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CANCER TREATMENT GUIDELINES

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Uganda Cancer Institute

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Copies may be obtained from Uganda Cancer Institute
Upper Mulago Hill Road
P.O Box 3935, Kampala, Uganda.
Tel: +256 414 540 410
+256 414 530 729
Website: www.uci.org.ug

This Treatment Guideline was generated by Uganda Cancer Institute team of Doctors and other Health Care Professionals Chaired and Co-chaired by Dr. Jackson Orem and Dr. Solomon Kibudde respectively.

Editorial Design:
Department of Medical Illustration,
Makerere University
P O.Box 7072 Kampala, Uganda
Tel: +256 414 540 228
Email: med.illustrationug@chs.mak.ac.ug

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FOREWORD

Cancer is a frightening diagnosis for any person or family or community regardless of social and economic strata. Globally, an estimated 14.1 million new cancer cases are diagnosed annually and of these approximately 8.2 million people die of cancer annually. Therefore cancer is a big public health problem locally and globally. Worldwide, an estimated 60 percent of all the new cancer cases occur in developing parts of the world.

In Uganda, according to data from Globocan in 2012, there were 29,400 new cancer cases, with an age-standardized rate of 169.7 and the risk of getting cancer before the age of 75 years was 17.6%. The number of cancer deaths was 21,500 and the risk of dying from cancer before the age 75 years was 14.1% and overall the 5-year prevalent cases among the adult population was 56,700. Among men, the top leading cancers are cancers of the prostate, oesophagus, Kaposi sarcoma, liver and colon in that order; while among women the 5 most frequent cancers are cervical cancer, breast cancer, kaposis sarcoma, oesophagus cancer and cancer of the ovary. Overall, the leading five cancers among both sexes in Uganda are cancer of cervix, Kaposi sarcoma, prostate cancer, breast cancer, and esophageal cancer; and this pattern is similar for other East African countries.

The top five cancers contribute over 60 percent of all the cancers seen at the Uganda Cancer Institute and similarly they are responsible for the 5 most frequent causes of cancer mortality in Uganda in the order Kaposi sarcoma (12.2%), cancer of cervix (10.6%), Prostate cancer (10.6%), Oesophagus cancer (10.0%) and breast cancer (5.5%) as per data from the Kampala Cancer Registry. Another observation about the 5 most frequent cancers is their etiological association with infections for instance cancer of the cervix and human papilloma virus, Kaposi sarcoma and human herpes virus 8, oesophagus cancer and human

papilloma virus infection. In addition, cancer of the cervix and Kaposi sarcoma are AIDS defining cancers and the leading type of cancer among people living with HIV infection in Uganda. Therefore, with proper coordination of resources and the existing infrastructure for communicable disease care in Uganda, we can improve detection, referral, treatment and follow-up of cancer patients with HIV/AIDS.

The guidelines for cancer care form a critical component of the national cancer control program (NCCP). The current guideline focuses on treatment of cancer in the context of Uganda and East Africa. The purpose is to promote quality management through a systematic decision making process during care, comprehensive approach and focusing on the needs of the patient. These guidelines are tailored to the current state of resources in terms of personnel, facilities, consumables, drugs and other services provided at the Uganda Cancer Institute and other countries within the East Africa Community.

The institute is also in final stages of implementing the referral guidelines for suspected cancer in Uganda as a strategy to curb late presentation and improve clinical outcomes. With adequate resources, we shall offer early diagnosis and screening services at our planned regional cancer centres and these shall network with the national referral centre for high tech and specialized care for our patients. This initiative will improve access, early diagnosis and referral; with a cardinal objective of improving cancer outcomes in Uganda.

This guideline offers the expected comprehensive approach to cancer and emphasizes the need for multi-disciplinary team discussions as a way to improve cancer outcomes. The Uganda cancer institute has teams of medical oncologist, radiation oncologists, gynecology oncologist, pediatric oncologist, surgical oncologists, oncology nurses, medical physicist, radiologists, medical counselors and

palliative care specialists all working as a team to improve cancer outcomes.

The current edition focuses on the 5 most frequent cancers in Uganda. This is a strategic start of initiating the cancer treatment guideline development process at Uganda Cancer Institute. After six to twelve months of implementation of these guidelines, we shall usher another edition encompassing the 10 most frequent cancers in Uganda. We are certain that these guidelines will play a big role in improving cancer care in Uganda and the rest of East Africa.

Dr. Jane Ruth Aceng
Hon. Minister of Health
Ministry of Health

PREFACE

Cancer is a major public health burden in Uganda. The burden of cancer cuts across age strata, economic strata and financial strata. The Uganda Cancer Institute is mandated to spearhead cancer control, research and care in Uganda. It is the epitome of cancer care in Uganda. The total new cancer cases seen annually are estimated to 4,000 new cases and this represents a small percentage of the new cancer cases in this country annually

The majority of cancer patients do not reach the National Cancer Treatment Center to receive the desired quality cancer care from the experts in the country. While we recognize efforts from medical doctors practicing at district and regional referral hospital to address the needs of cancer patients, there is a need to harmonize standards of care in the country.

The guidelines for care have been in place though not well outlined, and so we drafted this guideline to cover the commonly seen cancers as a strategy to build and extend to other cancers in the next edition. The motivation of the guideline is to standardize care in Uganda and the entire East Africa

The current and first edition of this guideline has five sections. The first section is a detailed outline of the treatment guidelines for the top five cancers in Uganda and the rest of East Africa namely cervical cancer, prostate cancer, Kaposi sarcoma, breast cancer and esophageal cancer. The second section of the guideline has cancer regimens for solid tumours, and the third section contains cancer treatment regimens for haematological cancers. The fourth section of the guidelines covers palliative care guidelines; and the fifth section of the guideline is dedicated to supportive care for cancer patients.

The purpose of the UCI cancer treatment guideline is to

harmonize care and communication between oncologists, medical doctors involved in cancer care and their communication to patients and their families. The guideline is pocket-size and easily readable during clinic hours and outside clinic hours. We hope that all oncology practitioners in Uganda and East-Africa will enjoy referring to the text as often as they see their patients

The guideline development process was initiated by the top management of the Uganda Cancer Institute under the leadership of Dr. Jackson Orem, who constituted a clinical practice guidelines working group spearheaded by Dr. Solomon Kibudde, Dr. Fred Okuku and Dr. Victoria Walusansa. During the guideline drafting process, one challenge we have observed is the need for protocols to support our local practices for which there is no established international evidence. We have included most of these 'practical' lessons as shared by the local experts and we have incorporated the current standards of care from other established guidelines particularly the National Cancer Comprehensive Network (NCCN) and the Cancer Therapeutic Adviser (CTA) guidelines.

However, in spite of these tremendous advances in oncology, this current guideline is tailored to our local priorities, resources and best practices given our socioeconomic context.

Lastly, we applaud the Uganda Cancer Institute and the African Development Bank for supporting the guideline development process.

Prof. Anthony K. Mbonye
Ag. Director General Health Services
Ministry of Health

- MESSAGE FROM THE DIRECTOR, UGANDA CANCER INSTITUTE
- MESSAGE FROM THE CHAIR, BOARD OF DIRECTORS, UGANDA CANCER INSTITUTE
- ACKNOWLEDGMENTS

At 50 years of the Uganda Cancer Institute, we recon the great history, and vividly envision a lustrous future...

Message from the Director, Uganda Cancer Institute

At 50 years of the Uganda Cancer Institute, we recon the great history, and vividly envision a lustrous future. As the center of excellence in oncology in East Africa, the Uganda Cancer Institute shall aspire to offer the state-of-the-art cancer care at local, regional and global platforms. Therefore, we celebrate yet another milestone, the Uganda Cancer treatment guidelines, as a key step towards cancer control in Uganda.

At the Uganda Cancer Institute, different specialists unite in teams that attend to specific cancers through clinics, ward-rounds, tumour board discussions and clinical-outcomes meetings with the sole aim of attaining improved outcome. We also offer health promotion through health education and cancer screening. Other cancer related services include diagnosis, surgery, chemotherapy, radiotherapy, immunotherapy, hormonal therapy and palliative care services.

The Uganda Cancer Institute (UCI) is leading the paradigm shift from cancer treatment to cancer prevention in Uganda. In 2012, the UCI founded the Comprehensive Community Cancer Program (CCCP) through which we connect with communities and empower them with knowledge and practices geared at cancer prevention, screening services and early diagnosis.

Additionally, the Uganda Cancer Institute is expanding its services to reach the entire country through its existing Mobile Cancer Clinics (MCC) that are to be scaled up into regional satellite cancer centres with the aim of improved access, early diagnosis, and effective referral.

This guideline is a start of a new era in clinical care in oncology in Uganda and East Africa; with emphasis on team work through tumour boards and/or disease-specific

multi-disciplinary clinics. The cardinal aim of the guideline is to improve outcomes of cancer care for all patients diagnosed with cancer and referred to us for treatment.

The guideline highlights the basic minimum standards for identifying pathognomic sings and symptoms, diagnosis, and approach to treatment, presented in form of algorithms for easy reference. Through the guidelines for cancer care in Uganda, we hope to improve communication amongst colleagues involved in cancer care for effective cancer outcomes for our patients. The guideline is available in hard copy and soft copy in form of an interactive pdf that will be free downloaded at the official Uganda Cancer Institute website.

The tool shall guard against malpractice that is currently infiltrating oncology in Uganda and other developing countries. Only trained physicians and surgeons are eligible to prescribe chemotherapy, and this should happen in a setting of recognized cancer treatment centres.

In future, we hope to incorporate personalized-treatment and more inclusion of targeted therapy and molecular tests in this guideline as a way of embracing advanced in clinical oncology. Thank you for reading and referring to this guideline.

“Research is our resource”

Dr. Jackson Orem
Director
Uganda Cancer Institute

Message from the Chair, Board of Directors, Uganda Cancer Institute

Allow me to congratulate the director, Uganda Cancer Institute, and the guidelines working group for putting together the first edition of the “Uganda Cancer Treatment guidelines”

“Oncology” is a dynamic subject and it cuts across all disciplines of medicine. What may be the practice today may be replaced by another approach tomorrow and therefore all users of this guideline must endeavor to keep up-to-date with literature

Cancer treatment guidelines sharply differ from cancer treatment protocols; what is presented here are treatment guidelines and are mere guideline and any clinician is free to change it depending on the circumstances. On the other hand, treatment protocols are for the clinical research and an individual is NOT at liberty to deviate and or change it at will.

From the guideline, it’s our hope that we shall stream several cancer treatment protocols to generate local evidence for cancer care in Uganda.

Each of the major tumours must have a tumour board. For instance a breast cancer tumour board should include a surgeon or surgical oncologist, a pathologist, radiologist, Medical oncologist, Radiation oncologist, Palliative care specialist, chemotherapy nurses as well as social workers

For each tumour the goal is to aim at cure, or prolonging life, or palliation. This should be stated at the start of a treatment plan.

Prof. Charles L. Olweny
Chair, Clinical Governance Committee
Chair, Board of Directors, Uganda Cancer Institute

ACKNOWLEDGMENTS

The management of the Uganda Cancer Institute would like to convey its heartfelt gratitude to the African Development Bank for the generous financial and technical support towards the development of these guidelines.

In the same spirit, special thanks go to the Director of the Uganda Cancer Institute, Dr. Jackson Orem for his visionary leadership and enormous support/contribution towards shaping oncology practice in Uganda today and in the future

The management would like to recognize the exceptional contribution from the guidelines working group coordinated by Dr. Solomon Kibudde, for the tireless efforts towards reviewing papers/articles, other guidelines and putting together existing best practices into this current clinical practice guideline.

Similarly, the expertise of key members of the guideline working group, including the Director, Dr. Fred Okuku and Dr. Victoria Walusansa; and the enormous contributions from the different tumour boards at the Uganda Cancer Institute, deserves outstanding credit.

The scope and detail of this work would not have been possible without the collective effort of the different cancer experts at the Uganda Cancer Institute and the management of the UCI is very grateful for each individual's contribution towards this document and pray that all the clinical teams shall adhere to this guideline as our standard of care.

Special thanks go to the following clinicians for their time and thoughts volunteered effortlessly during the process of compiling and editing this guideline;

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- Dr. Victoria Walusansa, consultant physician/oncologist, Uganda

Cancer Institute

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Cancer Institute

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- Dr. Jack Turyahikayo, palliative care specialist, Makerere University College of Health Sciences

Thanks you readers and clinicians in cancer care for using this guideline as a key step towards improving cancer outcomes in the Country and the rest of East Africa

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INTRODUCTION

Globally, cancer is the leading cause of mortality. In 2012 alone, there were an estimated 14.1 million new cancer cases diagnosed worldwide and an estimated 8.2 million cancer deaths[1]. By 2030, approximately 21.7 million new cancer cases are expected to be diagnosed and the death due to cancer is predicted to hit 13 million[1]. More than 70% of all cancer deaths occur in low- and middle-income countries, where resources available for prevention, diagnosis and treatment of cancer are limited or non-existent (WHO, 2012). In sub-Saharan Africa (SSA), cancer remains endemic in several countries and contributes significant morbidity and mortality. In Uganda, data from the Kampala Cancer Registry (KCR) shows an increase in the incidence of cancer in both sexes over the last two decades[2]. There are approximately 60, 000 cases of cancer per year, of which 45, 000 are incident cases.
And about 22, 000 deaths per year occur in Uganda due to cancer.

The Uganda Cancer Institute, which is the only comprehensive cancer treatment and referral centre in the country, handles approximately 4,000 new cancer cases per year, representing about 5% of all the new cancer cases in the country. The UCI offers cancer treatment including surgery, chemotherapy, radiotherapy, hormonal therapy and immunotherapy.
Largely, most patients are given chemotherapy either as neo-adjuvant or adjuvant or palliative by intent. Approximately 60% of patients at UCI need radiotherapy as part of the treatment by the teletherapy machine. Given the frequent late stage at presentation, most patients need radiotherapy for palliative intent. Lastly, surgical oncology services are relatively at infant stage due to several factors including trained human resource, service-strategy, and limited equipment/supplies for safe surgery at the UCI

Developing evidence-based clinical practice guidelines for cancer is a key component of a comprehensive National Cancer Control Programme (NCCP). With the rising number of patients in need of cancer treatment in Uganda, and several providers coming up to fill the cancer care gap, there is need for coordinated and standard care driven by standard national guidelines. Currently, several clinicians rely on other internationally drafted guidelines including the National Comprehensive Cancer Control Network (NCCN) guidelines, the American Society of Clinical Oncologists (ASCO) guidelines and the European Society of Medical Oncology (ESMO) guidelines, but these guidelines do not fully contextualize our challenges including costs of medicines, access to surgery, staging investigations capacity, limited cancer specialists and inadequate capacity for patient resuscitation and identification of chemotherapy associated toxicities.

While there have been efforts to have cancer treatment guidelines for Uganda, these have been published for only three cancers; breast cancer[3], Kaposi's sarcoma[4] and cutaneous T-cell lymphoma, and yet they remain remote and inaccessible to many health care providers. Traditionally, guidelines at the UCI have been based on consensus among experts, and they remain largely unpublished and inaccessible. This approach has been problematic because expert opinion does not always reflect the state of current medical knowledge[5]. Therefore the majority of patients do not receive treatment under uniform evidence-based guidelines and this challenge further magnifies as the UCI moves to establish satellite cancer clinics across the country. In addition, absence of treatment guidelines complicates care for patients referred to the UCI after partial treatment from private facilities within and neighboring Uganda. Additionally, with expert opinion being variable, it is difficult to measure cancer care outcomes since patients with the same type and stage of cancer will be managed differently.

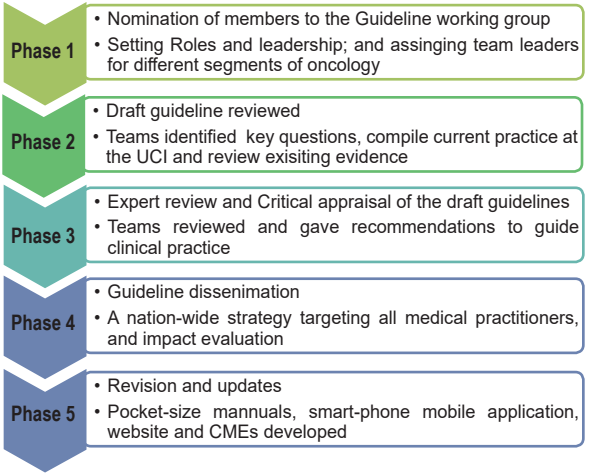
It is essential to develop patient care guidelines not only to standardize care but to also measure care outcomes as a basis for improvement

PURPOSE OF THE GUIDELINES

Cancer care requires a multidisciplinary team with a comprehensive approach and yet a common goal. To facilitate proper communication between the different specialists, there is need to establish a common agreement for the treatment of any particular patient with cancer, and this treatment plan is driven by the disease stage, tumour biology, available resources, treatment goals and patients' quality of life. The development of guidelines for cancer treatment in Uganda will enable proper treatment for every cancer patient, effective communication amongst different specialists, promote evidence based practice and allow for adequate planning for patient care. Through these guidelines, we hope to curb the unjustifiable variations in clinical practice; and respond to the increasing availability of evidence on new treatments and technologies, uncertainty about the effectiveness of many interventions in improving people's health, and a desire to make the best use of available health resources[12]

DEVELOPMENT OF THE GUIDELINES

The process of developing these guidelines consisted of five steps adopted from Thomson[13] ;



TARGET USERS

These will include all practitioners affiliated/working at cancer treatment centres in Uganda and East Africa. These will include;

- Medical oncologists
- Physicians practising Medical oncology
- Radiation oncologists
- Surgical oncologists
- Surgeons
- Palliative care experts – physicians, clinicians and nurses
- Oncology pharmacists
- Oncology nurses
- Medical officers
- Clinical officers
- Counsellors
- Gyn-oncologists
- Radiologists
- Nuclear Medicine physicians

ANTICIPATED IMPACT OF THE GUIDELINES

These guidelines are a key landmark on cancer care in Uganda and through the current edition; we hope to create a profound impact on cancer care in Uganda.

The following benefits are anticipated in the immediate and short-term implementation of these guidelines;

- Improvement in cancer referral in Uganda: The guidelines seek to reduce the delay from onset of symptoms to diagnosis and the duration from diagnosis of cancer to initiation of cancer treatment.
- Promoting rational use of chemotherapy: To ensure optimizing the available chemotherapy and improve clinical care, guidelines will promote better utilization of chemotherapy.
- Improving patient follow-up: Improving patients' awareness about cancer treatment will promote adherence to cancer treatment and patient follow-up.
- Leveraging communicable disease care platforms to improve cancer referral: Guidelines will enable linking existing services for care for HIV, TB, and Malaria in the country to support cancer screening, early diagnosis and timely referral.

This guideline is innovative in several ways;

- Tailored to available resources: The guidelines are intended to accommodate the local challenges in Uganda and the East Africa region, including limited access to chemotherapy, radiotherapy, immunotherapy, and surgery.
- Integration of on-going cancer control efforts in the country: Uganda has rolled-out several cancer prevention programs like HPV vaccination, HBV vaccination, Screening for cervix cancer, and breast cancer screening.
- Multi-disciplinary approach: These care guidelines will foster the process for the development of disease-specific teams at the UCI and nourish the set-up of disease-specific clinics and tumour-board meeting.

FUTURE PERSPECTIVES

Access to this guideline will be enhanced through modern Information Education Communication channels through several avenues including;

- Mobile phone technologies: The guideline will be made accessible to all practitioners in Uganda through enabling open access via the UCI website, and developing an interactive mobile smart-phone technologies and computer application for easy access.
- Easy download from local websites at cancer centres in East Africa
- Each disease specific guideline will have a supporting disease-specific patient-information booklet written in simple English with an attempt to explain all the important aspects of care for that particular cancer type and stage. The information will promote patient compliance and treatment and improve the dialogue between the doctors and the patients/their care takers.

REFERENCES

1. Ferley J, Soerjomataramł I, Ervik M, Dikshit R, Eser S. GLOBOCAN 2012 v1. 0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, Fr Int Agency Res Cancer. 2013.
2. Wabinga HR, Nambooze S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991-2010. Int J Cancer 2014;135:432-9.
3. Gakwaya A, Galukande M, Jombwe J, et al. Breast cancer guidelines for Uganda (2007). 2008.
4. Williams CK, Stefan DC, Rawlinson F, Simbiri K, Mbulaiteye SM. The African Organisation for Research and Training in Cancer and its conferences: a historical perspective and highlights of the Ninth. International Conference, Durban; 2013. p. 24.
5. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts: treatments for myocardial infarction. Jama 1992;268:240-8.
6. Coghill AE, Newcomb PA, Madeleine MM, et al. Contribution of HIV infection to mortality among cancer patients in Uganda. AIDS 2013;27:2933-42.
7. Menon MP, Coghill A, Mutyaba I, et al. Treatment Recommendations for Patients with NHL at the Uganda Cancer

Institute. Blood 2013;122:2960-.

8. De Boer C, Niyonzima N, Orem J, Bartlett J, Zafar Y. Prognosis, diagnostic delay, and patient characteristics associated with diagnostic delay among Kaposi sarcoma (KS) patients in Uganda. ASCO Meeting Abstracts 2013;31:6578-.
9. Galukande M, Mirembe F, Wabinga H. Patient Delay in Accessing Breast Cancer Care in a Sub Saharan African Country: Uganda. Br J Med Med Res 2014;4:2599-610.
10. Menon M, Coghill A, Mutyaba IO, et al. HIV and predictors of advanced cancer at presentation: Uganda. ASCO Meeting Abstracts 2014;32:6620-.
11. Orem J, Sandin S, Weibull CE, et al. Agreement between diagnoses of childhood lymphoma assigned in Uganda and by an international reference laboratory. Clin Epidemiol 2012;4:339-47.
12. Burgers JS, Grol R, KLAZINGA NS, MÄKELÄ M, Zaat J. Towards evidence-based clinical practice: an international survey of 18 clinical guideline programs. International Journal for Quality in Health Care 2003;15:31-045.
13. Thomson R, Lavender M, Madhok R. How to ensure that guidelines are effective. BMJ: British Medical Journal 1995;311:237.

PART ONE

TREATMENT GUIDELINES FOR THE FIVE MOST FREQUENT CANCERS IN UGANDA

BREAST CANCER

Clinical Evaluation

The following features should be explored during history taking and physical exam of a patient with suspected/ confirmed breast cancer

- Gender and Age
- Age at first parity
- Age at Menarche, and duration of menstrual cycle
- Type of contraceptive, and duration of use.
- Breast symptoms and signs
- Co-morbidity like HIV infection, Diabetes, hypertension and Heart Disease
- Family history of breast and/or ovarian cancer among 1st degree relatives
- Previous BRCA gene test among first degree relatives
- Prior irradiation to the chest wall
- Previous breast biopsy; and history of atypical ductal hyperplasia
- Alcohol and Tobacco use history
- Performance status using ECOG score
- Body Mass Index (BMI)
- Bimanual palpation of the breasts.
- Describe the tumor size and location, skin/chest wall changes and asymmetry and fixation to chest wall) and locoregional lymphnodes(mobility,matted or fixed)
- Complete physical exam

INVESTIGATIONS

Special Tests

Radiological tests

Before biopsy

- Plain chest radiograph (CXR), Bilateral mammogram for women above age 40 years

- Bilateral breast ultrasound scan and ultrasound of the regional lymphnodes.
- Breast MRI in case of early breast cancer where results will greatly infruence the management of the patient and in case of familial breast cancer.
- Breast implants, lobular cancer, suspicion of multifocality/ multicentricity

At Biopsy

- Trucut biopsy for histology (preferred). Review by at least two pathologists is recommended
- Fine Needle Aspirate for cytology (FNAC) in advanced cases may be done

After Biopsy

- Bone scan if clinically indicated Bone scan if symptomatic or elevated alkaline phosphatase (ALP) and stage III disease and above
- Abdomen ultrasound scan with focus on the Liver

Laboratory

- Immuno-histochemistry for the estrogen receptor(ER), Progesterone receptor (PR) and the Her2/Neu receptor status
- Complete Blood Count (CBC)
- HIV test (RCT)
- Hepatitis B surface antigen test (HepBsAg) and Hepatitis C virus serology
- Liver function tests (LFTs)
- Renal function tests (RFTs)
- Lactate dehydrogenase (LDH)
- Alkaline phosphatase (ALP)

Optional tests

- Oncogene assays
- Brain CT if suspicious CNS symptoms
- PET scan – Indicated for unsuspected nodal spread and distant metastases in selected cases

- ECG/ ECHO if treatment with anthracyclines and Trastuzumab is anticipated

STAGING

TNM clinical staging (AJCC 7th edition, 2010)

Primary tumour (T):

- TX: Primary tumour cannot be assessed
- T0: No evidence of primary tumour
- Tis: Carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no associated tumour.
  T1: Tumour 2.0 cm or less in greatest dimension
  - T1mic: Microinvasion 0.1 cm or less in greatest dimension
    T1a: Tumour more than 0.1 but not more than 0.5 cm in greatest dimension
    T1b: Tumour more than 0.5 cm but not more than 1.0 cm in greatest dimension
    T1c: Tumour more than 1.0 cm but not more than 2.0 cm in greatest dimension
- T2: Tumour more than 2.0 cm but not more than 5.0 cm in greatest dimension
- T3: Tumour more than 5.0 cm in greatest dimension
- T4: Tumour of any size with direct extension to (a) chest wall or (b) skin, only as described below.
  Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.
  - T4a: Extension to chest wall
    T4b: Oedema (including peaud'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
  - T4c: Both of the above (T4a and T4b)
    T4d: Inflammatory carcinoma

Regional lymph nodes (N):

- NX: Regional lymph nodes cannot be assessed (e.g., previously removed)
- N0: No regional lymph node metastasis

N1: Metastasis to movable ipsilateral level I, II axillary lymph node(s)
N2: Metastasis in ipsilateral level I, II axillary lymph node(s) that are clinically fixed or matted or in clinically detected ipslateral internal mammary nodes in the absence of clinically evident axillary lymphnode metastases

- N2a Metastases in ipslateral level I, II axillary lymphnodes fixed to one another (Matted) or to other structures
- N2b Metastases only in clinically detected ipslateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases.
- N3: Metastasis to ipsilateral infraclavicular (level III axillary) lymphnodes with or without level I, II axillary lymphnode involvement; or in clinically detected ipslateral internal mammary lymphnodes with clinically evident level I, II axillary lymphnode metastases or metastases in ipslateral supraclavicular lymphnodes with or without axillary, or internal mammary lymphnode involvement
- N3a Metastases in ipslateral infraclavicular lymph nodes
- N3b Metastases in ipslateral internal mammary lymphnodes with axillary lymphnodes
- N3c Metastases in ipslateral supraclavicular lymphnodes

Distant metastasis (M):

- MX: Presence of distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis present (includes metastasis to contralateral supraclavicular lymph nodes)

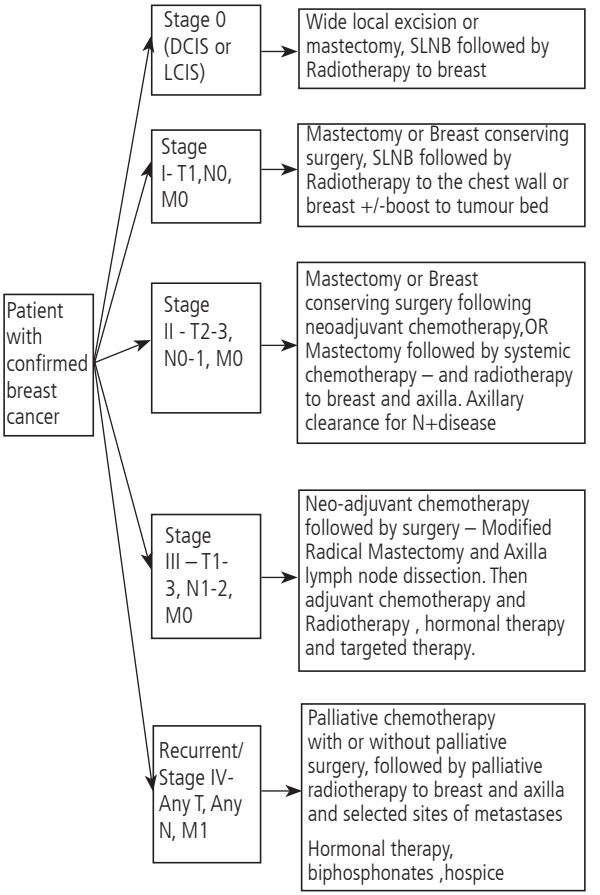
AJCC Staging

- Stage 0: Tis, N0, M0
- Stage I: T1, N0, M0
- Stage IIA: T0, N1, M0; T1, N1, M0; T2, N0, M0
- Stage IIB: T2, N1, M0; T3, N0, M0

- Stage IIIA: T0, N2, M0; T1, N2, M0; T2, N2, M0; T3, N1, M0; T3, N2, M0
  Stage IIIB: T4, Any N, M0
- Stage IIIC: Any T, N3, M0

  Stage IV: Any T, Any N, M1

Treatment guidelines



- Note; for DCIS.The following risk factors for recurence are considerd before giving adjuvant radiotherapy
- High grade , close or involved margins, size of the tumor, age<50yrs

Molecular Profiling

	ER/PR	HER2	Ki67%
LUMINAL A	5/8 or more	neg	<15%
LUMINAL B	<5/8	-/+	>15%
HER2	neg	pos	-
TRIPLE NEGATIVE (Basal Like)	neg	neg	-

Treatment of Breast cancer

Treatment should be carried out by a multidisciplinary team with at least one surgeon, radiologist, radiation oncologist, medical oncologist, pathologist,palliative care team and nurses . These processes of care should be coordinated by the primary doctor in the multidisplinary team prefelably an oncologists attending to patients in the breast cancer clinic.

Surgery for breast cancer

- Prophylactic Mastectomy
  - Risk reduction bilateral mastectomy with reconstruction should be offered to women with very high risk of breast cancer such as those who have tested positive for BRCA 1 and BRCA 2 Gene mutations alternatively breast conservation and mammographic surveillance can be an option
- Surgical options for Lobular carcinoma
  - Surgery for lobular carcinoma in situ should be considered only for those with pleomorphic variant after a tumor board discussion
- Surgical options for Ductal carcinoma in situ
  - The aim of the surgery for patients with ductal carcinoma in situ is to achieve negative margins. Negative margins are defined as greater than 2mm. Margins less than 1mm are considered inadequate.
  - This can be attained by a wide local excision followed with radiotherapy without lymph node dissection.
  - Oncoplastic breast surgery often using tissue displacement techniques to achieve a good

cosmetic outcome especially in patients with large breasts, a less favourable tumor/breast size ratio or cosmetically challenging (central or inferior) location of the tumor within the breast.

- Tumor bed should be marked with clips in a standardised way to facilitate accurate planning of the radiation boost field.
- Sentinel lymphnode biopsy (SLND) should be done for axillary node staging in clinically node negative breast cancer
- In presence of clinically node positive breast cancer and metastasis found in sentinel lymphnodes axillary clearance is indicated. clinically node negative breast cancer
- Mastectomy is indicated for large tumor relative to breast size, Tumor multicentricity, inability to achieve negative surgical margins after multiple resections, Prior radiation to the chest wall or breast, patients choice and other contraindications to radiotherapy.
- Breast reconstruction (immediate or delayed) should be available to those women requiring mastectomy
- Skin sparing mastectomy allows the skin envelope to be conserved for use in breast reconstruction

- **Surgical options for stage I and Stage II breast cancer**
  - Total mastectomy with axilla lymph node dissection is advised before initiation of chemotherapy. For selected patients, breast conserving surgery should be considered.
  - Neoadjuvant therapy may allow downsizing of a tumor so that Breast conserving surgery may be undertaken.
  - A breast MRI is preferable to assess the extent of disease pre and post neoadjuvant treatment.
  - When breast conserving procedure is anticipated, it is necessary to mark the primary site (using a marker clip or carbon localisation under ultrasound guidance) to facilitate accurate surgery

- Clinically negative axilla lymph nodes should be subjected to axilla imaging with ultrasound followed by FNAC or trucut biopsy of the lymph nodes
- Sentinel lymph node dissection (SNLD) should be performed among patients with breast cancer and clinically negative axilla nodes
- Sampled axilla lymph nodes should be well marked with clips to easy verification by the pathologist

- **Surgical options for stage III breast cancer**
  - Modified Radical Mastectomy (MRM) with level I and II axilla lymph node dissection is recommended. Patients should receive neo-adjuvant chemotherapy to improve surgical outcomes.

- **Surgical treatment for recurrence of breast cancer**
  - For local recurrence: consider surgical resection if possible followed by radiotherapy. All patients with known or suspected axillary lymph node metastases or T4 disease should have an axillary node dissection.
  - For regional or local regional recurrence: consider surgical resection if possible or attempt surgical resection after systemic chemotherapy; and this should be followed by radiotherapy
  - Patients with metastatic disease should not undergo radical mastectomy, unless motivated for by clinician for urgent local control palliation, or if metastases are isolated and stable. These patients should be discussed at the breast cancer tumour board before the decision to send them for surgery
    - Local recurrence may be amenable to wide local excision, even in the context of metastases. The decision to have surgery should be discussed in the breast cancer tumour board

- **Surgery for Metastatic breast cancer**
    - Toilet mastectomy should be performed to reduce tumor mass, palliate symptoms such as ulceration and bleeding

Radiotherapy for Breast cancer

- **Radiotherapy for Ductal/Lobular carcinoma in situ**
  - Breast conserving therapy with lumpectomy followed by Whole breast radiation should be considered standard treatment for DCIS
  - Special consideration for pts with <0.5cm tumor,low grade,completely excised with wide margin who opt for no radiotherapy.
  - Alternative is total mastectomy +/- LN dissection
- **Radiotherapy options for Stage I and Stage II**
  - Radiation therapy to the whole breast with or without boost to the tumour bed, and axilla. radiotherapy to the axilla will depend on the number of positive nodes compared to the extent of axillary clearance done
  - Positive margins will require a boost of 16Gys
  - Breast irradiation may be omitted in patients over 70 years of age, with hormone sensitive cancer and negative nodes.
  - All patients with breast conserving surgery must get radiotherapy to the breast.
  - Following mastectomy, RT will depend on the following; tumor size, axillary status,margins, histology and nodal status.
    - Sequential or concurrent hormonal therapy with radiation is acceptable.
- **Radiotherapy options for stage III breast cancer**
  - Radiation therapy is administered to the chest wall, infra-axilla region, supraclavicular region, internal mammary and the axilla bed
  - Dose prescriptions.
    - 45-50Gy at 1.8 to 2Gy per fraction using tangential fields to the breast or chest wall with not more than 2-3cm lung field involved, same dose and fractionation to the supraclavicular field and both fields must be treated daily Monday to Friday.
  - Boost the tumor bed with electrons or photons to a total dose of 64-66Gy

- For advanced disease,5-10cm tissue equivalent bolus is used till moist desquamation occurs.

- Radiotherapy options for IV breast cancer
- Locally advanced tumor can get palliative radiotherapy depending on the indication i.e.,
- Local bleeding, severe pain ,fungating ulceration 30Gy/10#,10Gy /1# ,20Gy /5# even higher doses can be given depending on the oncologist
- Metastatic stage !V
  - Palliative radiotherapy is indicated for sites of distant metastases including skin, nodes ,bones, spinal cord and brain. The typical doses for the different sites are as follows;
    - Bone and skin metastases
      - 8Gy/1# to single siteor 20Gy/5#
    - Cord compression
      - 20Gy/5# if good PS or residual power or
      - 8Gy/1# if poor PS or no power
    - Brain metastases
      - 20Gys/5# if good PS
      - 12Gy/2# over 3 days if poor PS

ADJUVANT ENDOCRINE THERAPY

Adjuvant Hormonal treatment for ER+ tumour patients

Type	DCIS/Stage I/II/III		Recurrent/Stage IV	
Treatment	1st line	2nd line	1st line	2nd line
Premenopausal	Tamoxifen for 5 years +/- ovarian ablation	AI for 5 years +/- ovarian ablation	Tamoxifen for 5 years +/- ovarian ablation	AI for 5 years +/- ovarian ablation
Postmenopausal	AI* or Tamoxifen for 5 years	Letrozole for 5 years	AI* or Tamoxifen for 5 years	Letrozole for 5 years

*AI – Aromatase Inhibitors like Anastrazole, Letrozole

A. **Adjuvant Hormonal therapy for patients with ER positive breast cancer**

TAMOXIFEN[1] — both pre and post-menopausal women

Tamoxifen	20 mg	PO Daily	5 to 10 years

Tamoxifen + Goserelin

Tamoxifen	20 mg	PO Daily	3 to 5 years
Goserelin	3.6mg	SC	Monthly

ANASTROZOLE[2] — post menopausal women

Anastrozole	1 mg	PO Daily	5 years

Anastrazole + Goserelin

Anastrazole	1 mg	PO Daily	3 to 5 years
Goserelin	3.6mg	SC	Monthly

LETROZOLE[3,4]- for post menopausal women

Letrozole	2.5 mg	PO Daily	5 years

Exemestane

Exemestane	25mg	PO Daily	5 years

EVEROLIMUS[5] (for pts who failed with Letrozole/ Tamoxifen/Anastrazole)

Everolirmus	10 mg	PO Daily	5 years

Pre-operative/ Adjuvant chemotherapy regimen

a. **Her2 negative breast cancer**

i. ***Preferred regimen***

CAF[6]

Adriamycin	50 mg/ m^2	IV	Day1
Cyclophosphamide	600 mg/ m^2	IV	Day 1
5-Fluorouracil	600 mg/ m^2	IV	Day 1

Repeat every 21days x 6 cycles

ii. ***Other regimens***

CMF[7-9]

Cyclophosphamide	600 mg/m^2	IV	Day1
Methotrexate	40 mg/m^2	IV	Day 1 & 8
5-Fluorouracil	600 mg/m^2	IV	Day 1

Repeat every 28 days x 6 cycles

FEC[10,11]

5FU	500mg/m^2	IV bolus	Day1
Epirubicin	75mg/m^2	IV	Day 1
Cyclophosphamide	500mg/m2	IV	Day 1

Repeat every 21 days x 6 cycles

Dose dense AC (Doxorubicin and cyclophosphamide)→T (Paclitaxel every two weeks) [12]

Doxorubicin	60mg/m^2	IV	Day 1
Cyclophosphamide	600mg/m^2	IV	Day 1

Repeat every 21days x 4 cycles

Followed by;

Docetaxel	100mg/m^2	IV	Day 1

Repeat every 21days x 4 cycles

OR

Paclitaxel	135mg/m^2	IV	Day 1

Repeat every 21days x 4 cycles

TAC[13]

Docetaxel	75mg/m^2	IV	Day1
Doxorubicin	50mg	IV	Day 1
Cyclophosphamide	500mg	IV	Day 1

Repeat every 21days x 6 cycles

Regimens for Her2 positive breast cancer

i. Preferred 1st line

TCH[14]

Docetaxel	75mg/m^2	IV	Day1
Carboplatin	AUC 5	IV	Day 1
Transtuzumab	4mg/Kg iv week 1	IV	Day 1

Repeat every 21days x 6 cycles

Followed by;

Transtuzumab	2mg/kg	IV	Day 1

Repeat every week x 17 weeks

Followed by;

Transtuzumab	6mg/Kg	IV	Day 1

Repeat every 21days x 1 year

Dose dense AC followed by Paclitaxel with Transtuzumab[15,16]

Doxorubicin	60mg/m^2	IV	Day 1
Cyclophosphamide	600mg/m^2	IV	Day 1

Repeat every 21days x 4 cycles

Followed by;

Paclitaxel	135mg/m^2	IV	Day 1

Repeat every 21days x 4 cycles

With

Transtuzumab	4mg/kg	IV	Day 1, Week 1

Followed by;

Transtuzumab	2mg/kg	IV	Day 1

Repeat every week x 17 weeks

Followed by;

Transtuzumab	6mg/Kg	IV	Day 1

Repeat every 21days x 1 year

ii. Other regimens

Docetaxol+ cyclophosphamide + Transtuzumab[17]

Docetaxel	75mg/m^2	IV	Day 1
Cyclophosphamide	600mg/m^2	IV	Day 1

Repeat every 21days x 4 cycles

Followed by;

Transtuzumab	4mg/kg	IV	Day 1, Week 1

Followed by;

Transtuzumab	2mg/kg	IV	Day 1

Repeat every week x 17 weeks

Followed by;

Transtuzumab	6mg/Kg	IV	Day 1

Repeat every 21days x 1 year

Paclitaxel + transtuzumab[18]

Paclitaxel	80mg/m^2	IV	Day 1

Repeat every week for 12 weeks

With

Transtuzumab	4mg/kg	IV	Day 1, Week 1

Followed by;

Transtuzumab	2mg/kg	IV	Day 1

Repeat every week x 17 weeks

Followed by;

Transtuzumab	6mg/Kg	IV	Day 1

Repeat every 21days x 1 year

Chemotherapy regimens for recurrent breast cancer

a. Preferred combination regimens

Gemcitabine + Carboplatin[19,20]

Gemcitabine	1,000mg/m^2	IV	Day1 and 8
Carboplatin	AUC 5	IV	Day 1

Repeat every 21days x 6 cycles

Gemcitabine + Paclitatel[21]

Gemcitabine	1,000mg/m^2	IV	Day1 and 8
Paclitexel	135mg/m^2	IV	Day 1

Repeat every 21days x 6 cycles

TC[22]

Docetaxel	75mg/m^2	IV	Day1
Cyclophosphamide	600mg/m^2	IV	Day 1

Repeat every 21days x 4 cycles

Docetaxel + Capecitabine

Docetaxel	75mg/m^2	IV	Day1
Capecitabine	950mg/m^2	PO BID	Day 1 – 14

Repeat every 21days x 6 cycles

Preferred single agent regimens

Capecitabine [23]

Capecitabine	1000mg/m^2	PO BID	Day 1 – 14

Repeat every 21days x 6 cycles

Paclitaxel [24]

Paclitaxel	175mg/m^2	IV	Day 1

Repeat every 21days x 6 cycles

Docetaxel [25,26]

Docetaxel	75mg/m^2	IV	Day 1

Repeat every 21days x 6 cycles

Gemcitabine[27,28]

Gemcitabine	725 mg/rn^2	IV over 30 minutes	Day 1 , 8 & 15

Repeat every 21days x 6 cycles

Important precautions regarding chemotherapy use for breast cancer patients

- All patients with recurrence or metastases must be discussed at the breast cancer tumour board meeting before deciding the treatment plan.
- For pregnant patients; systemic chemotherapy should be AVOIDED during the first trimester and when the decision is agreed to initiate treatment, the oncologist should liaise with the attending obstetrician for close monitoring of the mother and fetal wellbeing.
- For all the premenopausal women wishing to conceive after chemotherapy, fertility issues should be discussed with the oncologist and nurse counsellor before initiation of chemotherapy.
- Chemotherapy should be prescribed cautiously among patients aged > 70 years or else avoided. Among these patients, adjuvant hormonal therapy is advised after surgery or radiotherapy.
- Elderly patients with poor performance status and hormone receptor positive breast cancer should be given AI as first line treatment and assessed for operability at 3-6 months.

