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Management of Cancer in Low Income Countries

A guide to establishing cancer treatment - with a focus on pharmaceutical aspects of chemotherapy and handling of cytotoxic medicines

Experience from Kilimanjaro Christian Medical Centre, Moshi, Tanzania

Preface

About 15 years ago, DIFAEM was asked by Kilimanjaro Christian Medical Centre (KCMC) in Moshi, Tanzania, for support of cytotoxic medicines for the treatment of patients with AIDS related Kaposi sarcoma.

Up to then, the necessary cytotoxic medicines were not available at KCMC. DIFAEM started to provide bleomycin, doxorubicin and vincristine for specific cases and indications such as Kaposi sarcoma and later choriocarcinoma / gestational trophoblastic disease. Alongside the procurement and shipment of cytotoxic medicines to Tanzania, the question arose, how to make sure that these toxic medicines will be handled and administered properly. There were basically two answers to this question: To stop supplying the medicines because we knew that the local staff were not trained properly in handling cytotoxic medicines and feedback evaluations emphasized their lack of knowledge. The other option was to invest in training, capacity building and supervision of local staff to meet the standards of safe handling of cytotoxic medicines. DIFAEM decided to build up capacity and the project “Safe Handling of Cytotoxic Medicines” at KCMC was initiated.

Before launching this project, chemotherapies had been prepared by medical staff with poor or no personal protection in ward rooms, at the bedside, or in the outpatient setting just beside the patient. Together with our partners, we introduced training to pharmaceutical staff members on storing and preparing of cytotoxic medicines. Furthermore, we introduced the use of adequate Personal Protective Equipment (PPE). At the end of 2016, KCMC launched a new Cancer Care Centre. All rules and SOPs of “Safe Handling of Cytotoxic Medicines” that had been developed until then were shifted to this new centre. A safety cabinet became the most important tool for safe handling during preparation.

With this guide, we would like to share our experiences with decision makers who plan to set up a cancer treatment facility.

Tuebingen / Moshi, March 2020

Content

List of abbreviations

5-FU *5-Fluorouracil*

abl *Abelson murine leukemia viral oncogene*

AFP *Alpha-fetoprotein*

ALAT *Alanine aminotransferase*

ASAT *Aspartate aminotransferase*

bcr *breakpoint cluster region*

CA *Cancer antigen*

CEA *Carcinoembryonic antigen*

CMV *Cytomegalovirus*

CRP *C-reactive protein*

CSC *cytotoxic safety cabinet*

CT scan *computed tomography scan*

DNA *Deoxyribonucleic acid*

EBV *Epstein-Barr-virus*

EML *WHO Model List of Essential Medicines*

ESR *Erythrocyte sedimentation rate*

G-CSF *Granulocyte-colony stimulating factor*

HEPA *High-efficiency particulate air*

HIV *Human immunodeficieny virus*

HPV *Human papillomavirus*

INR *International normalized ratio*

IV *Intravenous*

KCMC *Kilimanjaro Christian Medical Centre*

LDH *Lactate dehydrogenase*

LIC *Low Income Country*

NCD *Non-communicable disease*

NGO *Non-governmental organization*

PCR *Polymerase chain reaction*

PO *per os (by mouth)*

PPE *Personal Protective Equipment*

PSA *Prostate-specific antigen*

PTT *Partial thromboplastin time*

SOP *Standard Operation Procedure, Standard Operating Procedure*

TB *Tuberculosis*

TLM *Their Lives Matter*

WHO *World Health Organization*

1 INTRODUCTION

1.1 Background

Cancer is one of the greatest public health challenges worldwide. The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. Cancer has a broad social impact in addition to the individual human tragedies, including productivity losses for cancer patients and their family caregivers.

Collective efforts in diagnosis and treatment have resulted in great improvements in survival rates. However, it continues to vary considerably by type of cancer and geographic region. According to the World Health Organization (WHO, 2018), over 80% of children diagnosed with cancer in high resource countries are cured of the disease, in contrast to rates as low as 10% among children diagnosed in Low and Middle Income Countries. These countries have almost 80% of the burden (as measured by disability-adjusted life years) but less than 5% share of global resources for combating cancer.

Non-Communicable Diseases (NCDs) and especially cancer are more in focus these days; cancer is more often diagnosed, and more cancer patients seek attention in hospitals. Major reasons are the ageing population, malignancies related to chronic infections such as HPV, hepatitis and HIV as well as life style changes and environmental pollution.

The more patients are diagnosed with cancer, the greater is the pressure on hospitals to address this challenge by introducing consistent cancer management. Due to efforts being directed to Communicable Diseases over the years, there has been less attention to NCDs in Low Income Countries (LICs), cancer in particular. It is thus that most hospitals are ill equipped to meet the increasing number of patients diagnosed with cancer, they lack resources and have limited staff to successfully meet the demand. Collaborative efforts and partnerships with international organizations have shown success in closing the gaps at KCMC Cancer Care Centre.

1.2 Objective and approach of this guide

The aim of this guide is not to display a comprehensive overview about global cancer care in detail – rather the authors aim to focus on challenges and questions prior to the establishment of cancer management and therapy in hospitals. The document targets decision makers and technical staff planning to start or to improve already existing cancer management.

To start cancer management in a hospital from the beginning and to run a cancer care unit are demanding tasks as well as complex medical and logistic challenges.

Objective: Decision makers in hospitals of Low Income Countries and others involved will receive information on the key points to consider and on the challenges when starting a cancer treatment facility.

A strong focus of this document is the pharmaceutical management of chemotherapy.

The guide intends to:

- assist hospitals in the necessary preparatory planning
- point out that the most important prerequisites must be met
- define a minimum of staff members and the range of specialists' training
- create awareness that sufficient budgeting is necessary
- create awareness that chemotherapy is a toxic therapy which needs safe handling measures
- create awareness that the preparation of cytotoxic medicines is much more demanding than the handling of other medicines
- share our experience, esp. in the field of pharmaceutical management of chemotherapy

Cancer has become an important field within the NCDs. Many hospitals are under pressure to address the growing numbers of patients by offering cancer care services. A hospital may also be better recognized by the public and by politicians if an oncology unit is planned or already available. But this also brings its challenges – monetary and loss of reputation - if the prerequisites are not met and the unit is not working properly.

Therefore, the starting point should be an analysis of the current state of cancer care in the hospital and the country as a whole. The following questions can serve as a guide.

