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Challenges associated with the Management of Haematological Malignancies in sub-Saharan AfricaShehu, A.R.*¹, Erhabor, O.¹, Hamid, K.², Umar Z.U.²School of Medical Laboratory Science, Usmanu Danfodiyo University Sokoto, Nigeria¹, College of Health Science Usmanu Danfodiyo University Sokoto, Nigeria²Author for Correspondence*: ralele922@gmail.com**Summary**

Haematological cancers or malignancies (leukaemia, lymphoma and myeloma) are a group of disorders that affect the production and function of blood cells. The aim of this review was to highlight the major challenges affecting the effective management of haematological malignancies particularly in sub-Saharan Africa (SSA). PubMed, Google Scholar, Science Direct and African Journals Online search was performed in January 2020 and studies on best practices on the diagnosis and management of haematological malignancies were sought. Search keywords included “haematological malignancies, management and evidenced-based global best practices”. In most SSA countries, advanced health care systems and technologies required for the effective management of patients are neither geographically nor economically accessible. There is poor access to chemotherapeutic agents and radiotherapy services due to socioeconomic realities. Modern diagnostic equipment and techniques (Immunophenotyping, Fluorescent In situ Hybridization, Cytochemical Stains and Polymerase Chain Reaction and Apheresis) required for the diagnosis and management are often unavailable. There is suboptimal access to safe and adequate supply of blood and components (fresh frozen plasma, cryoprecipitate, platelet concentrate, HLA and HPA matched platelets, irradiated, CMV negative and antigen negative blood products) required for the effective transfusion support of these patients. Capacity to carry out bone marrow and haemopoietic stem cell transplant is often unavailable. There is poor health

infrastructure, inadequacy of qualified staff (laboratory scientists, pathologists and oncologists) and suboptimal financial resources to support the running of effective haemato-oncology service. There is need for the establishment of a collaborative network among professionals responsible for the diagnosis and management of haematological malignancies. Pharmaceutical companies need to be humane by ensuring the availability, affordability and accessibility to life saving chemotherapeutics, radiotherapy and iron chelation agents. There is need to optimize health infrastructure both human (personnel) and material (equipment, reagent, consumables and physical) to facilitate the optimum management of haematological cancers in SSA.

Keywords: *Challenges, Management, Haematological Malignancies, Nigeria*

1.0 Introduction

Cancer is a major cause of death and disability in developing countries, where health systems are poorly equipped to deal with this challenge (Ferlay *et al.*, 2012). Of all cancers occurring in sub-Saharan Africa, haematologic malignancies have emerged as a major cause of morbidity and mortality. Sub-Saharan Africa, in particular, is experiencing a marked increase in burden, with more than 1 million incident of cancer and nearly 800 000 cancer-related deaths projected in the year 2030, representing an approximately 85% increase from 2008 (Satish *et al.*, 2012; Sylla and Wild, 2012). Haematological malignancies are a group of malignant clonal disorders that primarily affect the blood and blood producing

tissues (Arber *et al.*, 2016) including the bone marrow and lymphoid tissues. They are usually clonal in origin and are quite often associated with chromosomal abnormalities (Cairns, 1967).

These malignancies are induced by genetic damage or mutation in somatic cells, which can result from environmental agents such as chemicals, ionizing radiation and viral agents (Parsa, 2012). The pattern of clinical presentation of these malignancies is variable and depends largely on the nature of the disease and its extent. They have a worldwide distribution and can occur at all ages and in both genders (Xie *et al.*, 2003) Although, there are differences between the various types as regards the age and gender-related incidence, a changing pattern in the clinical presentation and distribution has been reported in various communities over the years (Wu *et al.*, 2005). According to the World Health Organization, the haematological malignancies are broadly classified into the myeloid and lymphoid malignancies. The myeloid malignancies include acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), polycythemia vera (PV), essential thrombocythaemia (ET), myelofibrosis (MF), myelodysplastic syndromes (MDS) and myelodysplastic syndrome/myeloproliferative neoplasms (MDS/MPNs) (Arber *et al.*, 2016) whereas the lymphoid malignancies include acute lymphoblastic leukemia (ALL) and the mature B-cell, T-cell, or NK-cell neoplasms including chronic lymphocytic leukemia (CLL), plasma cell neoplasms (PCNs), and Hodgkin's lymphoma (HL) (Swerdlow *et al.*, 2016).

Haematological malignancies are a significant cause of morbidity and mortality and constitute about 17.4%–18.05% of all cancers in Nigeria (Nwannadi *et al.*, 2010) The lymphomas have the highest prevalence; whereas among the leukaemias, chronic leukemias are more common (70.3%) than the acute leukemias (29.7%) with CML being the most common type of chronic leukemia (Omoti and Imiere, 2006) These diseases constitute an economic burden for the patients, their relatives, and the society at large because of the cost associated with their diagnosis and management, which is usually long-term. The cost of managing these disorders

is the sum of those incurred by patients and their families emanating directly through payment of hospital bills, procurement of blood and blood products, and chemotherapeutic drugs as well as indirectly through lost work time by way of absenteeism, disability or premature death, and unpaid care rendered by family members (Johnson and Zhou, 2011). Haematologic malignancies (leukemias and lymphomas) can arise from any stage of differentiation in the haematopoiesis cascade (Andrew *et al.*, 2009) Hematological malignancies are common, being the fourth most frequently diagnosed cancer in both males and females in the economically developed regions of the world (Ferlay, *et al.*, 2004). There are over 60 recognized disease subtypes, which differ widely in clinical presentation, treatment requirements and prognosis (WHO, 2008).

2.0 Classifications of Hematological Malignancies

In 1832, Thomas Hodgkin described the first haematologic malignancy. More than 30 years later, the particular type of lymphoma that he characterized was named Hodgkin disease in his honor. The published descriptions of other haematologic malignancies, such as leukaemia and multiple myeloma, soon followed. Since that time, these malignancies have been further described and attempts made to categorize various subtypes. With the assistance of immunophenotyping and cytogenetic and molecular genetic testing, it is now understood that haematologic malignancies include a very large number of genetically diverse diseases (Lichtman, 2008). The WHO classification applied the principles of the Revised European-American Lymphoma (REAL) classification from the International Lymphoma Study Group to all hematologic malignancies, incorporating morphology, immunophenotype, genetic features, and clinical features to define distinct types (Harris, *et al.*, 1999).

Leukaemia

The term leukemia is derived from Greek words “leukos” and “heima,” which refer to excess white blood cells in the body. Leukemia, once considered a single disease, was first recognized as a blood disease around the fourth or fifth

century BC. The first case was officially diagnosed by John Hughes Bennett and published in 1845 in the *Edinburgh Medical and Surgical Journal* (Bennett, 1845). Alfred Donné pioneered the use of microscopy to study blood diseases in the early to mid-1800s, and this coincided with the discovery of leukaemia as a blood cancer (Kampen, 2012). Then, in 1868, Ernst Neumann, a professor of pathologic anatomy, discovered a link between the source of blood and the bone marrow. This led to the knowledge that all blood cells derive from the bone marrow through haematopoiesis (Piller, 2001). In 1877, Paul Ehrlich invented a stain that could aid in the distinction of blood cells, which led to the subsequent classification of leukaemia (Piller, 2001). At the end of the 19th century, leukaemia was no longer considered a single disease and was classified into subtypes: chronic lymphocytic leukaemia, chronic myeloid leukaemia, acute lymphocytic leukaemia, and acute myeloid leukaemia. These four subtypes continue to be used as the basis for our understanding of these diseases. However, it is now known that leukaemia comprises a variety of haematopoietic neoplasms that are both complex and unique. Each subtype can be further distinguished by morphologic differences, cytogenetic abnormalities, immunophenotype, and clinical features. The exact cause of leukaemia is unknown. (Hamaker *et al.*, 2014) A combination of genetic factors and environmental (non-inherited) factors are believed to play a role. Risk factors include smoking, ionizing radiation, some chemicals (such as benzene), prior chemotherapy, and Down syndrome (Abel and Koreth, 2013) People with a family history of leukemia are also at higher risk.

Lymphoma

The first type of lymphoma was first described in “Some Morbid Appearances of the Absorbent Glands and Spleen,” a paper published in 1832 by Thomas Hodgkin. In 1898, Carl Sternberg

provided the first description of these malignant cells using a recently discovered staining technique. He referred to them as giant cells (Aisenberg, 2000). Just four years later, Dorothy Reed fully described the cells, which were termed Reed-Sternberg cells (Reed, 1902). For the next 60 years, more detailed clinical and pathologic descriptions of many different types of lymphoma emerged (Aisenberg, 2000). In 1942, Gall and Mallory developed the first lymphoma classification to categorize the other lymphomas that were not characterized by the Reed-Sternberg cells (Gall and Mallory, 1942). This classification system was quickly followed by the Rappaport Classification in 1956, which was based on cytology and the presence or absence of follicular structure (Rappaport *et al.*, 1956). Almost two decades later, the International Working Formulation was introduced, and lymphoma types were classified based on cell size, cell differentiation, and whether or not the cell was cleaved. This led to a classification scheme that distinguished lymphomas with low-grade clinical behavior (nodal follicular architecture maintained) from lymphomas with high-grade or aggressive behavior (nodal architecture replaced by a diffuse pattern of tumor involvement) (Non-Hodgkin's Lymphoma Pathologic Classification Project, 1982). In 1994, the REAL classification, defining immunophenotype and molecular genotype with morphology and clinical features, was developed for non-Hodgkin lymphoma (NHL) (Harris *et al.*, 1994). In 1965, Hodgkin lymphoma was classified into four staging categories at the Rye conference (Lukes and Butler, 1966). Prior to the development of these classifications, more than 50 different terms had been used in the literature to describe lymphoma (Lukes and Butler, 1966). Lymphomas can also be described as either low grade or high grade based on the growth tendency. Lymphomas can also be described broadly as Hodgkins (HL) and Non-Hodgkins Lymphoma (NHL).