Follow-up for breast cancer patients

Stage	Clinical	Investigations	Treatment options
DCIS/LCIS	History and physical exam every 6 months for 5 years then annually	Mammography every 12 months	Hormonal therapy – Tamoxifen or AI; - counselling on risk reduction
Stage I/II	History and Physical exam every three months for 5 years, then annually	Mammography every 12 months Monitor for osteoporosis and treat with Calcium and Vitamin D	Hormonal therapy – Tamoxifen or AI; - counselling on risk reduction
Stage III	History and Physical exam every three months for 5 years, then annually	Mammography every 12 months Monitor for osteoporosis and treat with Calcium and Vitamin D	Hormonal therapy – Tamoxifen or AI; - counselling on risk reduction -Avoid alcohol - lean body weight - regular exercise
Stage IV	History and Physical exam every three months for 5 years, then annually	Mammography every 12 months Monitor for osteoporosis and treat with Calcium and Vitamin D	Hormonal therapy – Tamoxifen or AI; -Bisphosphates for Stage IV with bone metastases

Special circumstances

Hypercalcemia

- Patients with hypercalcemia should be given bisposphonates. Patients with renal dysfunction require adequate hydration before administration of bisphosphonates

Bone metastases

- Patients with symptomatic/asymptomatic bone metastases should be given monthly zolendronic acid, and assess bone scan every six months

Pleural effusions

- Consider a standard drain for very ill patient with massive pleural effusion. Pleurodesis should be sought through a consultation to the cardiothoracic/ general surgeons.
- Pleurodesis: Bleomycin 45-60 units in 50-100ml normal saline. Turn every 2 minutes for 6 turns. Leave clamped for 2 hours then allow draining for at least 24 hours.

Local recurrence after mastectomy

- Perform FNAC and trucut biopsy for diagnosis and ER status. Restage with CXR, bloods tests, bone scan and abdominal ultrasound scan.
- If restaging is negative, offer chest wall RT if no previous radiotherapy
- If previous chest wall RT then consider second line hormonal therapy or chemotherapy as appropriate

Systemic relapse

- Second line hormonal therapy if bone only disease or limited visceral disease
- Chemotherapy if good performance status and/or ER negative

DOSE MODIFICATIONS & TOXICITY

- Delay chemotherapy by one week if Absolute Neutrophil Count (ANC) is below 1.0
- Delay chemotherapy by one week in patients with platelets <75,000
- Blood transfuse if hemoglobin drops below 8g/dl.
- Delay Chemotherapy by one week if hemoglobin below 8g/dl in patients with metastatic cancer
- Do not reduce dose unless persistent neutropenia, thrombocytopenia is leading to prolonged treatment delays, or associated with sepsis
- Dose reduced by 20% if necessary as above after

discussion with the senior Oncologist on duty.

Special considerations

- Cap all patients at body surface area of $2m^2$
- Avoid methotrexate in ascites or pleural effusions
- Instruct patients as to importance of high fluid intake during cyclophosphamide therapy. Discontinue cyclophosphamide if haemorrhagic cystitis occurs in spite of adequate hydration.
- Severe gastro-intestinal side effects (anorexia, nausea and vomiting, diarrhoea, stomatitis, dry mouth, epigastric pain) - postpone therapy until symptoms subside.
- Grade 3 or 4 vomiting or diarrhoea - reduce by 20% next cycle
- Grade 3 or 4 mucosal ulceration - Reduce methotrexate, 5-FU and anthracycline by 20%.

REFERENCES

1. Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. The Lancet 2010;374:2055-63.
2. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. The Lancet 2005;366:455-62.
3. Group BIG-C. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 2005;2005:2747-57.
4. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1–and/or ErbB-2–positive, estrogen receptor–positive primary breast cancer: evidence from a phase III randomized trial. Journal of Clinical Oncology 2001;19:3808-16.
5. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. New England Journal of Medicine 2012;366:520-9.
6. Hutchins LF, Green SJ, Ravdin PM, et al. Randomized, controlled trial of cyclophosphamide, methotrexate, and fluorouracil versus cyclophosphamide, doxorubicin, and

fluorouracil with and without tamoxifen for high-risk, node-negative breast cancer: treatment results of Intergroup Protocol INT-0102. Journal of Clinical Oncology 2005;23:8313-21.

7. Bonadonna G. Karnofsky memorial lecture. Conceptual and practical advances in the management of breast cancer. Journal of Clinical Oncology 1989;7:1380-97.
8. Buzzoni R, Bonadonna G, Valagussa P, Zambetti M. Adjuvant chemotherapy with doxorubicin plus cyclophosphamide, methotrexate, and fluorouracil in the treatment of resectable breast cancer with more than three positive axillary nodes. Journal of clinical oncology 1991;9:2134-40.
9. Goldhirsch A, Colleoni M, Coates A, Castiglione-Gertsch M, Gelber R, Group IBCS. Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: Are all CMFs alike? Annals of oncology 1998;9:489-93.
10. Levine MN, Pritchard KI, Bramwell VH, Shepherd LE, Tu D, Paul N. Randomized trial comparing cyclophosphamide, epirubicin, and fluorouracil with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: update of National Cancer Institute of Canada Clinical Trials Group Trial MA5. Journal of Clinical Oncology 2005;23:5166-70.
11. Levine MN, Bramwell VH, Pritchard KI, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. Journal of Clinical Oncology 1998;16:2651-8.
12. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. Journal of clinical oncology 2003;21:1431-9.
13. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. New England Journal of Medicine 2005;352:2302-13.
14. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. New England Journal of Medicine 2011;365:1273-83.
15. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. New England Journal of Medicine 2005;353:1673-84.
16. Dang C, Fornier M, Sugarman S, et al. The safety of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab in HER-2/neu overexpressed/amplified breast cancer. Journal of Clinical Oncology 2008;26:1216-22.
17. Jones SE, Collea R, Paul D, et al. Adjuvant docetaxel and

cyclophosphamide plus trastuzumab in patients with HER2-amplified early stage breast cancer: a single-group, open-label, phase 2 study. The Lancet Oncology 2013;14:1121-8.

18. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. New England Journal of Medicine 2015;372:134-41.
19. O'shaughnessy J, Schwartzberg L, Danso M, et al. A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). ASCO Annual Meeting Proceedings; 2011. p. 1007.
20. Albain K, Nag S, Calderillo-Ruiz G, et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall surviva. ASCO Annual Meeting Proceedings; 2004. p. 510.
21. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. Journal of Clinical Oncology 2008;26:3950-7.
22. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. Journal of Clinical Oncology 2006;24:5381-7.
23. Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. Journal of Clinical Oncology 2005;23:2155-61.
24. Seidman A, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. Journal of Clinical Oncology 1995;13:2575-81.
25. Ravdin PM, Burris H, Cook G, et al. Phase II trial of docetaxel in advanced anthracycline-resistant or anthracenedione-resistant breast cancer. Journal of clinical oncology 1995;13:2879-85.
26. Harvey V, Mouridsen H, Semiglazov V, et al. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. Journal of clinical oncology 2006;24:4963-70.
27. Brodowicz T, Kostler W, Möslinger R, et al. Single-agent gemcitabine as second-and third-line treatment in metastatic breast cancer. The breast 2000;9:338-42.
28. Spielmann M, Llombart-Cussac A, Kalla S, et al. Single-agent gemcitabine is active in previously treated metastatic breast cancer. Oncology 2001;60:303-7.

CERVICAL CANCER

Clinical evaluation of a patient with cancer of the cervix

- Age and Parity
- Nature and duration of per vaginal bleeding
  - Inter-menstrual bleeding
  - post-coital bleeding
  - post-menopausal bleeding
  - abnormal appearance of the cervix (suspicion of malignancy) vaginal discharge (blood stained)
- Other symptoms of cervical cancer
  - Pelvic pain
  - Vomiting
  - Hiccups
  - Bone pain
- Co-morbidity like HIV infection, diabetes, hypertension and heart disease
- Family history of cancer among 1st degree relatives
- Previous PAP smear or VIA or treatment for premalignant lesions
- Prior irradiation to the pelvis
- Alcohol and tobacco use history
- Performance status using ECOG score
  - ECOG 0: Fully active and able to carry on without restriction.
  - ECOG 1: Unable to carry out physically strenuous activities but ambulatory and able to complete work of a light or sedentary nature
  - ECOG 2: Ambulatory and capable of all self-care but unable to complete work activities. Up and about more than 50% of waking hours.
  - ECOG 3: Capable of only limited self-care and/ or confined to a bed or chair for more than 50% of waking hours.
  - ECOG 4: Completely disabled. Unable to carry out any self-care. Totally confined to a bed or chair.
- Body Mass Index (BMI)

- Nutritional assessment
- Complete physical exam
- Pelvic examination

INVESTIGATIONS

- Complete Blood Count (CBC)
- HIV test (RCT)
- Hepatitis B surface antigen Test (HepBsAg) and Hepatitis C virus serology (Optional)
- Liver function tests (LFTs)
- Renal function tests (RFTs)
- Lactate dehydrogenase (LDH)
- Alkaline phosphatase (ALP)
- Abdomen ultrasound scan with focus on the liver
- Plain chest radiograph (CXR)
- Cervical biopsy, and pathology review
- Colposcopy and excisional biopsy for Stage IA (e.g. cone biopsy).
- Cystoscopy: Only for stages II, III, IV. Biopsy suspicious lesions.
- Selected skeletal X-Rays and/or bone scan where indicated (clinical suspicion skeletal metastases).
- MRI/CT scans optional for early stage disease and if accessible, particularly useful for measurement of size of lesion and/or parametrial involvement.
- Pelvic CT assessment of pelvic/para-aortic nodal areas in stage IB2 or higher scheduled for curative chemo-radiotherapy.
- Consider FNAB of enlarged nodes or lesions if questionable findings.

FIGO STAGING (CLINICAL) 2009

- Stage I: The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded).
  - IA: Invasive cancer identified only microscopically. (All gross lesions even with superficial invasion are Stage IB cancers). Invasion is limited to measured

stromal invasion with a maximum depth of 5mm and no wider than 7mm.
    - IA1: Measured invasion of stroma no greater than 3mm in depth and no wider than 7mm.
    - IA2: Measured invasion of stroma > 3mm and < 5mm in depth and no wider than 7mm.
  - Stage IB: Clinical lesions confined to the cervix or preclinical lesions greater than stage IA.
    - IB1: Clinical lesions no greater than 4cm in size.
    - IB2: Clinical lesions > 4cm in size.
- Stage II: The carcinoma extends beyond the cervix, but has not extended onto the pelvic wall. The carcinoma involves the upper 2/3 of the vagina.
  - IIA: Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement.
    - IIA1: clinically visible lesion no greater than 4 cm.
    - IIA2: clinically visible lesion >4cm.
  - IIB: Obvious parametrial involvement but not onto the pelvic sidewall.
- Stage III: The carcinoma has extended onto the pelvic sidewall. On rectal examination, there is no cancer free space between the tumour and pelvic sidewall. The tumour involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes.
  - IIIA: Involvement of the lower vagina but no extension onto pelvic sidewall.
  - IIIB Extension onto the pelvic sidewall, or hydronephrosis / non-functioning kidney.
- Stage IV: The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
  - IVA: Spread to adjacent pelvic organs.
  - IVB: Spread to distant organs.

TREATMENT ALGORITHM FOR CERVICAL CANCER

	Stage	Treatment
IA	Stage IA1	**Conization** only, provided cone margins are negative, no vascular/lymphatic invasion, wishing to preserve fertility and patient available/prepared to return for regular follow up **Total hysterectomy** (TH) (abdominal/vaginal/ laparoscopic) provided cone margins negative and no vascular/lymphatic invasion. **TH + Pelvic Lymphadenectomy (PL)** if vascular/lymphatic invasion present. **Radical hysterectomy + PL** if cone margins are involved with cancer (perceived to be stage IB1). **Intracavitory brachytherapy** if not surgical candidate.
	Stage IA2	**Total hysterectomy (abdominal/vaginal/ laparoscopic) + PL** if cone margins clear and no vascular/lymphatic invasion. **Radical hysterectomy + PL** if cone margins are involved with cancer (perceived to be stage IB1). **Radical trachelectomy (+ Shirodkar suture) + PL** where preservation of fertility is desired. **Chemo-radiation** if not surgical candidate
IB	Stage IB1	**Radical hysterectomy + PL**. Individualise for age, obesity and co-existing medical conditions. If there is a suspicion of involved lymph nodes frozen section should be obtained. If positive, consider abandoning surgery. Discontinue hysterectomy if extra-cervical extension could compromise resection lines, in order to avoid two radical therapies i.e. surgery and adjuvant radiation. **Radical trachelectomy (+ Shirodkar suture) + PL** for tumours ≤ 2cm where preservation of fertility is desired. **Chemo-radiation + intracavitory brachytherapy** if medically unfit for surgery

	Stage IB2	**Chemo-radiation + intracavitary Brachytherapy**. **Radical hysterectomy and PLND** maybe an option in selected cases. Consider **salvage hysterectomy** if persistent central tumour can be histologically demonstrated 2-3 months post-treatment.
IIA	Stage IIA1	**Radical hysterectomy + PL** if minimal involvement of upper vagina
	Stage IIA2	**Chemo-radiation + intracavitary brachytherapy**.
IIB	Stage IIB	Chemo-radiation + intracavitary brachytherapy
III	Stage III	**Chemo-radiation + intracavitary brachytherapy**. **Palliative radiotherapy** should be considered if massive tumours with bilateral hydronephrosis, severe wasting/poor performance status, or patients with life threatening co-morbid conditions
IV	Stage IVA	Fit patients with low volume tumour: chemo-radiation + intracavitary brachytherapy. Patients with a bladder or rectal fistula must be referred for surgery and receive palliative radiotherapy thereafter. **Palliative radiotherapy** should be considered: Massive tumours with bilateral hydronephrosis, severe wasting/poor performance status, or patients with life threatening co-morbid conditions.
	Stage IVB	Palliative radiotherapy and/or trial of chemotherapy

	RECURRENT DISEASE.	If recurrence confined to pelvis and no previous RT: Chemoradiation. Small central recurrence and prior RT: Consider Exenteration or salvage hysterectomy. Large recurrence in radiation field: Consider chemotherapy and best supportive care. Distant recurrence: Individualise to chemotherapy, tumour directed RT or best supportive care

CHEMOTHERAPY REGIMENS FOR CANCER OF THE CERVIX

A. CONCURRENT CHEMORADIATION

CISPLATIN + XRT (CONCURRENT CHEMORADIATION)[1,2]

Before each cycle: CBC, RFTs, LFTs, Serum electrolytes (K+, Na+, Ca2+, Mg2+)

Pre-medications:

- Granisetron 3mg or Ondansetron 16 mg iv
  Dexamethasone 16 mg iv
  (All premedications are infused in 100mL NS over 10 mins)
  NB: The patient receiving Cisplatin should have creatinine clearance of 60mL/min (using Cockcroft-Gault formula) and urine output 100mL/hr or 20mg Furosemide iv prior to giving Cisplatin.

Cisplatin	40 mg/m^2	IV over 30 mins	Day 1
Concurrent RT:	50Gy/25#/5wks		

Repeat every week

B. NEOADJUANT CHEMOTHERAPY

CP (CISPLATIN + PACLITAXEL) [3]

Cisplatin	60 mg/m^2	IV over 30mins	Day 1
Paclitaxel	60 mg/m^2	IV	Day 1

Repeat every 21days x 3 cycles

C. CHEMOTHERAPY FOR STAGE IVB (METASTATIC) CANCER

PACLITAXEL + CISPLATIN[3]

Paclitaxel	135mg/m^2	IV over 60mins	Day 1
Cisplatin	50mg/m^2	IV	Day 1

Repeat every 21days x 6 cycles

CT (CARBOPLATIN + PACLITAXEL)[4,5]

Carboplatin	AUC 5	IV over 30mins	Day 1
Paclitaxel	135 mg/m^2	IV	Day 1

Repeat every 21days x 6 cycles

CT (CARBOPLATIN + DOCETAXEL)

Carboplatin	AUC 5	IV over 30mins	Day 1
Docetaxel	60 mg/m^2	IV	Day 1

Repeat every 21days x 6 cycles

D. RECURRENT OR PERSISTENT CANCER

MIC (MITOMYCIN + IFOSFAMIDE + CISPLATIN)

Mitomycin	6 mg/m^2	IV	Day 1
Cisplatin	50 mg/m^2	IV	Day 1
Ifosfamide + Mesna	3g/m^2	IV	Day 1

Repeat every 21days x 6 cycles

CT (CARBOPLATIN + DOCETAXEL)

Carboplatin	AUC 5	IV over 30mins	Day 1
Docetaxel	60 mg/m^2	IV	Day 1

Repeat every 21days x 6 cycles

FOLLOW-UP AFTER TREATMENT FOR CANCER OF THE CERVIX

Patients who have been treated for curative intent should undergo the following evaluation every 3 months for the first 3 years and every 6 months for the next 2 years

- Colposcopy
- CA 125
- Pelvic ultrasound scan or pelvic CT scan
- Complete history and physical exam

DOSE MODIFICATIONS & TOXICITY

- Delay chemotherapy by one week if Absolute Neutrophil count (ANC) is below 1.0
- Delay chemotherapy by one week in patients with platelets <75,000
- Transfuse if hemoglobin drops below 8g/dl.
- Delay one week if hemoglobin below 8g/dl in patients

with metastatic cancer

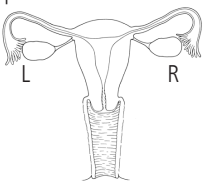
- Do not reduce dose unless persistent neutropenia, thrombocytopenia is leading to prolonged treatment delays, or associated with sepsis
- Dose reduced by 20% if necessary as above after discussion with senior.

SPECIAL CONSIDERATIONS

- Cap all patients at body surface area of $2m^2$
- Severe gastro-intestinal side effects (anorexia, nausea and vomiting, diarrhoea, stomatitis, dry mouth, epigastric pain) - postpone therapy until symptoms subside.
- Grade 3 or 4 vomiting or diarrhoea - reduce by 20% next cycle

REFERENCES

1. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. New England Journal of Medicine 1999;340:1154-61.
2. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. Journal of Clinical Oncology 1999;17:1339-.
3. Tewari KS, Sill MW, Long III HJ, et al. Improved survival with bevacizumab in advanced cervical cancer. New England Journal of Medicine 2014;370:734-43.
4. Moore KN, Herzog TJ, Lewin S, et al. A comparison of cisplatin/paclitaxel and carboplatin/paclitaxel in stage IVB, recurrent or persistent cervical cancer. Gynecologic oncology 2007;105:299-303.
5. Kitagawa R, Katsumata N, Shibata T, et al. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505. Journal of Clinical Oncology 2015;33:2129-35.

HISTOLOGY				
Date of biopsy _____/____/_____ *dd mm yy*			Histologic diagnosis:	
PHYSICAL EXAM				
Palpable or visible tumor location 			Tumor size_____cm	
Parametrial involvement	□ None	□ Right	□ Left	Signature
Pelvic sidewall involvement	□None	□ Right	□ Left	
Vaginal involvement	□ None	□ Upper 2/3	□ Lower 2/3	
Bladder mucosal involvement	□Yes	□ No	□ Not done	
Palpable rectal mucosal involvement	□Yes	□ No	□ Not done	Date of exam ____/___/__ *dd mm yy*
Enlarged lymph nodes	□L inguinal □R inguinal	□L supraclav □ R supraclav	□ L cervical □ R cervical	
Additional physical exam findings:				

IMAGING			
Chest x-ray	___/___/___ *dd mm yy*	□ Not done	□ Normal □Abnormal (describe)
Ultrasound (pelvic, abdominal)	___/___/___ *dd mm yy*	□ Not done	□ Normal □ Abnormal (describe) □ Hydronephrosis
Cystoscopy	___/___/___ *dd mm yy*	□ Not done	□ Normal □ Abnormal (describe) □ Bladder mucosa tumor
Proctoscopy	___/___/___ *dd mm yy*	□ Not done	□ Normal □ Abnormal (describe) □ Rectal mucosa tumor
Hysteroscopy	___/___/___ *dd mm yy*	□ Not done	□ Normal □ Abnormal (describe)
FINAL STAGE			

ADDITIONAL EVALUATION		
Diagnostic test	**Date**	**Value**
HIV	___/___/___ *dd mm yy*	□ Negative □ Positive □ Indeterminate
CD4 count	___/___/___ *dd mm yy*	____ cells/mm^3
Viral load	___/___/___ *dd mm yy*	____ copies/ml
Complete blood coun	___/___/___ *dd mm yy*	White blood cell _____ 10^3/µL Hemoglobin _____ g/dL Platelets _____ 10^3/µL Neutrophils _____ cells/µL
Creatinine	___/___/___ *dd mm yy*	____ µmol/L

Liver function tests	__/___/__ *dd mm yy*	ALP ___ U/L ALT _____ U/L AST _____ U/L
Potassium	___/___/__ *dd mm yy*	_____ mmol/L
Calcium	___/___/__ *dd mm yy*	_____ mmol/L
Magnesium	___/___/__ *dd mm yy*	_____ mmol/L
Phosphorous	___/___/__ *dd mm yy*	_____ mmol/L
LDH	___/___/__ *dd mm yy*	___ U/L
Audiometry	___/___/__ *dd mm yy*	□ Normal □ Abnormal (describe)

Stage	Description	Stage	Description
IA	Microscopic invasion	IIB	Obvious parametrial involvement but not onto the pelvic sidewall.
IA1	Stromal invasion ≤ 3 mm depth and ≤ 7 mm width	IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall.
IA2	Stromal invasion > 3 mm and < 5mm depth, ≤ 7mm width		
IB	Visible lesions confined to cervix and microscopic lesions greater than IA	IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney
IB1	No greater than 4 cm in size	IVA	Spread to adjacent pelvic organs
IB2	>4 cm in size	IVB	Spread to distant organs
IIA	Involvement of up to the upper 2/3 of the vagina. No obvious parametrial involvement		
IIA1	≤4 cm in size		
IIA2	>4 cm in size		

ESOPHAGEAL CANCER

Clinical evaluation of a patient with cancer of the Oesophagus

- Gender and age
- Degree of difficulty in feeding/dysphagia
  - Grade 0: Ability to eat normal food
  - Grade 1: Ability to eat some solid food
  - Grade 2: Ability to eat semi-solid food only
  - Grade 3: Ability to eat liquids only
  - Grade 4: Complete dysphagia
- Symptoms of oesophageal cancer
  - Chest pain
  - Weight loss
  - Hoarseness
  - Chronic cough
  - Hiccups
  - Bone pain
  - Vomiting blood
  - Loss of appetite
- Co-morbidity like HIV infection, diabetes, hypertension and heart disease
- Family history of cancer among 1st degree relatives
- Previous upper GI endoscopy findings
- Prior irradiation to the chest wall
- Alcohol and tobacco use history
- Performance status using ECOG score
  - ECOG 0: Fully active and able to carry on without restriction.
  - ECOG 1: Unable to carry out physically strenuous activities but ambulatory and able to complete work of a light or sedentary nature
  - ECOG 2: Ambulatory and capable of all self-care but unable to complete work activities. Up and about more than 50% of waking hours.
  - ECOG 3: Capable of only limited self-care and/ or confined to a bed or chair for more than 50% of waking hours.

- ECOG 4: Completely disabled. Unable to carry out any self-care. Totally confined to a bed or chair.

- Body Mass Index (BMI)
- Nutritional assessment
- Examination the orocavity, oropharynx and hypopharynx in smokers with SCC to rule out synchronous tumors.
- Complete physical exam

INVESTIGATIONS

- Complete Blood Count (CBC)
- HIV test (RCT)
- Hepatitis B surface antigen Test (HepBsAg) and Hepatitis C virus serology
- Liver function tests (LFTs)
- Renal function tests (RFTs)
- Lactate dehydrogenase (LDH)
- Alkaline phosphatase (ALP)
- Abdomen ultrasound scan with focus on the liver
- Plain chest radiograph (CXR)
- CT scan of neck, chest and abdomen
- Endoscopic examination (indicating the location of the tumor form the incisors, length of the tumor , nature of tumor ie polypoid, exophytic, ulcerated , extension into the stomach, percentage of circumference involved)
- Biopsy for histology (Her2/neu overexpression in patients with adenocarcinoma of gastroesophageal junction with distant metastasis.)
- Endoscopic ultrasound examination (EUS) in patients who are to benefit from surgical resection
- Tracheobronchoscopy in tumors at or above the tracheal bifurcation

STAGING

Depth of Tumour Penetration (T Stage):

Tis Carcinoma in situ or high-grade dysplasia

T1 Invasion into lamina propria or submucosa

T2 Invasion into muscularis propria

T3 Invasion into adventitia

T4a Invasion into resectable adjacent structures (e.g.: pleura, pericardium, and diaphragm)

T4b Invasion into unresectable adjacent structures (e.g.: aorta, vertebral body, and trachea)

Regional* Lymph Node Involvement (N Stage):
N0 No regional lymph node involvement

N1 Involvement of one or two regional lymph nodes

N2 Involvement of three to six regional lymph nodes

N3 Involvement of seven or more regional lymph nodes

* Regional refers to any peri-esophageal lymph node (from cervical to celiac regions)

Histologic Grade (G Stage):
G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

G4 Undifferentiated

Location of Squamous Cell Carcinomas:
U: Upper esophagus (20 to 25 cm from incisors)

M: Middle esophagus (>25 to 30 cm from incisors)

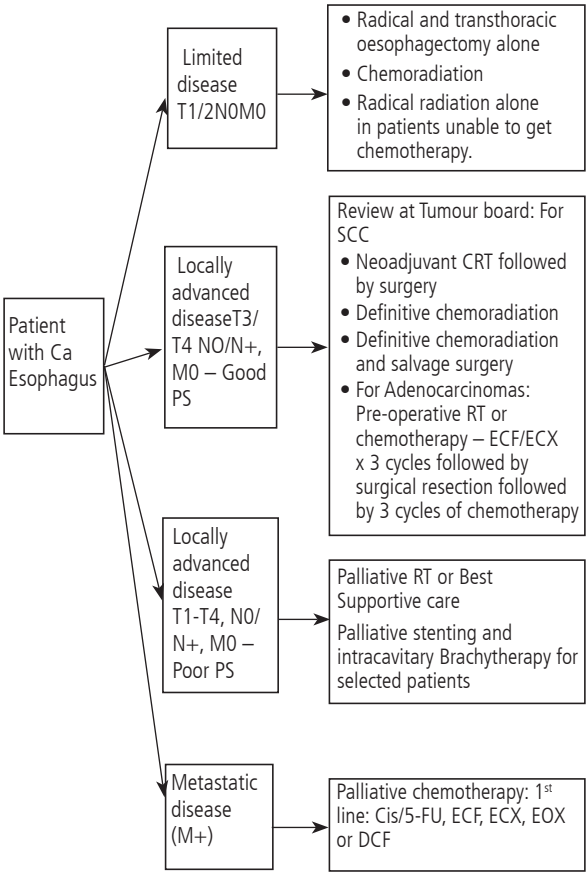
L: Lower esophagus (>30 to 40 cm from incisors)

EGJ: If the tumour arises from the esophagogastric junction or from the stomach within 5 cm from esophagogastric junction and crosses the esophagogastric junction.

Metastases (M stage)
M0: No metastases to distant organs or lymph nodes.

M1: Evidence of metastases to distant lymph nodes and/or other organs – liver and lungs.

TREATMENT ALGORITHM FOR CANCER OF THE OESOPHAGUS



RADIOTHERAPY OPTIONS FOR PATIENTS WITH CANCER OF THE ESOPHAGUS

Early disease (Stage T1/T2 N0 M0)

A. **Chemoradiation**: Definite chemoradiation is the treatment of choice for patients who are not fit for surgery or patients who decline surgery or

in patients with squamous cell carcinoma of the cervical esophagus. Chemoradiation with Cisplatin /5FU ×2 cycles followed by 2 more cycles of chemotherapy is recommended. Radiation doses range from 45 -50.4 Gy /25-28 fractions

B. **Radical Radiation**: Radical radiation alone to a dose of 54-60Gy in 1.8 to 2Gy/# may be considered in selected patients refusing or medically unfit for surgery and chemotherapy

Early disease (Stage T3/T4 N0/N+, M0) Good Performance status

A. Pre-operative chemoradiation can be given to eligible patients followed by surgery and radiotherapy. Cisplatin/5FU and external RT doses of 45-50.4 Gy in 25– 28 fractions followed by surgery in 4-6 weeks or weekly carboplatin/paclitaxel and RT (doses of 41.4 Gy in 23 fractions or 45 -50.4 Gy in 25 -28 fractions followed by surgery in 4-6 weeks).

B. Radical radiation alone to a dose of 54-60Gy in 1.8 to 2Gy/# may be considered in selected patients refusing or medically unfit for surgery and chemotherapy

Locally advanced disease stage: T1-T4, N0/N+, M0 Poor Performance status

A. Palliative radiotherapy to the affected segment is indicated for eligible patients (40Gy/ 16#, 36Gy/12 #, 30Gy/10#, 20Gy/5#, 8Gy/1#).

SURGICAL OPTIONS FOR PATIENTS WITH CANCER OF THE ESOPHAGUS

Early disease (Stage T1,T2/N0 M0)

Surgery alone may be the treatment of choice for patients with early oesophageal cancer.

Surgical resection is highly curative in early-stage esophageal cancer, but survival rates decline when tumors invade beyond the submucosa or are more advanced than Stage I. The most common surgical procedures performed are transthoracic esophageal resection using the right- or left-chest approach or transabdominal resection by blunt dissection. The esophagus is replaced with a new

esophagus constructed from the remaining stomach pulled up into the thoracic cavity or neck. The colon or jejunum can also be used for interposition if the stomach is not a suitable conduit.

Locally advanced disease stage (T3/4 N1 – 3 M0)
In locally advanced adenocarcinomas of the oesophagogastric junction infiltrating the cardia, laparoscopy can be done to rule out peritoneal metastases.

Neoadjuvant chemoradiation with planned surgery or definitive chemoradiation today with close and salvage surgery with local tumor persistence or progression is recommended for patients with squamous cell carcinoma of the oesophagus.

For adenocarcinoma of the oesophagus perioperative radiotherapy is followed by surgery.

Metastatic Disease
Surgery for patients in this category aims at restoring feeding and nutritional rehabilitation before definitive therapies through the following;

a. Feeding gastrostomy tube,
b. Stenting,
c. Percutaneous Endoscopic Gstrostomy (PEGs), or
d. NG Tube insertion

CHEMOTHERAPY REGIMENS FOR ESOPHAGEAL CANCER

A. Neo-adjuvant chemotherapy

Cisplatin and 5-Fluoro-uracil [1]

Cisplatin	80mg/m^2	IV	Day 1
5FU	1000 mg/m^2	IV	Day 1 – 4

Repeat every 21days x 2 cycles

ECF [2]

Epirubicin	50mg/m^2	IV	Day 1
Cisplatin	60mg/m^2	IV	Day 1
5FU	200 mg/m^2	IV	Day 1

Repeat every 21days x 3 cycles

ECX

Epirubicin	50mg/m^2	IV	Day 1
Cisplatin	60mg/m^2	IV	Day 1
Capecitabine	625mg/m^2	IV	Day 1

Repeat every 21days x 3 cycles

Concurrent chemoradiation for locally advanced cancer

Carboplatin + Taxol + RT[3]

Carboplatin	AUC2,	IV	Day 1
Docetaxel	50mg/m^2	IV	Day 1

Repeat every week for 5 weeks with Radiation therapy

Cisplatin + 5-FU + RT

Cisplatin	75mg/m^2	IV	Day 1
5FU	1000 mg/m^2	IV	Day 1 – 4
Concurrent RT			

Repeat every 21days x 2 cycles

B. **Palliative Chemotherapy**

ECF [2]

Epirubicin	50mg/m^2	IV	Day 1
Cisplatin	60mg/m^2	IV	Day 1
5FU	200 mg/m^2	IV	Day 1 – 4

Repeat every 21days x 6 cycles

ECX [4]

Epirubicin	50mg/m^2	IV	Day 1
Cisplatin	60mg/m^2	IV	Day 1
Capecitabine	625mg/m^2	Orally daily	Day 1-14

Repeat every 21days x 6 cycles

CF [1]

Cisplatin	75mg/m^2	IV	Day 1
5FU	1000 mg/m^2	IV	Day 1 – 4

Repeat every 21days x 6 cycles

CFH

Cisplatin	80mg/m^2	IV	Day 1
5FU	800 mg/m^2	IV	Day 1 – 5
Transtuzumab	8mg/kg	IV	Day 1

Repeat every 21days x 6 cycles

C. Adjuvant Chemotherapy

CISPLATIN + PACLITAXEL [5]

Cisplatin	75mg/m^2	IV	Day 1
Paclitaxel	200 mg/m^2	IV	Day 1

Repeat every 21days x 6 cycles

FOLLOW-UP AFTER TREATMENT FOR CANCER OF THE OESOPHAGUS

Patients who have been treated for curative intent should undergo the following evaluation every 3 months for the first 3 years and every 6 months for the next 2 years

- Upper GI endoscopy
- Carcinoembryonic Antigen (CEA)
- Dysphagia grade
- Complete history and physical exam

DOSE MODIFICATIONS & TOXICITY

- Delay chemotherapy by one week if Absolute Neutrophil Count (ANC) is below 1.0
- Delay chemotherapy by one week in patients with platelets <75,000
- Transfuse if hemoglobin drops below 8g/dl.
- Delay one week if hemoglobin below 8g/dl in patients with metastatic cancer
- Do not reduce dose unless persistent neutropenia, thrombocytopenia is leading to prolonged treatment delays, or associated with sepsis
- Dose reduced by 20% if necessary as above after discussion with senior.

SPECIAL CONSIDERATIONS

Cap all patients at body surface area of 2m^2

Severe gastro-intestinal side effects (anorexia, nausea and vomiting, diarrhoea, stomatitis, dry mouth, epigastric pain) - postpone therapy until symptoms subside.

Grade 3 or 4 vomiting or diarrhoea - reduce by 20% next cycle

REFERENCES

1. Lorenzen S, Schuster T, Porschen R, et al. Cetuximab plus cisplatin–5-fluorouracil versus cisplatin–5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Annals of Oncology 2009:mdp069.
2. Ross P, Nicolson M, Cunningham D, et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. Journal of clinical oncology 2002;20:1996-2004.
3. Li QQ, Liu MZ, Hu YH, Liu H, He ZY, Lin HX. Definitive concomitant chemoradiotherapy with docetaxel and cisplatin in squamous esopheageal carcinoma. Diseases of the Esophagus 2010;23:253-9.
4. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. New England Journal of Medicine 2008;358:36-46.
5. Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer journal (Sudbury, Mass) 1999;6:316-23.