A tool for structured documentation is attached as annex 1.

Hospital level:

- Is there an evident need/demand for a cancer care centre in the respective region? If yes, which type of cancer care services (medication incl. chemotherapy, surgery, radiation) should be prioritized and are feasible to start with?
- Is a sustainable financial source available? Which sources can be used to finance the new cancer treatment facility (government, faith based donors, NGOs, foundations, insurances etc.)?
- Will it be possible to acquire the necessary staff to deal with cancer diseases in an appropriate manner – oncologists, nurses with special training, specifically trained pharmaceutical and laboratory staff?
- Does the budget include continuing payment of staff in order to make sure that good quality services can be secured and follow up training will be possible?
- Does the budget include necessary specific equipment e.g. safety cabinet, and special consumables as well as maintenance and building infrastructure?

Country level:

- Which cancer entities are most prevalent in the region/country?
- Does the government support cancer care?
- Is a national cancer or NCD strategy available and implemented?
- Does a national treatment guideline for cancer exist?
- Does a central medical store provide cancer medicines?
- Is a health insurance system established – and does this cover chemotherapy as well?
- Which training programmes are available for staff involved in cancer management?
- Are there other cancer care centres in the country to facilitate cooperation and exchange? How many and where are they located? Which cancer care services do they offer? Are there possibilities to complement each other´s services?

The state of the wider health system needs to be considered as well. How does the Public Health Care system work? Are there community based services and what is the referral pattern in any given health system? These are important questions to answer, before getting into cancer care.

In addition, the health financing system is crucial to clarify. Nowhere can patients pay for cancer care out of pocket. So there must be a plan with the Ministry of Health for the provision of cancer care and the support of investigations, medicines and follow up care.

This guide is geared towards hospitals that are part of a national cancer care programme and who provide, or plan to provide, cancer care in the near future.

2 CLINICAL ASPECTS OF CANCER MANAGEMENT

2.1 Introduction

The word ”cancer” describes a large heterogeneous group of different disease entities. It ranges from non-aggressive and slow progressing tumours that might not need any directed therapy immediately to highly aggressive and fast proliferating tumours that need to be promptly addressed to avoid rapid progress and eventually death. The common factor of all entities is the cancer cells’ inability to regulate proliferation in a controlled way.

The treatment approach is determined by the type of cancer and the stage of the tumour, which describes its level of dissemination in the body. In general, the treatment modalities are surgery, radiation and/or medication (chemotherapy, antibody therapy, immuno-therapy etc.). Some entities demand only a single treatment option while others need all three of them. Combination of radiation and chemotherapy is common and often chemotherapy is combined with surgery to reduce the tumour volume before operation or to avoid dissemination of tumour cells after surgery.

The more complex a treatment plan is, the more specialists need to be involved and coordinated. This coordinating role is normally taken by oncologists who cooperate with radiographers, surgeons, radiation specialists and other health professionals. In both developed and developing countries, the extent of diagnostic and treatment capabilities at any given facility influences the scope of cancer service.

Therefore, it is crucial to evaluate the capabilities of cancer treatment facilities beforehand and determine what type of treatment can be offered depending on facilities, medication and the scope and training of personnel.

A hospital with a skilled surgeon and oncologist might be well capable of treating colon cancer and breast cancer, but will likely not be in a position to treat aggressive lymphoma or leukaemia without a haematologist, a blood bank and a specialized laboratory. And vice versa, if a hospital lacks skilled surgical capabilities, the treatment outcome of colon or breast cancer might be unfavourable even if all medication and radiation modalities are present.

Cooperation with other facilities (within a region or country) can be helpful to close service gaps and extend the scope of services.

2.2 Cancer in tropical countries / Low Income Countries

The reflection about cancer services in Low Income Countries is mostly related to countries that are geographically in the tropical belt. This implies not only limited (material and monetary) resources for cancer treatment, but also the influence of recurrent infections like malaria, viral infections and a high prevalence of HIV. As these factors influence the development of cancer cells, the patterns of cancer types differ from developed and mostly “Northern” countries.

Entities that occur rarely in Europe or the United States are seen commonly in tropical countries, including the HIV and herpesvirus-related Kaposi sarcoma, Burkitt’s lymphoma in endemic malaria regions, hepatitis-related hepatocellular carcinoma, and HPV-associated cervical cancer. The latter represents the most common cancer entity in women in East Africa, for example.

Other differences are due to the genetic diversity and environment of the respective population. Prostate cancer is known to be more aggressive in African men than in Caucasians and tends to be diagnosed in younger years, while lung cancer is rare in Africans and belongs to the most common

entities among Caucasians. Many cancers are diagnosed at earlier ages in tropical LICs than in developed countries.

The interplay of genetics and environmental factors is also important in respect of lower standards of occupational health, safety and environmental protection in developing countries. The unprotected use of pesticides and the lack of appropriate protective garments in mines are contributing to a higher prevalence of preventable cancer diseases.

Another aspect of cancer care in Low Income Countries is the lower level of health education. Many misconceptions about cancer, limited knowledge about the nature of cancerous tumours, and the widespread use of traditional medicine and spiritual healing contribute to late stage presentation. The majority of patients present with advanced and often non-curable tumours. Once a patient has started therapy, adherence to advice and loss to follow up are common challenges.

Due to the late stage presentation, palliative care plays an important role in these settings and should be implemented and supported in a comprehensive way. This will relieve patients from unnecessary suffering.

The linkage between late stage presentation, limited knowledge and misconceptions, prevalent infections, and weak health systems makes cancer care in these settings challenging. As every region and every country has different prerequisites and challenges for the establishment of cancer services, this document can only contribute to general reflections.

The most important consideration is priority setting:

- Who will receive cancer directed treatment (chemotherapy, radiation, surgery) and who will receive palliation (symptom-relief, palliative care)?
- What is the intended scope of the cancer service depending on available resources and demand?

These questions must be discussed on a national level with the Ministry of Health and other national/local health care providers. Once determined what services are given at what level of care, one can develop a strategy and operational plans in how to make it a reality.

2.3 Preparations of cancer care in a hospital in Low Income Countries

2.3.1 Staffing

Human resources are the basis for any new development in hospitals and early consideration of training of specialized health professionals is necessary, given the fact that training and specialisation of doctors can take several years.