Table 1: Classification of Lymphomas as either low grade or high grade based on the growth tendency.

Low Grade (Inert)	High Grade
Lower cellular proliferation	Higher cellular proliferation
Tend to grow slowly	Tend to grow rapidly
More difficult to treat	Less difficult to treat
If left untreated can lead to death less rapidly	If left untreated can lead to death rapidly

Table 2: Classification of Lymphomas into Hodgkin's and Non-Hodgkin's Lymphoma

Hodgkin (HL)	Non -Hodgkin (NHL)
Restricted essentially B lineage cells called Hodgkin or Reed- Sternberg cell	Large solid lymphoid tumours and diverse in nature (B or T-cell related)
Can be found in younger age	A disease of increasing age
More common in men than women	Affects men and women equally
Less encountered	More encountered

Multiple Myeloma

The first known case of a patient with multiple myeloma was documented by Solly in 1844; the patient was treated with a rhubarb pill and orange peel (Solly, 1844). Solly described the bones of a patient with multiple myeloma as soft and discolored. After the death of a 47-year-old man who presumably had multiple myeloma, Dr. Henry Bence Jones was asked to study the patient's urine and noted the presence of an abnormal protein. This protein was later called Bence-Jones protein (Kyle and Steensma, 2011). Interestingly, this 47-year-old man was initially treated with phlebotomy, leeches, steel, and quinine, and he lived for approximately two years (Kyle and Steensma, 2011). In the early 1900s, multiple myeloma was further characterized by pathologic fractures, proteinuria, anaemia, and chronic renal disease; however, erythrocyte sedimentation rate and blood protein abnormalities were not described at that time (Kyle and Steensma, 2011). Between 1922 and 1953, the discovery of two classes of Bence-Jones proteins, kappa and lambda, and serum monoclonal protein using electrophoresis

and immunofixation led to further understanding of this haematologic malignancy (Kyle and Steensma, 2011)

2.1 Diagnosis of Haematological Malignancies

The diagnosis of haematological malignancies has benefited enormously from recent scientific advances. In spite of this, morphology remains critically important and is the key front-line diagnostic technique which must not be overlooked. The light microscopy appearances may be diagnostic but, in addition, they are the foundation upon which decisions about further scientific assessment are based. In the modern era that utilizes a multi-parameter approach to disease classification, morphology is the screening test that determines the further investigations necessary (Swerdlow *et al.*, 2008).

Peripheral blood examination

Abnormalities on a full blood count (FBC), be they quantitative or qualitative, may be the first indication of a haematological malignancy and will generally lead to a blood film being

examined (Barnes *et al.*, 2005). Whereas currently FBC is most common type test that can give an indication of a potential haematological malignancy, light microscopy, automated image capture methods are increasingly being used (Briggs *et al.*, 2009). It is recommended for the assessment of neoplastic cells by morphological review be performed manually as a well-trained pair of eyes is more discriminating than a programmed computer. The abnormalities on the blood film may be diagnostic, or lead to a provisional diagnosis. Blood film examination requires a well-prepared smear made from a fresh blood sample (<2 hours in anticoagulant). The smear must be air-dried, fixed and stained with a Romanowsky stain (May– Grünwald, Leishman and Giemsa). A cover-slip, rather than oil, should be placed over the entire smear using mounting medium to provide permanent protection without interfering with the optics. Misidentification of significant and potentially diagnostic features can occur as a result of prolonged blood storage which causes EDTA-artefact, storage at the wrong temperature, poorly spread smears and poor-quality stain. The smear should be viewed macroscopically for its quality and staining appearances. Even without magnification, abnormal color, which may indicate the presence of proteinaemia, or pattern, due to red cell agglutination, may be evident. Microscopy should then commence with systematic scanning of the entire smear using a low-power ($\times 10$) objective, followed by $\times 20$ or $\times 25$ objectives to assess the following:

1. Background appearance of the blood (protein stain and abnormal agglutinates).
2. Erythrocyte distribution pattern (rouleaux or agglutination).
3. Manual assessment of the leukocyte count to detect discrepancies with the automated blood count.
4. Leukocyte distribution and presence of abnormal cells.

Blood film features that can aid in establishing the precise diagnosis are:

1. Number of blast cells: Circulating blast cells $\geq 20\%$ meets the WHO criteria for acute leukaemia. When there are fewer than 20% circulating blast cells a bone marrow examination is required to discriminate

between myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, myeloproliferative neoplasms and acute leukaemia.

2. Blast cell morphology: lymphoid or myeloid features. In some cases, the blast cells do not have any specific morphological features that allow lineage assignment. These cases, which may be merely undifferentiated lymphoid or myeloid blasts, or be of ambiguous lineage, will always require phenotyping by flow cytometry to resolve.
3. Accompanying cellular features, for example:
 - a. Leukoerythroblastic blood film may indicate bone marrow fibrosis or infiltration but not the cause.
 - b. Tear-drop poikilocytes may indicate presence of bone marrow fibrosis.
 - c. Neutrophil dysplasia (hypo lobulation and hypo granulation) may suggest myelodysplastic syndrome or acute myeloid leukemia.
 - d. Monocytosis may suggest chronic or juvenile myelomonocytic leukemia or acute myeloid leukemia with monocytoid differentiation.
 - e. Thrombocytosis with abnormal morphology may indicate myeloproliferative neoplasm (essential thrombocythaemia).
 - f. Dysplastic platelets (large size and hypogranular) may suggest myelodysplastic syndrome, myeloproliferative neoplasm or acute megakaryoblastic leukemia.
 - g. Erythroblastosis with dyserythropoietic features may suggest erythroleukemia or myelodysplasia (Simson *et al.*, 2008).

Bone marrow examination

The indications for performing a bone marrow examination have been formalized by the International Council for Standardization in Haematology (ICSH). A bone marrow examination is required whenever a haematological malignancy is suspected from the blood film. Bone marrow aspirate and trephine biopsy specimens provide complementary information and both are therefore valuable in the initial assessment of a possible haematological malignancy. The

aspirate gives detailed cytological detail, whereas the trephine biopsy provides more information about the overall marrow cellularity, architecture, cellular distribution and fibrosis. For some disorders the aspirate may provide sufficient information without the need for a trephine biopsy (acute leukemia). For others, the trephine biopsy is the prime diagnostic material (lymphoma staging) (Fend *et al.*, 2008). Bone marrow aspirate involves the removal of bone marrow fluid and cells by inserting a needle into the bone marrow and sucking out (aspirating) fluid and cells while bone marrow core biopsy involves the removal of an intact piece of bone marrow using a coring device (similar to a large diameter needle). In addition to morphology, the marrow samples can be used for ancillary biological tests required to reach a diagnosis and WHO classification (flow cytometry, polymerase chain reaction, immunocytochemistry and genetics) (Malempati *et al.*, 2009). Components of a normal bone marrow examination include; Cell: Fat ratio, Myeloid: Erythroid ratio, Nucleated cell differential count, Perl Blue (Prussian Blue Stain), megakaryocytes and Cellularity (Bain, 2005). In determining the cellularity, only nucleated cells (myeloid and erythroid precursors) are included in assessment (not mature RBCs or reticulocytes which could just indicate blood in the sample). Megakaryocytes do not contribute much to cellularity. In terms of cellularity, a marrow can be normoplastic, hypoplastic or hyperplastic (Syed *et al.*, 2007). The number of megakaryocytes is assessed subjectively. Aside from numbers; we look at maturation sequence (there should be more mature than immature megakaryocytes). Dysplasia in megakaryocytes could indicate abnormal or accelerated production and may yield clues as to mechanisms underlying a thrombocytopenia (Gandapur *et al.*, 2015).

Diagnosis for haematological neoplasms generally

The following blood test play a key role in the diagnosis of haematological neoplasms

- Full blood count
- Peripheral Blood Film
- Bone marrow Aspiration
- Bone marrow biopsy (Trephine)

- Immunophenotyping (lymphoma and myeloma)
- Cytochemistry
- Cell markers [Janus Kinase- 2 (JAK-2) diagnostic of MPD]
- Biopsy of the lymph node in patients presenting with lymphadenopathy
- Cytogenetics (AML and CML). BCR-ABL gene is diagnostic of CML.
- Florescent in situ hybridization (FISH)

Full Blood Count

- RBC: Low RBC count can be due to myelosuppression or bleeding particularly in thrombocytopenic patients. RBC count is increased in polycythaemia. In some B-cell malignancies, the presence of autoantibodies against RBC antigens can also result in low RBC count.
- MCV: Normochromic and normocytic picture can be seen in some cases, Raised MCV is often associated with cytotoxic therapy or those with MDS due to cell cycle arrest.
- MCHC: MCHC can be raised in patients with AIHA commonly seen in B cell malignancies, RBCs can lose their biconcave shape becoming spherical due to macrophages removing part of the autoantibodies-bound RBC membrane.
- WBC: Represent both mature and immature forms. Increased WBC may mean presence of circulating malignant cells or normal cells displaced from the BM by a malignant clone. Raised WBC count may mean increased proliferation or failure of apoptosis or both. A low WBC may mean myelosuppression, myelofibrosis (low or high possible).
- DLC: In lymphoid malignancy, there is reversed ratio between neutrophil and lymphocytes. Always remember that a reversed ratio can be seen in cases of viral infection in children that is not haematological malignancy. Basophilia is commonly seen in haematological malignancies.
- Platelet Count: Thrombocytopenia can be a consequence of myelosuppression. In splenomegaly, thrombocytopenia can occur (platelet trapping in the spleen).