KAPOSI'S SARCOMA

Clinical evaluation for patients with Kaposi's sarcoma

The clinical evaluation of patients with Kaposi's sarcoma should include the following;

- HIV status and date of diagnosis
- ART status – combination and start date
- CD4 count – current count and at the start of ART
- KS specific symptoms:
  - First skin lesion and its location
  - Appearance and distribution of the skin lesions
  - Onset of KS lesions relative to ART intake – before or after
  - Change in KS lesions while on ART
  - Presence of tumour-associated edema
  - Gastrointestinal KS symptoms like melena, oral lesions.
  - Pulmonary KS symptoms like cough, chest pain, hemoptysis
  - Document the presence of B- symptoms
    - Unexplained fevers
    - Unexplained night sweats
    - Unexplained weight loss
  - Medical/Medication history: History of TB & TB treatment, history other OIs, and chronic conditions like DM , HTN
- LNMP for women of reproductive age
- Confirm HIV status of their partner and children
- Targeted physical examination of skin, lymphnode areas and oropharynx for KS lesions
  - Type of skin lesions, location & number by location – lower limbs, upper limbs, trunk & Head .
    - Classification of number of lesions : <10 lesions or 10-50 lesions, or 50-100 lesions ,or >100 lesions on each of the affected body parts
    - This should be charted on the KS body Map

attached in Figure 1

- Oral Mucosal lesions – on soft or hard palate, gums, tonsils, or oropharynx
- Presence of tumour-associated edema
- Lymph node examination
- Oral exam commenting on location of lesions: soft or hard palate, tonsils, gums and oropharynx
- Eye conjunctiva and sclera exam

- Complete physical exam
  - vital signs (temperature, pulse, respiration rate, and blood pressure)
  - Look for pallor of mucosal & palmar surfaces
  - Score performance status using ECOG
  - measurement of weight and height
  - Systems examination of including chest, abdomen & CNS

Investigations

- Skin punch biopsy for histology
- HIV test, CD4 T-cell count and HIV-1 plasma viral load
- Complete blood count (CBC)
- Liver function tests (LFTs)
- Renal function test (RFTs)
- Stool fecal occult blood test (FOBT)
- Abdomen Ultrasonography
- Chest radiograph
- Urine analysis

Staging for AIDS KS

AIDS Clinical Trial Group classification criteria for Kaposi Sarcoma

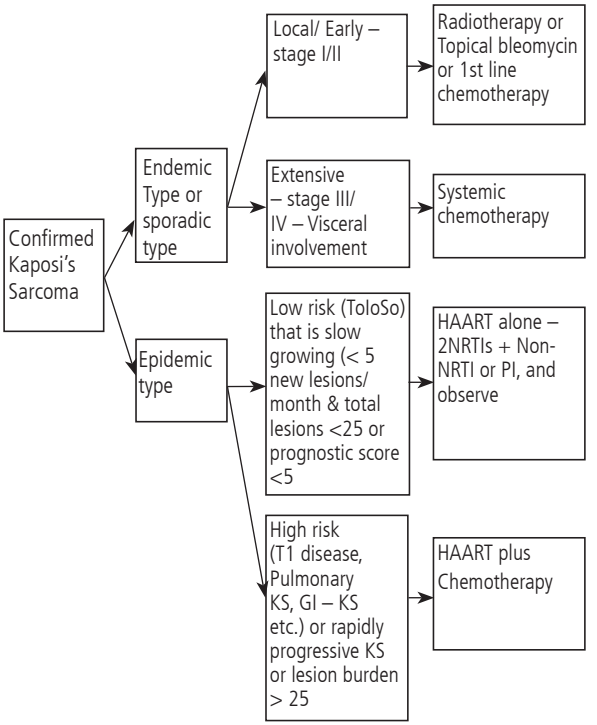
	Good prognosis	Poor prognosis
T – Tumour extent	T0	T1
	Localized to skin and/or lymph nodes and/or minimal oral disease[Note: Minimal oral disease is non-nodular KS confined to the palate.]	Tumor associated ulceration and/or edema
		KS in other non-nodal visceral
		Oral KS that is nodular or involves more than the palate
		Visceral involvement
I – immunosuppression	I0	I1
	CD4 > 200 cells/mm3 Cd4 > 15%	CD4 < 200cells/mm3 CD4 < 15%
S –Systemic illness	S0	S1
	No B symptoms	Presence of B-symptoms
	Karnofsky score > 70%	Karnofsky score < 70%
	No Opportunistic infections	Opportunistic infections
	No AIDS defining illnesses	Oral candidiasis
	No Oral ulcerations	

Staging of Classic KS

Stage	Cutaneous lesions	location	Behavior
I-Maculonodular	Macules or nodules or both	Lower limbs	Non-aggressive
II-Infiltrative	Plaques	Lower limbs	Locally aggressive
III-Florid	Angiomatous nodules and plaques	Extremities, particularly the lower ones	Locally aggressive
IV-Disseminated	Angiomatous nodules and plaques	Extremities, trunk, head	Disseminated, aggressive.

Epidemic KS prognostic score (Stebbing et al. 2006) Having KS as the first AIDS-defining illness (-3 points) and increasing CD4 cell count (-1 for each complete 100 cells/μL in counts at KS diagnosis) improved prognosis, whereas age at KS >50 years (+ 2) and S1 stage (+ 3) conveyed a poorer prognosis. On the basis of this index it was suggested that patients with a poor risk prognostic index (score >12) should be initially treated with HAART and systemic chemotherapy together whilst those with a good risk prognostic index (score <5) should be treated initially with HAART alone, even if they have T1 disease.

Treatment guideline for Kaposi's sarcoma at UCI



KAPOSIS SARCOMA TREATMENT REGIMENS

BV – 1st line (BLEOMYCIN + VINCRISTINE)[1] in patients with good risk disease

Bleomycin	15 IU/m^2	IV	Day 1
Vincristine	2 mg	IV	Day 1

Repeat cycle every 21 days for 6 cycles

PACLITAXEL – 1st line. [2,3] in patients with poor risk disease, good performance status, and ANC > 1500

Paclitaxel	100mg/m^2	IV	Day 1

Repeat cycle every 21 days for 6 cycles

May dose escalate if response unsatisfactory to

Paclitaxel	135mg/m^2	IV	Day 1

Repeat cycle every 21 days for 6 -8 cycles

Weekly VINCRISTINE – 1ST line among patients with visceral KS (Pulmonary & GI KS) who have poor PS and / or significant bone marrow suppression (severe anaemia or neutropenia)

Vincristine	1.4mg/m^2	IV	Day 1

Repeat cycle every week for 6 cycles

KAPOSI'S SARCOMA RESPONSE EVALUATION

The oncologist shall evaluate patients upon completion of their primary treatment for response to therapy and will objectively assess the response as defined in the following criteria

- Complete Remission
  - Complete response is defined as the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks. In some individuals, residual skin color changes may remain visible at one or more site(s) of lesions that were previously raised and/or red or violaceous
- Partial Response

  Partial response is defined as no new oral lesions or new or progressive visceral sites of involvement, or the appearance or worsening of tumor-associated edema or effusions or the development of five or more new cutaneous lesions in anatomic sites which were previously documented as having no evidence of cutaneous disease; AND
- A 50% or greater decrease in the number of all lesions present at entry (either total body or in the representative areas) lasting for at least 4 weeks; OR
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all nodular or plaque-like lesions become macules, either total body or in the representative areas) present at entry; OR

- A ≥ 50% decrease in the area of the five cutaneous marker lesions compared to entry.
- Stable Disease
  - Stable disease is defined as any response not meeting the criteria for CR, PR, or progressive disease
- Progressive Disease

  PD is defined as any one or more of the following:
  - ≥25% increase in the area of the five cutaneous marker lesions compared to entry or best response;
  - ≥25% increase in the total lesion count or a minimum of five new lesions, compared to entry or best response;
  - ≥25% increase in the number of raised lesions (minimum of five new raised lesions if there are very few raised lesions, for example <8), compared to entry or best response

Non-cutaneous Progressive Disease

- Noncutaneous progressive disease (PD) includes new oral or visceral sites of involvement or progression of oral or visceral disease or the development of new or increasing tumor-associated edema or effusion that interferes with the participant's normal activities lasting for at least two consecutive evaluations

KS IRIS

- KS-IRIS is defined as atypical progression of KS that occurs within 12 weeks of initiation of ART that is associated with an marked decrease in HIV VL of at least 1 log copy/mL from baseline and an increase in CD4+ count.

SPECIAL CONSIDERATIONS

- There are no differences in tumor resolution between PI and NNRTI based regimens. Prescribe ART as per national guidelines. Optimize ART by tracking HIV VL and confirming adherence. Bleomycin is

often complicated by infusion-related fever and chills, generally requiring pre-medication with dexamethasone and diphenhydramine for control, and is also associated with cutaneous toxicities.

- The maximum cumulative lifetime total dose of Bleomycin is 400 Units and so this should be computed regularly and patient's monitored for toxicity
- Grade 3 or 4 vomiting or diarrhoea - reduce by 20% next cycle
- Grade 3 or 4 mucosal ulceration - Reduce chemotherapy by 20%.
- With higher cumulative doses, pulmonary fibrosis may occur among patients receiving bleomycin. Asmptomoatic decreases in carbon monoxide diffusing capacity (DLCO) have been reported after lower doses of bleomycin.
- Vincristine frequently causes peripheral neuropathy (PN), and may cause jaw pain and constipation;maximum dose for every cycle should not exceed 2mg.
- Vincrisitne should NEVER be administered intrathecally because it is fatal. Vincristine infusions should be labelled "For intravenous use ONLY"Neither vincristine nor bleomycin is associated with significant hematologic toxicity and so treatment with bleomycin and vincristine may be initiated in a patient with lower haemoglobin level and platelate levels than usual.
- BV regimen is NOT inferior to ABV regimen and it has a lower side effect profile as compared to ABV regimen particularly haematological toxicities.
- Vinca alkaloids, including vincristine and vinblastine, are primarily metabolized by CYP3A isoenzymes. Several case reports and small series have suggested that co-administration of Vinca alkaloids with the potent CYP3A inhibitor, ritonavir, may be associated with increased hematologic and neurotoxicity
- Paclitaxel is metabolized in the liver predominantly by cytochromes P450 2C8 and 3A4 via saturable

elimination to less potent metabolites, indicating that modest changes in dose or metabolizing enzyme activity could result in disproportionately large alterations in systemic exposure, potentially influencing toxicity and response

- For HAART naive patients, the preferred first line regimen is; EFV/FTC/TDF (Atripla®) ®) 200 mg/300 mg/600 mg orally once daily on an empty stomach, preferably at bedtime or FTC/TDF 200 mg/300 mg (Truvada®) orally once daily plus nevirapine (NVP) 200 mg orally twice daily
- Women taking EFV and who are of reproductive potential are required to use two methods of acceptable birth control, to prevent the teratogic risk associated with Efavirence
- NVP should be started with the lead-in of 200 mg orally once daily for 14 days; then 200 mg orally twice daily. Health care providers must review signs and symptoms of NVP-related hypersensitivity and hepatitis with the participant prior to dispensing NVP
- Chemotherapy-associated anemia and neutropenia may be worsened by coadministration of zidovudine (ZDV)

DOSE MODIFICATIONS & TOXICITY

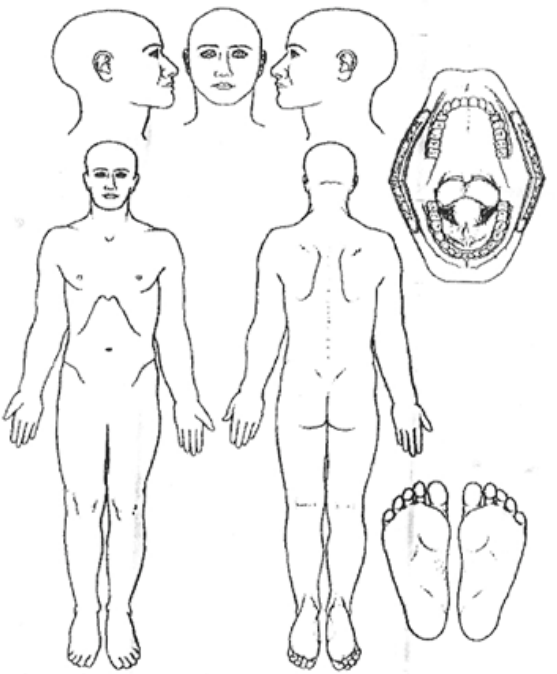
- Delay one week if Absolute Neutrophil count (ANC) below 1.0
- Delay one week if platelets <75,000
- Transfuse if haemoglobin drops below 8g/dl.
- Delay chemotherapy by one week if Haemoglobin below 8g/dl in patients with metastatic cancer
- Do not reduce dose unless persistent neutropenia, thrombocytopenia is leading to prolonged treatment delays, or associated with sepsis
- Dose reduced by 20% if necessary as above after discussion with senior.
- Cap all patients at body surface area of $2m^2$

REFERENCES

1. Gill P, Rarick M, Bernstein-Singer M, et al. Treatment of advanced Kaposi's sarcoma using a combination of bleomycin and vincristine. American journal of clinical oncology 1990;13:315-9.
2. Gill PS, Tulpule A, Espina BM, et al. Paclitaxel is safe and effective in the treatment of advanced AIDS-related Kaposi's sarcoma. Journal of clinical oncology 1999;17:1876-.
3. Tulpule A, Groopman J, Saville MW, et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. Cancer 2002;95:147-54.

Appendix

Appendix 1: Figure 1: KS Body Map



PROSTATE CANCER

Clinical evaluation of a patient with Prostate cancer

The following information should be documented during the clinical evaluation of a patient with suspected/ confirmed prostate cancer referred to the Uganda Cancer Institute

- Age at presentation
- Presence and duration of lower urinary tract symptoms
  - Frequency
  - Urgency
  - Nocturia
  - Intermittency
  - Straining
  - Incomplete emptying
  - Weak stream
- Past medical/medication history
- Co-morbidity including HIV infection, diabetes and hypertension
- First degree relatives with prostate cancer
- Alteration in erectile function
- Alcohol and Tobacco use
- History of recurrent urinary tract infection and prostatitis (history of dull perineal pain, low back pain, pain at the tip of the penis)
- Dietary history; a vegetarian diet and sea food diet is protective BUT does not alter the progression of prostate cancer
- Performance status - ECOG
- Complete physical exam
- Digital rectal exam: The clinician should report on the following; tenderness, size of the prostate, consistency, symmetry, mobility of the rectal mucosa, and presence of the 3 grooves (2 lateral grooves and 1 median groove)

The clinician evaluating the patient should attempt to score the severity of symptoms using the International Prostate Symptom Score (I-PSS). This score is important for the evaluation of patients with obstruction. It does not necessarily affect the treatment for prostate cancer.

Investigations

- Complete blood count (CBC)
- Renal function test (RFT)
- Liver function test (LFT)
- Lactate dehydrogenase test (LDH)
- Serum calcium
- Alkaline phosphatase (ALP)
- Prostate ultrasound scan (abdominal or Transrectal)
- Multiparametric Magnetic resonance imaging (MRI) of the prostate for anatomic details.
- Chest X-ray or chest CT scan
- Skeletal survey with plain X-rays to evaluate symptomatic regions of the skeleton
- Prostate Biopsy
    - With image guidance, aim at six (6) cores. While, with finger-guided blind biopsy, four (4) core biopsies should be taken. Any repeat biopsy should be done using image guidance.
        - For patients with low risk, 12 core biopsies is mandatory
    - Transrectal / Perineal Ultrasound guided biopsy using a 18G biopsy bilaterally from apex to base as far posterior and lateral as possible in the peripheral gland. Additional cores from DRE/TRUS suspected areas.
    - Transition Zone biopsies should be limited to repeat biopsies.
        - Finger guided blind biopsies are also acceptable.
    - Repeat Prostatic Biopsy after negative biopsy in the following situations;
        - Previous blind biopsy in case of clinical suspicion.

- Diagnostically inadequate tissue for histopathology
- Rising and/or persistent elevated PSA
- Suspicious digital rectal exam (DRE)
- Extensive High grade Prostatic intraepithelial neoplasia (PIN)
- Intraductal carcinoma
- Positive multiparametric MRI (mpMRI) findings. Before repeat biopsy perform mpMRI (where possible) when clinical suspicion of Prostate Cancer persist in spite of negative biopsies

Histopathology of prostate needle biopsies

Mandatory elements to be reported for a carcinoma positive prostate biopsy:

- Type of carcinoma
- Primary and secondary/ worst Gleason Grade
- Percentage high grade carcinoma
- Extent of carcinoma ie. percentage of prostate gland involved
- If present: extraprostatic extension, , lymphovascular invasion, intraductal carcinoma, perineural invasion
- International Society of Urological Pathology (ISUP) 2014 grade.

Histopathology of radical prostatectomy specimens

Mandatory elements provided by the pathology report

- Histopathological type
- Gleason score - Primary, secondary and tertiary grades after radical prostatectomy.
- International Society of Urological Pathology (ISUP) 2014 grade group
- Tumor substaging and surgical margin status: location and extent of extraprostatic extension, presence of bladder neck invasion, laterality of extraprostatic extension and seminal vesicle invasion, location and extent of positive surgical margins.
- Multifocality and diameter/volume and focal location

of the dominant tumor
  - Location and number of nodes retrieved, number of nodes involved
  - Presence of lymphovascular/ angio-invasion
  - Presence of intraductal carcinoma
- Clinical diagnosis of prostate cancer is acceptable in the following scenariosWhere there is radiological and clinical evidence of spinal cord compression.
- With a PSA > 100ng/ml

Prostatic Specific Antigen levels

- As a baseline, Total PSA should be documented;
- At surveillance or watchful waiting or monitoring of response to treatment; it is important to document the PSA doubling time,
- Only quantitative PSAs are acceptable.

Where possible the following PSA kinetics should be defined;

- PSA density: This is the level of serum PSA divided by the TRUS-determined prostate volume
- PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year)
- PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time
- Free/total (f/t) PSA ratio is widely used to differentiate BPH from Prostate Cancer (PCa). It stratifies the risk of PCa in men with 4-10 ng/mL total PSA and negative DRE
  - Prostate cancer was detected in 56% of men with free/total PSA <0.1 ng/mL
  - Qualitative PSA is not acceptable
- CT scan or MRI (optional) for assessment of cortical involvement not visible on x-ray
- Bone scan for symptomatic men or when there is high risk for osseous metastases

TNM classification of Ca Prostate

T – Primary Tumour

Clinical

TX: Primary tumour cannot be assessed

T0: No evidence of primary tumour

T1: Clinically inapparent tumour not palpable or visible by imaging

- T1a Tumour incidental histological finding in 5% or less of tissue resected
- T1b Tumour incidental histological finding in more than 5% of tissue resected
- T1c Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level)

T2: Tumour confined within the prostate

- T2a Tumour involves one half of one lobe or less
- T2b Tumour involves more than half of one lobe, but not both lobes
- T2c Tumour involves both lobes

T3: Tumour extends through the prostatic capsule

- T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
- T3b Tumour invades seminal vesicle(s)

T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall

Pathologic (pT)

- pT2 Organ confined
  - pT2a Unilateral involving one half of one side or less
  - pT2b Unilateral, involving more than one side but not both sides
  - PT2c Bilateral disease
- pT3 Extraprostatic extension
  - pT3a Extraprostatic extension or microscopic invasion of the bladder neck
  - pT3b Seminal Vesicle invasion
  - pT4 Invasion of Bladder, Invasion of rectum

N- Nodal involvement

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

M - Metastases

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
- M1a Non-regional lymph node(s)
- M1b Bone(s)
- M1c Other site(s)

Simplified AJCC Anatomic Stage/Prognostic Groups

Stage	Definition
Stage I	T1–T2a (Not palpable–≤1/2 of one lobe) + PSA <10 + Gleason ≤6
Stage II	T1–T2a PSA ≥10 &/or Gleason ≥7, or Any T2b (involving >1/2 of one lobe) or T2c (involving both lobes)
Stage III	T3
Stage IV	T4, N1, or M1

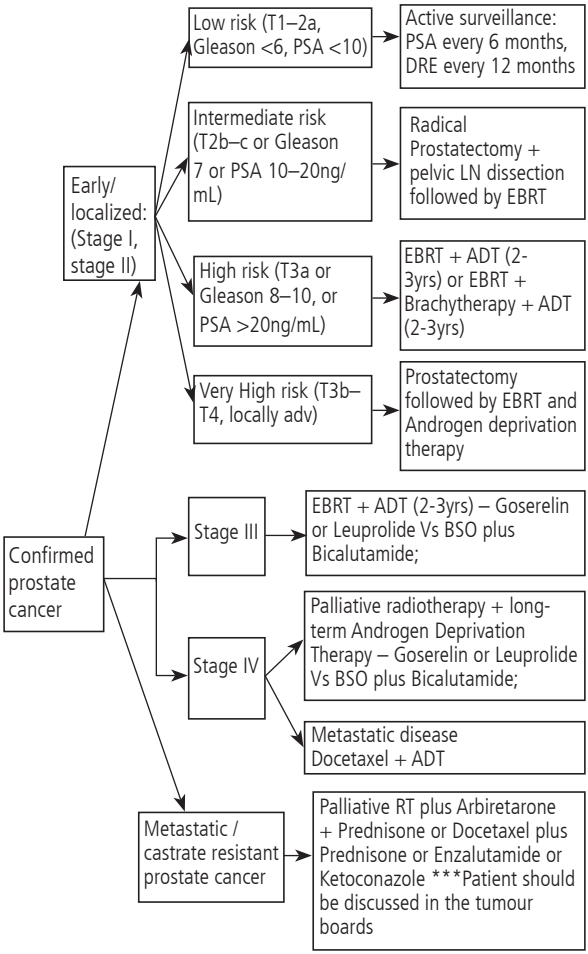
EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

	Localized			Locally advanced
Definition	Low risk	Intermediate risk	High risk	
	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10- 20 ng / mL and GS 7 and cT2b	PSA > 20 ng / mL and GS >7 and cT2c	any PSA any GS cT3-4 or cN+

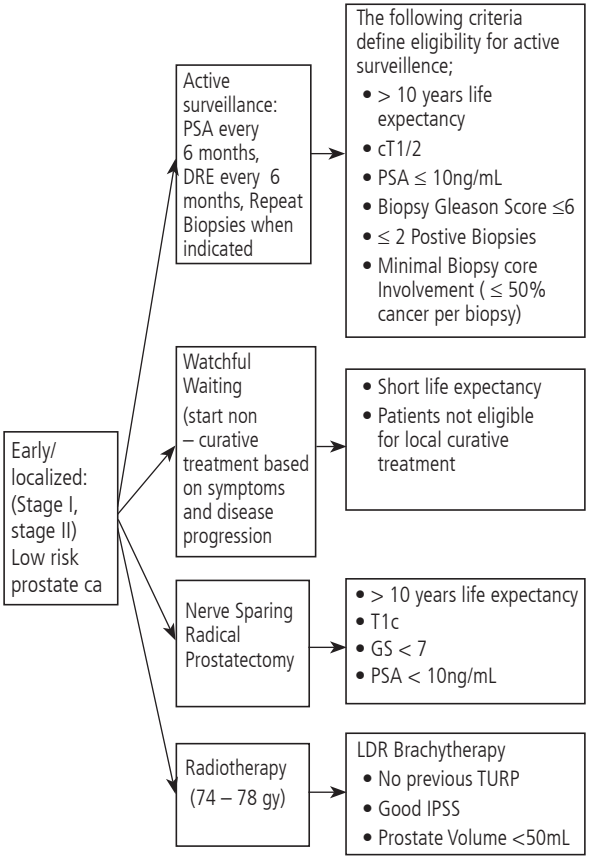
Interpretation of Gleason score

Score	Interpretation
Gleason X	Cannot be processed
Gleason ≤ 6	Well differentiated, good risk
Gleason 7	Moderately differentiated, Intermediate risk
Gleason 8-10	Poorly differentiated, Poor risk

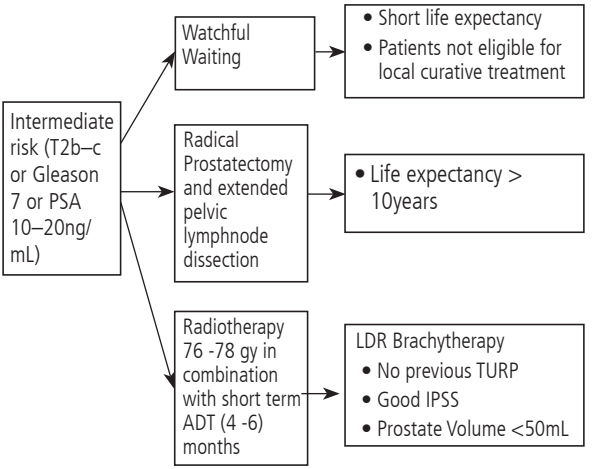
Treatment for Prostate cancer



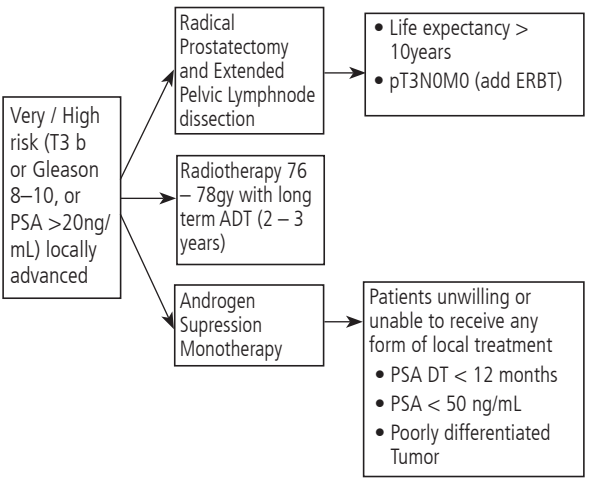
Treatment Algorithm for Early/localized Low risk prostate cancer



Treatment algorithm for Early/localized Intermediate risk Prostate cancer



Treatment Algorithm for early/localized veri high/high risk prostate cancer



SURGICAL OPTIONS IN MANAGEMENT OF PROSTATE CANCER

Radical prostatectomy

Radical prostatectomy (RP) involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain a negative margin. Often, this procedure is accompanied by bilateral pelvic lymph node dissection. The goal of RP by any approach must be eradication of disease, while preserving continence and whenever possible potency[1].

Generally there is no age threshold for radical prostatectomy[2]. However, patients with a life expectancy of > 10 years are more likely to benefit from the procedure. Radical prostatectomy is indicated in patients with localized cancer of the prostate of either low risk or intermediate risk. Other indications for RP include;

- High risk patients in a multimodality setting
- Locally advanced (cT3a – T4 N0 or Any T N1) in a multimodality setting
- Nerve sparing surgery for T1c, GS <7 and PSA <10ng/ml

In intermediate and High risk disease mpMRI is used as a tool to select patients for nerve sparing procedures. The following precautions should be taken into consideration.

- Do not offer Neoadjuvant hormonal therapy before RP
- Do not offer adjuvant therapy for pN0
- Offer any surgical approach available.
- Discuss active surveillance and radiotherapy with all patients who would be suitable for these treatment options

Pelvic lymph node dissection

The importance of pelvic lymph node dissection (PLND) is both prognostic and therapeutic. The dissection offers important prognostic information including; the number of

nodes involved, tumour volume within the lymph node, and capsular perforation of the node. The surgeon may opt to consider an extended PLND or sentinel LN dissection. The Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery. Besides being a staging procedure, pelvic LND may be curative, or at least beneficial, in a subset of patients with limited lymph node metastases [3-6]

BILATERAL ORCHIECTOMY

Surgical castration is still considered the primary treatment modality for ADT. It leads to a considerable decrease in testosterone levels: castration level

The castration level is < 50 ng/dl (1.7nmol/L) which was defined more than 40 years ago when testosterone testing was limited. Current methods have shown that the mean value after surgical castration is 15ng/dL. Therefore a more appropriate value is defined as 20ng/dL (1nmol/L)

Bilateral orchiectomy or subcapsular pulpectomy is a simple, cheap and virtually complication free surgical procedure. It is easily performed under local anaesthesia and is the quickest way to achieve a castration level within less than 12 hours, it is irreversible and does not allow for intermittent treatment.

CHANNEL TURP

Channel transurethral resection of the prostate (TURP) is a palliative measure to relieve urinary obstruction.

RADIOTHERAPY OPTIONS FOR THE TREATMENT OF PROSTATE CANCER

Radical radiotherapy

Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is the gold standard for EBRT

Regardless of the technique used, the choice of treatment is multidisciplinary. After the extent of the tumour has been properly assessed, the following are taken into account[7]:

- 2009 TNM classification;
- Gleason score, defined using an adequate number of core biopsies (at least 10);
- Baseline prostate-specific antigen (PSA);
- Age of the patient;
- Patient's comorbidity, life expectancy, and QoL;
- International Prostate Symptom Score (IPSS) and,
- the EAU prognostic factor classification.

The following criteria should be used to identify patients eligible for radical radiotherapy;EBRT to all risk groups of non metastatic prostate cancer

- Low risk cancer : Total dose 74 – 78gy
- Low Dose Radiation Brachytherapy : low risk prostate cancer, No previous TURP, IPSS <12, prostate Volume <50mL
- Intermediate risk prostate cancer: Total dose 76 – 78 gy in combination with short term ADT (4-6) months
- High risk prostate cancer: Total dose 76 – 78 gy in combination with long term ADT (2 – 3 years)
- Locally advanced cN0 prostate cancer: radioptherapy in combination with long term ADT (2-3) years
- Offer IMRT for definitive treatment of prostate cancer by EBRT
- cN+ prostate cancer: pelvic external irradiation in combination with immediate long term ADT
- pT3, N0, M0 prostate cancer and undetectable PSA following RP: Adjuvant EBRT however discuss with the patient the option of salvage EBRT when PSA starts to rise.

Brachytherapy

LDR brachytherapy is a safe and effective technique. There is a consensus on the following eligibility criteria:

- Stage cT1b-T2a N0, M0;
- A Gleason score < 6 assessed on an adequate number

of random biopsies;

- An initial PSA level of < 10 ng/mL;
- < 50% of biopsy cores involved with cancer;
- A prostate volume of < 50 cm3;
- An International Prostatic Symptom Score (IPSS) < 12[8]

SPECIAL CONSIDERATION

- In the absence of a radionuclide bone scan, plain radiographs can be used to evaluate symptomatic regions of the skeletal. Plain radiographs will only detect bone lesions when > 50% of bone mineral contact has been lost or gained.
- Bone scan is indicated in the initial evaluation of patients at high risk for bone metastases; T1 disease and PSA ≥ 20, T2 disease and PSA ≥ 10, gleason score > 8, T3 or T4 disease; and any disease stage with symptoms suggestive of bone metastases.
- Active surveillance refers to active monitoring of disease progression with the expectation to intervene with potentially curative approached in event of disease progression. This includes a PSA every 6 months, a DRE and Prostate biopsy every 12 months.
- The care for older men with prostate cancer should include the following;
  - Evaluate for life expectancy, comorbidity and health status
  - Evaluate for malnutrition
  - Evaluate for cognitive impairment
  - Offer only symptomatic palliative treatment to patients who are too sick with terminal illness
  - Evaluate bone mineral status and prevent osteoporosis related fractures

PROSTATE CANCER REGIMENS

HORMONAL THERAPY FOR METASTATIC CANCER

GOSERELIN [9]

Goserelin	3.6 mg	SC	Day 1

Repeat every 28days x 18 cycles

OR

Goserelin	10.8 mg	SC	Day 1

Repeat every 3 months x 6 cycles

NB: 1st dose is given with ant-androgen (Bicalutamide 50mg once daily) for 10-14 days to prevent flare

BICALUTAMIDE [10]

Bicalutamide	150 mg	PO	Day 1 - 28

Repeat every 28days x 18 cycles

LUPROLIDE[11,12]

Luprolide	7.5mg	IM	Day 1

Repeat every 28days x 18 cycles

OR

Luprolide	22.5mg	IM	Day 1

Repeat every 3 months x 6 cycles

KETOCONAZOLE [13]

Ketoconazole	400 mg	PO bid	Day 1 – 28

Repeat every 28days until normal PSA or hormonal refractory state

ABIRETARONE[14] – For Castrate Resistant Prostate Cancer

Abiraterone	1000mg	Orally daily	Day 1 – 21
prednisolone	10mg	Orally daily	Day 1 - 21

Repeat every 21days x 10 cycles

CABAZITAXEL[15] – For castrate resistant prostate cancer

Cabazitaxel	25mg/m^2	IV	Day 1

Repeat every 21days x 10 cycles

ENZALUTAMIDE[16]

Enzalutamide	160mg	Orally daily	Day 1 – 21

Repeat every 21days x 10 cycles

SPECIAL CONSIDERATIONS:

- Goserelin is associated with an initial “flare” and this can be avoided by initiating treatment in combination with an anti-androgen
- Bilateral subcapsular orchiectomy offers similar results as medical androgen deprivation therapy and should be preferred for long term androgen deprivation
- Antiandrogens are associated with painful gynecomastia. This condition can be prevented by

breast bud radiation

- Diethyl stilbetrol (DES) is associated with cardiovascular and thromboembolic side effects at any dose but frequently its dose and agent dependent. DES should be initiated at 1mg/day and increased gradually to achieve castrate levels of serum testosterone (<50ng/dL)
- High dose DES and Ketoconazole can be used in patients with impending spinal cord compression. DES is given at a dose of 120mg and tapered every after 2 days by 15mg until the dose reaches 5mg daily. Ketoconazole is given at 200mg three times a day for about two weeks

A. CHEMOTHERAPY FOR METASTATIC CANCER

Docetaxel+ Prednisone [17,18]

Docetaxel	75mg/m^3 d1
Prednisone	5mg bd d1-d21

Repeat cycle every 3 weeks x 10cycles

Docetaxel+ Goserelin

Docetaxel	75mg/m^3 d1
Goserelin	3.6mg STAT

Repeat cycle every 3 weeks x 10cycles

Mitoxantrone +Prednisone [19]

Mitoxantrone
Prednisolone 12mg/m2 IV over 30mins
Repeat cycle every 3 weeks x 6cycles

DOSE MODIFICATIONS & TOXICITY

- Delay one week if Absolute Neutrophil count below 1.0
- Delay one week if platelets <75,000
- Transfuse if Haemoglobin drops below 8g/dl.
- Delay chemotherapy by one week if Haemoglobin below 8g/dl in patients with metastatic cancer
- Do not reduce dose unless persistent neutropenia, thrombocytopenia is leading to prolonged treatment delays, or associated with sepsis
- Dose reduced by 20% if necessary as above after discussion with senior.

Special considerations

- Cap all patients at body surface area of $2m^2$
- Severe gastro-intestinal side effects (anorexia, nausea and vomiting, diarrhoea, stomatitis, dry mouth, epigastric pain) - postpone therapy until symptoms subside.
- Grade 3 or 4 vomiting or diarrhoea - reduce by 20% next cycle
- Grade 3 or 4 mucosal ulceration - Reduce chemotherapy by 20%.

B. TREATMENT OF OSTEOPOROSIS

BISPHOSPHATES —*for bone metastases*

Zolendronic acid 4mg iv for over 15minutes
Repeat every 3 months for one year then every 6 months

Alternative

Pamidronate 60mg iv over 90minutes STAT
Repeat every 3 months for one year then every 6 months

SPECIAL CONSIDERATIONS:

- When prescribing bisphospates, always ensure that serum creatinine clearance is ≥ 60mL/Min and AVOID the bisphosphates when serum creatinine clearance is ≤ 40ml/Min
- Clinicians should screen for osteoporosis and treat the condition among patients receiving androgen deprivation therapy.
- Zolendronic acid is preferred to pamidronate as the first choice for patients with high risk for skeletal related events
- Bisphosphates are associated osteonecrosis of the jaw. Patients may present with tooth ache and so we discourage dental entractions for patients receiving bisphosphates

FOLLOW UP

Active surveillence

The following criteria should be applied for identifying candidates for active surveillance;

- > 10 years life expectancy

- cT1/2 tumour size
- PSA ≤ 10ng/ml
- Biopsy Gleason Score <6
- Minimal Biopsy core involvement (≤ 50% cancer involvement)
- Follow up should be based on DRE, PSA, and repeat Biopsy
- Patient should be counseled on the possibility of needing further treatment in the future.
- Discuss surgery and radiotherapy as treatment options with patients suitable for such treatment

Age at presentation is very important when deciding on the intervals for active surveillance. Young patients tend to have aggressive forms of prostate cancer and therfore they require shorter intervals preferrably every month with a PSA reading, while the older patients should be seen at longer intervals ie. 3-6 months.

During active surveillance, older patients who are not fit for currative therapies should benefit from androgen deprivation therapy (ADT)

WATCHFUL WAITING

The following criteria should be used to identify patients who qualify for watchful waiting

- Patients not eligible for local curative treatment
- Start non curative treatment based on symptoms and disease progression

Clinical Evaluation on Follow up visits

Measurement of PSA is a cornerstone in follow-up after local treatment and PSA recurrence often precedes clinical recurrence [20,21]. A single, elevated, serum PSA level should be confirmed before starting second-line therapy based solely on PSA elevation

The PSA level for definition of treatment failure after RP and radiotherapy is defined by a PSA values > 0.2 ng/mL[22]

Prostate-specific antigen is expected to be undetectable within 6 weeks after successful RP

Rapidly increasing PSA level indicates distant metastases, whereas later, slowly increasing level most likely indicates local recurrence.

Patients should be followed-up more closely during the initial post-treatment period when risk of failure is highest. PSA measurement, disease-specific history and DRE are recommended at 3, 6 and 12 months postoperatively, every 6 months thereafter until 3 years, and then annually.

PSA persistence: PSA persistence is defined as failure of PSA to fall to undetectable levels. Patients should be re-evaluated to identify any sites of distant metastases including a bone scan and pelvic MRI scan. They are candidates for additional treatment with EBRT to sites of metastases or to the prostate in absence of distant metastases.

Biochemical failure after EBRT with or without Hormonal therapy: Biochemical failure is defined as a PSA increase by 2mg/mL or more above the nadir PSA after radiation. This should prompt further evaluation for local therapy like radical prostatectomy plus pelvic lymph node dissection followed by radiotherapy. This should be followed by androgen deprivation therapy for 2-3 years

TREATMENT OF PSA – ONLY RECURRENCE AFTER TREATMENT WITH A CURATIVE INTENT

A. Biochemical recurrence after radical prostatectomy

For patients with biochemical recurrence after radical prostatectomy, perform bone scan and /or abdomino-pelvic CT only in patients with PSA > 10ng/ml ar with PSA DT < 6months PSA Velocity >0.5ng/mL/month. Offer patients

with a PSA rise from the undetectable range and favourable prognostic factors surveillance and possibly delayed salvage radiotherapy. Other criteria for this treatment include;

- ≤pT3a
- Time to biochemical recurrence >3years
- PSA DT > 12 months
- Gleason score ≤ 7

Treat patients with a PSA rise from the undetectable range with salvage radiotherapy. The total dose of salvage radiotherapy should be atleast 66Gy and should be given early (PSA < 0.5ng/ml)

B. Biochemical recurrence after radiotherapy

This category of patients should benefit from salvage radical prostatectomy if possible, or considered for systemic salvage treatment

C. Systemic salvage treatment

Here patients are given Androgen Deprevation Therapy (ADT) however, this should be avoided under the following curcumstances;

- Absence of symptoms among men with biochemical recurrence
- Patients whose PSA Doubling Time (DT) >12 months
- Patients with confirmed Castration resistant prostate cancer (CRPC)

Castration recurrent prostate cancer (CRPC):
CRPC is defined as Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;

I. Biochemical progression: Three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, with PSA > 2 ng/mL or Radiological progression: The appearance of two or more new bone lesions on bone scan or enlargement of a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours)[23] Symptomatic progression alone must be

questioned and is not sufficient to diagnose CRPC

An alteration in normal androgen signaling is thought to be central to the pathogenesis of CRPC[24]. It is mediated through two main, overlapping, mechanisms. These are androgenreceptor (AR)-independent and AR-dependent

Follow up schedules

Evaluate patients every 3 – 6 months after treatment initiation

REFERENCES

1. Bianco FJ, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). Urology 2005;66:83-94.
2. Droz J-P, Balducci L, Bolla M, et al. Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults. Critical reviews in oncology/hematology 2010;73:68-91.
3. Seiler R, Studer U, Tschan K, Bader P, Burkhard F. 264 Removal of limited nodal disease in patients undergoing radical prostatectomy: Long term results confirm a chance for cure. European Urology Supplements 2014;1:e264.
4. Cheng L, Zincke H, Blute ML, Bergstralh EJ, Scherer B, Bostwick DG. Risk of prostate carcinoma death in patients with lymph node metastasis. Cancer 2001;91:66-73.
5. Aus G, Nordenskjöld K, Robinson D, Rosell J, Varenhorst E. Prognostic factors and survival in node-positive (N1) prostate cancer—a prospective study based on data from a Swedish population-based cohort. European urology 2003;43:627-31.
6. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. Jama 1999;281:1591-7.
7. Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. The Lancet Oncology 2014;15:464-73.
8. Ash D, Flynn A, Battermann J, de Reijke T, Lavagnini P, Blank L. ESTRO/EAU/EORTC recommendations on

permanent seed implantation for localized prostate cancer. Radiotherapy and Oncology 2000;57:315-21.

9. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. New England Journal of Medicine 1997;337:295-300.
10. Boccardo F, Barichello M, Battaglia M, et al. Bicalutamide monotherapy versus flutamide plus goserelin in prostate cancer: updated results of a multicentric trial. European urology 2002;42:481-90.
11. Group LS. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl J Med 1984;1984:1281-6.
12. Higano CS, Ellis W, Russell K, Lange PH. Intermittent androgen suppression with leuprolide and flutamide for prostate cancer: a pilot study. Urology 1996;48:800-4.
13. Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. Journal of Clinical Oncology 2010;28:1481-8.
14. De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. New England Journal of Medicine 2011;364:1995-2005.
15. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. The Lancet 2010;376:1147-54.
16. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. New England Journal of Medicine 2012;367:1187-97.
17. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. New England Journal of Medicine 2004;351:1513-20.
18. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. New England Journal of Medicine 2004;351:1502-12.
19. Wiseman LR, Spencer CM. Mitoxantrone. Drugs & aging 1997;10:473-85.
20. Horwitz EM, Thames HD, Kuban DA, et al. Definitions of biochemical failure that best predict clinical failure in patients with prostate cancer treated with external beam radiation

alone: a multi-institutional pooled analysis. The Journal of urology 2005;173:797-802.

21. Stephenson AJ, Kattan MW, Eastham JA, et al. Defining biochemical recurrence of prostate cancer after radical prostatectomy: a proposal for a standardized definition. Journal of Clinical Oncology 2006;24:3973-8.
22. Boccon-Gibod L, Djavan B, Hammerer P, et al. Management of prostate-specific antigen relapse in prostate cancer: A European consensus. International journal of clinical practice 2004;58:382-90.
23. Watanabe H, Okada M, Kaji Y, et al. New response evaluation criteria in solid tumours-revised RECIST guideline (version 1.1). Gan to kagaku ryoho Cancer & chemotherapy 2009;36:2495.
24. Schröder FH. Progress in understanding androgen-independent prostate cancer (AIPC): a review of potential endocrine-mediated mechanisms. European urology 2008;53:1129-37.

PART TWO

CHEMOTHERAPY REGIMENS FOR SOLID TUMORS

ANAL CANCER

A. LIMITED/LOCALIZED DISEASE (ANY T, ANY N, M0)

First line:

5FU/Mitomycin + XRT [1-3]

5-FU	1,000mg/m^2/day	IV infusion	Days 1–4, & 29–32
Mitomycin	10mg/m^2	IV bolus	Days 1 & 29

Plus Concurrent radiotherapy

Alternatives:

Capecitabine + mitomycin + radiotherapy [4,5]

Capecitabine	825mg/m^2	PO Twice daily	Monday–Friday
Mitomycin	10mg/m^2	IV bolus	Days 1 and 29

Plus Concurrent radiotherapy

B. METASTATIC ANAL CANCER (ANY T, ANY N, ANY M)

5-FU + CISPLATIN [6,7]

Cisplatin	100 mg/m^2	IV to run for 3 hours	Day 1
5-FU	500 mg/m^2/day	IV	Days 1-4

Repeat cycle every 4 weeks for 6 cycles

REFERENCES

1. Ajani JA, Winter KA, Gunderson LL, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. Jama 2008;299:1914-21.
2. Clark MA, Hartley A, Geh JI. Cancer of the anal canal. The lancet oncology 2004;5:149-57.
3. Party UACTW. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. The Lancet 1996;348:1049-54.
4. Goodman K, Rothenstein D, Lajhem C, Wu A, Cercek A, Saltz L. Capecitabine plus mitomycin in patients undergoing definitive chemoradiation for anal squamous cell carcinoma. International Journal of Radiation Oncology• Biology• Physics 2014;90:S32-S3.

5. Thind G, Johal B, Follwell M, Kennecke HF. Chemoradiation with capecitabine and mitomycin-C for stage I-III anal squamous cell carcinoma. Radiation Oncology 2014;9:1.
6. Ajani JA, Carrasco CH, Jackson DE, Wallace S. Combination of cisplatin plus fluoropyrimidine chemotherapy effective against liver metastases from carcinoma of the anal canal. The American journal of medicine 1989;87:221-4.
7. Faivre C, Rougier P, Ducreux M, et al. [5-fluorouracile and cisplatinum combination chemotherapy for metastatic squamous-cell anal cancer]. Bulletin du cancer 1999;86:861-5.

BLADDER CANCER

Intent: Perioperative (Neoadjuvant or adjuvant)

First line:

Gemcitabine + Cisplatin[1,2]

Cisplatin	70mg/m^2	IV	Day 1
Gemcitabine	1000mg /m^2	IV	Days 1,8,15

Repeat at 28 day intervals for 3 cycles prior to cystectomy

NB: Cisplatin can be substituted with carboplatin

Alternative:

Cisplatin + Methotrexate + Vinblastine (CMV)[3]

Methotrexate	30mg/m^2	IV bolus	Day 1
Vinblastine	4mg/m^2	IV bolus	Day 1
Cisplatin	100mg/m^2	IV infusion	Day 2
Leucovorin	15mg	PO or IV every 6 hours for 4 doses	
Methotrexate	30mg/m^2	IV bolus	Day 8
Vinblastine	4mg/m^2	IV bolus	Day 8
Leucovorin	15mg	PO every 6 hours for 4 doses	

Repeat every 3 weeks for 3 cycles.

MVAC[4]

Methotrexate	30mg/m^2	IV infusion	Days 1, 15 & 22
Vinblastine	3mg/m^2	IV infusion	Days 2, 15 & 22
Doxorubicin	30mg/m^2	IV infusion	Day 2
Cisplatin	70mg/m^2	IV infusion	Day 2

Repeat every 3 weeks for 6 cycles

Intent: Pallitive chemotherapy for metastatic bladder cancer

First line

Gemcitabine + Cisplatin[1,2]

Cisplatin	70mg/m^2	IV	Day 1
Gemcitabine	1000mg /m^2	IV	Days 1 & 8

Repeat at 21 day intervals for 6 cycles

Second line (palliative) chemotherapy for metastatic bladder cancer

Single agent taxane or gemcitabine

REFERENCES

1. Kaneko G, Kikuchi E, Matsumoto K, et al. Neoadjuvant gemcitabine plus cisplatin for muscle-invasive bladder cancer. Japanese journal of clinical oncology 2011:hyr068.
2. Ghadjar P, Burkhard FC, Gautschi O, Thalmann GN, Studer UE. Induction chemotherapy for unresectable urothelial carcinoma of the bladder. BJU international 2011;107:894-7.
3. Witjes JA, Compérat E, Cowan NC, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. European urology 2014;65:778-92.
4. Plimack ER, Hoffman-Censits JH, Viterbo R, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. Journal of Clinical Oncology 2014;32:1895-901.

BRAIN TUMOURS

A. GLIOBLASTOMA MULTIFORME

Intent: Adjuvant therapy

First line

Concomitant Temozolomide + XRT [1,2]

Temozolomide	75mg/m^2	PO daily	During XRT
Plus Radiotherapy			

Temozolomide

Temozolomide	150mg/m^2	PO daily	Day 1-5

Repeat at 28 day intervals maximum 6 cycles

Alternatives

Lomustine[3]

Lomustine (CCNU)	40mg	PO daily	Days 1-4

Repeat at 4-6 week intervals until progression / unacceptable toxicity

Second line

Temozolomide

Temozolomide	150mg/m^2	PO daily	Days 1-5

Repeat at 28 day intervals maximum 6 cycles

Third line options

Etoposide

Etoposide	50mg/m^2	PO BID	Days 1-14

Repeat at 21-28 day intervals maximum 6 cycles

B. OTHER BRAIN TUMOURS (OLIGODENDROGLIOMAS/MIXED TUMOURS)

First line

PCV [4,5]

Procarbazine	60mg/m^2	PO daily	Day 8-21
Lomustine (CCNU)	110mg/m^2	PO	Day 1
Vincristine	1.4mg/m^2	IV	day 8 & 29

Repeat at 6 weeks schedule

Second line

Consider radiotherapy

Third line

Temozolomide

Temozolomide	150mg/m^2	PO daily	Days 1-5

Repeat at 28 day intervals maximum 6 cycles

REFERENCES

1. Stupp R, Dietrich P-Y, Kraljevic SO, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. Journal of Clinical Oncology 2002;20:1375-82.

2. Stupp R, Mason WP, Van Den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. New England Journal of Medicine 2005;352:987-96.

3. Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. Journal of clinical oncology 2010;28:1168-74.

4. van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. Journal of Clinical Oncology 2006;24:2715-22.

5. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. Journal of Clinical Oncology 2013;31:344-50.

COLON CANCER

Intent: Advanced or metastatic colon cancer

First Line:

Modified FOLFOX6 [1,2]

Oxaliplatin	85 mg/m^2	IV Infusion	Day 1
Leucovorin	400mg/m^2	IV 2 hrs before 5-FU	Day 1
5-Fluorouracil	400mg/m^2	IV infusion for 2 hrs	Day 1
5-Fluorouracil	2400mg/m^2	46hr IV infusion	Days 1&2

Repeat at 14 day intervals for 12 cycles

Alternatives

mFOLFOX6 + Bevacizumab[3]

Oxaliplatin	85 mg/m^2	IV Infusion	Day 1
Leucovorin	400mg/m^2	IV 2 hrs before 5-FU	Day 1
5-Fluorouracil	400mg/m^2	IV infusion for 2 hrs	Day 1
5-Fluorouracil	1200mg/m^2	46hr IV infusion	Days 1&2
Bevacizumab	5mg/kg	IV infusion	Day 1

Repeat at 14 day intervals for 12 cycles

CapOX [4,5]

Oxaliplatin	130 mg/m^2	IV Infusion for 2hrs	Day 1
Capecitabine	850–1,000mg/m^2	PO twice daily	Day 1–14

Repeat at 21 day intervals for 12 cycles

Capox + Bevacizumab

Oxaliplatin	130 mg/m^2	IV Infusion for 2hrs	Day 1
Capecitabine	850–1,000mg/m^2	PO twice daily	Day 1–14
Bevacizumab	7.5mg/kg	IV infusion	Day 1

Repeat at 21 day intervals for 12 cycles

FOLFIRI[6]

Irinotecan	180mg/m^2	IV over 30–90 mins	Day 1
Leucovorin	400mg/m^2	IV infusion	Day 1
5-FU	400mg/m^2	IV infusion for 2 Hrs	Day 1
5-FU	2,400mg/m^2	IV for 46–48 hours	Days 1 & 2

Repeat at 14 day intervals for 12 cycles

Irinotecan[7,8]

Irinotecan	125mg/m^2	IV over 30–90 mins	Day 1 & 8

Repeat every 21 days

Cetuximab (*KRAS/NRAS* WT gene only) + irinotecan [9]

Cetuximab	500mg/m^2	IV over 30–90 mins	Day 1 & 8
Irinotecan	180mg/m^2	IV infusion	Day 1

Repeat at 14 day intervals for 12 cycles

Capecitabine[10]

Capecitabine	1,250mg/m^2	PO twice daily	Day 1 -14

Repeat every 21 days for 6 cycles

FOLFOX 4 [11]

Oxaliplatin	85 mg/m^2	IV Infusion for 2 Hrs	Day 1
Leucovorin	200mg/m^2	IV 2 hrs before 5-FU	Day 1 & 2
5-Fluorouracil	400mg/m^2	IV infusion for 2 hrs	Day 1
5-Fluorouracil	600mg/m^2	22hr IV infusion	Days 1&2

Repeat at 14 day intervals for 12 cycles

5-FU + LEUCOVORIN + BEVACIZUMAB (Roswell Park Regimen) [12,13]

Leucovorin	500mg/m^2	IV 2 hrs before 5-FU	Days 1,8,15,22,29 & 36
5-Fluorouracil	500mg/m^2	IV infusion for 2 hrs	Day 1,8,15,22,29 & 36
Bevacizumab	5 mg/kg	IV infusion over 30-90 mins	Days 1, 15, 29 & 43

Repeat at 14 day intervals for 12 cycles

REFERENCES

1. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. New England Journal of Medicine 2004;350:2343-51.
2. de Gramont Ad, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. Journal of Clinical Oncology 2000;18:2938-47.
3. Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. BMC cancer 2007;7:1.
4. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy

followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging–defined, locally advanced rectal cancer: grupo cáncer de recto 3 study. Journal of Clinical Oncology 2010;28:859-65.

5. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. Journal of Clinical Oncology 2008;26:2013-9.
6. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. Journal of Clinical Oncology 2004;22:229-37.
7. Cunningham D, Pyrhönen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. The Lancet 1998;352:1413-8.
8. Fuchs CS, Moore MR, Harker G, Villa L, Rinaldi D, Hecht JR. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. Journal of clinical oncology 2003;21:807-14.
9. Van Cutsem E, Tejpar S, Vanbeckevoort D, et al. Intrapatient cetuximab dose escalation in metastatic colorectal cancer according to the grade of early skin reactions: the randomized EVEREST study. Journal of clinical oncology 2012;30:2861-8.
10. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. New England Journal of Medicine 2005;352:2696-704.
11. André T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. Journal of Clinical Oncology 2009;27:3109-16.
12. Chen HX, Mooney M, Boron M, et al. Phase II multicenter trial of bevacizumab plus fluorouracil and leucovorin in patients with advanced refractory colorectal cancer: an NCI Treatment Referral Center Trial TRC-0301. Journal of Clinical Oncology 2006;24:3354-60.
13. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. Journal of Clinical Oncology 2005;23:3697-705.

ENDOMETRIAL CANCER

Intent: systemic chemotherapy for recurrent, metastatic endometrial cancer

FIRST LINE:

Carboplatin + paclitaxel[1,2]

Carboplatin	AUC 5–6	IV over 1 hour	Day 1
Paclitaxel	175mg/m^2	IV over 3 hours	Day 1

Repeat cycle every 3 weeks for 6 to 9 cycles

Alternatives

Doxorubicin/Cisplatin [3,4]

Doxorubicin	60mg/m^2	IV over 1 hour	Day 1
Cisplatin	50mg/m^2	IV over 3 hours	Day 1

Repeat cycle every 3 weeks for 6 cycles

Doxorubicin/Cisplatin + paclitaxel[3]

Doxorubicin	45mg/m^2	IV over 1 hour	Day 1
Cisplatin	50mg/m^2	IV infusion	Day 1
Paclitaxel	160mg/m^2	IV over 3 hours	Day 1

Repeat cycle every 3 weeks for 6 cycles

Carboplatin + docetaxel[5,6]

Docetaxel	60–75mg/m^2	IV over 3 hours	Day 1
Carboplatin	AUC 5–6	IV over 1 hour	Day 1

Repeat cycle every 3 weeks for 6 to 9 cycles

SECOND LINE:

Liposamal doxorubicin[7]

Liposomal doxorubicin	50mg/m^2	IV over 1 hour	Day 1

Repeat cycle every 4 weeks for 6 cycles

Paclitaxel[8]

Paclitaxel	110–200mg/m^2	IV over 3 hours	Day 1

Repeat cycle every 3 weeks for 6 cycles

Topotecan[9]

Topotecan	1.5mg/m2/day	IV over 1 hour	Day 1 - 5

Repeat cycle every 3 weeks for 6 cycles

Docetaxel[10]

Docetaxel	36mg/m^2	IV over 1 hour	Day 1, 8, and 15

Repeat cycle every 4 weeks for 6 cycles

Ifosphamide (for carcinosarcoma)[11]

Ifosfamide	2g/m^2/day	IV over 1 hour	Day 1 - 3
Mesna	2g	IV before Ifosphamide	Day 1–3

Repeat cycle every 3 weeks for 8 cycles

REFERENCES

1. Miller D, Filiaci V, Fleming G, et al. Late-Breaking Abstract 1: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. Gynecologic oncology 2012;125:771.
2. Sorbe B, Andersson H, Boman K, Rosenberg P, Kalling M. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel—long-term follow-up. International Journal of Gynecological Cancer 2008;18:803-8.
3. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. Journal of Clinical Oncology 2004;22:2159-66.
4. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study. Gynecologic oncology 2009;112:543-52.
5. Scribner DR, Puls LE, Gold MA. A phase II evaluation of docetaxel and carboplatin followed by tumor volume directed pelvic plus or minus paraaortic irradiation for stage III endometrial cancer. Gynecologic oncology 2012;125:388-93.
6. Nomura H, Aoki D, Takahashi F, et al. Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041). Annals of oncology 2011;22:636-42.

7. Muggia FM, Blessing JA, Sorosky J, Reid GC. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study. Journal of Clinical Oncology 2002;20:2360-4.
8. Lincoln S, Blessing JA, Lee RB, Rocereto TF. Activity of paclitaxel as second-line chemotherapy in endometrial carcinoma: a Gynecologic Oncology Group study. Gynecologic oncology 2003;88:277-81.
9. Wadler S, Levy DE, Lincoln ST, Soori GS, Schink JC, Goldberg G. Topotecan is an active agent in the first-line treatment of metastatic or recurrent endometrial carcinoma: Eastern Cooperative Oncology Group Study E3E93. Journal of clinical oncology 2003;21:2110-4.
10. Garcia AA, Blessing JA, Nolte S, Mannel RS. A phase II evaluation of weekly docetaxel in the treatment of recurrent or persistent endometrial carcinoma: a study by the Gynecologic Oncology Group. Gynecologic oncology 2008;111:22-6.
11. Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. Journal of Clinical Oncology 2007;25:526-31.

EWINGS SARCOMA

Intent: Primary chemotherapy: Neoadjuvant/ Adjuvant chemotherapy

First line:

VAC/IE (vincristine +doxorubicin + cyclophosphamide alternating with ifosfamide +etoposide)[1]

Alternating VAC and IE cycles

VAC cycles

Vincristine	2mg/m^2	IV over 1 hour	Day 1
Doxorubicin	75mg/m^2	IV infusion	Day 1
Cyclophosphamide	1,200mg/m^2	IV infusion	Day 1

Repeat cycle every 3 weeks

IE cycles

Ifosfamide	1,800mg/m^2	IV over 1 hour	Day 1-5
Mesna	2g	IV infusion	Days 1–5
Etoposide	100mg/m^2	IV infusion	

Repeat cycle every 3 weeks for 17 cycles

Alternatives:

VAIA (vincristine + dactinomycin [actinomycin D] + ifosfamide +doxorubicin)[2,3]

Vincristine	1.5mg/m^2	IV over 1 hour	Day 1
Ifosfamide	2,000mg/m^2	IV + mesna	Days 1-3
Dactinomycin	0.5mg/m^2	IV	Days 1, 3, & 5
Doxorubicin	30mg/m^2	IV	Days 2 & 4

Repeat cycle every 3 weeks for 4 cycles

Second line Therapy (Relapsed, Refractory disease or Metastatic Disease):

Cyclophosphamide + Topotecan[4-7]

Cyclophosphamide	250mg/m^2/day	IV over 1 hour	Day 1- 5
Topotecan	0.75mg/m^2/day	IV infusion	Day 1–5

Repeat cycle every 3 weeks for 12-14 cycles

Irinitecan +/- Temozolamide[8,9]

Temozolomide	100mg/m^2/day	PO daily	Day 1-5
Irinotecan	10–20mg/m^2/ day	IV at least 1 hour after temozolomide	Days 1–5 and 8–12

Repeat cycle every 3 weeks for 6 cycles

Ifosphamide (high dose) + Etoposide[10,11]

Ifosfamide	1,800mg/m^2/day	IV + Mesna	Day 1–5
Etoposide	100mg/m^2/day	IV	Days 1–5

Repeat cycle every 3 weeks for 12 cycles

Docetaxel + gemcitabine[12]

Gemcitabine	675mg/m^2	IV over 1 hour	Day 1 and 8
Docetaxel	75–100mg/m^2	IV	Day 8

Repeat cycle every 3 weeks for 13 cycles

REFERENCES

1. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. New England Journal of Medicine 2003;348:694-701.
2. Paulussen M, Craft AW, Lewis I, et al. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment—cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. Journal of Clinical Oncology 2008;26:4385-93.
3. Paulussen M, Ahrens S, Dunst J, et al. Localized Ewing tumor of bone: final results of the cooperative Ewing's Sarcoma Study CESS 86. Journal of Clinical Oncology 2001;19:1818-29.
4. Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/ Children's Cancer Group Phase II Study 9457—a report from the Children's Oncology Group. Journal of Clinical Oncology 2006;24:152-9.
5. Hunold A, Weddeling N, Paulussen M, Ranft A, Liebscher C, Jürgens H. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. Pediatric blood & cancer 2006;47:795-800.
6. Kushner BH, Kramer K, Meyers PA, Wollner N, Cheung NKV. Pilot study of topotecan and high-dose cyclophosphamide for resistant pediatric solid tumors. Medical and pediatric oncology 2000;35:468-74.
7. Saylors RL, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group phase II study. Journal of Clinical Oncology 2001;19:3463-9.
8. Casey DA, Wexler LH, Merchant MS, et al. Irinotecan and temozolomide for Ewing sarcoma: The Memorial

Sloan-Kettering experience. Pediatric blood & cancer 2009;53:1029-34.

9. McGregor LM, Stewart CF, Crews KR, et al. Dose escalation of intravenous irinotecan using oral cefpodoxime: a phase I study in pediatric patients with refractory solid tumors. Pediatric blood & cancer 2012;58:372-9.
10. Miser JS, Kinsella T, Triche T, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. Journal of Clinical Oncology 1987;5:1191-8.
11. Magnan H, Goodbody CM, Riedel E, Pratilas CA, Wexler LH, Chou AJ. Ifosfamide dose-intensification for patients with metastatic Ewing sarcoma. Pediatric blood & cancer 2015;62:594-7.
12. Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. Cancer 2008;113:419-25.

GALL BLADDER AND BILE DUCT CANCER

Intent: Primary treatment for unresectable disease

First line

Cisplatin + Gemcitabine[1]

Cisplatin	25mg/m^2	IV over 1 hour	Day 1 & 8
Gemcitabine	1,000mg/m^2	IV over 30 Minutes	Day 1
		Repeat cycle every 3 weeks for 6 cycles	

Alternatives:

GemOx[2,3]

Gemcitabine	1,000mg/m^2	IV over 30 Minutes	Day 1
Oxaliplatin	85mg/m^2		Day 2
		Repeat cycle every 2 weeks for 6 cycles	

Gemcitabine [4]

Gemcitabine	1,000mg/m^2	IV over 30 Minutes	Day 1
		Repeat cycle every 4 weeks for 6 cycles	

Capecitabine[5]

Capecitabine	1000 mg/m^2	PO BID daily	Days 1-14
		Repeat cycle every 3 weeks for 6 cycles	

REFERENCES

1. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. New England Journal of Medicine 2010;362:1273-81.
2. Jang J-S, Lim HY, Hwang IG, et al. Gemcitabine and oxaliplatin in patients with unresectable biliary cancer including gall bladder cancer: a Korean Cancer Study Group phase II trial. Cancer chemotherapy and pharmacology 2010;65:641-7.
3. Sharma A, Mohanti B, Raina V, et al. A phase II study of gemcitabine and oxaliplatin (Oxigem) in unresectable gall bladder cancer. Cancer chemotherapy and pharmacology 2010;65:497-502.
4. Tsavaris N, Kosmas C, Gouveris P, et al. Weekly gemcitabine for the treatment of biliary tract and gallbladder cancer. Investigational new drugs 2004;22:193-8.
5. Lozano R, Patt Y, Hassan M, et al. Oral capecitabine (Xeloda) for the treatment of hepatobiliary cancers (hepatocellular carcinoma, cholangiocarcinoma, and gallbladder cancer). Proc Am Soc Clin Oncol; 2000. p. 264a.

GASTRIC CANCER

Intent: Preoperative (esophagogastric and gastric cardia tumours)

First line:

Paclitaxel + carboplatin[1]

Paclitaxel	50mg/m^2	IV over 1 hour	Day 1
Carboplatin	AUC 2mg/min/mL	IV infusion	Day 1

Repeat cycle every week for 5 weeks

Alternatives

Cisplatin + 5-Fluorouracil[2,3]

Cisplatin	15mg/m^2	IV infusion	Day 1 - 5
5-FU	800mg/m^2/day	IV infusion	Day 1 - 5

Repeat cycle every 3 weeks for 2 cycles

Cisplatin + capecitabine[4]

Cisplatin	30mg/m^2	IV over 1 hour	Day 1
Capecitabine	800mg/m^2	PO twice daily	Days 1–5

Repeat cycle every week for 5 weeks

Intent: perioperative

First line:

5FU + Cisplatin[5]

Cisplatin	75-80mg/m^2	IV over 1 hour	Day 1
5-FU	800mg/m^2	IV over 24 Hrs daily	Day 1–5

Repeat cycle every 4 weeks for 2-3 cycles pre-operative and 3-4 cycles postoperative

Alternatives

Epirubicin + Cisplatin + capecitabine [6]

Epirubicin	50mg/m^2	IV	Day 1
Cisplatin	60mg/m^2	IV	Day 1
Capecitabine	625mg/m^2	PO twice daily	Day 1 - 21

Repeat cycle every 3 weeks for 3 cycles preoperatively & 3 cycles postoperatively

Epirubicin + Oxaliplatin + capecitabine[6]

Epirubicin	50mg/m^2	IV	Day 1
Oxaliplatin	130mg/m^2	IV	Day 1
Capecitabine	625mg/m^2	PO twice daily	Day 1 - 21

Repeat cycle every 3 weeks for 3 cycles preoperatively & 3 cycles postoperatively

Intent: Post operative

5-FU + Leucovorin[7]

Cycles 1, 3, and 4 (before and after radiation)

Leucovorin	20mg/m^2	IV infusion	Day 1 - 5
5-FU	425mg/m^2/day	IV infusion	Day 1 - 5

Repeat cycle every 28 days

Cycle 2 (with radiation)

Leucovorin	20mg/m^2	IV infusion	Day 1 – 4 and 31–33
5-FU	400mg/m^2/day	IV infusion	Day 1 - 4

Repeat cycle every 35 days

Intent: Palliative chemotherapy for unresectable locally advanced and metastatic gastric cancer

First line:

Cisplatin + 5 fluorouracil[8]

Cisplatin	75-100mg/m^2	IV infusion	Day 1
5-FU	1,000mg/m^2	IV over 24 hours daily	Day 1 - 4

Repeat cycle every 3 weeks for 6 cycles

Alternatives

Docetaxel + Cisplatin[9,10]

Docetaxel	70–85mg/m^2	IV infusion	Day 1
Cisplatin	70–75mg/m^2	IV infusion	Day 1

Repeat cycle every 3 weeks for 6 cycles

Paclitaxel + Cisplatin or carboplatin[11-13]

Paclitaxel	135–200mg/m^2	IV infusion	Day 1
Cisplatin	75mg/m^2	IV infusion	Day 2

Repeat cycle every 3 weeks for 6 cycles

Transtuzumab + Chemotherapy (For Her2 neu overexpressing adenocarcinoma)[14]

Trastuzumab	8mg/kg loading then 4mg/kg IV every 14 days	IV infusion	Day 1
Cisplatin	80mg/m^2	IV infusion	Day 1
Capecitabine	1000mg/m^2	PO twice daily	Days 1-14

Repeat cycle every 3 weeks for 2 cycles

REFERENCES

1. van Hagen P, Hulshof M, Van Lanschot J, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. New England Journal of Medicine 2012;366:2074-84.
2. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. Journal of Clinical Oncology 2008;26:1086-92.
3. Bedenne L, Michel P, Bouché O, et al. Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102. Journal of Clinical Oncology 2007;25:1160-8.
4. Lee SS, Kim S-B, Park S-I, et al. Capecitabine and cisplatin chemotherapy (XP) alone or sequentially combined chemoradiotherapy containing XP regimen in patients with three different settings of stage IV esophageal cancer. Japanese journal of clinical oncology 2007;37:829-35.
5. Ychou M, Boige V, Pignon J-P, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. Journal of Clinical Oncology 2011;29:1715-21.
6. Sumpter K, Harper-Wynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. British journal of cancer 2005;92:1976-83.
7. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. New England Journal of Medicine 2001;345:725-30.
8. Kim GM, Jeung H-C, Rha SY, et al. A randomized phase II trial of S-1-oxaliplatin versus capecitabine–oxaliplatin in advanced gastric cancer. European Journal of Cancer 2012;48:518-26.
9. Kim JY, Do YR, Park KU, et al. A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. Cancer chemotherapy and pharmacology 2010;66:31-6.
10. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. Journal of Clinical Oncology 2005;23:5660-7.
11. Ajani JA. Evolving chemotherapy for advanced gastric cancer. The Oncologist 2005;10:49-58.
12. Petrasch S, Welt A, Reinacher A, Graeven U, König M, Schmiegel W. Chemotherapy with cisplatin and paclitaxel

in patients with locally advanced, recurrent or metastatic oesophageal cancer. British journal of cancer 1998;78:511.

13. Ilson DH, Forastiere A, Arquette M, et al. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer journal (Sudbury, Mass) 1999;6:316-23.

14. Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. The Lancet 2010;376:687-97.

GASTROINTESTINAL STROMAL TUMOURS

Intent: Adjuvant or Palliative

First line for c-Kit Positive (CD117) tumour:

Imatinib (Glivec®) (Fiore, Palassini et al. 2009, McAuliffe, Hunt et al. 2009, Blesius, Cassier et al. 2011)

Imatinib 400mg orally once daily; increase to 400mg twice daily in patients withn documented KIT exon 9 mutation as clinically tolerated.

Second line:

Sunitinib (Sutent®) (Demetri, van Oosterom et al. 2006, George, Blay et al. 2009)

Sunitinib 50mg orally daily for 4 weeks followed by a two week break

Alternatives:

Regorafenib (Demetri, Reichardt et al. 2013)

Regorafenib 160mg orally once daily. Given in 4-week cycles with 3 weeks on and 1 week off.

Sorafenib(Kindler, Campbell et al. 2011, Park, Ryu et al. 2012, Montemurro, Gelderblom et al. 2013)

Sorafenib 400mg orally twice daily until disease progression or development of intolerance.

REFERENCES

1. Blesius, A., et al. (2011). “Neoadjuvant imatinib in patients with locally advanced non metastatic GIST in the prospective BFR14 trial.” BMC Cancer **11**(1): 1.
2. Demetri, G. D., et al. (2013). “Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial.” The Lancet **381**(9863): 295-302.
3. Demetri, G. D., et al. (2006). “Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial.” The Lancet **368**(9544): 1329-1338.

4. Fiore, M., et al. (2009). “Preoperative imatinib mesylate for unresectable or locally advanced primary gastrointestinal stromal tumors (GIST).” European Journal of Surgical Oncology (EJSO) **35**(7): 739-745.

5. George, S., et al. (2009). “Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure.” European journal of cancer **45**(11): 1959-1968.

6. Kindler, H., et al. (2011). Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): final results of a University of Chicago Phase II Consortium trial. ASCO Annual Meeting Proceedings.

7. McAuliffe, J. C., et al. (2009). “A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis.” Annals of Surgical Oncology **16**(4): 910-919.

8. Montemurro, M., et al. (2013). “Sorafenib as third-or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis.” European journal of cancer **49**(5): 1027-1031.

9. Park, S., et al. (2012). “Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group.” Investigational new drugs **30**(6): 2377-2383.

GERM CELL TUMOUR

Intent: Primary chemotherapy for germ cell tumours
First line:

Etoposide + Cisplatin (EP)[1]

Etoposide	100mg/m^2	IV	Day 1–5
Cisplatin	20mg/m^2	IV	Day 1–5

Repeat cycle every 3 weeks for 4 cycles

Alternatives:

Bleomycin + Etoposide + Cisplatin (BEP)[2]

Bleomycin	30 units	IV	Days 1, 8, and 15
Etoposide	100mg/m^2	IV	Day 1–5
Cisplatin	20mg/m^2	IV	Day 1–5

Repeat cycle every 3 weeks for 4 cycles

Etoposide + ifosphamide + Cisplatin + Mesna[3]

Mesna	120mg/m^2	IV slow infusion before ifosphamide	Day 1
Etoposide	75mg/m^2	IV	Day 1–5
Ifosphamide	1,200mg/m^2	IV + mesna 1,200mg/m^2 continuous infusion	Days 1–5
Cisplatin	20mg/m^2	IV	Day 1–5

Repeat cycle every 3 weeks for 4 cycles

Intent: second line chemotherapy for metastatic germ cell tumours

Gemcitabine + Oxaliplatin[4-6]

Gemcitabine	1,000mg/m^2	IV	Day 1and 8
Oxaliplatin	130mg/m^2	IV	Day 1

Repeat cycle every 3 weeks for 4 cycles

Gemcitbine + paclitaxel[7,8]

Gemcitabine	1,000mg/m^2	IV over 30 minutes	Days 1, 8 & 15
Paclitaxel	100mg/m^2	IV over 1 hour	Day 1

Repeat cycle every 4 weeks for 6 cycles

Gemcitabine + Paclitaxel + Oxaliplatin[9]

Gemcitabine	800mg/m^2	IV over 30 minutes	Days 1 and 8
Paclitaxel	80mg/m^2	IV over 1 hour	Day 1 and 8
Oxaliplatin	130mg/m^2	IV	Day 1

Repeat cycle every 3 weeks for 2 cycles

Etoposide [10]

Etoposlde	50mg/m^2	Orally daily	Day 1 – 28

Repeat cycle every 4 weeks until disease progression or unacceptable toxicity

REFERENCES

1. Xiao H, Mazumdar M, Bajorin DF, et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. Journal of clinical oncology 1997;15:2553-8.

2. Saxman SB, Finch D, Gonin R, Einhorn LH. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: the Indian University experience. Journal of Clinical Oncology 1998;16:702-6.

3. Nichols CR, Catalano PJ, Crawford ED, Vogelzang NJ, Einhorn LH, Loehrer PJ. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. Journal of Clinical Oncology 1998;16:1287-93.

4. Pectasides D, Pectasides M, Farmakis D, et al. Gemcitabine and oxaliplatin (GEMOX) in patients with cisplatin-refractory germ cell tumors: a phase II study. Annals of oncology 2004;15:493-7.

5. Kollmannsberger C, Beyer J, Liersch R, et al. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: a study of the German Testicular Cancer Study Group. Journal of Clinical Oncology 2004;22:108-14.

6. De Giorgi U, Rosti G, Aieta M, et al. Phase II study of oxaliplatin and gemcitabine salvage chemotherapy in patients with cisplatin-refractory nonseminomatous germ cell tumor. European urology 2006;50:1032-9.

7. Einhorn LH, Brames MJ, Juliar B, Williams SD. Phase II study of paclitaxel plus gemcitabine salvage chemotherapy for germ cell tumors after progression following high-dose chemotherapy with tandem transplant. Journal of clinical oncology 2007;25:513-6.

8. Mulherin B, Brames M, Einhorn L. Long-term survival with paclitaxel and gemcitabine for germ cell tumors after progression following high-dose chemotherapy with tandem transplants. ASCO Annual Meeting Proceedings; 2011. p. 4562.

9. Bokemeyer C, Oechsle K, Honecker F, et al. Combination chemotherapy with gemcitabine, oxaliplatin, and paclitaxel in patients with cisplatin-refractory or multiply relapsed germ-cell tumors: a study of the German Testicular Cancer Study Group. Annals of oncology 2008;19:448-53.

10. Miller JC, Einhorn LH. Phase II study of daily oral etoposide in refractory germ cell tumors. Seminars in oncology 1990;17:36-9.

GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

Intent: Curative systemic chemotherapy for low risk disease

Methotrexate[1]

Methotrexate	0.4 mg/kg	IV infusion	Day 1 - 5

Repeat cycle every 2 weeks for 6 cycles

Intent: Primary therapy for Medium risk group (WHO score 4-7)[2]

Course A

Etoposide	100 mg/m^2	IV infusion	Day 1 - 3

Course B

Hydroxyurea	500 mg	PO BID	Day 1
Methotrexate	50 mg	IM at Midday	Days 2,4,6,8
Folinic acid	6 mg	IM at 6pm	Days 3,5,7,9
6-MP	75 mg	PO daily	Days 3, 5,7,9

Course C

Dactinomycin	0.5 mg	IV infusion	Day 1 - 5

Course D

Vincristine	0.8 mg/m^2	IV infusion	Day 1 & 3
Cyclophosphamnide	400 mg/m^2	IV infusion	Day 1 & 3

Note: Courses A, B. & C are given in an eight course sequence in the order: A, B, C, B, A, B, C, B.

Intent: Primary therapy for High risk disease

EMA/CO [2-5]

Course A

Dactinomycin	0.5 mg/m^2	IV infusion	Day 1 & 3
Etoposide	100 mg/m^2	IV infusion	Day 1 & 3
Methotrexate	100 mg/m^2	IV bolus	Day 1
Methotrexate	200 mg/m^2	12 hour infusion	Day 1
Folinic acid	15 mg	PO bid	Days 3 and 4

Course B

Vincristine	1.0 mg/m^2	IV infusion	Day 8
Cyclophosphamide	600 mg/m^2	IV infusion	Day 8

Repeat cycle every 3 weeks for 6 cycles

Intent: Salvage therapy for resistant choriocarcinoma

PEBA [6]

Cisplatin	20 mg/m^2	IV infusion	Day 1 - 4
Etoposide	100 mg/m^2	IV infusion	Day 1
Bleomycin	10 IU/m^2	IV bolus	Day 1
Adriamycin	40 mg/m^2	IV infusion	Day 1

Repeat cycle every 3 weeks for 6-8 cycles

REFERENCES

1. Li MC, Hertz R, Spencer DB. Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma. Experimental Biology and Medicine 1956;93:361-6.
2. Newlands E, Bagshawe K, Begent R, Rustin G, Holden L, Dent J. Developments in chemotherapy for medium-and high-risk patients with gestational trophoblastic tumours (1979–1984). BJOG: An International Journal of Obstetrics & Gynaecology 1986;93:63-9.
3. Ross GT, Goldstein DP, Hertz R, Lipsett MB, Odell WD. Sequential use of methotrexate and actinomycin D in the treatment of metastatic choriocarcinoma and related trophoblastic diseases in women. American journal of obstetrics and gynecology 1965;93:223-9.
4. Bolis G, Bonazzi C, Landoni F, et al. EMA/CO regimen in high-risk gestational trophoblastic tumor (GTT). Gynecologic oncology 1988;31:439-44.
5. Newlands E, Bagshawe K, Begent R, Rustin G, Holden L. Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumours, 1979 to 1989. BJOG: An International Journal of Obstetrics & Gynaecology 1991;98:550-7.
6. Li-pai C, Shu-mo C, Jian-xuan F, Zi-ting L. PEBA regimen (cisplatin, etoposide, bleomycin, and adriamycin) in the treatment of drug-resistant choriocarcinoma. Gynecologic oncology 1995;56:231-4.