Depending on the desired scope of a new cancer care facility, it might be sufficient to train existing specialized doctors like gynaecologists or urologists in short programmes for oncology, if only certain entities should be addressed. If a comprehensive oncology service is desired, a fully specialized doctor in Oncology is needed. The master and fellowship programmes differ from country to country. Some countries offer programmes that combine Medical Oncology and Haematology, others offer Clinical and Radiation Oncology, or Haematology and Medical Oncology as separate specialisations. Also, the years of training will range from 3 up to 6 years.

Specialist doctors are important for a cancer centre, but it is equally important to consider other professionals such as nurses, who will administer chemotherapies, pharmacists who prepare

chemotherapies and social workers who deal with socio-economic implications such as fee exemptions and payment plans. These staff are equally important for a cancer department to run successfully.

Furthermore, as doctors tend to be the leading persons in departments, specifically trained administrative assistants are highly desirable. This is particularly important in low resource settings where specialized doctors are rare and their time should be dedicated to treatment as much as possible.

Also supporting staff working on procurement, cleaning, waste disposal and other related fields need to have special training to fulfil requirements that are linked to the field of oncology and chemotherapy handling and logistics.

To address the growing burden of cancer diseases, it is essential to have public health specialists for health education, early detection programmes, and palliative care workers to care for those who are incurable. The latter will pose the vast majority of patients attending a cancer care facility in any given low resource setting.

2.3.2 Diagnostics

Having access to diagnostic means is a necessary prerequisite for a cancer treatment facility. Pathology services as well as radiology services are indispensable. The extent of the diagnostic possibilities influences the treatment options. For example if a cancer treatment facility wants to offer antibody therapy, immunohistochemistry (e.g. CD20 for rituximab, Her2neu for trastuzumab etc.) must be available; for the treatment of CML patients with free tyrosine-kinase-inhibitors (see below "Targeted therapies"), PCR diagnostics are needed.

A list of required diagnostic laboratory methods and parameters at different levels of cancer care is available in annex 4.

It will be important to link basic and advanced facilities. Today this is easily possible and an oncologist at an advanced facility can easily supervise base facilities that will be involved in follow up care and also in the identification of suspect cases.

Therefore, not all diagnostic means need to be offered at the treatment facility itself. Availability through cooperation with far and nearby institutions (both private and governmental or faith based) are possible and will in most cases be the first step during the implementation phase.

Whenever possible, it is advisable to thoroughly evaluate the existing capacities within the hospital. As cancer care facilities are mostly based in large institutions like university hospitals or referral and specialized hospitals, it is very likely that many facilities are already equipped with diagnostic tools and machines that can be shared. Web-based alternatives offer solutions for facilities with limited number of professional staff, e.g. telepathology, teleradiology and online-tumour boards. The basis for the implementation is mostly cooperation with overseas universities or professional health societies.

2.3.3 Chemotherapy (see also chapter 3)

As the aim of this guide concerns chemotherapy, the following recommendations are focussed on this treatment modality and radiation and surgery will not be discussed in detail.

The field of oncology has grown and changed dramatically over the last few years. However, it will be unlikely to have all modern medications available from the beginning. Even established cancer medicines might be not available in every region/country due to lack of distributors, logistic issues, registration and/or bureaucratic obstacles.

It is advisable to first focus on simple non-complex treatment modalities to gain experience and to motivate staff for further development and innovations once the implementation phase of medical oncology/chemotherapy treatment has been achieved successfully.

Therefore, there is a need to establish a stepwise approach to cancer treatment. Develop a referral centre with specialist personnel and at the same time work with basic health facilities who can support follow up and the identification of suspect cases.

It is best to start chemotherapy programmes with well established and easy to administer protocols.

Examples of non-complex chemotherapy protocols are:

- simplified protocol for Burkitt´s Lymphoma in children: methotrexate IV and IT, vincristine IV, cyclophosphamide IV
- (neo-)adjuvant (perioperative) Breast Cancer treatment protocols: doxorubicin IV, cyclophosphamide IV and paclitaxel IV
- for endemic Kaposi Sarcoma: vincristine IV and bleomycin IV or paclitaxel IV monotherapy

It is important for staff to gain confidence in what they are doing and also for patients and their families to gain confidence in the treatment. As the risk of infection is much higher in Low Income Countries than in Western settings, there is also a need to accompany such a programme with intensive health education and community sensitisation so that patients can live in their respective communities without risk of stigma and discrimination.

Further advanced treatments can be introduced as training and confidence levels rise, such as:

- Adjuvant therapy for Colon Cancer: 5-FU IV or capecitabine PO and oxaliplatin IV and leucovorin IV

If a treatment facility aims for more complex therapies that are often accompanied by higher likelihood of side effects, the necessary medications to address those side effects need to be stocked as well (e.g. G-CSF to avoid neutropenic complications, broad spectrum antibiotics for neutropenic fever, potent antiemetics for platinum containing chemotherapies etc.).

2.3.4 Targeted therapies / antibodies

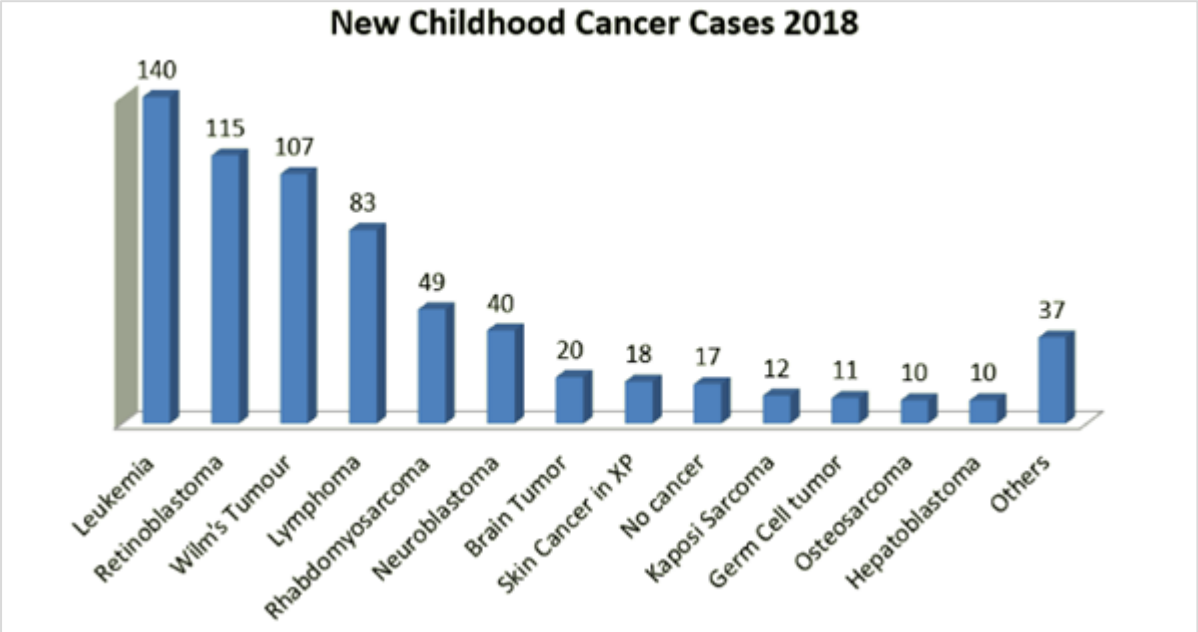
Antibody treatment like rituximab or trastuzumab, and their biosimilars, are currently available in many developing countries. These medications are effective and have fewer side effects than cytotoxic medication, but the high market prices limit the use to those who can afford to pay or for insured patients. Special precautions must be given to maintain cold chains for these sensitive antibodies.