Thrombocytosis may be associated with ET and PV (MPD). Also note that thrombocytosis (reactive) mediated can also occur as a consequence by inflammatory cytokines. Platelet may be decreased following haemorrhage.

- Blood Film: Look out for presence of dysplastic features in white cell morphology. For patients presenting with thrombocytopenia, rule out platelet clumping, fibrin strands and satellitism. Low platelet count should be technically validated before spreading a film (check for clot and

sample integrity). Check for dimorphic red cell population. Check cytoplasmic granular contents, size of haemoglobinization, cell size and number of platelets and presence of immature WBC forms. Look out for leucoerythroblastic picture presence of immature WBC and RBCs). If blast is present check for the presence of Auer rods (50% of myeloid malignancy exhibit Auer rods and may be evidence that blast is of myeloid origin and likely AML). Figure 1 shows the picture of a myeloblast with a characteristic auer rod.

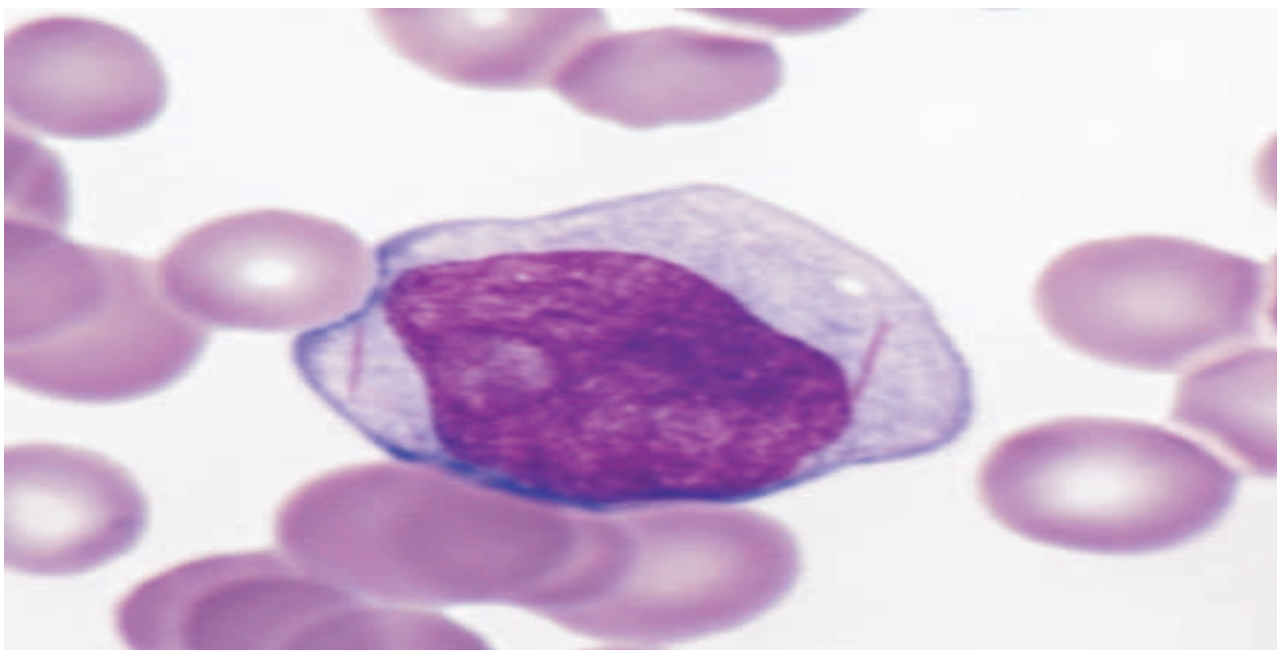


Figure 1: Auer Rods in a patient with AML (Krafts, 2011)

Bone Marrow Assessment

It is vital that BM findings are interpreted in context along with a recent FBC (last 24-48 hours) with a good quality blood smear. Bone marrow assessment in the management of haematological malignancy is important for several reasons:

- For a better understanding of the patient disease
- Determine BM involvement in lymphoma (extra nodal). Bone marrow infiltration
- Determine the distribution of cells in the BM
- Check for the presence of abnormal inclusions

Site for Bone marrow aspiration and trephine biopsy

- Anterior or posterior iliac crest
- Sternum (breastbone).
- In infants (shin bone or tibia)

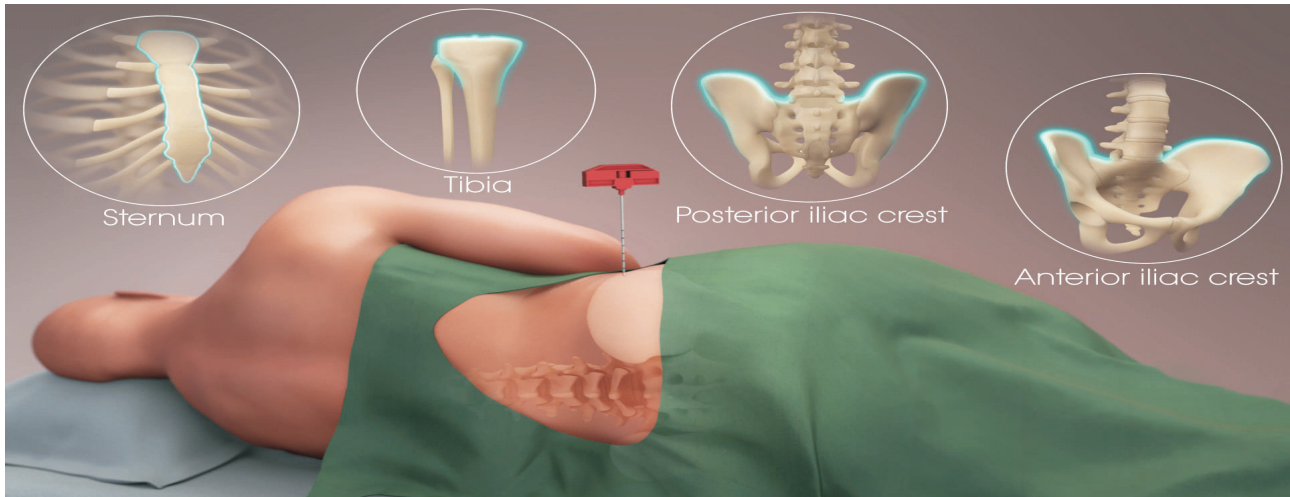


Figure 2: Site of Bone marrow Aspiration (www.wikiwand.com/en/Bone_marrow_examination#/References)

Bone marrow collection can either be

- Aspirate: A bone marrow aspiration removes only the marrow.
- Trephine Biopsy: Removes a small amount of bone and a small amount of fluid and cells

Test carried out on bone marrow aspirate

- **Perl's (Prussian) Blue stain** (check for iron stores/status). For diagnosis of iron deficiency anaemia. Iron is found within macrophages as haemosiderin. Iron is usually not seen in mature or immature RBCs. Presence of iron in BM (siderocytes if in mature RBCs and sideroblasts if in nucleated RBCs) is an abnormal finding.
- **Differential Leucocyte Count** (Count 500 nucleated and differentiate them into the various types). Examine by low power for cellularity, identification of abnormal cells and megakaryocytic cells for abnormality. Use high power to determination of maturation stage of myeloid and erythroid cell lines.
- **Myeloid: Erythroid Ratio.** There is a normal ratio of myeloid to erythroid precursors (approximately 4:1) with normal maturation of both cell lines. For the myeloid cells we count all the myeloid cells (all granulocytic and monocytic cells) excluding

lymphocytes, monocytes, macrophages, plasma cells, megakaryocytes, osteoclasts, osteoblasts, and other non-myeloid cells and for erythroid cell count all nucleated erythroid precursors in marrow. M:E ratio is low in:

- Myeloid hyperplasia (CML) in the absence of transient stress associated neutrophilia with a left shift
- Erythroid hypoplasia

▪ **Cellularity**

BM cellularity declines as one ages. Decline in BM cellularity accelerate after age 70 years. Guideline for computing marrow cellularity is calculated using the formula:

$$100 - \text{Age} = \text{Percentage of marrow cellularity}$$

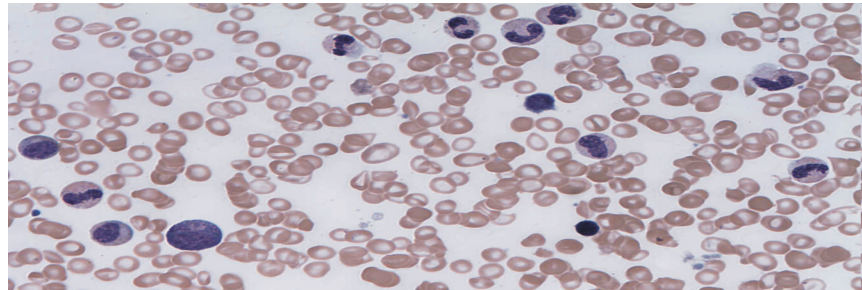
About 50% of normal healthy adult marrow aspirate is haemopoietic cells. In children and younger adults, the % is > 50%. Increased cellularity is seen in; Megaloblastic anaemia, Haemolytic anaemia (erythroid hyperplasia), Leukaemia (cellularity is greatly increased due to increased proliferation of white cells). A marked decrease in cellularity occurs; suppression by cytotoxic drugs (chemotherapy), aplastic Anaemia and BM failure.