HEAD AND NECK

Intent: induction chemotherapy for Head and Neck SCC

First line

Docetaxel + Cisplatin + 5-FU[1-3]

Docetaxel	75mg/m^2	IV infusion	Day 1
Cisplatin	75mg/m^2	IV infusion	Day 1
5-FU	750mg/m^2/day	IV infusion	Days 1–5

Repeat every 3 weeks for up to 4 cycles.

Alternatives

Cisplatin + 5-FU [1]

Cisplatin	75mg/m^2	IV infusion	Day 1
5-FU	750mg/m^2/day	IV infusion	Days 1–5

Repeat every 3 weeks for up to 4 cycles.

Paclitaxel + Cisplatin + 5 FU[4]

Paclitaxel	175mg/m^2	IV infusion for 3 hrs	Day 1
Cisplatin	100mg/m^2	IV infusion	Day 2
5-FU	500mg/m2/day	Iv infusion	Day 2–6

Repeat every 3 weeks for up to 3 cycles.

Docetaxel + Cisplatin[5]

Docetaxel	75mg/m^2	IV infusion	Day 1
Cisplatin	75mg/m^2	IV infusion	Day 1

Repeat every 3 weeks for up to 2 cycles.

Intent: Combination therapy for recurrent unresectable or metastatic disease (with No surgery or RT option)

Cisplatin or carboplatin + Decetaxel

Docetaxel	75mg/m^2	Infusion for 1 Hour	Day 1
Cisplatin	75mg/m^2	IV infusion	Day 1

Repeat every 3 weeks for up to 4 cycles.

Cisplatin or carboplatin + paclitaxel[6]

Paclitaxel	175mg/m^2	Infusion for 3 Hour	Day 1
Cisplatin	75mg/m^2	IV infusion	Day 1

Repeat every 3 weeks for up to 4 cycles.

Cispaltin + cetuximab (non-pharyngeal)[7]

Cetuximab	200mg/m^2	IV for 120 Mins	Day 1
Cisplatin	100mg/m^2	IV infusion	Day 1

Repeat every 4 weeks for up to 4 cycles.

Cisplatin + 5FU[8,9]

Cisplatin	100mg/m^2/day	Infusion for 1 Hour	Day 1
5-FU	500-1000mg/m^2	IV infusion	Day 1-4

Repeat every 3 weeks for up to 6 cycles.

Cisplatin + gemcitabine (nasopharyngeal)[10]

Gemcitabine	1,000mg/m^2	IV Infusion	Day 1 & 8
Cisplatin	80mg/m^2	IV infusion	Day 1-3

Repeat every 3 weeks for up to 4 cycles.

REFERENCES

1. Vermorken JB, Remenar E, Van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. New England Journal of Medicine 2007;357:1695-704.
2. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. New England Journal of Medicine 2007;357:1705-15.
3. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. Journal of the National Cancer Institute 2009.
4. Hitt R, López-Pousa A, Martínez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. Journal of Clinical Oncology 2005;23:8636-45.
5. Hui EP, Ma BB, Leung SF, et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. Journal of clinical oncology 2009;27:242-9.
6. Herbst RS, Arquette M, Shin DM, et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. Journal of Clinical Oncology 2005;23:5578-87.
7. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. Journal of Clinical Oncology 2005;23:8646-54.
8. Gibson MK, Li Y, Murphy B, et al. Randomized phase III

evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. Journal of Clinical Oncology 2005;23:3562-7.

9. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. Journal of Clinical Oncology 1992;10:1245-51.
10. Chen C, Wang F-h, Wang Z-q, et al. Salvage gemcitabine–vinorelbine chemotherapy in patients with metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. Oral oncology 2012;48:1146-51.

HEPATOCELLULAR CANCER

Intent: Palliative chemotherapy for advanced hepatocellular cancer

First line: for HCC with Child-Pugh Class a or B

Sorafenib [1]

Sorafenib	400mg	PO BID daily	Day 1

Repeat every 3 weeks until disease progression.

Alternatives:

Adriamycin

Adriamycin	60 mg/m^2	Iv infusion	Day 1

Repeat every 3 weeks for 6 cycles.

OR

Adriamycin	20 mg/m^2	Iv infusion	Day 1

Repeat every week for 12 cycles.

Capecitabine

Capecitabine	1000 mg/m^2	PO BID daily	Day 1- 14

Repeat every 3 weeks until disease progression

Bevacizumab

Bevacuzimab	5 mg/kg	Iv infusion	Day 1

Repeat every 2 weeks until disease progression

REFERENCES

1. Cheng A-L, Kang Y-K, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. The lancet oncology 2009;10:25-34.

LUNG CANCER

Intent: Neoadjuvant and adjuvant regimens

Cisplatin / Pemetrexed[1]

Cisplatin	75mg/m^2	IV infusion	Day 1
Pemetrexed	500mg/m^2	Iv infusion	Day 1

Repeat every 3 weeks for 4 cycles

Alternatives

Cisplatin + Etoposide[2]

Cisplatin	100mg/m^2	IV	Day 1
Etoposide	100mg/m^2	IV	Days 1–3

Repeat every 3 weeks for 4 cycles

Cisplatin + gemcitabine[3]

Cisplatin	75mg/m^2	IV	Day 1
Gemcitabine	1,250mg/m^2	IV	Day 1 & 8

Repeat every 3 weeks for 4 cycles

Cisplatin + docetaxel[4]

Docetaxel	75mg/m^2	IV	Day 1
Cisplatin	75mg/m^2	IV	

Repeat every 3 weeks for 4 cycles

Bevacizumab + Carboplatin + Paclitaxel[5]

Paclitaxel	200mg/m^2	IV	Day 1
Carboplatin	AUC 6mg/min/mL	IV infusion	Day 1
Bevacizumab	15mg/kg	IV	Day 1

Repeat every 3 weeks for 4 cycles

Bevacizumab + Cisplatin + Pemetrexed[6]

Pemetrexed	500mg/m^2	IV	Day 1
Cisplatin	75mg/m^2	IV infusion	Day 1
Bevacizumab	7.5mg/kg	IV	Day 1

Repeat every 3 weeks for 4 cycles

Erlotinib (EGFR Positive tumours)

Erlotinib	150mg	PO daily	Day 1 - 28

Repeat every 4 weeks until disease progression

Crizotinib (ALK positive tumours)

Crizotinib	250mg	PO twice daily	Day 1 - 28

Repeat every 4 weeks until disease progression

REFERENCES

1. Kreuter M, Vansteenkiste J, Fischer J, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. Annals of oncology 2012:mds578.
2. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon J, Vansteenkiste J. International Adjuvant Lung Cancer Trial Collaborative Group.. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60.
3. Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non–small-cell lung cancer. Journal of Clinical Oncology 2012;30:3516-24.
4. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non–small-cell lung cancer: The TAX 326 study group. Journal of Clinical Oncology 2003;21:3016-24.
5. Albain KS, Crowley JJ, Turrisi AT, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non–small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. Journal of clinical oncology 2002;20:3454-60.
6. Patel JD, Socinski MA, Garon EB, et al. PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non–small-cell lung cancer. Journal of Clinical Oncology 2013;31:4349-57.

LUNG CANCER - SCLC

Intent: Adjuvant chemotherapy for limited stage SCLC

FIRST LINE REGIMENS

Cisplatin + Etoposide [1,2]

Cisplatin	60-80mg/m^2	IV infusion	Day 1
Etoposide	100mg/m^2	IV infusion	Days 1-3

Repeat every 3 weeks for 6 cycles

Alternatives

Carboplatin + Etoposide[3]

Carboplatin	AUC 5–6mg/min/mL	IV infusion	Day 1
Etoposide	100mg/m2	IV infusion	Days 1-3

Repeat every 3 weeks for 6 cycles

Intent: Adjuvant chemotherapy for extensive stage SCLC

Carboplatin + Etoposide[4]

Carboplatin	AUC 5–6mg/min/mL	IV infusion	Day 1
Etoposide	100mg/m^2	IV infusion	Days 1-3

Repeat every 3 weeks for 6 cycles

Alternatives:

Cisplatin and Etoposide[5,6]

Cisplatin	60-80mg/m^2	IV infusion	Day 1
Etoposide	100mg/m^2	IV infusion	Days 1-3

Repeat every 3 weeks for 6 cycles

Carboplatin + Irinotecan[7]

Carboplatin	AUC 5–6mg/min/mL	IV infusion	Day 1
Irinotecan	50mg/m^2	IV infusion	Days 1,8 & 15

Repeat every 4 weeks for 6 cycles

SECOND LINE REGIMENS

Topotecan[8,9]

Topotecan	1.5mg/m^2	IV over 30 minutes.	Days 1-5

Repeat every 3 weeks for 6 cycles

Irinotecan[10]

Irinotecan	100mg/m^2	IV over 90 minutes	Days 1

Repeat cycle every week

Temozolamide[11]

Temozolomide	75mg/m^2	PO daily	Days 1-21

Repeat every 4 weeks for 6 cycles

Cyclophosphamide, doxorubicin and Vincristine (CAV)[12]

Cyclophosphamide	1,000mg/m^2	IV infusion	Day 1
Doxorubicin	45mg/m^2	IV	Day 1
Vincristine	2mg	IV infusion	Days 1

Repeat every 3 weeks for 6 cycles

Bendamustine[13]

Bendamustine	120mg/m^2	IV infusion	Day 1 & 2

Repeat every 3 weeks for 6 cycles

REFERENCES

1. Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. New England Journal of Medicine 1999;340:265-71.
2. Saito H, Takada Y, Ichinose Y, et al. Phase II study of etoposide and cisplatin with concurrent twice-daily thoracic radiotherapy followed by irinotecan and cisplatin in patients with limited-disease small-cell lung cancer: West Japan Thoracic Oncology Group 9902. Journal of Clinical Oncology 2006;24:5247-52.
3. Skarlos D, Samantas E, Briassoulis E, et al. Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). Annals of oncology 2001;12:1231-8.
4. Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase ii study of area under the plasma-concentration-versus-time curve–based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. Journal of clinical oncology 1999;17:3540-5.
5. Niell HB, Herndon JE, Miller AA, et al. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. Journal of Clinical Oncology

2005;23:3752-9.

6. Evans W, Shepherd F, Feld R, Osoba D, Dang P, Deboer G. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. Journal of Clinical Oncology 1985;3:1471-7.
7. Schmittel A, von Weikersthal LF, Sebastian M, et al. A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. Annals of oncology 2006;17:663-7.
8. O'Brien ME, Ciuleanu T-E, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. Journal of Clinical Oncology 2006;24:5441-7.
9. Eckardt JR, von Pawel J, Pujol J-L, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. Journal of Clinical Oncology 2007;25:2086-92.
10. Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. Journal of Clinical Oncology 1992;10:1225-9.
11. Zauderer MG, Drilon A, Kadota K, et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. Lung cancer 2014;86:237-40.
12. 12. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. Journal of clinical oncology 1999;17:658-.
13. Lammers PE, Shyr Y, Li C-I, et al. Phase II study of bendamustine in relapsed chemotherapy sensitive or resistant small-cell lung cancer. Journal of Thoracic Oncology 2014;9:559-62.

MELANOMA

Intent: systemic chemotherapy for metastatic or unresectable melanoma

First line in absence of immunotherapy

Dacarbazine[1]

Dacarbazine	250mg/m2/day	IV infusion	Day 1 –5

Repeat every 3 weeks for 6 cycles

Alternatives

Temozolamide[2]

Temozolomide	200mg/m2/day	PO daily	Day 1 –5

Repeat every 4 weeks for 6 cycles

Paclitaxel

Paclitaxel	250mg/m2	IV infusion for 24Hrs	Day 1

Repeat every 3 weeks for 6 cycles

Carboplatin + Paclitaxel[3-5]

Paclitaxel	100mg/m2	IV infusion	Day 1, 8, & 15
Carboplatin	AUC = 2		

Repeat every 4 weeks until disease progression

REFERENCES

1. Serrone L, Zeuli M, Sega F, Cognetti F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. Journal of experimental & clinical cancer research: CR 2000;19:21-34.
2. Middleton MR, Grob J, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. Journal of Clinical Oncology 2000;18:158-.
3. Rao RD, Holtan SG, Ingle JN, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. Cancer 2006;106:375-82.
4. Agarwala S, Keilholz U, Hogg D, et al. Randomized phase III study of paclitaxel plus carboplatin with or without sorafenib as second-line treatment in patients with advanced melanoma. ASCO Annual Meeting Proceedings; 2007. p. 8510.
5. Hauschild A, Agarwala SS, Trefzer U, et al. Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. Journal of Clinical Oncology 2009;27:2823-30.

MESOTHELIOMA

Intent: Induction chemotherapy or Palliative chemotherapy

Cisplatin / Pemetrexed [1]

Cisplatin	75mg/m^2	IV infusion	Day 1
Pemetrexed	500mg/m^2	IV infusion	Day 1

Repeat every 3 weeks for 6 cycles

Alternatives:

Carboplatin + pemetrexed[2,3]

Pemetrexed	500mg/m^2	IV infusion	Day 1
Carboplatin	AUC 5	IV infusion	Day 1

Repeat every 3 weeks for 6 cycles

Gemcitabine + Cisplatin[4,5]

Cisplatin	80–100mg/m^2	IV infusion for 1 Hr	Day 1
Gemcitabine	1000–1250mg/m^2	IV infusion	Day 1, 8, & 15

Repeat every 3 weeks for 6 cycles

Second line chemotherapy

Pemetrexed (if it was not used in the first line regimen)[6]

Pemetrexed	500mg/m^2	IV infusion	Day 1

Repeat every 3 weeks for 8 cycles

Gemcitabine[7-9]

Gemcitabine	1250mg/m^2	IV infusion	Day 1, 8, & 15

Repeat every 4 weeks for 10 cycles

REFERENCES

1. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. Journal of clinical oncology 2003;21:2636-44.
2. Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). Annals of oncology 2008;19:370-3.
3. Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma.

Journal of Clinical Oncology 2006;24:1443-8.

4. Nowak A, Byrne M, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. British journal of cancer 2002;87:491-6.
5. Van Haarst J, Baas P, h Manegold C, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. British journal of cancer 2002;86:342-5.
6. Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. Journal of Clinical Oncology 2008;26:1698-704.
7. Ettinger DS, Wood DE, Akerley W, et al. NCCN Guidelines Insights: Malignant Pleural Mesothelioma, Version 3.2016. Journal of the National Comprehensive Cancer Network 2016;14:825-36.
8. Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. Annals of oncology 2005;16:923-7.
9. van Meerbeeck JP, Baas P, Debruyne C, et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. Cancer 1999;85:2577-82.

OCCULT PRIMARY TUMOURS

Intent: Primary therapy for adenocarcinoma

First line:

Paclitaxel + Carboplatin[1]

Carboplatin	AUC 6mg/min/mL	IV infusion for 0.5 Hr	Day 1
Paclitaxel	200mg/m^2	IV infusion for 3 Hrs	Day 1

Repeat every 3 weeks for 6 cycles

Alternatives:

Paclitaxel + Carboplatin + Etoposide[2]

Paclitaxe	200mg/m^2	IV infusion for 3 Hr	Day 1
Carboplatin	AUC 6mg/min/mL	IV infusion	Day 1
Etoposide	50mg – 100mg	PO daily	Days 1–10

Repeat every 3 weeks for 4-8 cycles

Docetaxel + Carboplatin[3]

Docetaxel	65mg/m^2	IV infusion for 1 Hr	Day 1
Carboplatin	AUC 6mg/ in/mL	IV infusion	Day 1

Repeat every 3 weeks for 8 cycles

Docetaxel + Cisplatin[4]

Docetaxel	75mg/m^2	IV infusion for 1 Hr	Day 1
Cisplatin	75mg/m^2	IV infusion	Day 1

Repeat every 3 weeks for 6 cycles

Gemcitabine + Docetaxel[5]

Gemcitabine	1000mg/m^2	IV over 30 minutes	Day 1 & 8
Docetaxel	75mg/m^2	IV infusion for 1 Hr	Day 8

Repeat every 3 weeks for 6 cycles

mFOLFOX6[6,7]

Leucovorin	400mg/m^2	IV 2 hrs before 5-FU	Day 1
Oxaliplatin	85 mg/m^2	IV Infusion	Day 1
5-Fluorouracil	400mg/m^2	IV infusion for 2 hrs	Day 1
5-Fluorouracil	2400mg/m^2	46hr IV infusion	Days 1&2

Repeat at 14 day intervals for 24 cycles

CapOx[6]

Oxaliplatin	130 mg/m^2	IV Infusion for 2hrs	Day 1
Capecitabine	850–1,000mg/m^2	PO twice daily	Day 1–14

Repeat at 21 day intervals for 16 cycles

Intent: Primary therapy for squamous cell carcinoma of occult primary

First line:

Cisplatin + gemcitabine[8]

Cisplatin	100mg/m^2	IV Infusion	Day 1
Gemcitabine	1250mg/m^2	IV infusion	Day 1 & 8

Repeat at 21 day intervals for 4 cycles

Alternatives

mFOLFOX6[6,7]

Oxaliplatin	85 mg/m^2	IV Infusion	Day 1
Leucovorin	400mg/m^2	IV 2 hrs before 5-FU	Day 1
5-Fluorouracil	400mg/m^2	IV infusion for 2 hrs	Day 1
5-Fluorouracil	2400mg/m^2	46hr IV infusion	Days 1&2

Repeat at 14 day intervals for 24 cycles

Docetaxel + cisplain + 5fU[9]

Docetaxel	75mg/m^2	IV Infusion	Day 1
Cisplatin	75mg/m^2	IV infusion	Day 1
5-FU	750mg/m2/day	IV for 24 hours	Days 1–5

Repeat at 21 day intervals for 3 cycles

Cisplatin + fluorouracil[10]

Cisplatin	20mg/m^2	IV infusion	Day 1 - 5
5-FU	700mg/m^2/day	IV for 24 hours	Days 1–5

Repeat at 28 day intervals for 3 cycles

REFERENCES

1. Briasoulis E, Kalofonos H, Bafaloukos D, et al. Carboplatin plus paclitaxel in unknown primary carcinoma: a phase II Hellenic Cooperative Oncology Group Study. Journal of clinical oncology 2000;18:3101-7.
2. Greco F, Erland J, Patton J. Carcinoma of unknown primary site (CUPS): long-term follow-up after taxane-based chemotherapy. Proc Am Soc Clin Oncol; 2000.
3. Greco F, Erland J, Morrissey L, et al. Carcinoma of unknown primary site: phase II trials with docetaxel plus cisplatin or carboplatin. Annals of oncology 2000;11:211-5.
4. Demirci U, Coskun U, Karaca H, et al. Docetaxel and cisplatin in first line treatment of patients with unknown primary cancer:

a multicenter study of the anatolian society of medical oncology. Asian Pac J Cancer Prev 2014;15:1581-4.

5. Pouessel D, Culine S, Becht C, et al. Gemcitabine and docetaxel as front-line chemotherapy in patients with carcinoma of an unknown primary site. Cancer 2004;100:1257-61.
6. Cassidy J, Clarke S, Díaz-Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. Journal of Clinical Oncology 2008;26:2006-12.
7. Cheeseman S, Joel S, Chester JD, et al. A 'modified de Gramont'regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. British journal of cancer 2002;87:393-9.
8. Gross-Goupil M, Fourcade A, Blot E, et al. Cisplatin alone or combined with gemcitabine in carcinomas of unknown primary: results of the randomised GEFCAPI 02 trial. European Journal of Cancer 2012;48:721-7.
9. Pointreau Y, Garaud P, Chapet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. Journal of the National Cancer Institute 2009.
10. Kusaba H, Shibata Y, Arita S, et al. Infusional 5-fluorouracil and cisplatin as first-line chemotherapy in patients with carcinoma of unknown primary site. Medical Oncology 2007;24:259-64.

OSTEOSARCOMA

Intent: Neoadjuvant / Post operative schedule

First line:

Cisplatin/Doxorubicin [1-3]

Doxorubicin	25mg/m^2/day	IV Infusion	Day 1–3
Cisplatin	100mg/m^2	IV infusion	Day 1

Repeat at 21 day intervals for 6 cycles

Alternatives

Ifosphamide + Cisplatin + epirubicin[4]

Epirubicin	90mg/m^2	IV Infusion	Day 1
Cisplatin	100mg/m^2	IV infusion	Day 1
Ifosfamide	2.0g/m^2	IV infusion	Days 2–4

Repeat at 21 day intervals for 3 cycles

Second line chemotherapy for relapsed, metastatic and recurrent osteosarcoma

Carboplatin + Etoposide + ifosphamide[5]

Carboplatin	400mg/m^2/day	IV Infusion	Day 1 & 2
Ifosfamide	1,800mg/m^2/day	IV infusion + Mesna	Days 1 - 5
Etoposide	100mg/m^2/day	IV infusion	Days 1 – 5

Repeat at 21 day intervals for 3 cycles

Gemcitabine + docetaxel[6]

Gemcitabine	675mg/m^2	IV Infusion	Day 1 & 8
Docetaxel	75–100mg/m^2	IV infusion	Day 8

Repeat at 21 day intervals for 13 cycles

Ifosphamide + Etoposide[7]

Ifosfamide	2.0g/ m2	IV infusion	Days 1 – 5
Etoposide	100mg/m2/day	IV infusion	Day 1 – 5

Repeat at 21 day intervals for 12 cycles

REFERENCES

1. Bramwell V, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. Journal of Clinical Oncology 1992;10:1579-91.
2. Lewis IJ, Nooij MA, Whelan J, et al. Improvement in histologic

response but not survival in osteosarcoma patients treated with intensified chemotherapy: a randomized phase III trial of the European Osteosarcoma Intergroup. Journal of the National Cancer Institute 2007;99:112-28.

3. Souhami RL, Craft AW, Van der Eijken JW, et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. The Lancet 1997;350:911-7.
4. Basaran M, Bavbek ES, Saglam S, et al. A phase II study of cisplatin, ifosfamide and epirubicin combination chemotherapy in adults with nonmetastatic and extremity osteosarcomas. Oncology 2008;72:255-60.
5. Van Winkle P, Angiolillo A, Krailo M, et al. Ifosfamide, carboplatin, and etoposide (ICE) reinduction chemotherapy in a large cohort of children and adolescents with recurrent/refractory sarcoma: the Children's Cancer Group (CCG) experience. Pediatric blood & cancer 2005;44:338-47.
6. Navid F, Willert JR, McCarville MB, et al. Combination of gemcitabine and docetaxel in the treatment of children and young adults with refractory bone sarcoma. Cancer 2008;113:419-25.
7. Miser JS, Kinsella T, Triche T, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. Journal of Clinical Oncology 1987;5:1191-8.

OVARIAN CANCER

Intent: Adjuvant or Neo-adjuvant chemotherapy for ovarian cancer

First line:

Paclitaxel/Carboplatin[1]

Paclitaxel	175mg/m^2	IV over 3 hours	Day 1
Carboplatin	AUC 5/6	IV over 1 hour	Day 1

Repeat at 21 day intervals maximum 6 courses

Alternatives

Paclitaxel + Cisplatin[2]

Paclitaxel	135mg/m^2	IV over 3 hours	Day 1
Cisplatin	75–100mg/m^2	Intraperitoneal	Day 2
Paclitaxel	60mg/m^2	Intraperitoneal	Day 8

Repeat at 21 day intervals maximum 6 courses

Dose dense Paclitaxel + carboplatin[3]

Paclitaxel	80mg/m^2	IV over 1 hour	Day 1, 8 & 15
Carboplatin	AUC 5/6	IV over 1 hour	Day 1

Repeat at 21 day intervals maximum 6 courses

Paclitaxel + Carboplatin (For the elderly patients with poor PS)[4]

Paclitaxel	60mg/m^2	IV over 1 hour	Day 1
Carboplatin	AUC 2	IV over 30 minutes	Day 1

Repeat at 7 day intervals maximum 18 weeks

Second line chemotherapy

Single agent carboplatin

Carboplatin	AUC 5/6	IV over 1 hour	Day 1

Repeat at 28 day intervals maximum 6 courses

Carboplatin + Gemcitabine

Carboplatin	AUC 4	IV over 1 hour	Day 1
Gemcitabine	1000mg/m^2	IV over 3 hours	Day 1 & 8

Repeat at 21 day intervals maximum 6 courses

Carboplatin + Liposomal Doxorubicin

Carboplatin	AUC 5/6	IV over 1 hour	Day 1
Liposomal Doxorubicin	30mg/m^2	IV infusion	Day 1

Repeat at 28 day intervals maximum 6 courses

Third line chemotherapy options

Liposomal doxorubicin (Caelyx®)

Liposomal Doxorubicin	40-45mg/m^2	IV infusion	Day 1

Repeat at 28 day intervals maximum 6 courses

Topotecan

Topotecan	1.25mg/m^2 daily	IV over 30 minutes	Day 1 – 5

Repeat at 21 day intervals maximum 6 courses

Gemcitabine

Gemcitabine	1000mg /m^2	IV over 1 hour	Day 1, 8 &15

Repeat at 28 day intervals maximum 6 courses

Etoposide

Etoposide	50mg	PO BID diaily	Day 1 – 7

Repeat at 21 day intervals maximum 6 courses

REFERENCES

1. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. Journal of Clinical Oncology 2003;21:3194-200.
2. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. New England Journal of Medicine 2006;354:34-43.
3. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. The Lancet 2009;374:1331-8.
4. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. The Lancet Oncology 2014;15:396-405.

PANCREATIC CANCER

Intent: Palliative for metastatic pancreatic cancer with good performance status

First line

FOLRIRINOX(oxaliplatin +irinotecan + 5-fluorouracil[5-FU]/leucovorin)[1]

Oxaliplatin	85mg/m^2	IV over 1 hour	Day 1
Irinotecan	180mg/m^2	IV infusion	Day 1
Leucovorin	400mg/m^2	IV before 5 FU	Day 1
5-FU	400mg/m^2	IV over 2 hours	Day 1
5-FU	2,400mg/m^2	Iv over 46 hours	Days 1 & 2

Repeat at 21 day intervals maximum 6 courses

Alternatives

Gemcitabine + Erlotinib[2]

Cycle 1 (8-week cycle):

Gemcitabine	1000mg /m^2	IV over 1 hour	Days 1, 8,15, 22, 29, 36, and 43
Erlotinib	150mg	PO daily	Days 1–56

Subsequent cycles (4-week cycle):

Gemcitabine	1000mg /m^2	IV over 1 hour	Days 1, 8,& 15
Erlotinib	150mg	PO daily	Days 1–28

Gemcitabine + Cisplatin[3]

Gemcitabine	1000mg /m^2	IV over 1 hour	Days 1, & 15
Cisplatin	50mg/m^2	IV infusion	Days 1 & 15

Repeat every 4 weeks until disease progression

Gemcitabine + Capecitabine[4]

Gemcitabine	1000mg /m^2	IV over 1 hour	Days 1, 8 & 15
Capecitabine	825mg/m^2	PO BID daily	Days 1 - 21

Repeat every 4 weeks for up to 6 cycles

Intent: Palliative chemotherapy for metastatic pancreatic cancer with poor performance status

First line:

Gemcitabine[5]

Gemcitabine	1000mg /m^2	IV over 1 hour	Days 1, 8 & 15

Repeat every 4 weeks for up to 6 cycles

Capecitabine

Capecitabine	1,000mg/m^2	PO BID daily	Days 1 - 14

Repeat every 4 weeks for up to 6 cycles

REFERENCES

1. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. New England Journal of Medicine 2011;364:1817-25.
2. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. Journal of clinical oncology 2007;25:1960-6.
3. Oliver G, Sugar E, Laheru D, Diaz L. Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma. Gastrointestinal Cancers Symposium; 2010.
4. Cunningham D, Chau I, Stocken D, et al. Phase III randomized comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. Eur J Cancer Suppl 2005;3:12.
5. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. Jama 2013;310:1473-81.

RENAL CELL CARCINOMA

Intent: palliative

First Line:

Sunitinib[1]

Sunitinib	50mg	PO BID daily	Days 1 - 28

Repeat every 6 weeks until disease progression

Alternatives:

Sorafenib[2]

Sorafenib	400mg	PO BID daily	Days 1 - 28

Repeat every 4 weeks until disease progression

Pazopanib[3]

Pazopanib	800mg	PO BID daily	Days 1 - 28

Repeat every 4 weeks until disease progression

Temsirolimus[4]

Temsirolimus	25mg	IV infusion	Days 1

Repeat every week until disease progression

Everolimus[5]

Everolimus	10mg	PO BID daily	Days 1 - 28

Repeat every 6 weeks until disease progression

REFERENCES

1. Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. The lancet oncology 2009;10:757-63.
2. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. Journal of clinical oncology 2009;27:1280-9.
3. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. Journal of Clinical Oncology 2010;28:1061-8.
4. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. New England Journal of Medicine 2007;356:2271-81.
5. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma. Cancer 2010;116:4256-65.

SOFT TISSUE SARCOMA

Intent: systemic chemotherapy for soft tissue sarcomas

First line:

Doxorubicn + Ifosphamide + Mesna (AIM)[1-3]

Doxorubicin	30mg/m^2/day	IV infusion	Days 1 & 2
Ifosfamide	3,750mg/m^2/day	IV infusion	Day 1
mesna	750mg/m^2	IV infusion	Day 1

Repeat every 3 weeks for 6 cycles

Alternatives:

Doxorubicin + Dacarbazine (AD)[4,5]

Doxorubicin	15mg/m^2/day	IV infusion	Days 1 – 4
Dacarbazine	250mg.m^2	IV infusion	Day 1 – 4

Repeat every 3 weeks for 6 cycles

Doxorubicin + Ifosphamide + Mesna + Dacarbazine (MAID)[1-3,6]

Doxorubicin	20mg/m^2/day	IV infusion	Days 1 – 3
Ifosfamide	2,500mg/m^2	IV infusion	Day 1 – 3
mesna	2,500mg/m^2	IV infusion	Day 1 – 3
Dacarbazine	300mg/m^2	IV infusion	Day 1 – 3

Repeat every 3 weeks for 6 cycles

Second line

Gemcitabine + Docetaxel[7,8]

Gemcitabine	900mg/m^2	IV infusion	Days 1 & 8
Docetaxel	100mg/m^2	IV infusion	Day 8

Repeat every 3 weeks for 6 cycles

Alternatives

Gemcitabine + Dacarbazine[9]

Gemcitabine	1,800mg/m^2	IV infusion	Day 1
Dacarbazine	500mg/m^2	IV infusion	Day 1

Repeat every 2 weeks for 12 cycles

REFERENCES

1. Collaboration SM-a. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. The Lancet 1997;350:1647-54.
2. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113:573-81.
3. Edmonson J, Ryan L, Blum R, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. Journal of Clinical Oncology 1993;11:1269-75.
4. Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft-tissue sarcomas: a Southwest Oncology Group study. Journal of the National Cancer Institute 1991;83:926-32.
5. Antman K, Crowley J, Balcerzak SP, et al. An intergroup phase III randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue and bone sarcomas. Journal of Clinical Oncology 1993;11:1276-85.
6. Elias A, Ryan L, Sulkes A, Collins J, Aisner J, Antman KH. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. Journal of Clinical Oncology 1989;7:1208-16.
7. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. Journal of Clinical Oncology 2002;20:2824-31.
8. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. Journal of Clinical Oncology 2007;25:2755-63.
9. García-del-Muro X, López-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. Journal of Clinical Oncology 2011;29:2528-33.

THYMOMA

Intent: Systemic chemotherapy

First Line

CAP[1]

Cisplatin	50mg/m^2	IV infusion	Day 1
Doxorubicin	50mg/m^2	IV infusion	Day 1
Cyclophosphamide	500mg/m^2	IV infusion	Day 1

Repeat every 3 weeks for 8 cycles

CAP + prednisone[2]

Cyclophosphamide	500mg/m^2	IV infusion	Day 1
Cisplatin	30mg/m^2	IV infusion	Day 1 – 3
Doxorubicin	20mg/m^2	IV over 24 hours	Day 1 – 3
Prednisone	100mg	PO daily	Days 1–5

Repeat every 3 weeks for 3 cycles

PE[3]

Cisplatin	60mg/m^2	IV over 1 hour	Day 1
Etoposide	120mg/m^2	IV infusion	Day 1 – 3

Repeat every 3 weeks for 8 cycles

Cisplatin + Paclitaxel (Preferred for Thymic carcinoma)[4]

Cisplatin	60mg/m^2	IV over 1 hour	Day 1
Paclitaxel	135mg/m^2	IV over 3 hours	Day 1

Repeat every 3 weeks for 6 cycles

Second line:

Etoposide[3]

Etoposide	120mg/m^2	Iv infusion	Day 1 – 3

Repeat every 3 weeks for 8 cycles

Ifosphamide[5]

Ifosfamide	1.5g/m^2	Iv infusion	Day 1 – 5

Repeat every 3 weeks for 8 cycles

Pemetrexed[6]

Pemetrexed	500mg/m^2	Iv infusion	Day 1

Repeat every 3 weeks for 6 cycles

Sunitinib (for thymic carcinomas only)[7]

Sunitinib	50mg	PO daily	Day 1 – 28

Repeat every 6 weeks until disease progression

REFERENCES

1. Loehrer PJ, Kim K, Aisner SC, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. Journal of Clinical Oncology 1994;12:1164-8.
2. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung cancer 2004;44:369-79.
3. Giaccone G, Ardizzoni A, Kirkpatrick A, Clerico M, Sahmoud T, van Zandwijk N. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. Journal of Clinical Oncology 1996;14:814-20.
4. Lemma GL, Lee J-W, Aisner SC, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. Journal of Clinical Oncology 2011;29:2060-5.
5. Highley M, Underhill C, Parnis F, et al. Treatment of invasive thymoma with single-agent ifosfamide. Journal of clinical oncology 1999;17:2737-.
6. Loehrer Sr P, Yiannoutsos C, Dropcho S, et al. A phase II trial of pemetrexed in patients with recurrent thymoma or thymic carcinoma. ASCO Annual Meeting Proceedings; 2006. p. 7079.
7. Thomas A, Rajan A, Berman AW, et al. Phase II trial of sunitinib in patients with thymic epithelial tumors (TET). ASCO Annual Meeting Proceedings; 2014. p. 7525.

THYROID CANCER

Intent: Primary treatment for metastatic thyroid cancer not responding to RIA

First line:

Sunitinib[1]

Sunitinib	50mg	PO daily	Day 1 – 28

Repeat every 6 weeks until disease progression

Alternatives:

Sorafenib[2]

Sorafenib	400mg	PO BID daily	Day 1 – 28

Repeat every 4 weeks until disease progression

Second line:

Doxorubicin[3]

Dacarbazine based chemotherapy[4]

REFERENCES

1. Ravaud A, de la Fouchardière C, Asselineau J, et al. Efficacy of sunitinib in advanced medullary thyroid carcinoma: intermediate results of phase II THYSU. The oncologist 2010;15:212-3.
2. Sherman SI. Advances in chemotherapy of differentiated epithelial and medullary thyroid cancers. The Journal of Clinical Endocrinology & Metabolism 2009;94:1493-9.
3. Shimaoka K, Schoenfeld DA, Dewys WD, Creech RH, Deconti R. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 1985;56:2155-60.
4. Nocera M, Baudin E, Pellegriti G, et al. Treatment of advanced medullary thyroid cancer with an alternating combination of doxorubicin-streptozocin and 5 FU-dacarbazine. British journal of cancer 2000;83:715.

UTERINE SARCOMA

Intent: Primary therapy for locally advanced metastatic disease

First line therapy

Docetaxel + gemcitabine [1]

Gemcitabine	900mg/m^2	IV over 90 minutes	Day 1 & 8
Docetaxel	100mg/m^2	IV over 60 minutes	Day 8

Repeat every 3 weeks until disease progression

Alternatives

Doxorubicin + ifosphamide[2]

Doxorubicin	50mg/m^2	IV over 15 minutes	Day 1
Ifosfamide	5g/m^2	IV over 24 hours	Day 1
Plus: Mesna (admixed)	6g/m^2	IV over 36 hours	Day 1

Repeat every 3 weeks for 6 cycles

Doxorubicin + dacarbazine[3]

Doxorubicin	15mg/m^2	IV infusion	Day 1 – 4
Dacarbazine	250mg/m^2	IV infusion	Day 1 – 4

Repeat every 3 weeks for 6 cycles

Gemcitabine + dacarbazine[4]

Gemcitabine	10mg/m^2/min	IV over 180 minutes	Day 1
Dacarbazine	500mg/m^2	IV over 20 minutes	Day 1

Repeat every 2 weeks for 12 cycles

Second line therapy:

Liposaomal doxorubicin[5]

Liposomal doxorubicin	50mg/m^2	IV infusion	Day 1

Repeat every 4 weeks for 6 cycles

Temozolamide[5]

Temozolomide	50–75mg/m^2	PO daily	Day 1 - 42

Repeat every 6 weeks until disease progression

Docetaxel[6]

Docetaxel	36mg/m^2	IV over 1 hour	Day 1, 8 & 15

Repeat every 4 weeks until disease progression or unacceptable toxicity

REFERENCES

1. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecologic oncology 2008;109:329-34.
2. Sutton G, Blessing JA, Malfetano JH. Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcomas of the uterus: a Gynecologic Oncology Group study. Gynecologic oncology 1996;62:226-9.
3. Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus infusion in patients with soft-tissue sarcomas: a Southwest Oncology Group study. Journal of the National Cancer Institute 1991;83:926-32.
4. García-del-Muro X, López-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. Journal of Clinical Oncology 2011;29:2528-33.
5. Amant F, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I. Clinical management of uterine sarcomas. The lancet oncology 2009;10:1188-98.
6. Garcia AA, Blessing JA, Nolte S, Mannel RS. A phase II evaluation of weekly docetaxel in the treatment of recurrent or persistent endometrial carcinoma: a study by the Gynecologic Oncology Group. Gynecologic oncology 2008;111:22-6.

VULVAL CANCER

Intent: Primary chemotherapy for unresectable, recurrent Metastatic disease

First line therapy:

Cisplatin + 5 Fluorouracil [1,2]

Cisplatin	60mg/m^2	IV infusion	Day 1
5-FU	1,000mg/m^2/day	IV infusion	Days 1–4, & 29–32

Plus Concurrent radiotherapy

Alternatives:

Mitomycin C + 5FU[3]

Mitomycin C	12mg/m^2(max 20mg)	IV infusion	Day 1
5-FU	1,000mg/m^2/day	IV infusion	Days 1–4, & 29–32

REFERENCES

1. Cunningham MJ, Goyer RP, Gibbons SK, Kredentser DC, Malfetano JH, Keys H. Primary radiation, cisplatin, and 5-fluorouracil for advanced squamous carcinoma of the vulva. Gynecologic oncology 1997;66:258-61.

2. Eifel PJ, Morris M, Burke TW, Levenback C, Gershenson DM. Prolonged continuous infusion cisplatin and 5-fluorouracil with radiation for locally advanced carcinoma of the vulva. Gynecologic oncology 1995;59:51-6.

3. Landoni F, Maneo A, Zanetta G, et al. Concurrent preoperative chemotherapy with 5-fluorouracil and mitomycin C and radiotherapy (FUMIR) followed by limited surgery in locally advanced and recurrent vulvar carcinoma. Gynecologic oncology 1996;61:321-7.