Modern treatment options are expensive and often unavailable in low resource settings but through humanitarian aid organizations, a number of state-of-the-art medications are available on donation basis or for discount prices, depending on the country.

2.4 Paediatric Oncology

Paediatric Oncology needs special knowledge and experience. In case of interest we advise readers to contact the Tanzanian based NGO "WeAreTLM" (TLM = Their Lives Matter), www.wearetlm.org, dedicated in providing free and curative care for all children with cancer in Tanzania, based at Muhimbili National Hospital in Dar-es-salaam. All treatment offered by TLM is provided entirely free of charge.

The most common conditions seen in 2018 are as follows:



Children with cancer should be managed within a paediatric ward/service if at all possible. Some conditions are extremely complicated to treat and require extensive medical services and years of experience. However other conditions are relatively easy to manage given a number of simple resources.

With this in mind TLM are working with the government to support as many clinical care sites as possible. This allows those children with straight forward conditions to be managed close to home. In addition, those requiring specialist care will rapidly access this service through the growing network.

Four different levels of care for childhood cancer treatment which have been identified range from quaternary or the highest level of comprehensive sub-specialized treatment; to the lowest level centres who are trained to suspect, stabilize and rapidly transfer children appropriately. Implementation of this model will ensure that children in need are fast-tracked to the most appropriate treatment centres avoiding current systematic referral delays. In many cases children will access cancer care closer to their homes and families.

The four levels of care and support are as follows:

Quaternary Care (Hub)

This is the control centre or Hub of the entire network and will provide the following to all participating sites either directly or using IT technology:

- Central Pathology Services for children as required to confirm pre-treatment diagnosis.
- Specialist procurement of chemotherapy, chemotherapy-protection, diagnostic and supportive care equipment and consumables for patients.
- Daily (as required) and weekly (regular) specialist case conference support to each individual centre.
- Centralised development of all treatment protocols.
- Provision of a National Paediatric Oncology Electronical Medical Record System for all centres.
- Inpatient services for all children who require complex sub-specialist Oncology care.
- Training for doctors (MSc in Paediatric Oncology), nurses (Clinical Oncology Nurse Training Certificate), Pharmacists, Laboratory technicians, Dieticians, and Psychosocial support staff.
- Access to the innovative SAFE Chemo Highly Automated Chemotherapy Prescribing Platform.
- National awareness campaigns regarding early warning signs and symptoms of childhood cancer.
- Nationwide transport coordination and support for rapid referral of sick children across the network.
- Access to all medical guidelines, pocket guides, nutritional recipes, Play Therapy manuals and storybooks created by WeAreTLM.

Tertiary Care

These care centres will provide Paediatric Oncology for all childhood cancer diagnoses unless Quaternary (Hub) level care is required. They will rely on the Hub for system strengthening, procurement and some pathology services (until their labs have been sufficiently strengthened). They will act as a primary point of contact for all regional Secondary and Primary Level Care Facilities. These are University Hospitals based at the six main zones around Tanzania.

Secondary Care

All regional centres with sufficient capacity and interest will be linked into this network to treat pre-agreed ‘easy to treat’ cancers and also work with other higher-level centres for follow up cases. They will also provide support to Primary Level Facilities.

Primary Care

These centres will be responsible for suspecting, stabilizing and safely and rapidly transferring any child suspected of a childhood malignancy to the appropriate regional or national centre where definitive treatment will be available. They will be a vital point of palliative care at a community level for children where curative efforts are unsuccessful. These centres will also help with awareness campaigns in the community on Early Warning Signs of childhood cancer.

National Children's cancer Guidelines are available on request including guidelines on:

- Chemotherapy treatment
- Supportive care concerns
- Parent support

Please let TLM know if your site might be interested in participating.

3 PHARMACEUTICAL ASPECTS OF CANCER MEDICINES

3.1 Introduction

Cancer medicines comprise cytotoxic medicines, targeted therapies, immunomodulators, hormones and antihormones. A number of cancer medicines belong to the "essential medicines" according to WHO, 35 different products are listed in the current Essential Medicines List (EML) (WHO 2019).

"Chemotherapy" in the context of cancer care means treatment with cytotoxic medicines. This is often the mainstay of cancer-directed treatment.

It is important to know and to be aware that cytotoxic medicines are ***toxic*** medicines themselves.

Cytotoxic medicines are classified as CMR medicines:

C = Carcinogenic, M = Mutagenic, R = Reprotoxic.

Carcinogenic chemicals can cause or promote cancer diseases. Mutagenic chemicals can cause genetic mutations. Reprotoxic chemicals can harm the reproductive process.

Cytotoxic medicines belong to the most toxic category of substance classes into which hazardous chemicals can be subdivided.

Cytotoxics interact with DNA and can cause harm also to healthy body cells. Therefore, special precautions are required while handling cytotoxic medicines. Spills of cytotoxics must be avoided. If they occur, they must be documented and reported.

Spills of cytotoxic medicines cause contamination with toxic material which may harm staff preparing and administering medication, caregivers, patients and others. No regulatory dosage limits are defined like for other chemicals. Any contamination and contact with the skin, airways, mucous membranes and eyes of the human body must be strictly avoided as well as contamination of the environment.