Figure 3: Cellularity of Bone Marrow

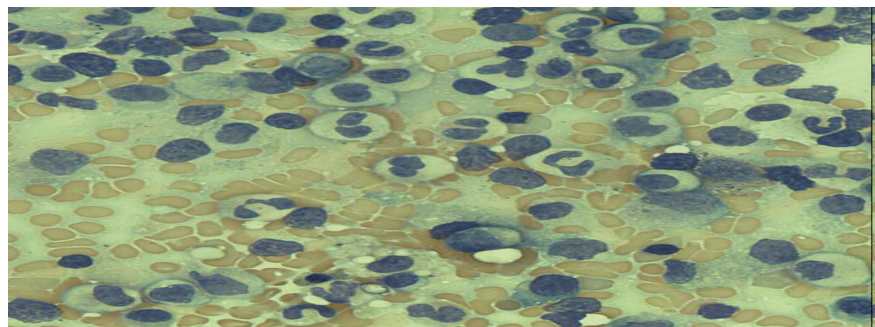
Bone Marrow Plasticity

w Marrow Picture

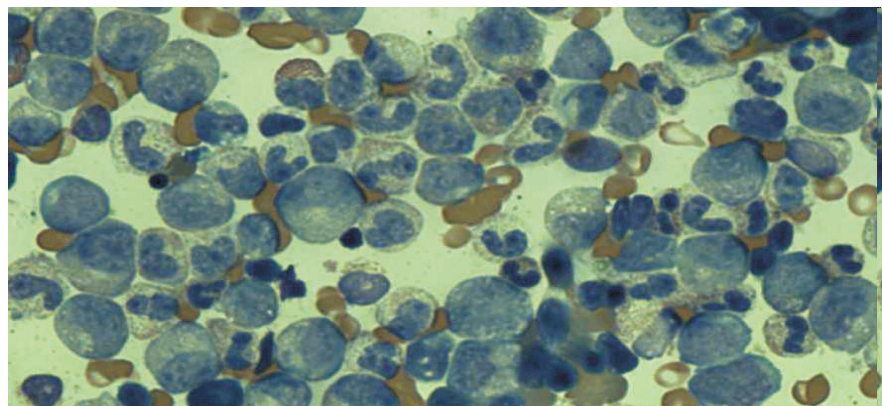
Hypoplastic



Normoplastic



Hyperplastic



Other Parameters to look out for in Bone Marrow Examination

- Presence of megakaryocytes (Giant cell with multi-lobulated nucleus in BM-develop into platelets).
- Presence of diagnostic features (sideroblast diagnose sideroblastic anaemia).
- Excess iron (haemochromatosis) or too little iron (Fe deficiency anaemia).
- Look out for signs of Cancer cells (leukaemia, lymphoma, or multiple myeloma).
- Disease staging [check if disease is active, if a patient in CMR (No residual disease) or if there is Relapse (resurfacing of clonal malignancy)].
- Fat to Cell Ratio (In children < 10 years 10% fat to 90% cells while in adult: 30% - 70% fat to 70% - 30% cell).
- Marrow cell composition: Erythroid Cells (18 to 39%), Plasma Cells (0.4 to 3.9%) and Myeloid Cells: 60-75% of nucleated cells in marrow.
- Nucleated Cell Count (Count at least 500 cells and categorize them into; blast cells, promyelocytes, myelocytes, metamyelocytes, band forms, segmented neutrophils, eosinophils, basophils, promonocytes and monocytes, lymphocytes and plasma cells and erythroblasts).

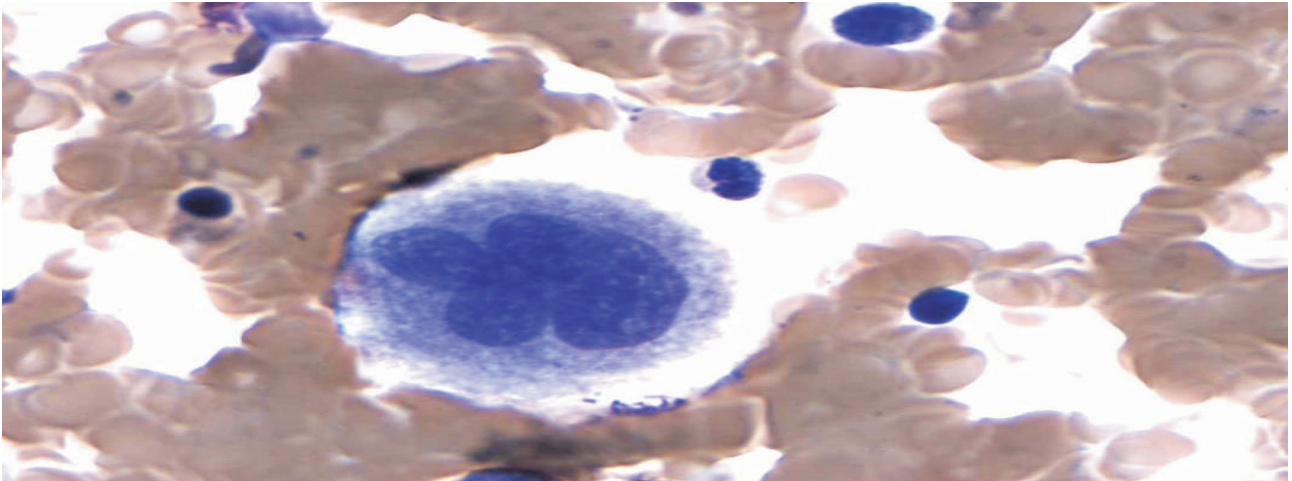
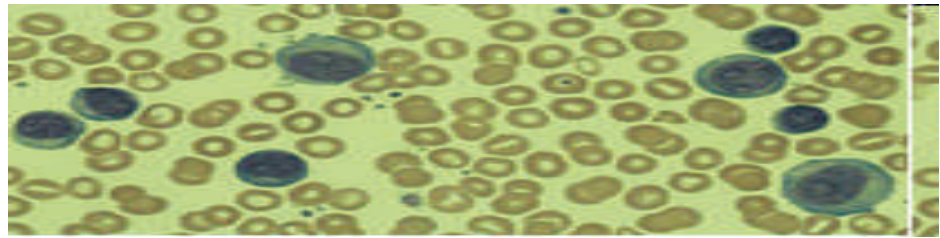


Figure 4: A Megakaryocyte in a Bone Marrow Film

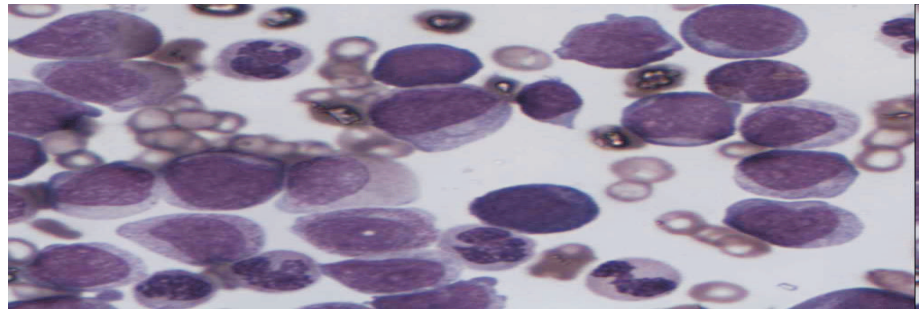
Figure 5: Bone Marrow Film in Haematological Malignancy

Haematological Malignancy	Peripheral/Bone Marrow Picture
Chronic Myelomonocytic Leukaemia (CMML)	
Chronic Lymphocytic Leukaemia (CLL)	
Chronic Myelocytic Leukaemia (CML)	
Multiple Myeloma (MM)	

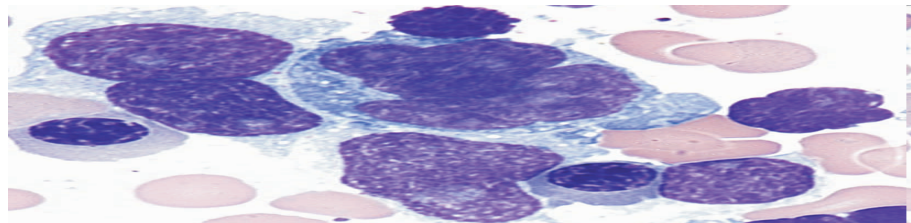
Acute Lymphoblastic Leukaemia (ALL)



Acute Myeloblastic Leukaemia (AML)

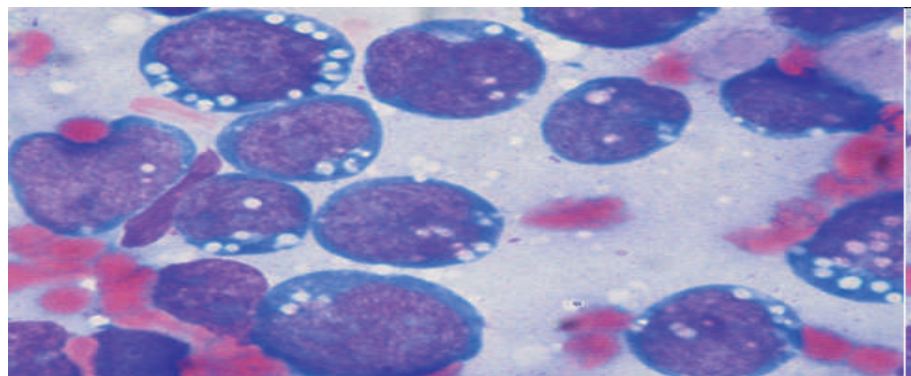


Diffuse Large B Cell Lymphoma (DLBCL)



(Maslak, 2009)

Burkitt Lymphoma



(Uthman, 2006)

Immunophenotyping

Immunophenotyping plays a significant role in the diagnosis of haematological malignancies. Peripheral blood and BM aspirate can be used for immunophenotyping using flow cytometers. It involves the use of monoclonal antibodies (mAb) directed against intracellular and extracellular Cluster Differentiation (CD) antigens (Zola, H. *et al.*, 2006). Immunophenotyping can be used to accurately diagnose haematological malignancy. Irrespective of their morphological features. There are up to 350 CD antigens currently

known. Some CD are more specific with:

- Lineage
- Particular stage of maturation

CD antigens are expressed on all lineages. Monoclonal antibodies directed against CD antigens are anti-CD followed by the number of the CD antigen (anti-CD53). According to specific cluster of differentiation (CD) markers, lymphocyte population can also be divided into three main subgroups:

- Natural killing cells (CD3-/CD16+56+)
- B cells (CD19+) and T cells (Cd3+).