PART THREE

CHEMOTHERAPY REGIMENS FOR HEAMATOLOGICAL CANCERS

ACUTE LYMPHOBLASTIC LEUKEMIA

Intent: Primary therapy for Ph (-) Adult ≥ 40 years of Age

Linker 4-drug regimen[1]

Induction

Daunorubicin	50mg/m^2/day	IV infusion	Day 1–3
Vincristine	2mg	IV infusion	Days 1, 8, 15, & 22
Prednisone	60mg/m^2/day	PO daily	Days 1–28
L-asparaginase	6,000IU/m^2/day	IM	Days 17–28

If bone marrow on day 14 has residual leukemia:

Daunorubicin	50mg/m^2/day	IV infusion	Day 15

If bone marrow on day 28 has residual leukemia:

Daunorubicin	50mg/m^2/day	IV infusion	Day 29 & 30
L-asparaginase	6,000IU/m^2/day	IM	Days 29 – 35
Prednisone	60mg/m^2/day	PO daily	Days 29 – 42

Consolidation

Cycles 1, 3, 5, and 7:

Daunorubicin	50mg/m^2/day	IV infusion	Day 1 & 2
Vincristine	2mg	IV infusion	Days 1, & 8
Prednisone	60mg/m^2/day	PO daily	Days 1–14
L-asparaginase	12,000IU/m^2/day	IM	Days 4, 7, 9, 11, 14

Cycles 2, 4, 6, & 8:

Teniposide	165mg/m^2	IV infusion	Day 1, 4, 8, & 11
Cytarabine	300mg/m^2	Iv infusion	Days 4 & 6

Cycle 9:

Methotrexate	690mg/m^2	IV over 42 hours	Day 1
Leucovorin	15mg/m^2	IV every 6 hours	12 doses
Methotrexate	20mg/m^2	PO weekly	30 months
6-Mercaptopurine	75mg/m^2	PO daily	30 months

Intent: Primary therapy for Ph (-) Adult ≥ 40 years of Age

CALBG 8811 (Larson Regimen)[2]

Induction

Cyclophosphamide	1,200mg/m^2	IV infusion	Day 1
Daunorubicin	45mg/m^2	IV infusion	Days 1- 3
Vincristine	2mg	Iv infusion	Days 1, 8, 15, & 22
Prednisone	60mg/m^2/day	PO daily	Days 1–21
L-asparaginase	6,000IU/m^2.	SC	Days 5, 8, 11, 15, 18, 22

Consolidation

Methotrexate	15mg	IT	Day 1
Cyclophosphamide	1,000mg/m^2	IV	Day 1
6-Mercaptopurine	60mg/m^2/day	Po daily	Days 1–14
Cytarabine	75mg/m^2/day	SC	Days 1–4 & 8–11
Vincristine	2mg	IV	Days 15 & 22
L-asparaginase	6,000IU/m^2	SC	Days 15, 18, 22, 25

Repeat cycle every 4 weeks for 2 cycles, followed by

Cranial irradiation	2,400cGy		Days 1–12
Methotrexate	15mg	IT	Days 1, 8, 15, 22,29
6-Mercaptopurine	60mg/m^2/day	PO daily	Days 1–70
Methotrexate	20mg/m^2	PO daily	Days 36, 43, 50, 57,64

Followed by;

Doxorubicin	30mg/m^2	IV	Days 1, 8, & 15
Vincristine	2mg	IV	Days 1, 8 & 15
Dexamethasone	10mg/m^2/day	PO daily	Days 1–14
Cyclophosphamide	1,000mg/m^2	IV	Day 29

6-Thioguanine	60mg/m^2/day	PO daily	Days 29–42
Cytarabine	75mg/m^2/day	SC	Days 29–32 & 36–39
Followed by			
Vincristine	2mg	IV	Day 1
Prednisone	60mg/m^2/day	PO daily	Days 1–5
Methotrexate	20mg/m^2	PO daily	Days 1, 8, 15, and 22
6-Mercaptopurine	60mg/m^2/day	PO daily	Days 1–28

Repeat cycle every 4 weeks until 24 months from diagnosis

Intent: chemotherapy for Ph (-) young adults (15-39 years)

CALGB 10403[3]

Induction

Cytarabine	IT	Day 1
Methotrexate	IT	Days 8 and 29
Daunorubicin	IV	Days 1, 8, 15, & 22
Vincristine	IV	Days 1, 8, 15, & 22
PEG-asparaginase.		Day 4

Consolidation

Methotrexate	IT	Days 1, 8, 15, 22
Cyclophosphamide	IV	Days 1 and 29
Cytarabine		Days 1–4, 8–11, 29–32, 36–39
6-Mercaptopurine	PO	Days 1–14, 29–42
Vincristine	IV	Days 15, 22, 43, 50
PEG-asparaginase		Day 15, 43

Interim Maintenance

Methotrexate	IT	Days 1 and 31
Vincristine	IV	Days 1, 11, 21, 31, and 41
Methotrexate	IV	Days 1, 11, 21, 31, and 41
PEG-asparaginase		Days 2 and 22

Delayed Intensification

Methotrexate	IT	Days 1, 29, and 36
Dexamethasone	PO	Days 1–7 and 15–21
Doxorubicin	IV	Days 1, 8, and 15
PEG-asparaginase		Days 4 and 43
Cyclophosphamide	IV	Day 29
Cytarabine	IV	Days 29–32 & 36–39
6-Thioguanine	PO	Days 29–42

Maintenance

Methotrexate	IT	Days 15 and 29
Vincristine	IV	Days 1, 29, and 57
Methotrexate		Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78
For Females		
Dexamethasone	PO for 2 years	Days 1–5, 29–33, and 57–61
For Men		
6-Mercaptopurine	PO for 3 years	Days 1–84

REFERENCES

1. Linker C, Damon L, Ries C, Navarro W. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. Journal of Clinical Oncology 2002;20:2464-71.
2. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. Blood 1995;85:2025-37.
3. Stock W, Luger SM, Advani AS, et al. Favorable outcomes for older adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL): early results of US Intergroup Trial C10403. Blood 2014;124:796-.

ACUTE MYELOID LEUKEMIA

Intent: Induction therapy for AML among patients Age ≤ 60 years

3+7 regimen [1-3]

Induction

Daunorubicin	45-90mg/m^2	IV	Day 1–3
Cytarabine	100–200mg/m^2	IV infusion	Days 1–7

Intent: Induction therapy for patients Age ≥ 60 years;

Performance Status 0–2 Favorable cytogenetic markers without prior MDS/Therapy-related AML[4-6]

Induction

Daunorubicin	45-90mg/m^2	IV	Day 1 – 3
Cytarabine	100–200mg/m^2	IV infusion	Days 1–7

OR

Low-intensity therapy

Cytarabine	20mg	SC daily	Day 1–10

OR

5-azacytidine	75mg/m^2	IV infusion every 28 days	Days 1–7

Intent: Induction therapy for patients Age ≥ 60 years

Performance Status 0–2 Unfavorable cytogenetic markers with prior MDS/Therapy-related AML[7,8]

Induction

Low-intensity therapy (as above)

OR

Daunorubicin	45–60mg/m^2	IV infusion	Days 1–3

OR

Cytarabine	100–200mg/m^2	IV infusion	Days 1–7

Intent: Induction therapy for patients Age ≥ 60 years Performance Status >2 or 0–3 with significant co morbidities or age ≥75 years[9]

Induction

Low-intensity therapy

(as above)

OR

Hydroxyurea	10–70mg/kg/day	PO	Days 1 - 28

Intent: Post remission therapy

Age > 60 years with complete response [10,11]

Cytarabine	100–200mg/m^2	IV for 1-2 cycles	Days 1 – 5

Intent: Post remission therapy for patients Age ≥ 60 years with induction failure

Reduced-intensity HSCT in context of clinical trial

OR

Best supportive care

REFERENCES

1. Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. New England Journal of Medicine 2009;361:1249-59.
2. Kern W, Estey EH. High-dose cytosine arabinoside in the treatment of acute myeloid leukemia. Cancer 2006;107:116-24.
3. Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. Blood 1996;88:2841-51.
4. Krug U, Röllig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. The Lancet 2010;376:2000-8.
5. Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose

daunorubicin in older patients with acute myeloid leukemia. New England Journal of Medicine 2009;361:1235-48.

6. Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer 2007;109:1114-24.
7. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. The lancet oncology 2009;10:223-32.
8. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. Journal of Clinical Oncology 2010;28:556-61.
9. Kantarjian HM, Erba HP, Claxton D, et al. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. Journal of Clinical Oncology 2010;28:549-55.
10. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. New England Journal of Medicine 1994;331:896-903.
11. Löwenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. New England Journal of Medicine 2011;364:1027-36.

CHROMIC LYMPHOCYTIC LEUKEMIA

Intent: Primary treatment for CLL/SLL

Chlorambucil + Rutuximab[1]

Cycle 1			
Chlorambucil	8mg/m^2/day	PO	Days 1–7
Cycle 3			
Rituximab	375mg/m^2	IV	Day 1
Chlorambucil	8mg/m^2/day	PO	Days 1–7
Cycle 4–8			
Rituximab	500mg/m^2	IV	Day 1
Chlorambucil	8mg/m^2/day	PO	Days 1–7

Repeat cycle every 28 days; administer rituximab at dose of 375mg/m2 IV every 2 months for 2 years as maintenance therapy.

Bendamustine +/- Rutuximab[2-4]

Rituximab	375mg/m^2	IV	Day 0
Bendamustine	70mg/m^2	IV	Days 1 and 2

Repeat cycle every 28 days for 6 cycles

Chlorambucil[5,6]

Chlorambucil	0.4mg/kg/day with an increase to 0.8mg/kg	PO	Days 1–28

Repeat cycle every 28 days for 12 cycles.

Rutuximab[7]

Rituximab	375mg/m^2/day	IV	Day 1, 8, 15, & 22

Intent: Age ≤ 65 years without significant comorbidities

Rituximab + Fludarabine + Cyclophosphamide (FCR)[8-10]

Rituximab	375mg/m^2	IV	Day 1
Fludarabine	25mg/m^2/day	IV	Days 1–3
cyclophosphamide	250mg/m^2/day	IV	Day 1 – 3

Repeat cycle every 28 days for 6 cycles

Fludarabine + Rituximab[11]

Fludarabine	25mg/m^2/day	IV	Days 1–5
Rituximab	50mg/m^2	IV	Day 1
Rituximab	325mg/m^2		Day 3 and 5

Repeat cycle every 28 days for 6 cycles

REFERENCES

1. Foà R, Giudice I, Cuneo A, et al. Chlorambucil plus rituximab with or without maintenance rituximab as first-line treatment for elderly chronic lymphocytic leukemia patients. American journal of hematology 2014;89:480-6.
2. Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. Journal of Clinical Oncology 2012;30:3209-16.
3. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. Journal of Clinical Oncology 2009;27:4378-84.
4. Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine in the Treatment of Chronic Lymphocytic Leukemia-Consistent Superiority Over Chlorambucil in Elderly Patients and Across Clinically Defined Risk Groups. Blood 2009;114:2367-.
5. Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. New England Journal of Medicine 2000;343:1750-7.
6. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009;114:3382-91.
7. Huhn D, von Schilling C, Wilhelm M, et al. Rituximab therapy of patients with B-cell chronic lymphocytic leukemia. Blood 2001;98:1326-31.
8. Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. Journal of Clinical Oncology 2005;23:4079-88.
9. MONTSERRAT E, TAM CS, O'BRIEN S, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Commentary. Blood 2008;112.
10. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. The Lancet 2010;376:1164-74.
11. Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6-14.

CHRONIC MYELOID LEUKEMIA

Intent: Primary treatment for CML

Category: Ph+ or BCR-ABL positive [1-8]

Imatinib	400mg	PO daily	Day 1 – 28

Repeat cycle every 28 days for 6 cycles

OR

Nilotinib	300mg	PO BID daily	Day 1 – 28

Repeat cycle every 28 days for 6 cycles

OR

Dasatinib	100mg	PO daily	Day 1 – 28

Repeat cycle every 28 days for 6 cycles

Intent: primary treatment for accelerated phase[9-12]

Imatinib	600mg	PO daily	Day 1 – 28

Repeat cycle every 28 days for 6 cycles

OR

Dasatinib	140mg	PO daily	Day 1 – 28

Repeat cycle every 28 days for 6 cycles

OR

Nilotinib	400mg	PO BID daily	Day 1 – 28

Repeat cycle every 28 days for 6 cycles

AND

Consider HSCT based on response.

Intent: Primary treatment for blast phase – lymphoid[13-19]

ALL-type induction chemotherapy, plus TKI followed by HSCT, if feasible

OR

TKI followed by HSCT, if feasible.

Intent: Primary treatment for blast phase – myeloid[13-19]

AML-type induction chemotherapy, plus TKI followed by HSCT, if feasible.

OR

TKI followed by HSCT, if feasible.

REFERENCES

1. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine 2010;362:2260-70.
2. Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood 2012;119:1123-9.
3. Hochhaus A, Kim D-W, Shah NP, et al. Four-year (yr) follow-up of patients (pts) with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP) receiving dasatinib or imatinib: efficacy based on early response. Blood 2013;122:653-.
4. Larson R, Hochhaus A, Hughes T, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia 2012;26:2197-203.
5. Hughes TP, Saglio G, Kantarjian HM, et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. Blood 2013:blood-2013-06-510396.
6. O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine 2003;348:994-1004.
7. Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. New England Journal of Medicine 2010;362:2251-9.
8. Cortes JE, Jones D, O'Brien S, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. Journal of Clinical Oncology 2010;28:398-404.
9. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99:1928-37.
10. Kantarjian HM, Cortes J, O'Brien S, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome–positive chronic myelogenous leukemia in blast phase. Blood 2002;99:3547-53.
11. Kantarjian HM, O'Brien S, Cortes JE, et al. Treatment of Philadelphia chromosome-positive, accelerated-phase chronic myelogenous leukemia with imatinib mesylate. Clinical Cancer Research 2002;8:2167-76.
12. Sawyers CL, Hochhaus A, Feldman E, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood 2002;99:3530-9.
13. Palandri F, Castagnetti F, Testoni N, et al. Chronic myeloid leukemia in blast crisis treated with imatinib 600 mg: outcome

of the patients alive after a 6-year follow-up. Haematologica 2008;93:1792-6.

14. Palandri F, Castagnetti F, Alimena G, et al. The long-term durability of cytogenetic responses in patients with accelerated phase chronic myeloid leukemia treated with imatinib 600 mg: the GIMEMA CML Working Party experience after a 7-year follow-up. haematologica 2009;94:205-12.
15. Silver RT, Cortes J, Waltzman R, Mone M, Kantarjian H. Sustained durability of responses and improved progression-free and overall survival with imatinib treatment for accelerated phase and blast crisis chronic myeloid leukemia: long-term follow-up of the STI571 0102 and 0109 trials. Haematologica 2009;94:743-4.
16. Apperley JF, Cortes JE, Kim D-W, et al. Dasatinib in the treatment of chronic myeloid leukemia in accelerated phase after imatinib failure: the START A trial. Journal of clinical oncology 2009;27:3472-9.
17. Le Coutre P, Giles F, Hochhaus A, et al. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. Leukemia 2012;26:1189-94.
18. Gambacorti-Passerini C, Cortes J, Khoury H, et al. Safety and efficacy of bosutinib in patients with AP and BP CML and ph+ ALL following resistance/intolerance to imatinib and other TKIs: Update from study SKI-200. ASCO Annual Meeting Proceedings; 2010. p. 6509.
19. Cortes JE, Kim D-W, Pinilla-Ibarz J, et al. Long-term follow-up of ponatinib efficacy and safety in the phase 2 PACE trial. Blood 2014;124:3135-.

AIDS RELATED LYMPHOMAS

Intent: primary chemotherapy for AIDS related

Burkitts lymphoma

CDE (cyclophosphamide +doxorubicin + etoposide) +rituximab [1,2]

Cyclophosphamide	187.5–200mg/m^2	IV	Days 1–4
Doxorubicin	12.5mg/m^2	IV	Days 1 – 4
Etoposide	60mg/m^2	IV	Days 1 – 4

Repeat cycle every 28 days for 6 cycles

Alternatives

Dose-adjusted EPOCH (etoposide + prednisone +vincristine + cyclophosphamide+ doxorubicin) + rituximab [3-5]

Etoposide	50mg/m^2	IV	Days 1–4
Prednisone	60mg/m^2	PO	Days 1 – 4
Vincristine	0.4mg/m^2	IV	Days 1 – 4
Doxorubicin	10mg/m^2	IV	Days 1 – 4
Rituximab	375mg/m^2	IV	Day 1
Cyclophosphamide	375mg/m^2	IV	Day 5

Repeat cycle every 21 days for 6 cycles

NB: If CD4 cells ≥100/mm3 OR 187mg/m2 IV if CD4 cells <100/mm3.

Cyclophosphamide dose-adjustment (after Cycle 1):

- If nadir ANC >500/mcL, then increase by 187mg above previous cycle.
- If nadir ANC <500/mcL, or platelets <25,000/mcL, then decrease by 187mg below previous cycle.

Intent: Primary therapy for AIDS related Diffuse Large B-cell lymphoma

CHOP + rituximab[6,7]

Option 1—Modified CHOP

Cyclophosphamide	375mg/m^2	IV	Day 1
Doxorubicin	25mg/m^2	IV	Day 1
Vincristine	1.4mg/m^2	IV	Day 1
Prednisone	100mg	PO	Days 1 – 5
Rituximab	375mg/m^2	IV	Day 1

Repeat cycle every 21 days for 6 cycles

Option 2—Standard-dose CHOP

Cyclophosphamide	750mg/m^2	IV	Day 1
Doxorubicin	50mg/m^2	IV	Day 1
Vincristine	1.4mg/m^2	IV	Day 1
Prednisone	100mg	PO	Days 1 – 5
Rituximab	375mg/m^2	IV	Day 1

Repeat cycle every 21 days for 6 cycles

Alternatives:

Dose-adjusted EPOCH (etoposide + prednisone +vincristine + cyclophosphamide+ doxorubicin) + rituximab[3-5]

Etoposide	50mg/m^2	IV	Day 1 – 4
Prednisone	60mg/m^2	PO	Day 1 – 4
Vincristine	0.4mg/m^2	IV	Day 1 – 4
Doxorubicin	10mg/m^2	IV	Days 1 – 4
Rituximab	375mg/m^2	IV	Day 1

Repeat cycle every 21 days for 6 cycles

NB: If CD4 cells ≥100/mm3 OR 187mg/m2 IV if CD4 cells <100/mm3.

Cyclophosphamide dose-adjustment (after Cycle 1):

- If nadir ANC >500/mcL, then increase by 187mg above previous cycle.

- If nadir ANC <500/mcL, or platelets <25,000/mcL, then decrease by 187mg below previous cycle.

Intent: primary therapy for AIDS related Plasmablastic lymphoma

CODOX-M/IVAC (modified) (cyclophosphamide + vincristine+ doxorubicin + high-dose methotrexate alternating with ifosfamide + etoposide +high-dose cytarabine) [8-10]

Cyclophosphamide	800mg/m^2	IV	Day 1
Cyclophosphamide	200mg/m^2	IV	Day 2 – 5
Doxorubicin	40mg/m^2	IV	Day 1
Vincristine	1.5mg/m^2	IV	Days 1 & 8
MTX	1,200mg/m^2	IV over 1 hour followed by 240mg/m^2/hour over 23 hours	Day 1
Cytarabine	70mg	IT	Days 1 and 3
Rituximab	375mg/m^2	IV	Day 1
MTX	12mg	IT	Day 15
Alternate with:			
Ifosfamide	1,500mg/m^2	IV	Days 1–5
Etoposide	60mg/m^2	IV	Days 1 – 5
Cytarabine	2,000mg/m^2	IV every 12 hours for 4 doses	Days 1 and 2
Rituximab	375mg/m^2	IV	Day 1
MTX	12mg	IT	Day 15

REFERENCES

1. Sparano JA, Lee S, Chen MG, et al. Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma: an Eastern Cooperative Oncology Group Trial (E1494). Journal of Clinical Oncology 2004;22:1491-500.

2. Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. Blood 2005;105:1891-7.

3. Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome–related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. Blood 2003;101:4653-9.

4. Barta SK, Lee JY, Kaplan LD, Noy A, Sparano JA. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. Cancer 2012;118:3977-83.

5. Bayraktar UD, Ramos JC, Petrich A, et al. Outcome of patients with relapsed/refractory acquired immune deficiency syndrome-related lymphoma diagnosed 1999–2008 and treated with curative intent in the AIDS Malignancy Consortium. Leukemia & lymphoma 2012;53:2383-9.

6. Boué F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. Journal of Clinical Oncology 2006;24:4123-8.

7. Ribera JM, Oriol A, Morgades M, et al. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. British journal of haematology 2008;140:411-9.

8. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for human immunodeficiency virus–associated Burkitt lymphoma. Cancer 2003;98:1196-205.

9. Barnes J, Lacasce A, Feng Y, et al. Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Annals of Oncology 2011:mdq677.

10. Noy A, Kaplan L, Lee J, Cesarman E, Tam W. Modified dose intensive R-CODOX-M/IVAC for HIV-associated burkitt (BL)(AMC 048) shows efficacy and tolerability, and predictive potential of IRF4/MUM1 expression. Infectious Agents and Cancer 2012;7:1.

BURKITTS LYMPHOMA

Intent: induction therapy for Low risk/High risk Burkitts Lymphoma

R-CHOP[1-3]

Rituximab	375mg/m^2	IV 7 days prior CHOP	Day 1, 22, and 43
Cyclophosphamide	750mg/m^2	IV	Day 1
Doxorubicin	50mg/m^2	IV	Day 1
Vincristine	2mg	IV	Day 1
Prednisone	100mg	Orally	Days 1–5

Repeat cycle every 3 weeks for 3 cycles followed by radiotherapy

Alternatives

CALGB 10002[4]

Cycle 1:

MTX+araC+Hydrocort		IT	Day 1
Cyclophosphamide	200mg/m^2	IV	Days 1–5
rednisone	60mg/m^2	PO	Days 1–7

Cycles 2 (beginning Day 8), 4, and 6:

MTX +araC+Hydrocort		IT	**Day 1**
Ifosfamide	800mg/m^2	IV dexamethasone 10mg/m^2	Days 1–5
Methotrexate	1.5g/m^2	IV+ vincristine 2mg IV	Day 1
Cytarabine	1g/m^2	IV+ etoposide 80mg/m^2	Days 4 & 5
Rituximab	375mg/m^2	IV	Day 8

Repeat cycle every 21 days for 6 cycles

Cycles 3, 5, and 7:

MTX +araC+Hydrocort		IT	Day 1
Cyclophosphamide	200mg/m^2	IV	Day 1 – 5
Dexamethasone	10mg/m^2	IV	Day 1 – 5

Methotrexate	1.5g/m^2	IV	Days 1
Vincristine	2mg	IV	Day 1
Doxorubicin	25mg/m^2	IV	Days 4 and 5
Rituximab	375mg/m^2	IV.	Day 8

Repeat cycle every 21 days for 6 cycles

HyperCVAD (cyclophosphamide + vincristine + doxorubicin + dexamethasone alternating with high-dose methotrexate and cytarabine)[5]

Cycles 1, 3, 5, and 7—HyperCVAD

Cyclophosphamide	300mg/m^2	IV every 12 hours for 6 doses	Days 1–3
Mesna	600mg/m^2	IV infusion	Days 1–3
Vincristine	2mg	IV	Days 4 and 11
Doxorubicin	50mg/m^2	IV	Day 4
Dexamethasone	40mg	IV daily	Days 1–4 and 11–14
Rituximab	375mg/m^2	IV	Days 1 and 11

Cycles 2, 4, 6, 8—High-dose MTX and Cytarabine

MTX	1g/m^2	IV over 24 hours	Day 1
Cytarabine	3g/m^2	IV every 12 hours for 4 doses	Days 2 and 3
Rituximab	375mg/m^2	IV	Days 2 and 8

Repeat cycle every 21 days for 8 cycles

Intent: second line therapy

Dose-adjusted EPOCH (etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin) + intrathecal MTX + rituximab [6-8]

Rituximab	375mg/m^2	IV	Day 1
Etoposide	50mg/m^2	IV	Days 1–4
Vincristine	0.4mg/m^2	IV	Days 1–4
Doxorubicin	10mg/m^2	IV	Days 1–4
Prednisone	60mg	Orally	Days 1–5

Cyclophosphamide	750mg/m^2	IV	Day 5
Methotrexate	12mg	intrathecally	Days 1 & 5

Repeat cycle every 3 weeks for 6 cycles

Alternatives

RICE (rituximab + ifosfamide + carboplatin + etoposide)[9]

Rituximab	375mg/m^2	IV	Day 1
Ifosfamide	5g/m^2	IV over 24 hours	Days 2
Mesna	5,000mg/m^2	IV	Day 2
Carboplatin	AUC 5mg·min/mL	IV	Days 2
Etoposide	100mg/m^2	IV bolus	Days 1–3

Repeat cycle every 2 weeks for 3 cycles

HDAC + rituximab[10]

Cytarabine	3g/m^2	IV every 12 hours	Days 1, 3 & 5
Rituximab	375mg/m^2	IV	Day 1

Repeat cycle every 21 days for 4 cycles

REFERENCES

1. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-5.
2. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. Journal of Clinical Oncology 2005;23:4117-26.
3. He X, Jia B, Shi Y. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in patients with stage I diffuse large B-cell lymphoma. ASCO Annual Meeting Proceedings; 2014. p. e19513.
4. Rizzieri DA, Johnson JL, Byrd JC, et al. Efficacy and toxicity of rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or Burkitt–like leukemia/lymphoma:

Cancer and Leukemia Group B (Calgb) study 10002. Blood 2010;116:858-.

5. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 2006;106:1569-80.
6. Dunleavy K, Wayne A, Little R, et al. The Addition of Rituximab to Dose-Adjusted EPOCH with HAART Suspension Is Highly Effective and Tolerable in AIDS-Related Lymphoma (ARL) and Allows the Delivery of Abbreviated Chemotherapy. Blood 2005;106:930-.
7. Dunleavy K, Little R, Pittaluga S, et al. A prospective study of dose-adjusted (DA) EPOCH with rituximab in adults with newly diagnosed Burkitt lymphoma: a regimen with high efficacy and low toxicity. Annals of Oncology; 2008: OXFORD UNIV PRESS GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND. p. 83-4.
8. Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 2002;99:2685-93.
9. Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: A report from the Children's Oncology Group. Pediatric blood & cancer 2009;52:177-81.
10. Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. New England Journal of Medicine 1994;331:896-903.

DIFFUSE LARGE B-CELL LYMPHOMA

Intent: primary chemotherapy for DLBCL

R-CHOP[1-3]

Rituximab	375mg/m^2	IV 7 days prior CHOP	Day 1, 22, and 43
Cyclophosphamide	750mg/m^2	IV	Day 1
Doxorubicin	50mg/m^2	IV	Day 1
Vincristine	2mg	IV	Day 1
Prednisone	100mg	orally	Days 1–5

Repeat cycle every 3 weeks for 3 cycles followed by radiotherapy

Alternatives

Dose-adjusted EPOCH +rituximab[4-6]

Rituximab	375mg/m^2	IV	Day 1
Etoposide	50mg/m^2	IV	Days 1–4
Vincristine	0.4mg/m^2	IV	Days 1–4
Doxorubicin	10mg/m^2	IV	Days 1–4
Prednisone	60mg	orally	Days 1–5
Cyclophosphamide	750mg/m^2	IV	Day 5

Repeat cycle every 3 weeks for 6 cycles

Intent: Primary therapy for patients with poor left ventricular function or very frail

RCEPP[7]

Cyclophosphamide	600mg/m^2	IV	Days 1 and 8
Etoposide	70mg/m^2	IV	Day 1
Etoposide	140 mg/m^2	Orally	Days 2 and 3
Procarbazine	60mg/m^2	orally	Days 1–10
Prednisone	60mg/m^2	orally	Days 1–10

Repeat cycle every 4 weeks for 6 cycles

Alternatives (for patients with poor LV function)

RCNOP[8,9]

Cyclophosphamide	600mg/m^2	IV	Days 1
Liposomal doxorubicin	30mg/m^2	IV	Day 1

Vincristine	2mg	IV	Days 1
Prednisone	60mg/m^2	orally	Days 1–5
Rituximab	375mg/m^2	IV for cycle 1	Day 8

Repeat cycle every 3 weeks for 6-8 cycles

Intent: primary therapy for patients > 80 years with co-morbidity

R-mini-CHOP[10]

Rituximab	375mg/m^2	IV for cycle 1	Day 1
Cyclophosphamide	400mg/m^2	IV	Day 1
Doxorubicin	25mg/m^2	IV	Day 1
Vincristine	1mg	IV	Day 1
Prednisone	40mg/m^2	orally	Days 1–5

Repeat cycle every 3 weeks for 6 cycles

Intent: second line therapy

DHAP ± rituximab[11,12]

Cisplatin	100mg/m^2	IV over 24 hours	Days 1
Cytosine arabinoside	2g/m^2	IV over 12 hours	Days 2
Dexamethasone	40mg	IV or orally	Days 1–4
± Rituximab	375mg/m^2	IV prior to DHAP	Day 0

Repeat cycle every 3 weeks for 6 -10 cycles

Alternatives:

ESHAP ± rituximab[13,14]

Etoposide	40mg/m^2	IV	Days 1–4
Cisplatin	25mg/m^2	IV over 24 hours	Days 1–4
Methylprednisolone	250-500mg	IV	Days 1–5
Cytarabine	2g/m^2	IV over 2–3 hours	Days 5
± Rituximab	375mg/m^2	IV prior to ESHAP	Day 0

Repeat cycle every 3-4 weeks for 6-8 cycles

GDP ± rituximab[15,16]

Cisplatin	75mg/m^2	IV over 1 hour	Days 1
Gemcitabine	100mg/m^2	IV over 30 minutes	Days 1 & 8
Dexamethasone	40mg	PO in divided doses	Days 1–4
± Rituximab	375mg/m^2	IV prior to GCD	Day 0

Repeat cycle every 3 weeks for 6 cycles

ICE ± rituximab[12,17,18]

Ifosfamide	5g/m^2	IV over 24 hours	Days 1
Etoposide	100mg/m^2	IV bolus	Days 1–3
Carboplatin	AUC 5mg·min/mL	IV	Days 2
± Rituximab	375mg/m^2	IV prior to ICE	Day 1 & 3

Repeat cycle every 2 weeks for 3 cycles

Bendamustine ± rituximab[19-21]

Rituximab	375mg/m^2	IV	Day 1
Bendamustine	90mg/m^2	IV over 30–60 minutes	Day 1 & 2

Repeat cycle every 4 weeks for 6 cycles

CEPP ± rituximab[7]

Cyclophosphamide	600mg/m^2	IV	Days 1 and 8
Etoposide	70mg/m^2	IV	Day 1
Etoposide	140 mg/m^2	Orally	Days 2 and 3
Procarbazine	60mg/m^2	Orally	Days 1–10
Prednisone	60mg/m^2	Orally	Days 1–10
± Rituximab	375mg/m^2	IV prior to CEPP	Day 1 & 3

Repeat cycle every 4 weeks for 6 cycles

Rituximab[22]

Rituximab	375mg/m^2	IV	Day 1, 8, 15 and 22

Repeat cycle every 4 weeks for 52 weeks

REFERENCES

1. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-5.
2. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. Journal of Clinical Oncology 2005;23:4117-26.

3. He X, Jia B, Shi Y. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in patients with stage I diffuse large B-cell lymphoma. ASCO Annual Meeting Proceedings; 2014. p. e19513.
4. Purroy N, López A, Vallespi T, Gironella M, Bergua J, Sancho JM. Dose-Adjusted EPOCH Plus Rituximab (DA-EPOCH-R) in Untreated Patients with Poor Risk Large B-Cell Lymphoma. A Phase 2 Study Conducted by the Spanish PETHEMA Group. Blood 2009;114:2701-.
5. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. Journal of Clinical Oncology 2008;26:2717-24.
6. Wilson WH, Jung S-H, Porcu P, et al. A Cancer and Leukemia Group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. Haematologica 2012;97:758-65.
7. Chao NJ, Rosenberg S, Horning S. CEPP (B): an effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. Blood 1990;76:1293-8.
8. Martino R, Perea G, Caballero MD, et al. Cyclophosphamide, pegylated liposomal doxorubicin (Caelyx), vincristine and prednisone (CCOP) in elderly patients with diffuse large B-cell lymphoma: results from a prospective phase II study. Haematologica 2002;87:822-7.
9. Zaja F, Tomadini V, Zaccaria A, et al. CHOP-rituximab with pegylated liposomal doxorubicin for the treatment of elderly patients with diffuse large B-cell lymphoma. Leukemia & lymphoma 2006;47:2174-80.
10. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. The lancet oncology 2011;12:460-8.
11. Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-22.
12. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. Journal of Clinical Oncology 2010;28:4184-90.

13. Velasquez W, McLaughlin P, Tucker S, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. Journal of Clinical Oncology 1994;12:1169-76.
14. Martín A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica 2008;93:1829-36.
15. Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma. Cancer 2004;101:1835-42.
16. Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leukemia & lymphoma 2010;51:1523-9.
17. Zelenetz A, Hamlin P, Kewalramani T, Yahalom J, Nimer S, Moskowitz C. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Annals of Oncology 2003;14:5-10.
18. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood 2004;103:3684-8.
19. Weidmann E, Kim S-Z, Rost A, et al. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. Annals of Oncology 2002;13:1285-9.
20. Vacirca J, Tabbara I, Acs P, Shumaker G. Bendamustine+ Rituximab as Treatment for Elderly Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Blood 2010;116:2806-.
21. Ohmachi K, Niitsu N, Uchida T, et al. Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. Journal of Clinical Oncology 2013;31:2103-9.
22. Grillo-López AJ, Hedrick E, Rashford M, Benyunes M. Rituximab: ongoing and future clinical development. Seminars in oncology; 2002: Elsevier. p. 105-12.

EXTRANODAL NK/T-CELL LYMPHOMA

Intent: primary chemotherapy for extranodal NK/T cell lymphomas

AspaMetDex[1]

Methotrexate	3g/m^2	IV	Day 1
Dexamethasone	40mg	orally	Days 1–4
Pegaspargase	6000 U/m^2	IM	Days 2, 4, 6, and 8

Repeat cycle every 3 weeks for 3 cycles

SMILE[2,3]

Methotrexate	2g/m^2	IV	Day 1
Dexamethasone	40mg	orally	Days 2–4
Leucovorin	15mg	× 4 doses/day IV or orally	Days 2–4
Ifosfamide	1500mg/m^2	IV	Days 2–4
Etoposide	100mg/m^2	IV	Days 2–4
L-asparaginase	6000 U/m^2	IV	Days 8, 10, 12, 14, 16, 18, and 20

Repeat cycle every 3 weeks for 3 cycles

GELOX[4]

Oxaliplatin	130mg/m^2	IV	Day 1
Pegaspargase	2500U/m^2	IM	Day 1
Gemcitabine	1000mg/m^2	IV	Days 1 and 8

Repeat cycle every 3 weeks for 6 cycles

REFERENCES

1. Jaccard A, Gachard N, Marin B, et al. Efficacy of L-asparaginase with methotrexate and dexamethasone (AspaMetDex regimen) in patients with refractory or relapsing extranodal NK/T-cell lymphoma, a phase 2 study. Blood 2011;117:1834-9.

2. Yamaguchi M, Suzuki R, Kwong YL, et al. Phase I study of

dexamethasone, methotrexate, ifosfamide, l-asparaginase, and etoposide (SMILE) chemotherapy for advanced-stage, relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma and leukemia. Cancer science 2008;99:1016-20.

3. Yamaguchi M, Kwong Y-L, Kim WS, et al. Phase II study of SMILE chemotherapy for newly diagnosed stage IV, relapsed, or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type: the NK-Cell Tumor Study Group study. Journal of Clinical Oncology 2011;29:4410-6.

4. Gao Y, QiChun C, Wang X, et al. Efficacy and safety of pegaspargase with Gemcitabine and Oxaliplatin in patients with treatment-naïve, refractory extranodal natural killer/T-Cell lymphoma: a single-centre experience. Blood 2013;122:642-.

FOLLICULAR LYMPHOMA

Intent: primary chemotherapy for follicular lymphoma

Bendamustine + rituximab[1]

Rituximab	375mg/m^2	IV	Day 1
Bendamustine	90mg/m^2	IV over 30–60 minutes	Day 1 & 2

Repeat cycle every 4 weeks for 6 cycles

RCHOP [2,3]

Rituximab	375mg/m^2	IV	**Day 0**
Cyclophosphamide	750mg/m^2	IV	Day 1
Doxorubicin	50mg/m^2	IV	Day 1
Vincristine	2mg	IV	Day 1
Prednisone	100mg	Orally	Days 1–5

Repeat cycle every 3 weeks for 6 cycles

RCVP [4,5]

Rituximab	375mg/m^2	IV	**Day 1**
Cyclophosphamide	750mg/m^2	IV	Day 1
Vincristine	2mg	IV	Day 1
Prednisone	100mg	Orally	Days 1–5

Repeat cycle every 3 weeks for 8 cycles

LENALIDOMIDE + RITUXIMAB[6,7]

Lenalidomide	20mg	Orally	Days 1–21
Rituximab	375mg/m^2	IV	Day 1

Repeat cycle every 4 weeks for 12 cycles

Intent: second line therapy

Fludarabine + rituximab[8]

Fludarabine	25mg/m^2	IV	Days 1–5
Rituximab	375mg/m^2	IV	Day 1

Repeat cycle every 4 weeks for 12 cycles

LENALIDOMIDE ± RITUXIMAB[9]

Lenalidomide	25mg	Orally	**Days 1–21**

Rituximab	375mg/m^2	IV	**Day 1, 8, 15 and 22**

Repeat cycle every 4 weeks for 52 weeks

RITUXIMAB[10,11]

Rituximab	375mg/m^2	IV	**Day 1, 8, 15 and 22**

Repeat cycle every 4 weeks for 52 weeks

RFND[12]

Rituximab	375mg/m^2	IV	**Day 1, 8, 15, and 22**
Fludarabine	25mg/m^2	IV	**Days 1–3**
Mitoxantrone	10mg/m^2	IV	**Days 1–3**
Dexamethasone	20g/m^2	IV or Orally	**Days 1–5**

Repeat cycle every 4 weeks for 2-5 cycles

REFERENCES

1. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. The Lancet 2013;381:1203-10.

2. Czuczman MS, Weaver R, Alkuzweny B, Berlfein J, Grillo-López AJ. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. Journal of clinical oncology 2004;22:4711-6.

3. WILSON WH, HIDDEMANN W, KNEBA M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxombicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Commentary. Blood 2005;106.

4. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. Journal of Clinical Oncology 2008;26:4579-86.

5. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417-23.

6. Martin P, Jung S-H, Johnson JL, et al. CALGB 50803 (Alliance): A phase II trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma. ASCO Annual Meeting Proceedings; 2014. p. 8521.

7. Fowler NH, Davis RE, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. The Lancet Oncology 2014;15:1311-8.

8. Czuczman MS, Koryzna A, Mohr A, et al. Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma. Journal of Clinical Oncology 2005;23:694-704.

9. Leonard J, Jung S-H, Johnson JL, et al. CALGB 50401: A randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma. ASCO Annual Meeting Proceedings; 2012. p. 8000.

10. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. Journal of clinical oncology 1998;16:2825-33.