Examples of contamination and spills during preparation

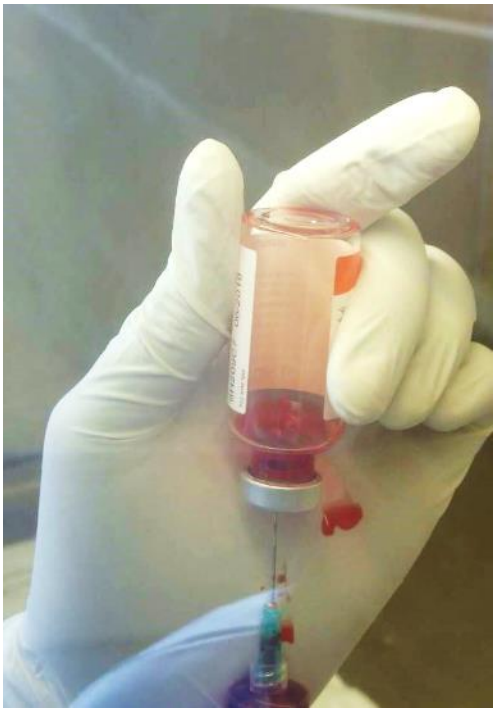


Figure 1: Only double gloving provides protection of the skin (© Peter Vollmer)

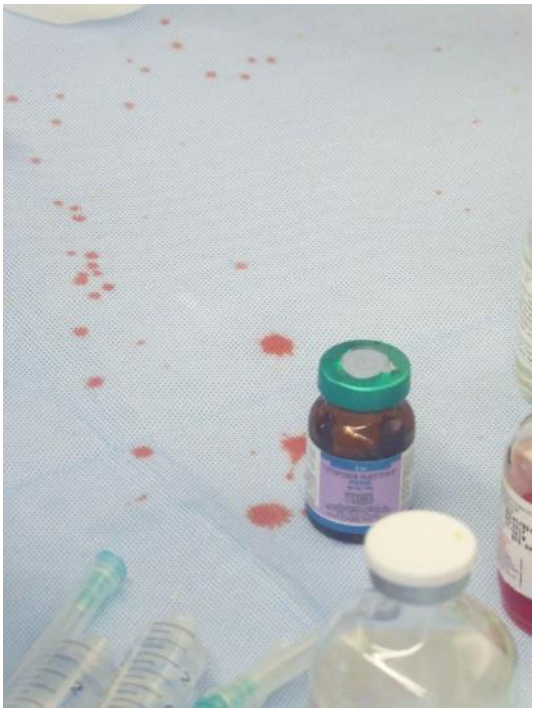


Figure 2: Special drape absorbs cytotoxic spill - this picture shows a spill from a pressurized syringe (© Peter Vollmer)

Figure 3: Visible contamination of vials (© Peter Vollmer)

3.2 Availability and procurement of cancer medicines

A good cancer programme should aim to have a constant supply of all necessary cancer medicines in sufficient quantities.

In preparation of any programme, one must decide in a stepwise fashion which cases the programme can handle and which diseases must be referred to a higher level.

Once the level of care has been decided then it is necessary to ensure a constant supply of all those medications that are part of the programme.

Because of stock outs, the patient's treatment protocol, and hence the effectiveness of therapy, is at risk. Once patients buy such medicines from private pharmacies, it will be at much higher cost. At the same time, the quality of the medicines cannot be guaranteed.

Cytotoxic medicines are expensive, prices for therapies like rituximab are extraordinarily high. This is true for the original products as well as for biosimilars (highly similar to another already approved biological medicine). Ideally, the hospital should run an Oncology Pharmacy where an experienced pharmacist purchases good quality cancer medicines from reliable wholesalers or pharmaceutical companies.

Our experience from Tanzania shows that it is a challenge to get all the necessary cancer medicines from local sources only - even for big hospitals in major cities. Prices for cancer medicines vary a lot in different places, e.g. DIFAEM could provide quite a number of European quality-assured cancer medicines to KCMC for lower prices than those available on the Tanzanian market.

Chemotherapy has a big financial impact on the running costs of a cancer unit in a hospital. A system has to be in place to relieve the patients from any significant out of pocket expenses.

Some organizations and companies provide donations for a selected range of cancer medicines or offer them on a discount rate. The Max Foundation (www.themaxfoundation.org) delivers free tyrosine-kinase-inhibitors for several indications, Clinton Health Initiative (www.clintonhealthaccess.org) offers a set of frequently used chemotherapy for reduced prices in many African countries.

However, as one develops a cancer treatment centre, one needs to look at sustainability and medicine donations can only be a temporary way of care. Therefore, further lobbying and advocacy is needed for lowering prices on such medicines and to generate respective resources for the treatment.

Another strategy is to pool procurement of cancer medicines in any given region. Once a number of Cancer Centres can bring their orders together, it will reduce the prices and at the same time can ensure a good standard of quality. However, this demands a high standard of cooperation and alignment between different centres.

Cancer medicines might be purchased locally. But quality checks of cancer medicines in most African countries are almost impossible because of lack of specific technical equipment and limited capacities at the local Medicine Regulatory Authorities. This can be an open door for substandard or even falsified products.

Therefore, the selection of reliable, internationally well-known suppliers is the key, even if the products are more expensive compared to other options. The selection of a generic (or biosimilar) alternative may lower the cost.

The pharmacist in charge needs to be skilled in this special procurement. He/she needs to be trained on the criteria to identify or suspect a substandard or falsified product including insufficient packing, poor labelling, missing important elements like manufacturing company, discrepancies in batch/expiry date seen outside the package and at the blister, suspect colour of the substance in the vial or of the tablet among other. A list with criteria for visual inspection of sensitive cancer medicines can be provided by DIFAEM upon request.

An experience that underlines this critical visual inspection: During preparation of a cyclophosphamide infusion we found vials with a melted yellow-brownish mass instead of the usual white crystalline powder. Asking the supplying pharmacist in charge about the situation, he replied that this happens sometimes, but has no consequence for the effectiveness. Some vials were taken to Germany for quality analysis and the laboratory could prove that these vials contained only 20 % of the declared active ingredient. We don't think the product had been falsified, the reason might have been high temperature during transport. Cyclophosphamide is temperature sensitive and should be kept not above 25°C. Thus, strong advice followed to this hospital and to the supplier to guarantee accurate transport and storage conditions as well as visual inspection on arrival of the consignment.