- T cells can be sub-divided into helper T cells (CD4+) and cytotoxic T cells (Cd8+).
- B Cell CLL is positive for CD5, 19, 23

For mAbs to be able to bind to the CD antigens, 2 requirements must be met:

- Fixation is necessary to prevent cell lysis
- Permeabilization allows mAbs to penetrate the cell

Principle of flow cytometry

For the CD antigens to be detected by flow cytometry, fluorochromes are joined to the mAbs. If the specific CD antigen to which the monoclonal is specific is present on the cell, the fluorochrome bound mAbs binds to the antigen (target cell). Laser light of a particular

wavelength excites the cell to which the mAbs linked fluorochrome is bound emitting light of a particular wavelength. The principle is based of fluorescence. The light emitted by each fluorochrome are measured simultaneously by using a flow cytometer with multi-channel capabilities.

Immunophenotyping differentiate:

- Myeloid from lymphoid
- Differentiated or undifferentiated
- Whether a cell express both myeloid and lymphoid lineage
- Define stage of maturation arrest within malignant
- Differentiate T and B cell lineage marker or both

Table 3: Types of Fluorochromes used on Flow Cytometers for diagnosis of Haematological Malignancies

Fluorochromes	Excitation Max (nm)	Emission Max (nm)
Allophycocyanin (APC)	650	660
Fluorescein Isothiocyanate	490	520
Peridinin Chlorophyll Protein (Percp)	488	578
Phycoerythrin (PE)	564	576
Rhodamine	550	573
Texas Red	596	615

Flow Cytometry

In flow cytometry, a sample containing cells or particles is suspended in a sheath fluid and injected into the flow cytometer instrument. The sheath fluid allows for hydrodynamic focusing which allows the cells to pass as a single file through the light beam (laser) for sensing. Modern flow cytometers have multiple lasers and fluorescence detectors. Components of a flow cytometer include:

1. Fluidics system
2. Optical system (light system)
3. Detector/electronics

Flow cytometers utilize lasers as light sources to produce both light scatter and fluorescent light signals that are read by detectors (photodiodes or photomultiplier tubes). Cell populations can be analyzed and/or purified based on their fluorescent or light scattering characteristics.

How Flow cytometer works?

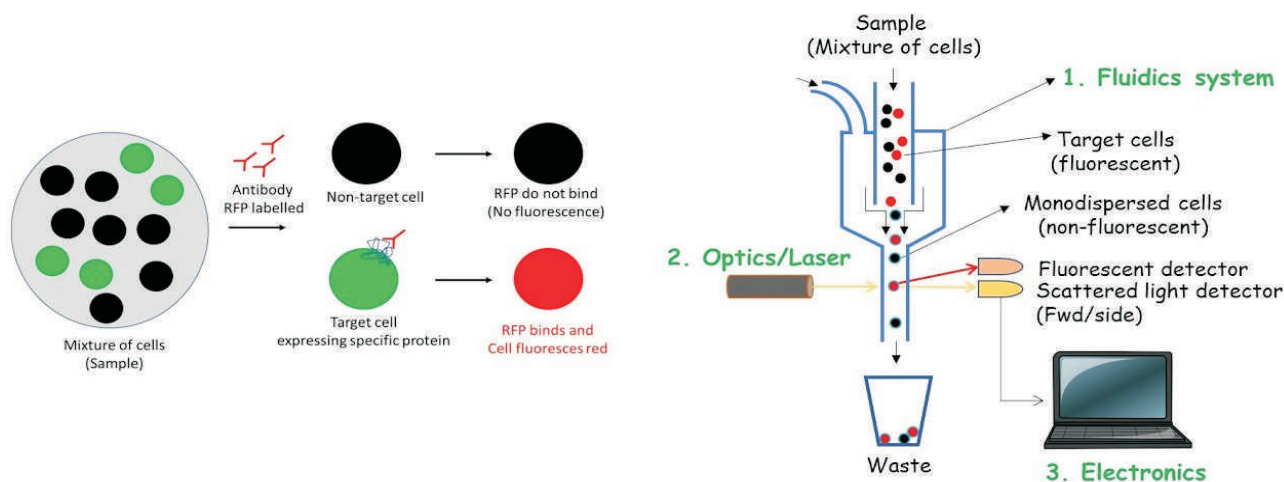


Figure 6: Principle of Flow Cytometry for diagnosis of Haematological Malignancies (www.youtube.com/watch?v=CueDs0U-Jdc)

Cytochemistry

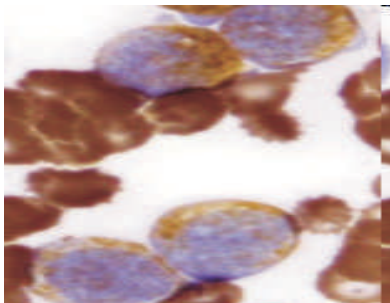
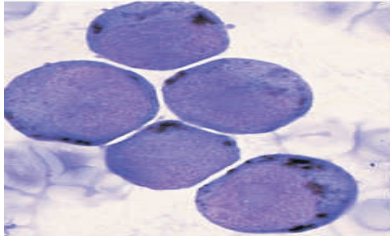
Cytochemistry confirms the presence or absence of a diagnostic marker (enzymes) within the cells. With the use of cytochemistry we can determine the following:

- Cell lineage (It is very difficult to

differentiate between a myeloblast and lymphoblast if Auer rods are absent. It is also difficult to differentiate erythroblast from monoblast and megakaryoblast on a film without use of cytochemistry)

- Classification of the malignancy

Table 4: Examples of Cytochemical Stains

Cytochemical Stains	Nature and Uses	Result	Picture
Myeloperoxidase (MPO)	<ul style="list-style-type: none"> Brown Peroxidase enzyme found with azurophilic granules of granulocytes Utilizes 3,3, Diaminobenzidine (DAB) 	Pos- Myeloid myeloblast, promyelocyte, myelocyte, metamyelocyte, granulocytes and monocytes Neg- ALL	 <p>AML Patient</p>
Sudan Black B (SBB)	<ul style="list-style-type: none"> Black Lipophilic stain, Bind lipid membrane of granules in granulocytes and monocyte 	Pos- Myeloid myeloblast, promyelocyte, myelocyte, metamyelocyte, granulocytes and monocytes Neg- ALL	 <p>AML with Sudan Black B</p>

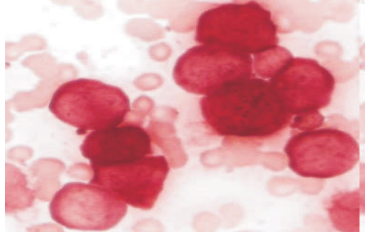
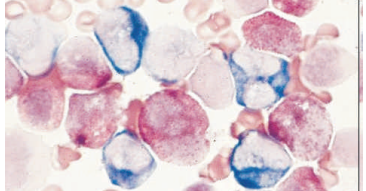
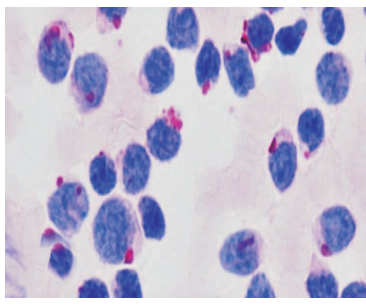
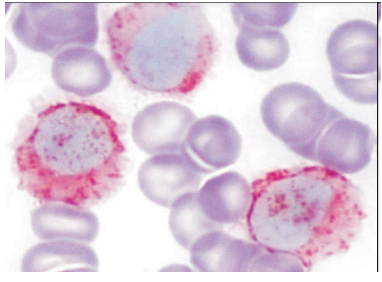
Alpha Naphthyl Acetate Esterase (ANAE)	<ul style="list-style-type: none"> Red Brown Identify leukaemic monoblast and granulocytes. Myeloblast stain negative 	Pos- Monoblast and granulocytes	
Chloro Acetate Esterase (CAE)	<ul style="list-style-type: none"> Bright Blue Identify leukaemic monoblast and granulocytes. Myeloblast stain negative 	Pos-Granulocytes Neg- Myeloblast	
Periodic Acid Schiff (PAS)	<ul style="list-style-type: none"> Red Pink React with 1, 2, glycol groups found in carbohydrate in glycogen. Early erythroblast, mature RBCs and immature granulocyte stain negative 	Pos-Mature granulocytes, monocyte, megakaryocyte, platelets and leukaemic erythroblast	
Acid Phosphatase (AP)	<ul style="list-style-type: none"> Produces red granules Differentiate T cells (++) and B cells (+) Identify AML with monocytic involvement. 	Pos- T cells (++) , B cells (+), granulocytes (++) , megakaryocytes (++) and plasma cells (++)	

Table 5: Diagnostic Utility of cytochemical stains in diagnosis of haematological malignancies

Cytochemical Stain	Myeloblast	Lymphoblast
Myeloperoxidase	Positive	Negative
Specific Esterase (Cae)	Positive	Negative
Sudan Black B	Positive	Negative
Periodic Acid Schiff	Variable	Block Positivity
Acid Phosphatase	Negative	Positive in T Lymphoblasts

Follow up of patients

Patient with haematological neoplasms should be followed up regularly. Treatment can either be successful (complete molecular response/remission or partial remission), a patient should be followed up regularly to rule out any recurrence and monitor for development of secondary malignancy.