11. Ghielmini M, Schmitz S-FH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly× 4 schedule. Blood 2004;103:4416-23.

12. McLaughlin P, Hagemeister FB, Rodriguez MA, et al. Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma. Seminars in oncology; 2000. p. 37-41.

HODGKIN'S LYMPHOMA

Intent: first line therapy for stage IA and stage IIA
Favourable

Adriamycin + Bleomycin + Vincristine + Dacarbazine – ABVD [1-4]

Doxorubicin	25mg/m^2	IV push	Days 1 & 15
Bleomycin	10units/m^2	IV push	Days 1 & 15
Vinblastine	6mg/m^2	IV over 5-10 minutes	Days 1 & 15
Dacarbazine	375mg/m^2	IV over 60 minutes	Days 1 & 15

Repeat cycle every 4 weeks for 2-4 cycles followed by radiation

Alternatives:

Doxorubicin + Vinblastine + Mechlorethamine + Etoposide + Vincristine + Bleomycin + Prednisone (Stanford V)[5-7]

Doxorubicin	25mg/m^2	IV push	Days 1 & 15
Vinblastine	6mg/m^2	IV over 5-10 minutes	Days 1 & 15
Mechlorethamine	6mg/m^2	IV push	Day 1
Vincristine	1.4mg/m^2	IV over 5–10 minutes	Days 8 & 22
Bleomycin	5units/m^2	IV push	Days 8 & 22
Etoposide	60mg/m^2	IV over 60 minutes	Days 15 and 16
Prednisone	40mg/m^2	orally every other day	Days 1–28

Repeat cycle every 4 weeks for 2 cycles followed by radiation

Intent: first line therapy for stage I/II Unfavourable

Doxorubicin + Bleomycin + Vinblastine + Dacarbazine (ABVD) [1-4,8]

Doxorubicin	25mg/m^2	IV push	Days 1 & 15
Bleomycin	10units/m^2	IV push	Days 1 & 15
Vinblastine	6mg/m^2	IV over 5-10 minutes	Days 1 & 15
Dacarbazine	375mg/m^2	IV over 60 minutes	Days 1 & 15

Repeat cycle every 4 weeks for 2-4 cycles followed by radiation

Alternatives

Doxorubicin + Vinblastine + Mechlorethamine + Etoposide + Vincristine + Bleomycin + Prednisone (Stanford V) [5-7]

Doxorubicin	25mg/m^2	IV push	Days 1 & 15
Vinblastine	6mg/m^2	IV over 5-10 minutes	Days 1 & 15
Mechlorethamine	6mg/m^2	IV push	Day 1
Vincristine	1.4mg/m^2	IV over 5–10 minutes	Days 8 & 22
Bleomycin	5units/m^2	IV push	Days 8 & 22
Etoposide	60mg/m^2	IV over 60 minutes	Days 15 and 16
Prednisone	40mg/m^2	orally every other day	Days 1–28

Repeat cycle every 4 weeks for 2 cycles followed by radiation

Bleomycin + Etoposide + Doxorubicin + Cyclophosphamide + Vincristine + Procarbazine + Prednisone (Escalated BEACOPP)[8,9]

Cyclophosphamide	1,250mg/m^2	IV over 60 minutes	Day 1
Doxorubicin	35mg/m^2	IV push	Day 1
Etoposide	200mg/m^2	IV over 2 hours	Days 1–3
Procarbazine	100mg/m^2	orally	Days 1–7
Vincristine	1.4mg/m^2	IV over 5–10 minutes	Day 8
Bleomycin	10units/m^2	IV push	Day 8
Prednisone	40mg/m^2	orally daily	Days 1–14

Repeat cycle every 3 weeks for 2 cycles followed by ABVD then radiation therapy

Intent: primary therapy for stage III and IV

Doxorubicin + Bleomycin + Vinblastine + Dacarbazine (ABVD) [1-4]

Doxorubicin	25mg/m^2	IV push	Days 1 & 15
Bleomycin	10units/m^2	IV push	Days 1 & 15
Vinblastine	6mg/m^2	IV over 5-10 minutes	Days 1 & 15
Dacarbazine	375mg/m^2	IV over 60 minutes	Days 1 & 15

Repeat cycle every 4 weeks for 2-4 cycles followed by radiation

Intent: second line therapy

Cyclophosphamide + Vincristine + Procarbazine + Prednisone (C-MOPP)[10,11]

Cyclophosphamide	650mg/m^2	IV over 30 minutes	Day 1
Vincristine	1.4mg/m^2	IV	Day 1
Procarbazine	100mg/m^2	orally daily	Days 1–7
Prednisone	40mg/m^2	orally daily	Days 1–14

Repeat cycle every 4 weeks for 4-8 cycles

Alternatives

Dexamethasone + Cytarabine + Cisplatin (DHAP)[12,13]

Cisplatin	100mg/m^2	IV over 24 hours	Days 1
Cytarabine	2g/m^2	IV over 12 hours	Days 2
Dexamethasone	40mg	IV or orally	Days 1–4

Repeat cycle every 3 weeks for 4 -8 cycles

Etoposide + Methylprednisolone + Cytarabine + Cisplatin (ESHAP)[14,15]

Etoposide	40mg/m^2	IV	Days 1–4
Cisplatin	25mg/m^2	IV over 24 hours	Days 1–4
Methylprednisolone	500mg	IV	Days 1–5
Cytarabine	2g/m^2	IV over 2–3 hours	Days 5

Repeat cycle every 3-4 weeks for 4-8 cycles

Gemcitabine + Carboplatin + Dexamethasone (GCD)[16]

Gemcitabine	100mg/m^2	IV over 30 minutes	Days 1 & 8
Carboplatin	AUC 5mg • min/mL	IV over 60 minutes	Day 1
Dexamethasone	40mg	PO in divided doses	Days 1–4

Repeat cycle every 3 weeks for 6 cycles

Ifosfamide + Carboplatin + Etoposide (ICE)[13,17]

Ifosfamide	5g/m^2	IV over 24 hours	Days 1
Etoposide	100mg/m^2	IV bolus	Days 1–3
Carboplatin	AUC 5mg·min/mL	IV	Days 2

Repeat cycle every 2-3 weeks for 4-8 cycles

REFERENCES

1. Eich H, Mueller R, Diehl V, et al. Intensified Chemotherapy and Dose-Reduced Involved Field Radiotherapy in Patients with Early Unfavorable Hodgkin Lymphoma: Final Analysis of the German Hodgkin Study Group (GHSG) Randomized HD11 Trial. International Journal of Radiation Oncology* Biology* Physics 2010;78:S1.
2. Engert A, Plütschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. New England Journal of Medicine 2010;363:640-52.
3. Meyer RM, Gospodarowicz MK, Connors JM, et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. New England Journal of Medicine 2012;366:399-408.
4. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. Journal of Clinical Oncology 2004;22:2835-41.
5. Gordon LI, Hong F, Fisher RI, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). Journal of Clinical Oncology 2013;31:684-91.
6. Advani RH, Hoppe RT, Baer DM, Mason J, Rosenberg SA, Horning SJ. Efficacy of Abbreviated Stanford V Chemotherapy and Involved Field Radiotherapy in Early Stage Hodgkin's Disease: Mature Results of the G4 Trial. Blood 2009;114:1670-.
7. Edwards-Bennett S, Jacks L, Moskowitz C, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. Annals of oncology 2009:mdp337.
8. von Tresckow B, Plütschow A, Fuchs M, et al. Dose-intensification in early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD14 trial. Journal of Clinical Oncology 2012:JCO. 2011.38. 5807.
9. Engert A, Haverkamp H, Kobe C, et al. Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin's lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial. The Lancet 2012;379:1791-9.
10. Montoto S, Camós M, López-Guillermo A, et al. Hybrid

chemotherapy consisting of cyclophosphamide, vincristine, procarbazine, prednisone, doxorubicin, bleomycin, and vinblastine (C-MOPP/ABV) as first-line treatment for patients with advanced hodgkin disease. Cancer 2000;88:2142-8.

11. Takenaka T, Mikuni C, Miura A, et al. Alternating combination chemotherapy C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) and ABVd (adriamycin, bleomycin, vinblastine, dacarbazine) in clinical stage II–IV Hodgkin's disease: a multicenter phase II study (JCOG 8905). Japanese journal of clinical oncology 2000;30:146-52.
12. Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Annals of Oncology 2002;13:1628-35.
13. Abalı H, Ürün Y, Öksüzoğlu B, et al. Comparison of ICE (ifosfamide-carboplatin-etoposide) versus DHAP (cytosine arabinoside-cisplatin-dexamethasone) as salvage chemotherapy in patients with relapsed or refractory lymphoma. Cancer investigation 2008;26:401-6.
14. Aparicio J, Segura A, Garcera S, et al. ESHAP is an active regimen for relapsing Hodgkin's disease. Annals of Oncology 1999;10:593-5.
15. de Larrea CF, Martinez C, Gaya A, et al. Salvage chemotherapy with alternating MINE–ESHAP regimen in relapsed or refractory Hodgkin's lymphoma followed by autologous stem-cell transplantation. Annals of Oncology 2010;21:1211-6.
16. Gopal AK, Press OW, Shustov AR, et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leukemia & lymphoma 2010;51:1523-9.
17. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001;97:616-23.

PERIPHERAL T-CELL LYMPHOMA

Intent: primary chemotherapy for ALCL, ALK+ histology peripheral T-cell lymphoma

CHOP-21[1-3]

Cyclophosphamide	750mg/m^2	IV	Day 1
Doxorubicin	50mg/m^2	IV	Day 1
Vincristine	2mg	IV	Day 1
Prednisone	100mg	orally	Days 1–5

Repeat cycle every 3 weeks for 6 cycles

CHOEP [1,3]

Cyclophosphamide	750mg/m^2	IV	Day 1
Doxorubicin	50mg/m^2	IV	Day 1
Vincristine	2mg	IV	Day 1
Etoposide	100mg/m^2	IV	Days 1–3
Prednisone	100mg	orally	Days 1–5

Repeat cycle every 3 weeks for 6 cycles

Intent: first line therapy for other histologies (ALCL, ALK, PTCL, NOS, AITL, EATL)

CHOEP [1,3]

Cyclophosphamide	750mg/m^2	IV	Day 1
Doxorubicin	50mg/m^2	IV	Day 1
Vincristine	2mg	IV	Day 1
Etoposide	100mg/m^2	IV	Days 1–3
Prednisone	100mg	orally	Days 1–5

Repeat cycle every 3 weeks for 6 cycles

CHOP-14[1-3]

Cyclophosphamide	750mg/m^2	IV	Day 1
Doxorubicin	50mg/m^2	IV	Day 1
Vincristine	2mg	IV	Day 1
Prednisone	100mg	orally	Days 1–5

Repeat cycle every 2 weeks for 6 cycles

CHOP-21[1-3]

Cyclophosphamide	750mg/m^2	IV	Day 1
Doxorubicin	50mg/m^2	IV	Day 1

Vincristine	2mg	IV	Day 1
Prednisone	100mg	orally	Days 1–5

Repeat cycle every 3 weeks for 6 cycles

Dose-adjusted EPOCH[4-6]

Etoposide	50mg/m^2	IV	Days 1–4
Vincristine	0.4mg/m^2	IV	Days 1–4
Doxorubicin	10mg/m^2	IV	Days 1–4
Prednisone	60mg	orally	Days 1–6
Cyclophosphamide	750mg/m^2	IV	Day 6

Repeat cycle every 3 weeks for 6 cycles

Second line therapy

DHAP [7,8]

Cisplatin	100mg/m^2	IV over 24 hours	Days 1
Cytosine arabinoside	2g/m^2	IV over 12 hours	Days 2
Dexamethasone	40mg	IV or orally	Days 1–4

Repeat cycle every 3 weeks for 6 -10 cycles

ESHAP[9]

Etoposide	40mg/m^2	IV	Days 1–4
Cisplatin	25mg/m^2	IV over 24 hours	Days 1–4
Methylprednisolone	500mg	IV	Days 1–5
Cytarabine	2g/m^2	IV over 2–3 hours	Days 5

Repeat cycle every 3-4 weeks for 6-8 cycles

GDP [10-12]

Cisplatin	75mg/m^2	IV over 1 hour	Days 1
Gemcitabine	100mg/m^2	IV over 30 minutes	Days 1 & 8
Dexamethasone	40mg	PO in divided doses	Days 1–4

Repeat cycle every 3 weeks for 6 cycles

ICE[13]

Ifosfamide	5g/m^2	IV over 24 hours	Days 1
Etoposide	100mg/m^2	IV bolus	Days 1–3
Carboplatin	AUC 5mg·min/mL	IV	Days 2

Repeat cycle every 2 weeks for 3 cycles

REFERENCES

1. Savage K, Chhanabhai M, Gascoyne R, Connors J. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. Annals of Oncology 2004;15:1467-75.
2. Pfreundschuh M, Trümper L, Kloess M, et al. Two-weekly or

3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood 2004;104:634-41.

3. Schmitz N, Trümper L, Ziepert M, et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010;116:3418-25.
4. Dunleavy K, Shovlin M, Pittaluga S, et al. DA-EPOCH chemotherapy is highly effective in ALK-positive and ALK-negative ALCL: results of a prospective study of PTCL subtypes in adults. Blood 2011;118:1618-.
5. Wilson WH, Bryant G, Bates S, et al. EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. Journal of Clinical Oncology 1993;11:1573-82.
6. Peng Y-L, Huang H-Q, Lin X-B, et al. [Clinical outcomes of patients with peripheral T-cell lymphoma (PTCL) treated by EPOCH regimen]. Ai zheng= Aizheng= Chinese journal of cancer 2004;23:943-6.
7. 7. Velasquez WS, Cabanillas F, Salvador P, et al. Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP). Blood 1988;71:117-22.
8. Mey UJ, Orlopp KS, Flieger D, et al. Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma. Cancer investigation 2006;24:593-600.
9. Velasquez W, McLaughlin P, Tucker S, et al. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. Journal of Clinical Oncology 1994;12:1169-76.
10. Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma. Cancer 2004;101:1835-42.
11. Dong M, He X-h, Liu P, et al. Gemcitabine-based combination regimen in patients with peripheral T-cell lymphoma. Medical Oncology 2013;30:1-6.
12. Connors JM, Sehn LH, Villa D, et al. Gemcitabine, Dexamethasone, and Cisplatin (GDP) As Secondary Chemotherapy In Relapsed/Refractory Peripheral T-Cell Lymphoma. Blood 2013;122:4345-.
13. Zelenetz A, Hamlin P, Kewalramani T, Yahalom J, Nimer S, Moskowitz C. Ifosfamide, carboplatin, etoposide (ICE)-based second-line chemotherapy for the management of relapsed and refractory aggressive non-Hodgkin's lymphoma. Annals of Oncology 2003;14:5-10.

MULTIPLE MYELOMA

Intent: primary therapy for transplant candidates

Bortezomib + dexamethasone[1-4]

Bortezomib	1.3mg/m^2	IV bolus	Days 1, 4, 8, and 11
Dexamethasone	40mg	orally daily	Days 1–4 and 9–12

Repeat cycle every 3 weeks for 3–4 cycles

Alternatives

Bortezomib + doxorubicin + dexamethasone[5,6]

Bortezomib	1.3mg/m^2	IV bolus	Days 1, 4, 8, and 11
Doxorubicin	9mg/m^2	IV infusion	Days 1–4
Dexamethasone	40mg	orally daily	Days 1–4, 9–12, 17-20

Repeat cycle every 3 weeks for 3–4 cycles

Bortezomib + thalidomide + dexamethasone[3,7-9]

Bortezomib	1.3mg/m^2	IV bolus	Days 1, 4, 8, and 11
Thalidomide	50–200mg	orally daily at bedtime	Days 1–21
Dexamethasone	40mg	orally daily	Days 1–4 and 9–12

Repeat cycle every 3 weeks for 3–4 cycles

Lenalidomide + dexamethasone[10,11]

Lenalidomide	25mg	orally daily	Days 1–21
Dexamethasone	40mg	orally daily	Days 1, 8, 15 and 22

Repeat cycle every 3 weeks for 3–4 cycles

Thalidomide + dexamethasone[12-15]

Thalidomide	50–200mg	PO daily at bedtime	Days 1–28
Dexamethasone	40mg	orally daily	Days 1–4, 9–12, 17-20

Repeat cycle every 3 weeks for 3–4 cycles

Intent: primary therapy for non-transplant candidates

Lenalidomide + dexamethasone[1-4]

Lenalidomide	25mg	orally daily	Days 1–21
Dexamethasone	40mg	orally daily	Days 1, 8, 15 and 22

Repeat cycle every 3 weeks for 3–4 cycles

Lenalidomide + low dose dexamethasone[10]

Lenalidomide	25mg	orally daily	Days 1–21
Dexamethasone	40mg	orally daily	Days 1, 8, 15 and 22

Repeat cycle every 4 weeks until maximal response

Melphalan Prednisone + bortezomib (MPB)[16,17]

Melphalan	9mg/m^2	orally daily	Days 1–4
prednisone	60mg/m^2	orally	Days 1 – 4
Bortezomib	1.3mg/m^2	IV bolus	Days 1, 4, 8, 11, 22, 25, 29, and 32

Repeat cycle every 6 weeks until disease progression

Melphalan + prednisone + lenalidomide (MPL)[18,19]

Melphalan	0.18mg/kg	orally daily	Days 1–4
Prednisone	2mg/kg	orally	Days 1 – 4
Lenalidomide	10mg	orally daily	Days 1–21

Repeat cycle every 4 weeks until disease progression

Melphalan + prednisone + thalidomide (MPT)[20-23]

Melphalan	0.2–0.25mg/kg	orally daily	Days 1–4
Prednisone	2mg/kg or 100mg	orally	Days 1 – 4
Thalidomide	50–200mg	orally daily at bedtime	Days 1–42

Repeat cycle every 6 weeks until disease progression

Liposomal doxorubicin + Vincristine + dexamethasone[24]

Pegylated liposomal doxorubicin	40mg/m^2	IV over 60 minutes	Day 1
vincristine	1.4mg/m^2	IV over 5–10 minutes	Day 1
Dexamethasone	40mg	orally daily	Days 1–4

Repeat cycle every 4 weeks until disease progression

Melpalan + prednisone (MP)[17,19,20,22,25]

Melphalan	8–9mg/m2	orally daily	Days 1–4
Prednisone	60mg/m	orally	Days 1 – 4

Repeat cycle every 6 weeks until disease progression

Vincristine + doxorubicin + dexamethasone (VAD)[26]

Doxorubicin	9mg/m^2	IV over 60 minutes	
Vincristine	0.4mg/m^2	IV over 5–10 minutes	
Dexamethasone	40mg	orally daily	Days 1–4, 9–12,17–20

Repeat cycle every 4 weeks until disease progression

Intent: Maintenance therapy

Bortezomib[4,6]

Bortezomib	1.3mg/m^2	IV bolus	Days 1, 4, 8, & 11

Repeat cycle every 2 weeks for 2 years or until disease progression

Lenalidomide[18,27-29]

Lenalidomide	10mg	orally daily	Days 1–28

Repeat cycle every 4 weeks until disease progression

Thalidomide [30,31]

Thalidomide	50–200mg	orally daily	Days 1–28

Repeat cycle every 4 weeks until disease progression

REFERENCES

1. Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients with t (4; 14) myeloma but not outcome of patients with del (17p). Journal of Clinical Oncology 2010;28:4630-4.
2. Harousseau J-L, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. Journal of Clinical Oncology 2010;28:4621-9.
3. Moreau P, Avet-Loiseau H, Facon T, et al. Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma. Blood 2011;118:5752-8.
4. Niesvizky R, Flinn IW, Rifkin R, et al. Efficacy and safety of three bortezomib-based combinations in elderly, newly diagnosed multiple myeloma patients: results from all randomized patients

in the community-based, phase 3b UPFRONT study. Blood 2011;118:478-.

5. Popat R, Oakervee HE, Hallam S, et al. Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: updated results after long-term follow-up. British journal of haematology 2008;141:512-6.

6. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. Journal of Clinical Oncology 2012;30:2946-55.

7. Kaufman JL, Nooka A, Vrana M, Gleason C, Heffner LT, Lonial S. Bortezomib, thalidomide, and dexamethasone as induction therapy for patients with symptomatic multiple myeloma. Cancer 2010;116:3143-51.

8. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. The Lancet 2010;376:2075-85.

9. Rosiñol L, Cibeira MT, Mateos MV, et al. A phase III PETHEMA/GEM study of induction therapy prior autologous stem cell transplantation (ASCT) in multiple myeloma: superiority of VTD (bortezomib/thalidomide/dexamethasone) over TD and VBMCP/VBAD plus bortezomib. Blood 2010;116:307-.

10. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. The lancet oncology 2010;11:29-37.

11. Zonder JA, Crowley J, Hussein MA, et al. Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232). Blood 2010;116:5838-41.

12. Rajkumar SV, Rosiñol L, Hussein M, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. Journal of clinical oncology 2008;26:2171-7.

13. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. Journal of clinical oncology 2006;24:431-6.

14. Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. Journal of Clinical Oncology 2003;21:16-9.

15. Rajkumar SV, Hayman S, Gertz MA, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. Journal of Clinical Oncology 2002;20:4319-23.

16. Harousseau J-L, Palumbo A, Richardson PG, et al. Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. Blood 2010;116:3743-50.

17. Mateos M-V, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. Journal of Clinical Oncology 2010;28:2259-66.

18. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. New England Journal of Medicine 2012;366:1759-69.

19. Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA—Italian Multiple Myeloma Network. Journal of Clinical Oncology 2007;25:4459-65.

20. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial. The Lancet 2007;370:1209-18.

21. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. Journal of Clinical Oncology 2009;27:3664-70.

22. Palumbo A, Bringhen S, Caravita T, et al. Oral melphalan and

prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. The Lancet 2006;367:825-31.

23. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study. Journal of Clinical Oncology 2010;28:3160-6.

24. Rifkin RM, Gregory SA, Mohrbacher A, Hussein MA. Pegylated liposomal doxorubicin, vincristine, and dexamethasone provide significant reduction in toxicity compared with doxorubicin, vincristine, and dexamethasone in patients with newly diagnosed multiple myeloma. Cancer 2006;106:848-58.

25. Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. Blood 2010;116:1405-12.

26. Dimopoulos M, Pouli A, Zervas K, et al. Prospective randomized comparison of vincristine, doxorubicin and dexamethasone (VAD) administered as intravenous bolus injection and VAD with liposomal doxorubicin as first-line treatment in multiple myeloma. Annals of oncology 2003;14:1039-44.

27. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. New England Journal of Medicine 2012;366:1770-81.

28. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. New England Journal of Medicine 2012;366:1782-91.

29. Kneppers E, van der Holt B, Kersten M-J, et al. Lenalidomide maintenance after nonmyeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 Trial. Blood 2011;118:2413-9.

30. MERLINI G, ATTAL M, HAROUSSEAU J-L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Commentary. Blood 2006;108.

31. Brinker BT, Waller EK, Leong T, et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. Cancer 2006;106:2171-80.

ACRONYMS AND ABBREVIATIONS

5-FU 5-fluorouracil
AJCC American Joint Committee on Cancer
ALL Acute lymphoblastic leukemia
ALP Alkaline phosphatase
ALT Alanineaminotransferase
AML Acute myeloid leukaemia
APL Acute Promyelocytic leukemia
AST Aspartate aminotransferase
BCC Basal cell carcinoma
BCLC Barcelona Clinic for Liver Cancer
BRCA Breast cancer
BSO Bilateral salpingo-oopherectomy
BSO Bilateral subcapsular orchiectomy
CIS carcinoma in Situ
CLL Chronic lymphocytic leukemia
CML Chronic Myeloid Leukemia
CRC Colorectal cancer
CT scan Computed Tomography scan
CXr Chest X-ray
DLBCL Diffuse Large B-cell lymphoma
EBRT External Beam Radiation therapy
EGFR Epidermal growth factor receptor
FIGO International Federation of Gynecology and Obstetrics
FISH Fluorescent in situ hybridization
FOBT Fecal Ocult Blood Test
FNAC Fine Needle Aspiration and cytology
GIST Gastrointestinal stromal tumour
GTD Gestational Trophoblastic Diseases
IHC Immunochemistry
IMRT Intensity modulated radiotherapy
KS Kaposi's sarcoma
LDH Lactate dehydrogenase
LEEP Loop electrosurgical excision procedure
LFT Liver function tests
MDT Multi-Disciplinary Teams
MRI Magnetic Resonance Imaging

NCCN	National Comprehensive cancer Network
NPC	Nasopharyngeal cancer
NHL	Non-Hodgkin's lymphoma
NSCLC	Non-small cell lung cancer
PC	Palliative care
PCR	Polymerase chain reaction
PEG	Percutaneous Endoscopic Gastrostomy
PET	Positron Emission Tomography
PL	Pelvic Lymphadenectomy
PR	Progesterone Receptor
RECIST	Response Evaluation Criteria in Solid Tumours
RFA	Radiofrequency ablation
RT	Radiation Treatment
SCCHN	Squamous cell carcinoma Head and Neck
SCLC	Small cell lung cancer
SLL	Small lmphocytic lymphoma
TACE	Trans-arterial chemoembolization
TAH	Total abdominal hysterectomy
TMZ	Temozolamide
TNM	Tumour, node, metastasis
U/S	Ultrasound
VEGF	Vascular endothelial growth factor

ANNEX

PART FOUR

PALLIATIVE CARE GUIDELINES

CONSTIPATION MANAGEMENT

Principles:

- Constipation refers to the passage of small, hard faeces infrequently and with difficulty.
- Stool frequency varies considerably in the normal population and an understanding of the patient's usual bowel habit is essential for management.
- Constipation is often overlooked despite being an important symptom that can cause distress and complications for many patients. Aim to anticipate and prevent constipation, especially when prescribing regular opioids.
- If evidence of bowel obstruction see separate guideline.

Assessment:

- Take a clinical history of the constipation. This should include the patients current bowel pattern compared to their normal, associated symptoms of constipation (e.g. abdominal pain, nausea, PR bleeding), any dietary changes and a list of current medications.
- Perform an abdominal examination including digital rectal examination unless the patient is too weak or likely to suffer undue pain or bleeding as a result.
- Request any appropriate investigations.

Management:

- Good holistic care requires a combination of general non-clinical measures and advice, investigation and treatment of any underlying cause(s) and appropriate symptomatic treatment(s). All three aspects of care are important and ideally should occur concurrently, however for certain patients the underlying cause of the constipation may be unclear.

Management for these patients should focus on improving symptoms and quality of life whilst regularly reassessing.

Most patients respond best to a combination of a softening and stimulant laxative.

General measures	• Encourage fluid intake • Increase fibre in diet. Consider vegetable oil or margarine (1 tablespoon at breakfast) and/or dried crushed paw-paw seeds • Encourage exercise/ ambulation where possible • Assess and manage any pain appropriately
Treat underlying cause(s)	• History, examination and investigations should focus on finding or excluding underlying causes for constipation. Common causes include: - Medication e.g. opioids, anticholinergics - General body weakness/ immobility - Reduced food intake and/ or dehydration - Low residue diet • Reverse/ treat any underlying cause(s) identified appropriately
Treatment (Start with one laxative and titrate dose according to symptoms before adding a second. Often a combination of two laxatives will be required, e.g. bisacodyl and liquid paraffin)	**Oral medication:** • Bisacodyl 5-15mg nocte (start with 5mg nocte and titrate up) • Liquid Paraffin 10mls od (increase to bd if required)
	Rectal measures: • Rectal measures are sometimes necessary but should never replace prescription of an appropriate oral laxative • If hard faecal mass present at digital rectal examination manual removal of faeces may be required • Glycerine suppositories one suppository PR od

DELIRIUM (ACUTE CONFUSIONAL STATE) MANAGEMENT

Principles:

- Delirium is a clinical syndrome, typically acute in onset that involves abnormalities of thought, perception and fluctuating levels of consciousness.
- Both hyperactive and hypoactive forms of delirium have been identified and patients may exhibit features of either.
- Delirium is common in patients with advanced disease, especially the elderly and those approaching end of life.

Assessment:

- Take a full history including MMSE. Often a collateral history is required from the patient's caretaker.
- Examine the patient thoroughly looking for signs of an underlying cause and request any appropriate investigations e.g. CBC, RFTs, urinalysis.

Management:

- Good holistic care requires a combination of general non-clinical measures and advice, investigation and treatment of any underlying cause(s) and appropriate symptomatic treatment(s). All three aspects of care are important and ideally should occur concurrently, however for certain patients the underlying cause of the delirium may be unclear. Management for these patients should focus on improving symptoms and quality of life whilst regularly reassessing.

<table>
<tr><th></th><th colspan="2"></th></tr>
<tr><td>General measures</td><td colspan="2">• Ensure patient safety and optimise environment
• A care taker should remain with the patient
• Remove any objects that could be harmful
• Correct any sensory impairments, e.g. inadequate lighting
• Ideally the environment should be familiar and not over stimulating
• Educate the family regarding delirium and provide support both emotionally and psychologically.</td></tr>
<tr><td>Treat underlying cause(s)</td><td colspan="2">• History, examination and investigations should focus on finding or excluding underlying causes for delirium.
• Common causes include:
o Medications e.g. Opiate toxicity, anticholinergics, hypnotics
o Infections
o Urinary retention
o Constipation
o Metabolic abnormalities e.g. renal impairment,Ca^{2+}, dehydration
o Cerebral metastases or other intracranial event
o Alcohol or drug withdrawal</td></tr>
<tr><td rowspan="3">Treatment</td><td colspan="2">Antipsychotics</td></tr>
<tr><td>First line:
• Haloperidol 1.25-5mg up to tds po or sc</td><td>Second line:
• Chlorpromazine 25-50mg up to tds po or sc
OR
• Risperidone 2mg po od (increased by 1mg daily to maximum of 6mg daily)</td></tr>
<tr><td colspan="2">Benzodiazepines:
(Generally not recommended for delirium unless it is related to alcohol withdrawal, however can be used second line for patients with an agitated delirium in addition to haloperidol or chlorpromazine)
• Diazepam 5-10mg nocte po or sc</td></tr>
</table>

BREATHLESSNESS MANAGEMENT

Principles:

- Breathlessness (dyspnoea) is a distressing symptom experienced by many patients with advanced disease.
- It is a subjective experience and should not be confused with tachypnoea that is an objective clinical sign.

Assessment:

- Take a full, holistic history from the patient and complete a clinical examination.
- Order any appropriate investigations e.g. CXR, CBC.

Management:

- Good holistic care requires a combination of general non-clinical measures and advice, investigation and treatment of any underlying cause(s) and appropriate symptomatic treatment(s). All three aspects of care are important and ideally should occur concurrently, however for certain patients the underlying cause of the breathlessness may be unclear. Management for these patients should focus on improving symptoms and quality of life whilst regularly reassessing.

General measures	• Reassure the patient – breathlessness can be extremely frightening, and is exacerbated by anxiety. Explore the patient's fears and concerns. • Breathing exercises and relaxation techniques are often beneficial and should be taught to the patient: o Explain that their breathing will improve if they slow it down. Show them how to slow their breathing by pursing their lips as if they were going to whistle when they breathe out. o Teach the patient to breathe with their diaphragm rather than the top of the chest by putting one hand on their chest and one on the top of their abdomen so they can feel where they are breathing from. The hand on the abdomen should move more if they are breathing with their diaphragm. • Find the most comfortable position for the patient (usually sitting up). • Ensure good ventilation – open windows and/ or use a fan. Loosen any tight clothing. • Conserve energy by limiting or reducing activities.
Treat underlying cause(s)	• History, examination and investigations should focus on finding or excluding underlying causes for breathlessness. • Reverse/ treat any underlying cause(s) identified appropriately.

Symptomatic treatment	• Low dose morphine e.g. 2.5-5mg po 4 hourly can improve symptoms of breathlessness (if already on morphine for pain control, increase the dose by 20% and advise on taking breakthrough doses as required). • Diazepam 2.5-5mg po up to tds. This can be very helpful when the breathlessness is associated with significant anxiety or panic attacks. • Consider oxygen if hypoxic (however there is no evidence to support the use of palliative oxygen in patients with normal oxygen saturations). • Regular nebulised saline 0.9% may be helpful for patients with sticky bronchial secretions.

END OF LIFE CARE MANAGEMENT PART 2: PRESCRIBING

Principles:

- Most patients find taking medication a burden especially towards the end of life.
- Focus on giving medication that will improve the patient's quality of life and discontinue any unnecessary medications, e.g. anti-hypertensives.

Assessment:

- If the patient is unable to swallow choose an appropriate route to give necessary medications e.g. via NG tube, parenteral or PR.
- Subcutaneous (SC) is recommended when the enteral route is not possible e.g. patient has bowel obstruction. It is preferred over intravenous and intramuscular access due to its reduced trauma and pharmacokinetics.
- If repeated injections are anticipated or experienced a butterfly needle can be inserted and used as a route for regular SC injections.

Management:

- Common symptoms encountered towards the end of life include pain, agitation, nausea and excessive respiratory secretions. Management of these symptoms is highlighted below.
- Consider prescribing medications pre-emptive to symptoms arising, also referred to as anticipatory prescribing. This can avoid delays in administration but must also be assessed on a case by case basis.
- Morphine concentrations can vary between establishments depending on the preparation used - remember that SC morphine is twice the potency of oral morphine.

Symptom	Enteral Route	Subcutaneous Route
Pain	Morphine 5 – 7.5 mg 4hrly	Morphine 2.5 – 5 mg 4hrly
Morphine dose will depend on the patient, clinical problem and previous opioid use. If the patient is already taking opioids 1/6th of 24 hour oral dose can be given orally PRN or 1/12th of the 24 hour oral dose can be given SC PRN.		
Nausea and Vomiting	Haloperidol 2.5mg od titrated to bd	Haloperidol 2.5mg od titrated to bd
Anxiety or Agitation	Diazepam 5-10mg od titrated to tds	Diazepam 5mg od titrated to tds
Excessive bronchial secretions		Hyoscine butylbromide 20mg od titrated to tds
Anti-secretory medication should be given when symptoms first occur and will be less helpful if given later.		
Issues of Hydration and Nutrition	• Patients should eat and drink as they wish and take sips of water as long as they are able. • Families should be educated that it is normal for patients to lose their appetite, sense of thirst and stop feeding towards the end of life. They should not feed patients if they are no longer able to swallow as this may cause choking and distress. • Intravenous fluids at this stage will not prolong life and will not prevent thirst. Over hydration may contribute to distressing respiratory secretions or generalised oedema and are generally discouraged; good regular mouth care is the best way to keep the patient comfortable. • Intravenous dextrose for calorie supplementation is unlikely to be of benefit. • If there is a reduced level of consciousness patients should be not be fed due to the risk of aspiration and artificial nutrition is generally discouraged at the end of life.	

END OF LIFE CARE MANAGEMENT PART 1: GENERAL MEASURES

Principles:

- At the end of life goals of care change to prioritise comfort and quality of life.
- Listening to the patient and their family is paramount. Empowering families with basic nursing skills and knowledge to care for their loved one can bring union, peace and comfort at an otherwise difficult time.

Assessment:

- Clinical signs found towards the end of life may include:
  - Patient becomes bedbound and is increasingly drowsy or in a semi-conscious state
  - Minimal oral intake; patient not managing oral medication and sips of fluid only
  - The patient's condition is deteriorating rapidly, e.g. day by day or hour by hour
  - Breathing becomes irregular +/- noisy (death rattle)
  - Changes in skin colour and/ or temperature

Management:

- Exclude/ treat any reversible causes of the patient's deterioration such as dehydration, infections, drug toxicity and/ or biochemical abnormalities.
- Good holistic care requires a combination of general non-clinical measures and advice, investigation and treatment of any underlying cause(s) and appropriate symptomatic treatment(s) which may or may not include anticipatory prescribing (ref. Part 2)

General measures	
Comfort Nursing Care	• Keep the patient clean and dry. • Regularly clean the mouth with a moist cloth wrapped round a spoon (ref. Mouth Care Guideline). • Prevent and manage pressure sores (bed sores) appropriately. Pressure sores arise when an area of skin is placed under too much pressure for a prolonged period of time often as a result of immobility such as in bedbound patients. Remember that pressure sores can occur in numerous conditions and settings, not just end of life. The recommendations below can be applied regardless of the prognosis of the patient and underlying diagnosis. • Check the patient's skin regularly looking for early signs of pressure sores such as skin discolouration. • Patients should be turned regularly (at least every two hours) and soft cushioning placed beneath common pressure areas such as the heels. • Avoid positioning patients directly on pressure ulcers or bony prominences. • Optimise nutritional status which will assist healing. • Discourage smoking; this can prevent healing by reducing oxygen levels in the blood. • Manage any associated pain (ref. Pain Guideline) and infection (ref. Wound Management Guidelines). Topical antibiotics are recommended over systemic treatments for infected pressure ulcers unless there is evidence of underlying osteomyelitis. • If severe the patient may need a surgical review for consideration of debridement.

Discontinue Interventions that are not providing symptomatic benefit	• The benefit versus burden should be assessed for all interventions. o Always ask “will this test change my management plan or the outcome for the patient?” • Interventions such as venepuncture, vital signs monitoring and frequent blood glucose tests are generally discouraged unless they will influence patient management and overall quality of life. • Intravenous dextrose for calorie supplementation is unlikely to be of benefit.
Psychological, Social and Spiritual Needs	• The end of life is an emotional time for all involved and requires health care professionals to be considerate and compassionate. Take time to listen to the concerns of the patient and their family: break bad news sensitively. • Encourage the family to be present, holding a hand or talking to the patient even if there is no visible response - the patient may be able to hear even if they cannot respond. • Consider spiritual support. • Consider the best place of death for the patient and their family, would discharge home be best?

FUNGATING WOUNDS MANAGEMENT

Principles:

- Fungating wounds can cause social isolation and low self esteem. However, with the appropriate support the majority of patients and their family members can manage even the most difficult of wounds.
- Good treatment manages all aspects of wound care including exudates, malodour and pain as well as promoting the emotional well being of the patient and family.

Assessment:

- Take a history from the patient and examine the wound.
- Consider the potential for serious complications such as catastrophic haemorrhage.
- Explore the psychological, social and spiritual effects the wound has on the patient and family.

Management:

- Good holistic care requires a combination of general advice, wound treatment and appropriate symptomatic treatment(s). All three aspects of care are important and ideally should occur concurrently, however for certain patient's treatment of the wound itself may be limited due to e.g. advanced disease status. Management for these patients should focus on improving symptoms and quality of life whilst regularly reassessing.

General measures	• Clean the wound regularly (at least daily) using a simple salt solution (dissolve 1 teaspoon of salt per pint of cooled boiled water – this is approximately equivalent to 0.9% saline). • Apply clean dressings daily. These can be made from local materials. • Protect the normal skin around the wound with barrier creams.