Transport and storage of cytotoxic medicines need to strictly follow the directions of the manufacturer. Similar to the procurement of vaccines, one needs to keep the cold chain if indicated. Exceeding the upper temperature limit may harm or even destroy cytotoxic agents which eventually results in treatment failure.

3.3 Sterility of prepared cytotoxic medicines

The quality of the prepared cytotoxic medicines is crucial; all parenteral preparations have to be sterile. Similar to the rules in an operating room, sterile procedures in preparing cytotoxic medicines are a must.

Preparations contaminated by microorganisms put the patients at high risk of getting serious, life-threatening infections.

All staff preparing cytotoxic medicines must be well trained in aseptic technique. Cytotoxic medicines must be prepared in a separated preparation room with an anteroom. A cytotoxic safety cabinet has to be used so that contamination can be avoided at all cost.

In High Income Countries the preparation of cytotoxic medicines is performed in so-called "clean rooms" only (rooms with filtered air and controlled environment to avoid contamination by germs). A cytotoxic safety cabinet or an isolator is necessary in order to prevent contamination of the product and to protect staff against contamination with the drug. Staff must be trained and supervised and the environment kept extremely clean.

Critical awareness and well-defined handling procedures are necessary to assure that all preparations are sterile and meet high quality standards.

4 SAFE HANDLING OF CYTOTOXIC MEDICINES / SAFE HANDLING CONCEPT

4.1 Handling cytotoxic medicines - risk assessment

All persons handling along the total supply and application chain are at risk of contamination. This includes:

- Logistical staff in the medicine supply chain management in case of improper packaging, leakage or damage.
- Pharmaceutical staff and nurses are at risk when preparing/handling these medicines without proper protection.
- Nurses and doctors are at risk when administering cytotoxic medicines.
- The patients might be in danger in case of unsterile preparations, improper handling or in case of extravasation (severe irritation or tissue damage may happen).
- Cleaning staff and waste-disposal staff, e.g. those putting waste into the incinerator, are at risk of contamination.

4.2 Measures to control the risk – safe handling

Strict safety regulations must be implemented and followed.

A "**Safe Handling of Cytotoxic Medicines Training**" and the implementation of a "**Safe Handling Concept**" are needed. Non-cytotoxics, such as antibodies, may also need special handling and training. Standard Operation Procedures (SOPs) have to be implemented for all key procedures. Continued update-training and monitoring is important, too. A model list of SOPS can be found as annex 2.

All staff involved in any handling of cytotoxic medicines should attend a "Safe Handling of Cytotoxic Medicines Training". Most important is to create awareness, to give all necessary information and to train practically for all procedures related to safe handling.

A "Safe Handling Concept" should be established which includes SOPs for all steps from the receipt of consignments, storage, preparation, administration and handling of spills to the management of cytotoxic wastes. The aim is to implement all steps of cytotoxic handling in a professional way under safety conditions to minimize all sources of contamination and contact with the human body.

Our experience is that it needs time and effort on all sides to build up such a concept, starting with creating awareness, spreading the necessary information, and then implementing in daily practice (most important!). It is essential to have all the key staff "on board".

One needs to look at the following issues:

Key aspects of a Safe Handling Concept:

4.2.1 Transport and storage of cytotoxic medicines

4.2.2 Safe handling during preparation of cytotoxic medicines

4.2.3 Safe handling during administration of cytotoxic medicines

4.2.4 Cytotoxic spills/Use of spill kits

4.2.5 Cytotoxic waste management

4.2.1 Transport and storage

Transport and storage must always be performed strictly as directed by the manufacturer. All handling has to be done cautiously. Packaging must be kept safe during the transport. All medicines must be shipped and handled in the original packaging.

Temperature checks should be performed according to the requirements of the manufacturer and the cold chain must be kept where necessary.

Clear documentation should accompany all transport and storage, so it is documented where the medicine comes from, who has handled it, and at what time.

Any broken package must be reported and documented (picture) and reported to the next higher level of responsibility.

4.2.2 Safe handling during preparation

Cytotoxic medicines should be prepared only by specifically trained pharmacists or pharmacy technicians in a separate preparation room with an anteroom/a sluice. Staff must wear Personal Protective Equipment (PPE).

In this context, to prepare cytotoxic medicines means to use liquid parenteral medicines or to reconstitute solutions from sterile dry powders in vials. Cytotoxic medicines must be prepared for each patient separately according to the individually prescribed doses. The method of preparation should be described in an approved master protocol document that is available at all times. The right amount of dilution and the correct amount of solution must be used. The documentation of each preparation must be clearly stated.

Use Luer Lock syringes (see c.) to prepare the medicines.

The final preparations are usually contained in Luer Lock syringes, in infusion bottles/bags or in containers for long-term infusion and should be administered without delay.

We found that infusion bottles without rubber stopper were used. The wall of the bottles was punched to inject the cytotoxic medicine. The resulting hole couldn't be closed again tightly or remained wide open, so sterility of the chemotherapy couldn't be guaranteed anymore and spills happened during administration.

To use infusion bags with two ports (one for adding cytotoxic medicines, the other as infusion port) is most appropriate.

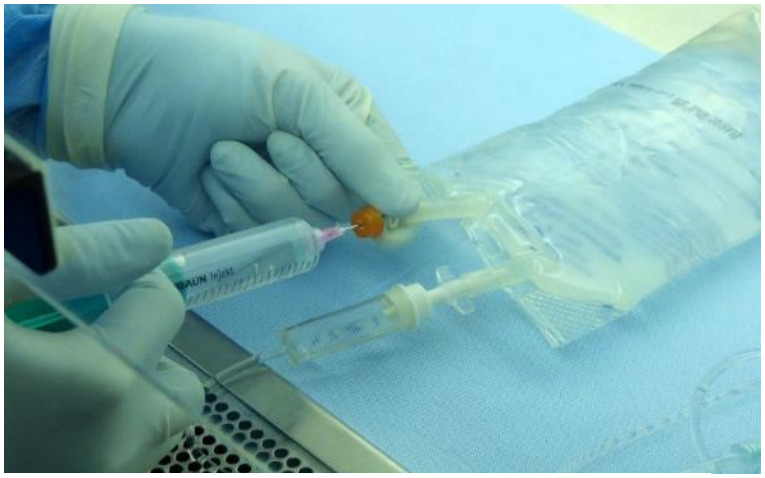


Figure 4: Infusion bag with two ports (© Peter Vollmer)

What is state of the art in preparing cytotoxic medicines?

a. To use of a cytotoxic safety cabinet (CSC) with HEPA filters and laminar air flow.