Patient presentation in Haematological Malignancies

Common presenting symptoms in haematological malignancies include:

- Pallor (sign of anaemia). Note anaemia can sometimes be normochromic and normocytic)
- Lethargy (sign of anaemia and poor tissue perfusion)
- Pharyngitis
- Recurrent infection (consequence of dysfunction immune system). The WBC count may also be raised and may not indicate the functional status. Leucocytosis may indicate presence of circulating leukaemic cells or displacement of non-malignant WBC by clonal cells in the BM)
- Easy bruising-ecchymosis or petechiae (sign of thrombocytopenia and dysfunctional platelets)
- Pyrexia (fever) night sweats and weight loss: Often due to malignant B cells and precursors produced in response to the synthesis of cytokines (IL1, Tumour necrosis Factor alpha (TNF- α) and IL6). During infection WBC increases in number and secrete cytokines that:
 - Potentiate white cell colony
 - Stimulate the hypothalamus to increase body temperature
 - Stimulate the proliferation of haematopoietic stem cells
 - Stimulate the proliferation of B cells
- Palpable Organomegaly (spleen and liver):
- Lymphadenopathy: Painless and rubbery
- Bone pains (Due to increased BM cellularity can compress the nerves running through the bones). In myeloma malignant plasma cell secretes osteoclast activators which degrade the bones
- Flu like symptoms

- Some patient may present as asymptomatic and only suspected following routine basic haematology test (FBC)
- Myelosuppression [failure of myeloid cells in the BM to produce RBC, WBC and platelets (pancytopenia) due to proliferation of malignant cells in the BM or the effect of a therapeutic agent (chemotherapy)]

Haematopoietic cell differentiation and antigen expression

The availability of monoclonal antibodies to leukocyte differentiation antigens has led to an explosion in our knowledge and understanding of normal hematopoietic cell differentiation. Through this we have learned that the antigenic profile of the majority of the malignancies mimics that of the normal equivalent cell. This phenotypic association between normal and malignant cells is the guiding principle of the WHO classification; it uses the antigen profile to class neoplasms by cell lineage and their stage of differentiation (Swerdlow, S.H. *et al.*, 2008).

3.0 Management of Haematological Malignancies

Although recent years have seen an explosion in new treatments for haematologic malignancies such as chronic lymphocytic leukemia (CLL) (Hallek, 2017) and multiple myeloma, (Warren *et al* 2013) including the expansion of age limits for haematopoietic cell transplantation (HCT) for acute leukemia and myelodysplastic syndromes (MDS) (Abel and Koreth, 2013). There is overall little specific evidence to guide treatment decisions for older adults. This is largely because they are underrepresented in cancer-related clinical trials (Scher and Hurria, 2012). Indeed, about one-third of haematology trials listed in the National Institutes of Health registry include lineage-based exclusions (Hamaker, *et al.*, 2014). Moreover, even when there are no age restrictions, older patients who are eligible are most often not representative of the older patients commonly seen in practice. Haematologists are thus left with great clinical uncertainty, and must either assume that new treatments will be effective despite data that hail primarily from younger patients, or avoid such treatments altogether for their older patients.

Immunotherapy

The field of immunotherapy in cancer treatments has been accelerating over recent years and has entered the forefront as a leading area of ongoing research and promising therapies that have changed the treatment landscape for a variety of solid malignancies. Prior to its designation as the Science Breakthrough of the Year in 2013 (Couzin-Frankel, 2013), cancer immunotherapy was active in the treatment of haematologic malignancies. One of the oldest forms of cancer immunotherapy: allogeneic haematopoietic stem cell transplantation (HCT). The first allogeneic transplant was performed in 1968 by E. Donnall Thomas, who would go on to win the Nobel Prize for being a pioneer in this technology and the father of stem cell transplantation. Although it has been referred to as “the chemotherapist's bluntest weapon” (Mukherjee, 2010), as it indeed aims to eradicate the haematopoietic and immune systems of a patient. It is often the only curative option for many patients with haematologic malignancies. Moreover, with widening clinical indications and the use of alternative donors, its use only continuous to increase (Pasquini and Zhu, 2017). In addition, allogeneic HCT has provided a model of immunotherapy in haematologic malignancies, offering invaluable information that can be used as the field moves forward. For example, we have learned about the sensitivity of haematologic malignancies to the “graft-versus-leukemia” or “graft-versus tumor” effect, and thus, we know these are appropriate targets for immunotherapy (Horowitz *et al.*, 1990; Weiden *et al.*, 1979). This sensitivity has been demonstrated by several factors: (1) the efficacy of allogeneic transplant in chemo-refractory disease (Duval *et al.*, 2010), (2) the use of donor lymphocyte infusions to treat relapse after transplant (Ali *et al.*, 2016), and (3) the use of reduced intensity or non-myeloablative conditioning regimens (“mini-transplant”) (Carella *et al.*, 2000), where the reliance of efficacy and disease eradication is primarily on the graft-versus leukemia effect, with little contribution from high-dose chemotherapy. The overall survival after allogeneic transplant has improved significantly over the past several decades (Gooley *et al.*, 2010), although this is mainly due to improvements in non-relapse

mortality and advances in supportive care (treatment and prevention of infections or graft-versus-host disease (GVHD)).

Monoclonal antibodies

Rituximab, an anti-CD20 monoclonal antibody targeting B cells, was the first monoclonal antibody to be approved by the United States Food and Drug Administration (FDA) for the treatment of cancer in 1997 and since has become the prototype for anti-CD20 monoclonal antibodies and a backbone of B cell malignancy treatment regimens. It is a type I antibody and thus exhibits complement-dependent cytotoxicity and antibody-dependent cytotoxicity. Since rituximab, newer monoclonal antibodies directed against CD20 have been developed for use in B cell malignancies, including of ofatumumab and Obinutuzumab. Ofatumumab is a second generation, fully humanized anti-CD20 monoclonal antibody that binds to a different site than rituximab, and is also a type I antibody. This agent was FDA approved for the treatment of previously treated chronic lymphocytic leukemia (CLL) in 2009 or in combination with chlorambucil for the treatment of previously untreated CLL in 2014 (Hillmen *et al.*, 2015; Wierda *et al.*, 2010). Obinutuzumab is another second-generation anti-CD20 monoclonal antibody that is a glycol engineered type II antibody, which differs from the others in that it induces direct cell death, along with enhanced antibody-dependent cytotoxicity. This agent was FDA approved in combination with chlorambucil for the treatment of previously untreated CLL in 2013 and in combination with bendamustine for the treatment of relapsed/refractory follicular lymphoma (FL) in 2016 (Goede *et al.*, 2014; Sehn *et al.*, 2016). Studies are ongoing with both of these agents, which may highlight the best role of these agents in the context of current B cell malignancy regimens. Multiple myeloma (MM) had been long left out of the monoclonal antibody arena until recently, with the surge in development of effective monoclonal antibody therapies based on identification of target antigens. Two of these agents have been FDA approved in the treatment of relapsed/refractory multiple myeloma and show much promise. Daratumumab is an anti-CD38 monoclonal

antibody that was FDA approved for the treatment of MM in patients who received at least three prior therapies including a proteasome inhibitor and an immunomodulatory agent. CD38 is a transmembrane glycoprotein that is ubiquitously expressed on MM cells, and other monoclonal antibodies targeting this antigen are in development. Daratumumab induces overall response rates (ORR) of 29–36% in heavily pretreated patients as a single agent (Usmani *et al.*, 2016). In two recent randomized controlled trials, there was significantly improved ORR of 83–93% when daratumumab was added to bortezomib or lenalidomide and dexamethasone, compared to these agents alone, with 61–63% reduction in risk of progression or death (Dimopoulos *et al.*, 2016; Palumbo *et al.*, 2016).

Antibody-drug conjugates

Antibody-drug conjugates take monoclonal antibodies a step further by linking the targeting antibody with a cytotoxic agent. The initial excitement of these direct drug delivery systems rose and fell with the approval and subsequent withdrawal of Gemtuzumab Ozogamicin (Mylotarg[®]) (GO) in 2000 and 2010, respectively. However, a recent meta-analysis from five randomized controlled trials that included 3325 patients with acute myeloid leukemia (AML) demonstrated that the use of GO improved 5-year overall survival and reduced the risk of relapse (Hills *et al.*, 2014). The absolute survival benefit was especially apparent in patients with favorable and intermediate risk cytogenetics. These data among others have prompted reconsideration of the withdrawal of GO. Nonetheless, recent momentum has been gained in haematologic malignancies again with the development of Brentuximab, an anti-CD30 antibody linked to a microtubule inhibitor, MMAE. Because of its efficacy in the treatment of relapsed/refractory Hodgkin lymphoma (HL) (either after autologous stem cell transplant or in patients who are not transplant candidates) and in relapsed systemic anaplastic large cell lymphoma, which are both malignancies in which CD30 is highly expressed, brentuximab received FDA approval for the treatment of both of these diseases in 2011 (Younes *et al.*, 2012). It

also received approval for post-autologous stem cell transplant consolidation in patients with HL at high risk of relapse or progression in 2015, based on data showing a median PFS of 43 months compared to 24 months for patients who received placebo (Moskowitz C.H. 2015).