Treat underlying cause(s)		• Consider what treatment options are available. Local or systemic treatment may be possible and could include surgery, radiotherapy and/ or chemotherapy. • Liaise with the appropriate colleagues to organize such treatments
Symptomatic treatment		
Pain	**General constant pain**	• Ensure that the pain is not caused by infection or dressings. Prescribe appropriate analgesia (see separate pain guideline).
	Pain with dressing changes only	• Soak dressings off with a simple salt solution. • Give an extra dose of analgesia 30mins before dressing change.
Malodour +/- Exudate		• Prescribe non-enteric coated metronidazole tablets. These should be crushed and the powder applied directly to the wound when changing the dressing, ideally daily. • For foul smelling PV discharge use metronidazole pessaries or non-enteric coated metronidazole tablets inserted PV.
Infection	**Systemic upset or cellulitis**	• Continue management above AND • Prescribe an appropriate antibiotic (may need to be give parenterally).
Bleeding	**Mild**	• Avoid trauma especially when changing dressings that should be soaked off with a simple salt solution.
	Moderate to severe	• Consider palliative radiotherapy, surgery or chemotherapy • Consider adding tranexamic acid tablets po 500mg-1g tds

MOUTH CARE MANAGEMENT

Principles:

- Good mouth care is a vital part of palliative care; it not only improves comfort but helps maintain a patient's ability to eat, drink and communicate effectively.
- All patients should have regular screening for mouth complications.
- High risk patients, e.g. those with oro-pharyngeal disease, receiving head and neck radiotherapy or immunocompromised patients should be given advice about mouth care preemptive to symptoms arising.

Assessment:

- Take a full, holistic history from the patient and examine the mouth looking for signs of dryness, coating, ulceration, infection or tumour.
- Order any appropriate investigations e.g. mouth swab particularly for patients with persistent or recurrent symptoms.

Management:

- Good holistic care requires a combination of general non-clinical measures and advice, investigation and treatment of any underlying cause(s) and appropriate symptomatic treatment(s). All three aspects of care are important and ideally should occur concurrently, however for certain patients the underlying cause of the oral symptoms may be unclear. Management of these patients should focus on improving symptoms and quality of life whilst regularly reassessing.

General measures
• Patients should maintain a moist mouth by sipping fluids regularly throughout the day. If the patient is unable to swallow they should rinse their mouth regularly with a simple saline or bicarbonate solution (add 1 teaspoon of salt or bicarbonate to a glass of warm water and stir well to dissolve). • Brush teeth and clean tongue at least twice daily using a small soft toothbrush and toothpaste. • Advise patients to suck fresh cold pineapple cubes once or twice daily; this can help lift debris from the tongue. • Adjust foods to aid eating e.g. soft foods with lots of sauce/ gravy and avoid too many sugary foods and drinks. • Advise regular application of lip balm or 'Vaseline' to dry cracked lips. • Review the patient's medications and adjust as appropriate; certain drugs can exacerbate oral symptoms e.g. anticholinergics cause a dry mouth.

Specific oral problems	
Candidiasis	• Ketoconazole 200mg od for 7 days OR Fluconazole 200mg od for 7 days.
Painful Mouth	• Oral morphine 4hrly (for dose refer to pain management guideline). Patients should hold the morphine in their mouth and use as a mouthwash for at least 30 seconds before swallowing. • Analgesic and antiseptic gel (e.g. bonjela): apply topically to mouth ulcers 4hrly. Has limited use for patients with generalised oral pain.

Mucositis +/- Ulceration	• Assess carefully for evidence of infection and treat appropriately. o For gingivitis or anaerobic lesions (often associated with significant halitosis) treat with metronidazole mouthwash. This can be made by mixing 50mls of intravenous metronidazole with 450mls of water (50mls of water can be replaced with juice or other flavouring if required). Educate patients to use this solution tds as a mouthwash for 1 minute before spitting out. • Increase the frequency of mouth cleaning with a saline solution, up to hourly in severe cases. • For severe cases of mucositis or aphthous ulceration consider a course of steroids. Prescribe Dexamethasone 8mg orally od for 5 days and then review. • Review the patient's management plan with the oncology or palliative care teams. If mucositis is secondary to chemo/ radiotherapy the dose of treatment may need reducing or in severe cases a break in treatment may be advised to allow healing of the mucous membranes.
Herpes Simplex Infection	• Oral Acyclovir 200mg, 5 times a day for 5-10 days depending on severity. • Treat lip ulcers with Acyclovir ointment: apply topically to lesions for 5-10 days.

NAUSEA AND VOMITING MANAGEMENT

Principles:

- Nausea and vomiting is a distressing symptom that is common in the palliative care population however often underreported by patients.

Assessment:

- Take a full, holistic history from the patient and complete a clinical examination.
- Order any appropriate investigations e.g. CXR, CBC.

Management:

- Good holistic care requires a combination of general non-clinical measures and advice, investigation and treatment of any underlying cause(s) and appropriate symptomatic treatment(s). All three aspects of care are important and ideally should occur concurrently, however for certain patients the underlying cause of the nausea and vomiting may be unclear. Management for these patients should focus on improving symptoms and quality of life whilst regularly reassessing.

General measures	• Good frequent mouth care (see mouth care guideline) • Patients should be encouraged to eat and drink as they wish. Regular sips of fluid and small low fibre meals are recommended over larger meals. • Ensure the patient is adequately hydrated.
Treat underlying cause(s)	• History, examination and investigations should focus on finding or excluding common underlying causes for nausea and vomiting. • Reverse/ treat any underlying cause(s) identified appropriately

Treatment

- The choice of first line anti-emetic will be determined by the likely underlying cause of the nausea and vomiting (see below).
- Avoid combining drugs with similar mode of action or antagonistic effects e.g. prokinetics and anticholinergics.
- Consider giving medication via a non-oral route (sc or iv) if actively vomiting or severe nausea.
- Prescribe the chosen antiemetic regularly.

Pattern	Causes	Suggested medication
Gastric stasis or delayed bowel transit time • Early satiety • Nausea is typically relieved by vomiting	• Medications, e.g. morphine • Constipation • Gastric outflow obstruction "squashed stomach syndrome"	• Metoclopramide 10-20mg 8 hourly 30 mins before meals (same dose sc or iv)
Metabolic disturbance or toxins • Intractable nausea that is typically not relieved by vomiting	**Metabolic:** • Renal failure, liver failure, hypercalcaemia **Toxic:** • Medications e.g. morphine • Chemotherapy +/- Radiotherapy	• Haloperidol 1.25 -2.5mg nocte (po or sc)
Raised intracranial pressure • Typically worse in the mornings and often associated headaches	• Intracranial tumours • Infections e.g. toxoplasmosis meningitis	• Dexamethasone 8-16mg od (caution in patients with untreated infections)
Visceral stretch/ compression • Nausea and vomiting accompanied by abdominal pain	• If inoperable conservative management of malignant bowel obstruction can improve symptom burden – refer patient to MPCU • Intra abdominal or pelvic malignancy • Bowel obstruction	• Promethazine 25mg tds • Hyoscine butylblomide 20-40mgs qds

PAIN MANAGEMENT FOR ADULTS

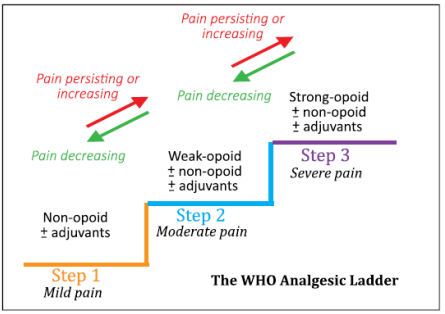
Principles:

- Pain is what the patient says it is and can have physical, psychological, social and spiritual components.
- Aim to control pain quickly and safely. Regularly re-evaluate pain and monitor its response to treatment.
- Benefits and burdens alongside affordability and accessibility are important factors in the choice of analgesic.

Assessment:

- Evaluate the cause of the pain using a holistic history, thorough examination and appropriate investigations. Pain severity should be assessed using an appropriate pain evaluation tool such as the hand scale below.

Management:



- Good holistic care requires a combination of general non-clinical measures and advice, investigation and treatment of any underlying cause(s) and appropriate symptomatic treatment(s). All three aspects of care are important and ideally should occur concurrently, however for certain patients the underlying cause of the pain may be unclear. Management for these patients should focus on improving symptoms and quality of life whilst regularly reassessing.
- Pain management is based on the WHO analgesic ladder.
- Medications should be given regularly throughout the day and

orally unless contraindicated.

- Patients started on a regular opioid should have a laxative co-prescribed unless contraindicated

Step	Analgesics	Comments	Adjuvants
Step 1 (non-opioid)	Paracetamol 1g 6 hourly or Diclofenac 50mg 8 hourly	• Continue with step 1 analgesic when moving on to step 2 and 3	• Amitriptyline 12.5-25mg nocte for neuropathic pain (can be increased to 50-75mg if tolerated) • Clonazepam 0.5-1mg nocte for neuropathic pain second line • Dexamethasone 4-8mg od for swelling/ oedema e.g. liver capsular stretch • Hyoscine Butylbromide (buscopan) 20mg qds for smooth muscle spasm • Diazepam 5-20mg nocte for painful skeletal muscle spasm
Step 2 (Weak Opioid)	Morphine 2.5-5mg 4 hourly during the day with a double dose at night or Codeine Phosphate 30-60mg 6 hourly or Tramadol 50-100mg 6 hourly	• Low dose morphine is considered a step 2 analgesic and is recommended first line if available as it is cheaper than codeine or tramadol • Discontinue step 2 analgesics when starting step 3	
Step 3 (Strong Opioid)	Morphine 7.5-10mg 4 hourly during the day with a double dose at night if breakthrough pain occurs give an equivalent additional dose. Increase the dose as required to control the patient's pain	• The elderly and/or those with renal impairment may require a dose adjustment • (For children see separate guideline)	

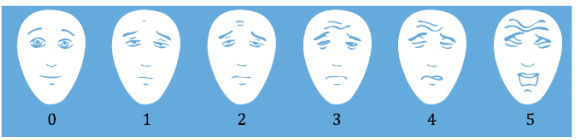
PAIN MANAGEMENT FOR CHILDREN

Principles:

- Pain is what the child says it is and can have physical, psychological, social and spiritual components. No child should be withheld adequate and safe analgesia.
- Aim to control pain quickly and safely. Regularly re-evaluate pain and monitor its response to treatment.

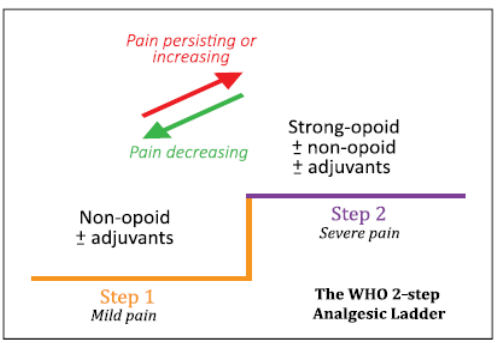
Assessment:

- Evaluate the cause of the pain using a holistic history, thorough examination and appropriate investigations.
- Pain severity should be assessed by using an appropriate pain evaluation tool such as the hands or faces scale below. Scores are from 0, 1, 2, 3, 4, 5 (0 = no pain and 5 = very, very much in pain).



Management:

- Good holistic care requires a combination of general non-clinical measures and advice, investigation and treatment of any underlying cause(s) and appropriate symptomatic treatment(s)



- Pain management for children is based on the WHO analgesic ladder using a two-step strategy
- Medications should be given regularly throughout the day and

orally unless contraindicated.

- Patients started on a regular opioid should have a laxative co-prescribed unless contraindicated.

Step	Analgesics	Comments	Adjuvants
Step 1 (non-opioid)	**Infants from 1 to 3 months** • Paracetamol 10mg/kg every 4-6 hrs max 4 doses/day **Children from 3 months to 12 years** • Paracetamol 10-15mg/kg every 4-6 hrs max 4 doses/day, max 1g at a time. Ibuprofen 5-10mg/kg every 6-8 hours	• Aspirin is rarely used in children	• Amitriptyline - children from 2-12 years, 0.2-0.5mg/kg (max 25mg) at night – increase if needed to max 1mg/kg twice a day • Carbamazepine – 5-20mg/kg/day in 2 or 3 divided doses, increase gradually to avoid side effects. • Diazepam (used for associated anxiety) o 1-6 years: 1mg/day in 2-3 divided doses • 6-14 years: 2-10mg/day in 2-3 divided doses • Hyoscine Butylbromide • 1month – 2 years: 0.5mg/kg po 8hrly • 2-5 years: 5mg po 8hrly • 6-12 years: 10mg po 8hrly • Prednisone – 1.2mg/kg/day
Step 2 (Opioid)	**Infants from 1 to 3 months** Oral morphine – 0.08-0.2mg/kg every 4 hrs **Children from 1 to 2 years** Oral morphine – 0.2-0.4mg/kg every 4 hrs **Children from 2 to 12 years** Oral morphine 0.2-0.5mg/kg every 4hrs	• **Titration:** After a starting dose, the dosage should be adjusted to the level that is effective with a maximum dosage increase of 50% per 24 hours.	

MALIGNANT SPINAL CORD COMPRESSION

Principles:

- Malignant spinal cord compression (MSCC) is defined as compression of part of the spinal cord through a malignant process such as direct tumour pressure, oedema, vascular disturbance or vertebral instability.
- It is most commonly seen in metastatic lung, breast, prostate cancer or myeloma.
- MSCC is a palliative care emergency requiring urgent assessment and management. Late diagnosis and/ or delays in treatment can result in paraplegia, loss of bowel/ bladder control, impaired quality of life and reduced survival.

Assessment:

- Take a full, holistic history from the patient and complete a clinical examination. Key signs and symptoms of MSCC include:
    - **Pain** – Severe progressive back pain (particularly thoracic) +/- neuropathic or radicular pain. Pain is typically exacerbated by coughing, straining or lying flat. Pain usually precedes any sensory or motor deficit.
    - **Motor +/- Sensory Deficit** – Reduced power and sensation primarily of the lower limbs but may effect upper limbs depending on the level of compression.
    - **Autonomic dysfunction** – Bladder and/ or bowel disturbance (loss of sphincter control is a late sign with a poor prognosis).
- Order imaging investigations urgently – ideally these should be done within 24 hours for patients with neurological symptoms
    - MRI is the gold standard though access and cost limit its use in Uganda. If MRI is available aim to image the whole spine as multiple levels of cord compression can occur.

- If MRI unavailable consider CT of the vertebral column.
- Always consider plain x-rays of the whole spine but remember these may not show the compression.

Management:

- Good holistic care requires a combination of general non-clinical measures and advice, investigation and treatment of MSCC and appropriate symptomatic treatment(s). All three aspects of care are important and ideally should occur concurrently.

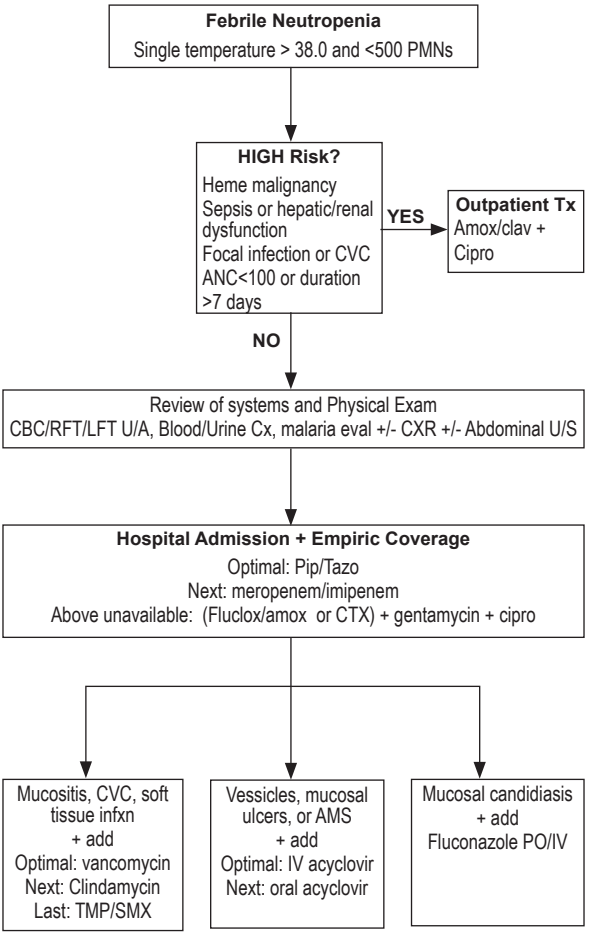
General measures	• Pain should be assessed and managed using the WHO analgesic ladder (see pain management guidelines). • Assess for concurrent problems such as pressure sores, bladder/ bowel incontinence and psychosocial distress. • Remember to involve OT and physiotherapy in the management of these patients.
Corticosteroids	• High dose steroids should be commenced immediately with any clinical suspicion of MSCC until a decision regarding treatment is made. • Unless contraindicated prescribe Dexamethasone 16 mg stat po followed by 16mg once daily while treatment is being planned and implemented. • Once radiotherapy treatment has started the dose should be reduced over 5-7 days and then stopped. • Dexamethasone should not be taken after midday as it may cause insomnia. • Consider monitoring blood sugars, especially diabetic patients. • Advise patients to take after food to reduce the risk of gastric irritation.

Radiotherapy	• Radiotherapy is the definitive treatment for MSCC. If appropriate patients with MSCC should be discussed with a radio-oncologist urgently for consideration of treatment. • If there is complete paraplegia and loss of sphincter control, radiotherapy may improve pain control but is unlikely to restore function. Patients who are too frail or unfit for specialist treatment should not be transferred unnecessarily to a tertiary referral centre for radiotherapy.

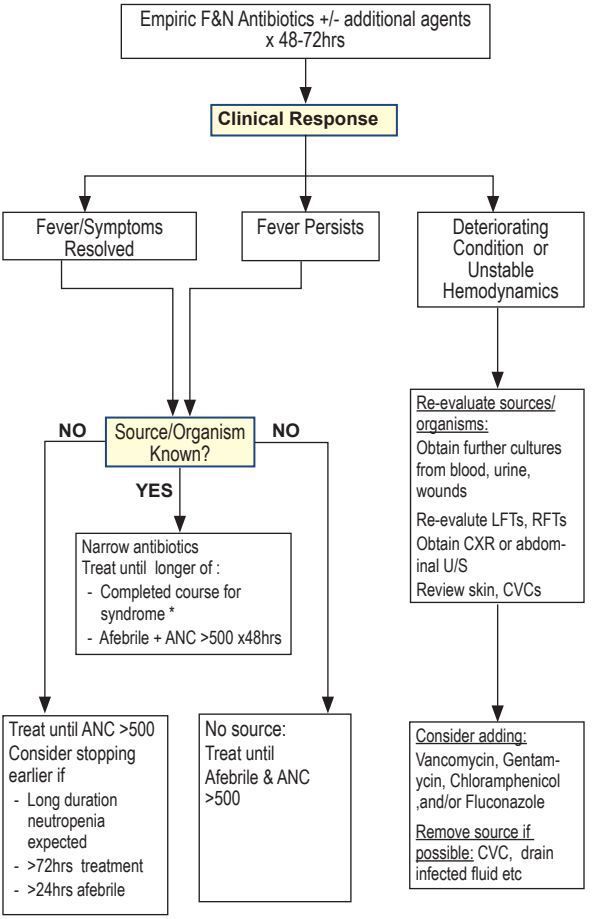
PART FIVE

SUPPORTIVE CARE GUIDELINES

Initial F&N management



Ongoing therapy management * ie: 14 days for bacteremia or 7 days for pneumonia or cellulitis



MANAGEMENT AND PREVENTION OF FEBRILE NEUTROPENIA

1. Purpose

The purpose of this guideline is to provide recommendations for prophylaxis, diagnosis, and management of febrile neutropenia among adult and pediatric patients with malignancies at the Uganda Cancer Institute.

2. Definitions

2.1 Fever: Single oral or tympanic temperature >38^{0}C
Note: Axillary temperatures are discouraged and rectal temperatures are contraindicated in patients with chemotherapy-induced febrile neutropenia

2.2 Afebrile Neutropenic Sepsis: Fever equivalents, such as rigors or sweats, or focal signs of infection and/or unstable hemodynamics in the setting of neutropenia. These conditions should be treated as if febrile neutropenia despite absence of fever.

2.3 Neutropenia:

a) Absolute neutrophil count (ANC) < 500 cells/mm^3

b) ANC <1000 cells/mm^3, which is expected to decrease to <500 cells/mm^3 within 48 hours

c) “Functional neutropenia”: Qualtitative defects in ciruculating neutrophils as a result of a hematologic malignancy; Patients with high blast counts or dysplastic cells may be functionally neutropaenic regardless of the neutrophil count on their CBC.

3. Risk Assessment:

Assessment of risk for severe infection in a patient with febrile neutropenia is crucial for determining the appropriate choice of antimicrobial therapy, including type, route (intravenous vs oral) and duration. Factors influencing risk of severe infection include type of malignancy, chemotherapy received, medical history and comorbidities, and presenting signs and symptoms.

3.1 <u>High Risk:</u> A patient is considered high risk if he/she meets ANY of the criteria below:

a) Oral or tympanic temperature > 390C

b) Underlying cancer diagnosis: i) AML, ii) Bone marrow involvement, or iii) Relapsed malignancy

c) Medical comorbidity: i) Hepatic insufficiency (LFTs >5x normal), or ii) Renal insufficiency (CrCl<30) d) "Septic" clinical presentation: i) hypotension, ii) respiratory distress, iii) hypoxemia, iv) new-onset abdominal pain, or v) neurologic changes

e) Evidence of focal infection: i) mucositis, ii) pneumonia, iii) perianal tenderness, or iv) presence of central venous line

f) Laboratory findings: i) ANC <100 cells/mm3, ii) Platelet count <50,000 cells/mm3, or iii) C-reactive protein >90 mg/L

g) Anticipated duration of neutropenia >7 days

<u>3.2 Low Risk:</u>

a) Clinically stable

b) Neutropenia expected to resolve within 7 days

c) No active comorbidities

Note: Any patient who does not clearly meet criteria for low-risk status should be considered high risk

4. Clinical Assessment

A focused history, physical exam, laboratory tests, and imaging should be completed with attention to likely sources of infection and evidence of shock.

4.1 Exam

a) Obtain and document vital signs: Temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, urine output

b) Carefully examine skin, line sites, sinuses, oropharynx, lungs, abdomen, perineum, genitalia. Assess difficulty or pain with eating, swallowing, or defecating, or genital pain, as these may be signs of mucositis, invasive herpesvirus infections, or mucosal candidiasis.

c) *Per rectum exam is contraindicated in a neutropenic patient*

4.2 Laboratory Testing

a) CBC, RFT, LFT
b) Urinalysis and microscopy
c) Urine culture (“clean catch”)
d) Blood slide for malaria parasites and/or malaria rapid test
e) Peripheral blood cultures (bacterial and fungal)

4.3 Imaging

a) Chest X-ray only if respiratory signs or symptoms
b) Abdominal X-ray or ultrasound only if abdominal signs or symptoms

5. Empiric Antibiotic Therapy

5.1 Basic Principles

a) Antibiotics should be administered to a patient with suspected neutropenic fever without delay. All patients should receive antibiotics within 30 minutes of initial recognized fever.

b) Confirmation of laboratory neutropenia should not delay initiation of antibiotics if suspected neutropenia. Antibiotics can be discontinued if CBC result does not meet criteria of neutropenia.

c) Cultures (blood and urine) should ideally be obtained prior to antibiotic administration, but should not delay treatment.

d) Optimal empiric antibiotic therapy should include an agent(s) with bactericidal activity, especially against *Pseudomonas aeruginosa*, and have a favorable toxicity profile.

e) If a source of possible or definite infection is identified, additional initial agents may be warranted (see 5.4 “Signs of focal infection”) to cover additional organisms.

f) The presence of malaria does not rule out a bacterial source of sepsis and should not affect empiric antibiotic treatment.

5.2 High Risk Patients

a) 1st Line: **Pipericillin-tazobactam**.
If evidence of sepsis/shock: add **gentamycin**.

Agent	Dose	
	Pediatric (age <15)	Adult
Pipericillin-tazobactam	100 mg pipericillin/ kg IV q 6 hours, up to maximum does of 4.5 g	4.5 g IV q 6 hours
Gentamycin	2.5 mg/kg IV q 8 hours	2mg/kg IV x 1; then 1.7 mg/kg IV q 8 hours

b) 2nd Line: **Meropenem** or **imipenem**.

Agent	Dose	
	Pediatric (age <15)	**Adult**
Meropenem	**≤50 kg**: 20 mg/kg IV q 8 hours; do not exceed 1 g q 8 hours **>50 kg**: 1 g IV q 8 hours	1 g IV q 8 hours
Imipenem	20 mg/kg IV q 6 hours	500 mg IV q 6 hours *(1 g IV q 8 hours)*

c) 3rd Line: If first or second line regimens unavailable:

i) Ceftriaxone + ciprofloxacin + gentamycin

If suspect intrabdominal source: add **metronidazole**

Agent	Dose	
	Pediatric (age <15)	**Adult**
Ceftriaxone	50 mg/kg IV q 24 hours	2 g IV q 24 hours
Ciprofloxacin	10 mg/kg IV q 8 hours	400 mg IV q 8 hours
Gentamycin	2.5 mg/kg IV q 8 hours	2mg/kg IV x 1; then 1.7 mg/kg IV q 8 hours
Metronidazole	10 mg/kg IV q 8 hours	500 mg IV q 8 hours

ii) If high suspicion for multi-drug resistant organism: **Chlorampenicol**

Agent	Dose	
	Pediatric (age <15)	**Adult**
Chlorampenicol	50-100 mg/kg/day IV in 4 divided doses	50-100 mg/kg/day IV in 4 divided doses

d) If severe penicillin/beta-lactam allergy*: **Clindamycin + ciprofloxacin+ gentamycin**

**risk of penicillin cross-reaction is <5% in carbapenems and should be challenged in life-threatening infections unless reliable history of anaphylaxis to a PCN or*

cephalosporin

Agent	Dose	
	Pediatric (age <15)	Adult
Clindamycin	10 mg/kg IV q 6-8 hours	450 mg IV q 6-8 hours
Ciprofloxacin	10 mg/kg IV q 8 hours	400 mg IV q 8 hours
Gentamycin	2.5 mg/kg IV q 8 hours	2mg/kg IV x 1; then 1.7 mg/kg IV q 8 hours

5.3 Low-Risk Patients

a) 1st line: **Ciprofloxacin oral + amoxicillin/clavulanate syrup or ampicillin/cloxacillin capsules**

b) 2nd line: **Ciprofloxacin oral + clindamycin oral**

c) If beta lactam allergy: **Levofloxacin oral**

Agent	Dose	
	Pediatric (age <15)	Adult
Ciprofloxacin	20 mg/kg po q 12 hours	400 mg po q 12 hours
Amoxicillin/ clavulanate	45 mg/kg po in divided doses twice daily	875 mg po q 12 hours
Flucloxacillin	<2 yrs: 62.5mg po q 6h 2-10 years: 125mg po q 6h	500 mg po q 6 hours
Clindamycin	20 mg/kg/day po divided q 6-8 hours	450 mg po q 8 hours
Levofloxacin	<5 yrs: 8-10mg/kg po twice daily >5 yrs: 10mg/kg po q day; max 750mg	500 mg po q day

5.4 Signs and Symptoms of Focal Infection

a) If skin/soft tissue infection, mucositis, or concern for serious catheter related infection:

Add coverage for gram positive bacteria (including MRSA) to empiric regimen above.

First line: Vancomycin IV

Second line: Clindamycin IV or Trimethoprim-sulfa

(TMP) IV or po.

Third line: Chloramphenicol (Consider for unstable patients or for MRSA resistant to clindamycin and TMP when vancomycin is not available)

Agent	Dose	
	Pediatric (age <15)	**Adult**
Vancomycin	40 mg/kg/day in 4 divided doses	1 g IV q 12 hours
Clindamycin	10 mg/kg IV q 6-8 hours	450 mg IV q 6-8 hours *(600 mg IV q 8 hours)*
Trimethoprim-sulfa	5mg/kg IV or po q 6 hours	5mg/kg IV or po q 6 hours
Chlorampenicol	50-100 mg/kg/day IV in 4 divided doses	50-100 mg/kg/day IV in 4 divided doses

b) If any vesicular skin, genital, perianal, oropharyngeal lesions, or severe dysphagia or odynophagia, or concern for encephalitis: Add or increase acyclovir to treat for herpes simplex virus (HSV) or varicella zoster virus (VZV) infection:

Agent	Dose	
	Pediatric (age <15)	**Adult**
Acyclovir	< 2 years: 30 mg/kg/day IV divided q 8 hours; or 80 mg/kg/day po divided q 6 hours >2 years: 30 mg/kg/day IV divided q 8 hours; or 1000 mg/day po divided q 6 hours	800 mg po q 6 hours

c) If oral thrush or severe genial/perineal candidiasis: 6-mg/kg q24hrs PO/IV (12mg/kg if any sepsis signs for concern of candidemia)

d) If any signs/symptoms of pneumonia: Add either erythromycin 50mg/kg daily in 4 doses PO (max 4g daily) or clarithromycin 15mg/kg/day divided q12hrs (max 1g/day) * clarithro is better tolerated, preferable

if available. NOT NEEDED if Ciprofloxacin or levofloxacin is used!

e) If concern for Pneumocystis pneumonia: bilateral infiltrates, inappropriately quiet chest for degree of hypoxemia, generally sub-acute in onset, history of prolonged neutropenia or high-dose steroids: Add Trimethoprim-sulfa IV 5mg/kg/dose TMP content q6hrs or TMP-SMX (Cotrimoxazole) PO same dosing.

6. Ongoing Management and Duration of Antimicrobial Therapy

6.1 Basic Principles: Duration of antibiotic therapy depends on clinical circumstances and response to therapy. In general, prefer to continue antibiotic therapy until neutropenia is resolved (ANC>500 cells/mm^3) and patient is afebrile x 48hrs. If a documented infection is present, treat full course as appropriate (ie 14 days for bacteremia or 10 days for pneumonia) or ANC>500, whichever is *longer*.

6.2 Clinical evaluation: Patients should be assessed at least daily to evaluate for evidence of focus of infection and response to therapy. Assessment should include vital signs (minimum of temperature recording) every 8 hours and a daily physical exam and review of investigations

6.3 Ongoing Management:

a) Do not modify initial empiric antimicrobial regimen based solely on persistent fever in patients who are clinically stable.

b) In patient who is clinically unstable despite empiric antibiotics and sepsis management:
   1) Repeat thorough clinical exam (including mucosa and lines/cannulas)
   2) Request CXR if not done initially, even if there are no focal symptoms
   3) Perform blood and urine cultures if not already done
   4) Broaden antimicrobial coverage:
      i) If patient initially on piperacillin/tazobactam only, add second gram-negative agent such as gentamycin. Move to carbapenem if not

already on one. Cipro/levofloxacin are not adequate single “broadening agents” because of resistance.

ii) If the patient is unstable after 48hrs of carbapenem and/or gentamycin, strongly consider resistant infection and replace regimen with chloramphenicol 25mg/kg IV

iii) If on any regimen other than chloramphenicol (which treats MRSA) add vancomycin (pharmacy dosing), clindamycin, or IV TMP-SMX

iv) Consider early empiric antifungal therapy if duration of neutropenia >7 days or continues to be clinically unstable despite appropriate fluids and empiric antibiotics: fluconazole 12mg/kg q24hrs IV

6.4 If documented focus of infection:

a) Therapy may be tailored to treat site of infection and pathogen identified

b) Directed antimicrobial therapy should be continued until ANC > 500 cells/mm3, afebrile for 48hrs, and patient has received full course of treatment for documented infection (ie 14 days for bacteremia, 10 days for UTI or pneumonia)

6.5 If unknown source of infection:

a) Continue empiric antibiotic until ANC >500 cells/mm3

b) If expect prolonged neutropenia (> 7 days), could consider discontinuing therapy if:
Afebrile at least 24-48 hours; treated with IV antibiotics at least 72 hours; well-appearing;
sterile blood cultures, any local infection under control, and evidence of bone marrow recovery

7. Antifungal Therapy

7.1 Basic Principles:

a) In general, antifungal therapy is not part of initial empiric treatment for neutropenic fever.

b) *Candida* (yeast) and *Aspergillus* (mold) are the most common fungal pathogens causing infection, although infection with mold is more common in patients with profound neutropenia (ANC<100 cells/mm^3) and fevers lasting beyond 7-10 days.

c) Strongly consider anti-mold therapy for patients with pulmonary compromise/infiltrates on chest X-ray not improving on appropriate antibiotics, persistent altered mental status with signs of meningitis/ increased ICP, or evidence of skin embolic phenomena with longer durations of neutropenia.

7.2 High Risk Patients:

a) Consider adding antifungal therapy if fever persists or recurs at 4-7 days.

i) 1st line: Fluconazole 12mg/kg q24hrs IV, PO acceptable alternative if IV not available

ii) If patient previously on fluconazole prophylaxis, concern for fluconazole-resistant *Candida* species (*C. krusei* or *C. glabrata*), or risk for mold: Amphotericin B 3mg/kg

q24hrs IV for suspected resistant yeast or 5mg/kg q24hrs for mold

b) Duration of therapy:

i) Documented fungal infection: Continue until ANC > 500 cells/mm^3 and patient has received full course of treatment for documented infection.

ii) Unknown source of fever: Continue empiric antifungal until resolution of fever and ANC>500 cells/ mm^3

iii) Documented or suspected mold therapy: Longer periods of therapy often warranted and ID specialist involvement is highly suggested.

7.3 Low Risk Patients

a) Empiric antifungal therapy is not recommended

8. Prophylaxis of Neutropenic Infections

8.1 Chemoprophylaxis

1. Chemoprophylaxis should be considered for all patients with expected duration of neutropenia of >7 days and/or ANC nadir of <100 cells/ mm

Specific patient populations who should receive prophylaxis:

a) Those receiving leukemia induction-remission or relapse-induction chemotherapy.

b) Those presenting with neutropenia or functional neutropenia due to the primary disease ie: leukemias or marrow-invasive lymphomas or other solid tumors

2. Bacterial prophylaxis: All chemoprophylaxis routinely should cover Gram negative rods including pseudomonas and should be oral and well tolerated. Gram positive coverage is not routinely indicated and has shown no additional benefit in several studies. However, some studies have demonstrated benefit of co-amoxiclavulanate alone, despite no anti-pseudomonal properties.

   Recommended regimens:

   a) Ciprofloxacin at 10-15mg/kg/dose q12 hrs PO
   b) Levofloxacin at 10mg/kg q12hrs if age <5 or q24hrs if age >5 PO
   c) Alternate: if quinolone not acceptable only: co-amoxiclavulanate

3. Fungal prophylaxis: Generally indicated for AML induction-remission or relapse-induction only. May be considered for individual patients with history of recurrent mucocutaneous candidiasis during prior cycles, but otherwise should not be routine.

Recommended regimen:

a) Fluconazole 3-6mg/kg/day PO, maximum dose 200mg/day (adult equivalent)

4. Antiviral prophylaxis: Prophylaxis for herpes simplex virus is indicated in patients receiving induction-remission therapy or relapse-remission therapy in AML. May also be considered for specific individuals with other malignancies who describe a history of recurrent oral or ano-genital ulcers (presumed HSV-1 or HSV-2 infected) prior to receiving chemotherapy, whether HIV-infected or not.

   Recommended regimen:
   a) Acyclovir 40mg/kg/day divided in 2 doses, or up to 400mg PO q12hrs.

8.2 Patient-based, family, and community interventions to reduce infection

Family members and caretakers should be educated to promote good hygiene practices in patients, family members, and all visiting community members at the home or hospital while a patient is undergoing cancer treatment.

1) Patients and care providers should wash hands after toileting and before preparing or eating food with soap and water
2) All visitors to the home or ward should wash hands with soap and water or alcohol before approaching patient
3) Patients with mucositis or extensive oral ulcers should not brush teeth with a brush, but should rather rinse their mouth thoroughly and regularly (twice daily or preferably after each meal) with toothpaste and treated water or an anti-septic mouth rinse if available
4) All drinking water or water used for oral care should be boiled for a minimum of 3 minutes or otherwise filtered/purified. A particle filter is not sufficient for killing viruses, so dilute bleach drops are recommended in the case the water is not boiled or

commercially purchased

5) Bed nets should be used when possible

6) All patients at risk for neutropenia should be fed a "modified neutropenic diet" including:
   a) Consuming no raw whole fruits or vegetables unless they have a peel or skin which can be removed, the skin and knife are first washed in safe water before cutting, and the child only handles the prepared fruit or vegetable section without the skin.
   b) All vegetables, starches, meats, and fishes should be thoroughly cooked, preferably stewed, steamed, or baked, and served hot immediately after preparing.
   c) Avoid consumption of street foods and foods previously cooked and left standing or reheated after some time.
   d) Dairy product, and fruit juices when possible, should be pasteurized rather than consumed fresh

7) Patients should be bathed regularly when at home and the hospital, taking care to avoid disturbing any canula. Ideally, chlorhexidine gluconate solution could be applied from neck to feet 2-3 times weekly. In the absence of prepared chlorhexidine solution, a dilute bleach bath (sodium hypochlorite or chlorox at 6% concentration) can be prepared using 10ml of the commercial 6% solution for every 4L of water used. The patient should be cleansed with cloths or sponges or should soak in the solution for 10 mins and then rinsed with fresh water after the bleach bath is completed. *keep undiluted bleach away from children's reach* (Seattle Childrens' Hospital Dermatology Recommendations)

8) Educate caretakers to perform symptom screens on all potential visiting family or community members, whether in the ward or home. This includes asking

about running nose, coughing, sneezing, fever, or rashes in any potential visitors before they enter the patient's area and requesting they visit once their symptoms have completely resolved in order to protect their child and other children.

8.3 Reduction of Health-care associated infections

1. All health care providers of any job description should wash hand with soap and water or alcohol gel prior to and after any contact with patients.
   a) All health care providers should wash hands/ alcohol cleanse between each patient in the case of rounds or when multiple children are being examined sequentially
   b) Soap and water must be used in the case of visible contamination to the hands or gloves, including contact with blood, vomitus, feces, or wound care.
   c) Soap and water strongly preferred when an examined child has diarrhea, as alcohol gels do not safely remove C. difficile spores or viral pathogens such as norovirus.
   d) Use of gloves is not an adequate replacement for hand washing/alcohol gel before and after patient contact.
2. All patients with diarrhea or respiratory viruses should attempt to be either cohorted with patients who have similar symptoms or isolated. In the case that isolation is not possible, move the patient to an area with good ventilation (respiratory viruses) and ask that all patient attendants care only for their child and not assist with others' care.
3. Bed nets should be provided when possible
4. A regular scheme of ward sanitizing should be

performed with a simple bleach solution and water.

a) After any patient discharge or death, the vacated bed/crib and surrounding floor area should be liberally cleansed before the next occupant

b) The ward may be routinely cleansed on a rotating basis. Patients and families should remove their belongings from the floor such that a thorough cleaning can be done, after which, any floor mats etc may be moved back.

5. Any health care workers with respiratory illnesses and/or fever should be encouraged to take sick leave or moved to non-patient care duties for the duration of rhinitis, cough, and sneezing.
6. At such time that patient spacing is possible and the ward is not open to the community, the use of face masks and gloves for all health care workers and attendants is recommended. Unfortunately, this intervention is not useful in the current cohorted situation, but may be considered in the future.
7. Care should be used to avoid blood stream infections by careful management of cannulas.

a) Wide and thorough cleansing of the skin (minimum of 10cm around the site) with alcohol or iodine should be performed prior to insertion of the canula.

b) All cannulas should be evaluated daily by medical/ nursing staff and replaced immediately if the bandage is loosened, soiled, or the surrounding skin is appearing inflamed

9. Appendix

9.1 Flow Diagram/Decision Tree for Initial Management

9.2 Flow Diagram/Decision Tree for Ongoing Antibiotic Management

9.3 Local Organisms, Antibiotic Resistance, and Discussion of Antibiotic Rationale

NOTES