A CSC provides optimal protection of the preparing staff, of the product and of the environment.

Figure 5: Cytotoxic safety cabinet (CSC) with HEPA filters and laminar air flow (© Peter Vollmer)

All particulate contamination from the preparation procedures is kept within the CSC and filtered by the HEPA (High Efficiency Particulate Air) filters. The HEPA filters and the laminar air flow create clean room conditions inside the CSC. In addition, aseptic technique has to be applied to make sure that all preparations are sterile.

The appropriate type of safety cabinet for the preparation of cytotoxic medicines is a cytotoxic safety cabinet with a third HEPA filter directly below the working area.

A good quality CSC costs about 15,000 USD.

Every CSC must be serviced at least once a year by a specifically trained and experienced technician using the correct equipment (air velocity measurement tool, particle generator, particle counter). It can be a real challenge to identify a qualified technician with the necessary tools in Low Income Countries, but it is necessary for the quality of the preparations.

The following experience shows how important it is to have a proper working safety cabinet: We found a very old donated safety cabinet in a Cancer Care Centre looking suspicious because the surface of the pre-filter was almost black in colour – an indication that it had not been exchanged for a long time. A service check was performed which showed that even the main blower was not working properly. So, there was no more protection, it was even dangerous to use this safety cabinet.

Is a safety cabinet mandatory for the preparation of cytotoxic medicines?

A cytotoxic safety cabinet is state of the art and international standard in the preparation of cytotoxic medicines.

To guarantee high quality chemotherapies this investment is necessary. If there is no other way, preparation of chemotherapies may be started without a CSC, but has to be done in a suitable separate room with an anteroom (to change clothes and to put on PPE) and without any further activities inside. The following points b. to d. have to be followed rigorously from the beginning. The aim must be to implement a CSC as soon as possible if not available from the beginning.

b. To use Personal Protective Equipment (PPE) properly.

Figure 6: Correct PPE (© Peter Vollmer)

All staff involved in the preparation procedure need to wear impervious protective gowns, double gloving or purpose made gloves, special respiratory protection masks, filtering out effectively dust and aerosols, safety goggles with side protection or face shield, and hair covering. A detailed list of PPE is attached (annex 3).

PPE is an effective way to protect skin, airways and eyes from any contact with cytotoxics.

As PPE is expensive, a SOP has to be established with a clear description of doffing and donning. It must also be clearly indicated which parts of the PPE (e.g. gowns and respiratory protection masks) can be reused and if so, how often. The protocol must state which PPE products have to be used for the preparation and administration of each cytotoxic item (e.g. the preparing person should use special Chemo-gloves, the administering staff double gloving with usual gloves because those have to be changed frequently).

c. For all cytotoxic medicines preparations except intrathecal preparations it is mandatory to use Luer Lock syringes to minimize the risk of separation of connections.

Figure 7: Luer Lock syringe with needle

The big advantage of this type of syringe is that the needle cannot disconnect from the syringe which avoids big spills/contamination (example see picture on page 14) because it is screwed on the syringe.

The following additional protective materials increase safety and make the preparation work easier:

Use wide-bore needles (18G), air venting devices and absorbing two-layer drapes to cover the surface of the work area within the safety cabinet.

d. To apply aseptic technique.

Aseptic technique maintains sterility of the product by providing a barrier between the microorganisms in the environment and the product. Aseptic technique includes "no touch" technique avoiding touching any part of the sterile equipment like needles, tips of syringes and sterile connections. A prerequisite of aseptic technique is to use sterile equipment only inside the safety cabinet. **Aseptic technique can be done only by a two-person team: a preparing person and an assisting person.** The preparing person must remain with her/his sterile gloved hands in the safety cabinet, the assisting person has to hand over all necessary materials in an aseptic way.

We found in several places that professionals had some theoretical knowledge about asepsis but couldn't apply it. E.g. the preparing pharmacist went out of the safety cabinet to collect medicines and consumables for the next preparations touching door handles etc. Then he continued preparing in the safety cabinet wearing the same, now highly contaminated, gloves.

4.2.3 Safe handling during administration

The administration of cytotoxic medicines always has to be done under safety conditions.

The person administering them should wear PPE and should apply aseptic technique to maintain sterility. Contamination of the patient and the surroundings by cytotoxics should be avoided. For cases of extravasation an SOP with all steps to be followed immediately needs to be implemented and known. An extravasation kit has to be accessible close to the point of accident.

4.2.4 Cytotoxic spills / Use of spill kit

Spills of concentrated or diluted cytotoxic medicines may happen. It is necessary to keep spill kits close to the places where spills might happen. Spill kits can be purchased and contain everything necessary to remove bigger spills in a professional way.

4.2.5 Cytotoxic waste management

All contaminated wastes have to be collected separately in strong plastic bags or containers, both have to be clearly labelled with a warning symbol for cytotoxic waste. All contaminated needles need to be collected in puncture resistant containers with warning symbols. Cytotoxic waste has to be brought directly and separated from other waste to the incinerator and burned at high temperature (should be at least 800°C) as soon as possible.

5 CONCLUSION AND CONTACT

We hope that all aspects elaborated in this document will assist especially faith-based hospitals in Low Income Countries in the decision-making process of starting cancer care, and especially chemotherapy, in their setting. We would like to emphasize once again that in all aspects of cancer management, well trained staff is essential. That means specialists are needed in all involved departments, continuous upgrade training, supervision, monitoring and evaluation have to be guaranteed to secure the quality of the services. The implementation of SOPs is required.

This guide has been prepared together with pharmaceutical senior experts Mr. Peter Vollmer and Mr. Albert Petersen as well as haematologist and medical oncologist Dr. Oliver Henke and paediatric oncologist Dr. Patricia Scanlan. We sincerely appreciate their input and commitment. We also thank pharmacist Dr. David Scott for proofreading the document.