Chimeric antigen receptor T cells (CAR T cells)

An incredibly promising area for immunotherapy in haematologic malignancies has been the development and refinement of CAR T cell therapy, which is a field that is moving at an accelerated pace. This therapy involves not only targeting tumor antigens directly but also augmentation of these targeted immune effectors. CAR T cells are autologous T cells that are engineered to express chimeric antigen receptors against a specific tumor surface antigen, thus are antigen specific and HLA independent, and therefore are independent of MHC expression. The general anatomy of CARs includes a single-chain variable fragment derived from an antibody, linked by a hinge and trans membrane domain to an intracellular T cell signaling domain with a costimulatory domain (number and type depending on the specific CAR) (Weinkove *et al.*, 2019; Maude *et al.*, 2015; Moskowitz *et al.*, 2014). This strategy has been particularly successful in haematologic malignancies, given several advantages compared to solid tumors: there are established cell surface antigens to target (e.g., CD19 on B cell malignancies); tumor sampling is straightforward and less invasive than in solid tumors, as discussed previously; and importantly, there is already a natural homing of T cells to the areas where the malignancy is located, e.g., blood, bone marrow, lymph nodes, thus making the road for these CARs straightforward. The process by which patients undergo CAR T cell therapy begins with collection of autologous T cells by leukapheresis. The CAR is then introduced into the T cells through one of the several mechanisms, most commonly using viral vectors, and then, the cells undergo culture for expansion. Usually, patients undergo lympho depleting chemotherapy prior to CAR T cell infusion, which can enhance in vivo expansion of T cells through the expression of homeostatic

cytokines, such as IL-7 and IL-15. This in vivo expansion has been correlated with response to therapy, thus may be more significant than the actual dose of T cells that are infused (Lee *et al.*, 2015; Maude *et al.*, 2014). The engagement of tumor antigen by CAR to the T cells then leads to cytotoxicity and massive T cell proliferation, which again is going to be independent of MHC expression.

Positron emission tomography (PET)/computerized tomography (CT)

A positron emission tomography scan is known as a PET scan. PET scan is a type of test that may be used in cancer treatment. It uses 2-(18F) fluorodeoxyglucose (FDG-PET) which were tested for the first time in malignant lymphomas 20 years ago (Paul, 1987). During the following years the value of PET-scans in the staging, prognostication, treatment planning, and response evaluation of lymphomas was extensively investigated, and PET became increasingly important in the management of several lymphoma types, particularly Hodgkin lymphoma (HL) and aggressive non-Hodgkin lymphoma (NHL). The role of PET in other types of hematological malignancies has not been evaluated as extensively. The present article will review the evidence for the use of PET in hematological malignancies.

PET in the planning of radiotherapy for lymphomas

For most lymphoma types, radiotherapy is today used in a combined modality setting. In this setting radiotherapy has changed from extended fields developed for single modality treatment to more and more conformal fields designed for combined modality treatment, encompassing only the initially macroscopically involved tissue volumes in early-stage disease and residual masses after chemotherapy in advanced disease (Girinsky *et al.*, 2016 and Yahalom *et al.*, 2005). These changes have led to dramatic reductions in the volume of normal tissue being irradiated in most lymphoma patients, leading to equally dramatic reductions in the risk of serious long-term sequelae of radiotherapy. However, with increasing conformality of radiotherapy for lymphomas the risk of geographical misses will also increase. Hence, the timing and the

anatomical accuracy of the imaging procedures used for treatment planning are essential. Accurate determination of the extent of disease at diagnosis (pre chemotherapy, radiotherapy planning and post chemotherapy) is critical for the planning of modern lymphoma radiotherapy. CT scans are employed for treatment planning, because the CT numbers are correlated with the electron density of the corresponding tissues at each voxel relative to the electron density of water. The information from the planning CT scan can therefore be employed by the dose-planning algorithm for calculation of the absorption and scattering of the radiation in the tissues. As PET has been shown to be more accurate for staging of HL and aggressive NHL, it is by implication also more precise in defining the initially involved regions which are intended to be irradiated in patients with early-stage disease. However, although virtually all lymphomatous masses are PET positive, it is not uncommon to see variable parts of clearly involved volumes that are CT positive but PET negative. We do not at present know the significance of this finding, which may be more common in some types of lymphoma than others. A recent publication on PET scan in early-stage HL showed that on average only 25% of the lymphoma volumes were FDG avid (Girinsky *et al.*, 2007). In this publication an automated segmentation method was used based on fixed thresholds originally developed for head and neck cancer. Other methods of segmentation may yield different percentages of FDG avid volumes. Interestingly, rates of chemotherapy induced shrinkage were similar for the PET-positive and PET-negative lymphoma masses. This may be taken as an indication that both contained active lymphoma tissue, although non-malignant reactive parts of the lymph node masses might also shrink due to chemotherapy. No diagnostic modality has 100% sensitivity and specificity, and the delineation of the lymphoma volume must be based on all the diagnostic information available of both anatomy and physiology of the disease (Gregoire, V. 2004). Therefore, treatment planning using a combined PET/CT scan is preferable (Jarritt *et al.*, 2006).

3.0 Challenges of Management in Developing Countries

Cancer is a major cause of death and disability in developing countries, where health systems are poorly equipped to deal with this challenge. Sub-Saharan Africa, in particular, is experiencing a marked increase in burden, with more than 1 million incidence of cancers and nearly 800 000 cancer-related deaths projected in the year 2030, representing an approximately 85% increase from 2008. By comparison, HIV is responsible for 1.2 million deaths, tuberculosis for 250 000 deaths, and malaria 709 000 deaths annually across sub-Saharan Africa, with mortality declining for each of these infectious diseases in recent years (Ferlay *et al.*, 2008; WHO, 2010).

As a result, cancer figured prominently in the recent United Nations General Assembly meeting on non-communicable diseases. Of all cancers occurring in sub-Saharan Africa, haematologic malignancies have emerged as a major cause of morbidity and mortality. Non-Hodgkin lymphoma (NHL), leukaemia, Hodgkin lymphoma (HL), and multiple myeloma together accounted for 8.7% of incident cancer diagnoses and 9.9% of cancer deaths in 2008, with NHL being the sixth most common cancer in the region. (Ferlay *et al.*, 2008) Treatment of haematologic malignancies in resource-rich settings is increasingly associated with unprecedented rates of long-term cure and control. Conversely, and despite their increasing impact, mechanisms for diagnosing, treating, and palliating these conditions in sub-Saharan Africa are inadequate. Despite numerous obstacles, haematologic malignancies can be effectively treated and cured in resource-limited settings.

GLOBOCAN 2008 estimates and 2030 projections summarizing the burden of haematologic malignancies. Despite serving as the reference standard for cancer burden worldwide, GLOBOCAN estimates suffer from several limitations with respect to sub-Saharan Africa. First, projections are derived from population growth and aging assuming stable cancer-specific incidence rates. Second, cancer registration is sparse because of difficulties defining and enumerating populations residing

in a particular area, as well as challenges obtaining accurate cancer diagnoses. Cancer registries covered only 11% of Africa in 2006 (Parkin, 2006) and data from small regions of only 2 countries in sub-Saharan Africa (Uganda and Zimbabwe) are included in the most recent Cancer Incidence in 5 Continents. Third, mortality statistics are similarly limited with only 3 countries (Mauritius, Seychelles, and South Africa) contributing to the WHO mortality registry (WHO, 2012).

Impact of endemic infections

Of cancers occurring in Africa, 36% result from infection, which is double the world average. (Parkin, 2006) In this context, the impact of several endemic infections on haematologic malignancies deserves examination.

HIV

In resource-rich countries, HIV confers a higher risk of NHL, HL, and leukemia (Patel *et al.*, 2008; Grulich A.E. *et al.*, 2007). A similarly increased risk of NHL and HL has been reported in sub-Saharan Africa (Mbulaiteye *et al.*, 2006). In the antiretroviral therapy (ART) era in developed countries, NHL incidence declined but has since stabilized, whereas HL incidence has been stable and possibly even increased (Engels *et al.*, 2006). Cancer has increased as a proportional contributor to HIV mortality and now accounts for 25% to 35% of deaths, with NHL being the most frequent cancer-related cause (Simard and Engels, 2010). Risk factors for NHL include lower CD4 count and cumulative HIV viremia (Engels *et al.*, 2010). Interestingly, risk for HL may be highest during the first months after ART initiation and with moderate rather than severe CD4 lymphopenia (Lanoy *et al.*, 2011). Despite having 12% of the world's population, sub-Saharan Africa is home to 22.9 million (68%) of the 34.0 million people worldwide living with HIV (UNAID, 2011). Although there have been significant achievements scaling up access to ART, there remain many obstacles. HIV-infected persons in sub-Saharan Africa initiate ART at lower CD4 counts than developed countries. Delayed ART initiation leads to greater lifetime CD4 lymphopenia and HIV viremia, placing patients at higher risk for haematologic malignancies

(Guiguet *et al.*, 2009). Revised 2010 WHO guidelines recommend ART at CD4 counts less than 350 cells/mm³ in resource-limited settings, replacing the prior threshold of less than 200 cells/mm³ (WHO,2010). However, even if updated WHO guidelines are universally implemented, there will remain a significant “treatment gap” between developing and developed countries, where many guidelines now recommend ART at CD4 counts more than 500 cells/mm³ (Thompson *et al.*, 2010) The risk of malignant haematologic disorders may also be enhanced by higher frequency of endemic oncogenic co infections in sub-Saharan Africa. As the global epidemic evolves, haematologic cancers may therefore become major contributors to HIV morbidity and mortality in the region, to an equal or even greater degree than resource-rich settings. Consistent increases in NHL, and to a lesser extent HL, have been noted across the region since the onset of the HIV epidemic, and HIV prevalence among NHL and HL patients in many settings ranges from 30% to 70% (Wiggill T.M. *et al.*, 2011; Mwakigonja *et al.*, 2010).