The practical experience results from cooperation with the Kilimanjaro Christian Medical Centre. We are grateful for this collaboration, and we sincerely appreciate KCMC´s commitment to get involved in cancer care and to establish a Cancer Care Centre. We are glad to see the significant progress that has been achieved at KCMC over the last 15 years!

For further advice, information and inquiries, especially on pharmaceutical aspects of cancer care, please do not hesitate to contact DIFAEM:

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6 REFERENCES AND FURTHER LITERATURE

- **Examples for Safe Handling of Cytotoxics Guidelines:**
  https://www.hse.gov.uk/healthservices/safe-use-cytotoxic-drugs.htm;
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4324350/#!po=20.8333
- **World Health Organization (2018). Technical Report. Pricing of cancer medicines and its impacts.**
  https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?sequence=1&isAllowed=y
- **WHO Model List of Essential Medicines 2019**
  https://www.who.int/medicines/publications/essentialmedicines/en/
- **Standard Treatment Guidelines (STG) and National Essential Medicines List (NEMLIT). Tanzania Mainland, 2017**
  STG: Chapter 22"Malignant Disease Conditions". pages 339-369.
  NEMLIT: "8. Antineoplastics and Immunosuppressives". pages 424-426.
  http://apps.who.int/medicinedocs/en/m/abstract/Js23541en/
- **WHO Database on Palliative Care:** https://www.who.int/ncds/management/palliative-care/en/
- **ESMO-Magnitude of clinical benefit scale**
  The ESMO-MCBS is a standardised, generic, validated tool to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies at the time of approval.
  https://www.esmo.org/guidelines/esmo-mcbs/esmo-magnitude-of-clinical-benefit-scale
- **The International Network for Cancer Treatment and Research (INCTR)**
  a not-for-profit organization dedicated to helping build capacity for cancer research and treatment in developing countries.
  http://www.inctr.org/
- **WHO Technical Report series 1021 - The selection and use of essential medicines 2019**.
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  https://apps.who.int/iris/bitstream/handle/10665/330668/9789241210300-eng.pdf?ua=1
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  https://apps.who.int/iris/bitstream/handle/10665/255262/9789241565462-eng.pdf?sequence=1
- **WHO CANCER DATABASE** "WHO CANCER Diagnoses and Treatment"
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- **National Comprehensive Cancer Network**
  https://www.nccn.org/professionals/physician_gls/default.aspx

7 ANNEXES

Annex 1: Tool for structured documentation

Hospital level:

A Demand

Is there evident need / demand for cancer care in the respective region? ☐yes ☐no

If yes, which type of cancer care services to start with:

- Medication incl. chemotherapy ☐yes ☐no
- Surgery ☐yes ☐no
- Radiation ☐yes ☐no

Which cancer entities are most prevalent?

_____

_____

What is the intended scope of the cancer services?

_____

B Budget

Is sustainable financing available for intended scope of cancer service? ☐yes ☐no

If yes, which sources?

_____

Resources available for:

- Payment of specified staff ☐yes ☐no
- Follow up trainings, supervision, monitoring and evaluation ☐yes ☐no
- Specific equipment like cytotoxic safety cabinet ☐yes ☐no
- Building infrastructure ☐yes ☐no
- Medicines ☐yes ☐no
- PPE Materials ☐yes ☐no
- Special consumables ☐yes ☐no
- Maintenance ☐yes ☐no

C Staff

Is recruitment of qualified staff possible? ☐yes ☐no

- Oncologists ☐yes ☐no
- Nurses with special training ☐yes ☐no
- Specifically trained pharmaceutical staff ☐yes ☐no
- Specifically trained laboratory staff ☐yes ☐no

Country level:

Government supports cancer care	☐yes	☐no
National cancer or NCD strategy available and ready for implementation at hospital level	☐yes	☐no
Existence of National treatment guideline for cancer	☐yes	☐no
Central medical store provides cancer medicines	☐yes	☐no
Health insurance system established	☐yes	☐no
• Insurance covering chemotherapy as well	☐yes	☐no
Training programmes available for staff involved in cancer management	☐yes	☐no
Are there other cancer care centres in the country to cooperate with?	☐yes	☐no
• In which fields is a cooperation possible (e.g. laboratory, pooled procurement, …)?		

_____

_____

Annex 2:

List of SOPs:

- Who is allowed to handle and to prepare cytotoxic medicines?
- Transport and storage of cytotoxic medicines
- Written prescription/checking of a written prescription
- Hygiene and cleaning procedures
- General preparation procedure
- SOPs for each cytotoxic medicine
- Use of PPE
- Use of special disposable material for the preparation of cytotoxic medicines
- Administration of cytotoxic medicines
- Cytotoxic spills / Use of spill kit
- Cytotoxic waste management
- Removal of body excretions of patients under chemotherapy

Annex 3:

List of PPE

Personal Protective Equipment for handling cytotoxic medicines	
Item	**Specification**
Gown	Made from impervious material, closed-front, long sleeved with knit or elastic cuffs; the cuffs should be tucked under the gloves.
Gloves	For preparing cytotoxic medicines: purpose made chemo-gloves with a long breakthrough time; for administration and other handling: double gloving with nitrile, polyurethane, neoprene or latex gloves. Gloves must be long enough to cover the wrist cuffs of the gown while the arm is being bent or stretched.
Respiratory protection mask	N95, N100, FFP2 or FFP3 face masks are suitable. Standard surgical mask are not suitable, these offer protection against the inhalation of powder, but not liquids and aerosols. No inhaled air should bypass the mask.
Safety goggles	With side protection or face shield.
Hair covering	Necessary only during preparation of cytotoxic medicines. Caps must contain hair and should fit snugly around the head.

Annex 4:

List of diagnostic laboratory methods and parameters required on different levels of cancer care

Basic Level	**Intermediate Level**	**Advanced tests for specialization**
Full blood count	Peripheral blood smear	Protein serum electrophoresis
Creatinine, Uric acid	Bone marrow aspirates	Beta-2-microglobulin
ASAT, ALAT, Bilirubin	LDH, Lipase, Urea	Kappa/lambda light chains
Potassium, Sodium, Calcium	Vitamin B12, Folic Acid, Ferritin	bcr-abl PCR
ESR (or CRP)	PSA, CEA, CA15-3, CA19-9, AFP	Cytology
Glucose	INR, PTT	Methotrexate levels and others
HIV	Virus serology (CMV, EBV, Hepatitis)	Low cytometry
		Immunohistochemistry