Epstein Barr Virus (EBV)

The discovery of EBV as the first virus to be pathogenically implicated in human cancer originated in sub-Saharan Africa nearly 50 years ago, when specimens collected by Denis Burkitt from Ugandan children with a newly described jaw tumor were cultured and examined via electron microscopy by colleagues in London. EBV has since been recognized for its ability to immortalize B lymphocytes, as well as its association with Burkitt lymphoma (BL), HL, nasal NK-T cell lymphoma, and B-cell NHL in patients with immunosuppression, including HIV (Thorley-Lawson and Gross, 2004). The kinetics of EBV acquisition differ in sub-Saharan Africa from developed countries. Infection occurs via contact with oral secretions, and seroprevalence is nearly universal throughout sub-Saharan Africa with acquisition in early childhood, whereas seroprevalence is approximately 75% in developed countries with acquisition later in life coincident with sexual activity (Cohen, 2000). Although the majority of the world's population is infected with EBV, there are marked global variations in the

incidence of EBV-associated cancers, perhaps resulting from host genetics, environmental factors, or viral genetic variation, with EBV having a striking and geographically unique association with BL and HL in sub-Saharan African (Chang *et al.*, 2009). EBV-encoded RNA has been demonstrated in more than 50% of unselected lymphomas from sub-Saharan Africa, with BL, HL, and plasmablastic lymphoma having the highest rates of association (Naresh *et al.*,2011).

Malaria

Sub-Saharan Africa's share of global malaria (□ 90%) is even more disproportionate than its share of HIV (WHO, 2010). Endemic childhood Burkitt Lymphoma (BL) has been ecologically linked to malaria since its earliest description (Kafuko and Burkitt, 1970) In addition, elevated levels of non-protective whole schizont antibodies, reflecting malaria-related immune activation, have been demonstrated among children with BL whereas protective antibodies against *Plasmodium falciparum* serine repeat antigen have been associated with lower BL risk in Africa (Guech-Ongey *et al.*, 2012). A clear etiologic link has not been established, yet *P falciparum* induces polyclonal expansion of B cells, impairs EBV-specific T-cell immune responses and may preferentially stimulate EBV replication and expansion of EBV-positive B-cell expression by its cysteine-rich interdomain region 1 α , all of which suggest a possible etiologic role. Alternatively, malaria transmission is influenced by pesticides, bed-nets, sociocultural practices, and other ecologic factors, which may modulate BL risk by affecting immune responses to EBV or malaria, or by influencing additional cofactors, such as intestinal parasites (Ogwang *et al.*, 2008).

Available resources

Despite increasing burden, resources to diagnose, treat, and palliate haematologic malignancies in sub-Saharan Africa are scarce. Moreover, services are concentrated within major population centers in more economically advanced countries, despite the fact that 63% of the population lived in rural areas in 2010 (World Bank,2012)

Haematopathology

Diagnostic haematopathology remains limited, and Laboratory Haematologist and Pathologist scarcity is symptomatic of critical health worker shortages in the SSA. These key workers tend to be concentrated in major cities and tertiary health institution (Benediktsson *et al.*, 2007). By comparison, there are more of these key professional in developed countries. The International Network for Cancer Treatment and Research (INCTR) convened a panel, which visited national referral hospitals in Kenya, Nigeria, Tanzania, and Uganda, to evaluate infrastructure for diagnosing lymphoma (Naresh *et al.*, 2011). Key findings included highly variable equipment and personnel, overuse of suboptimal fine needle aspiration specimens, variable turnaround times, variable histology and cytology preparations with lower standards than developed countries, a tendency for BL over diagnosis, and absence of immunohistochemistry. Cytogenetic, molecular, and FISH techniques, which are core elements of haematopathology in the developed world, are non-existent. Laboratory Haematologist and Pathologists were well trained and adequate in number for institutional workloads, but too few at the national level with inadequate numbers of trainees, and suffered from limited reference materials and training opportunities. Of 467 histologic samples interpreted as lymphoma by participating centers, 393 (84%) were assessable by the panel, with 364 (93%) assessed specimens confirmed as lymphoma on independent review, suggesting a high level of diagnostic accuracy when specimen quality was sufficient.

Chemotherapeutic agents

Twenty-two chemotherapeutic agents are included in March 2011 WHO Model Lists of Essential Medicines for adults and children, 20 of which are active in haematologic malignancies. The median year of US Food and Drug Administration approval for included medicines is 1969, and it has been proposed that cisplatin, imatinib, melphalan, and rituximab be added. Imatinib is available in some settings under a donation program and has been used with good results in chronic myelogenous leukemia in Kenya (Kiarie *et al.*, 2009). Developed countries have recently suffered from critical shortages of

many generic chemotherapeutic agents designated as WHO essential medicines. Although the impact of global shortages on cancer programs in sub-Saharan Africa is difficult to quantify, governments may be less able to secure adequate quantities of cancer medicines when competing with developed countries under conditions of limited international supply. Pharmacy stock-outs have long hampered HIV and tuberculosis treatment programs in sub-Saharan Africa. Drug shortages have similarly interfered with lymphoma treatment even in the context of an internationally funded clinical trial (Bateganya *et al.*, 2011; Mwanda *et al.*, 2009).

Radiotherapy

In sub-Saharan Africa, 64% of patients with NHL, 75% with HL, and 38% with myeloma have been estimated to need radiotherapy at diagnosis (Barton *et al.*, 2006). The International Atomic Energy Agency has set a global minimum standard of one radiotherapy unit per million persons, whereas developed countries may have up to 6 units per million persons (Salminen *et al.*, 2011). Currently, 18% of radiotherapy need in Africa is fulfilled, and 21 countries in sub-Saharan Africa have no operational units. Among radiotherapy centers, there are wide variations in staff and equipment, as well as occasional absence of simulators and treatment-planning systems. (Salminen *et al.*, 2011)

Haemopoietic Stem Cell Transfusion (HSCT)

HSCT is available in 6 centers in sub-Saharan Africa, all in South Africa (Pasquini and Wang, 2011). Between 1995 and 2011, 902 HSCTs (44% autologous, 43% matched sibling, 9% unrelated) were performed in South Africa and reported to the Center for International Bone Marrow Transplant Research, with leading indications being NHL, multiple myeloma, acute myeloid leukemia, and chronic myelogenous leukemia (Sandra, 2011). Outcomes were comparable to developed countries, with 5-year survival rates of 52% for autologous HSCT and 50% for allogeneic HSCT. Even within South Africa, availability is less than 50 HSCTs per 10 million population, compared with more than 300 HSCTs per 10 million population in developed countries (Gratwohl *et al.*, 2010).

Supportive and Palliative Care

In addition to better cancer treatments, many of the recent survival gains among patients with haematologic malignancies in developed countries have resulted from improved supportive care. In sub-Saharan Africa, where endemic infectious burden is high, and where patients frequently have HIV and other immunosuppressive conditions, such as malnutrition, infectious complications of cancer therapy present a significant obstacle. Cancer treatment increases risk of tuberculosis in endemic areas (Wu *et al.*, 2011). Bacteremia studies from sub-Saharan Africa are scarce and have focused on community-acquired bacteremia. Few existing nosocomial bacteremia studies suggest a distinct microbiologic spectrum from community-acquired bacteremia, similar to developed countries (Aiken *et al.*, 2011; Allegranzi *et al.*, 2011). Finally, palliation is a core function of oncologists in the developed world, and patients often die of cancer even when optimally treated. Palliative services in sub-Saharan Africa are scarce. They are constrained by opioid availability, as well as regulatory barriers that interfere with opioid administration even when available, despite the fact that morphine has been a WHO essential medicine since 1977 (Harding and Higginson, 2005). Scaling up palliative care has recently become an international priority, including WHO-sponsored initiatives to develop comprehensive palliative care programs with a community health approach.

Blood Transfusion Support

Effective blood transfusion service is fundamental in managing patients with haematologic malignancies (Ddungu *et al.*, 2020). The need for the safe and adequate supply of blood products for patients with haematological malignancies cannot be over emphasized. Thrombocytopenic and anaemic patient will need platelet and red cell concentrate including irradiated red cells where indicated respectively. Patients with alloantibodies with need to be transfused with antigen negative donor red cells, patients with platelets refractoriness will need HLA and or HPA matched platelets. In Nigeria, there is suboptimal access to safe and adequate supply of blood and specialized blood components (fresh frozen

plasma, cryoprecipitate, platelet concentrate, HLA and HPA matched platelets, irradiated, CMV negative and antigen negative blood products) required for the effective transfusion support of these patients (Erhabor and Adias, 2011).

4.0 Conclusion

In conclusion, given the enormous challenges and rapidly increasing burden, some may feel pessimistic about prospects for controlling haematologic malignancies in sub-Saharan Africa. Modern diagnostic equipment and techniques are often unavailable, there is suboptimal access to safe and adequate supply of blood and components, capacity to carry out bone marrow and haemopoietic stem cell transplant is often unavailable, there is poor health infrastructure and suboptimal financial resources to support the running of effective haemato-oncology service. There is need for the establishment of a collaborative network among professionals responsible for the diagnosis and management of haematological malignancies. Pharmaceutical companies need to be humane by ensuring the availability, affordability and accessibility to life saving chemotherapeutics, radiotherapy and iron chelation agents as well as the optimization of health infrastructure both human and materials to facilitate the optimum management of haematological cancers in SSA.

5.0 Recommendations

1. There is need to develop conventional and novel diagnostics adapted to the West African setting: There is a critical need to expand histopathology, improve tissue sampling and processing, and implement basic immunohistochemistry. However, grafting pathology systems from developed countries into dissimilar settings without modification is unlikely to be successful. Conventional procedures may need to be supplemented, and even supplanted in some instances, by diagnostic algorithms, tissue microarrays, and digital microscopy approaches suited to local conditions, as promoted by the INCTR and Sub-Saharan Africa Lymphoma Consortium (Naresh *et al.*, 2011).
2. There is need to make cancer medicines and iron chelation medication to be affordable as well as the integration of newer treatments:

The molecular age has catalyzed a shift away from cytotoxic treatment toward “targeted” therapies directed at immunophenotypes, mutations, and gene products. Non-cytotoxic agents, which have augmented the armamentarium for haematologic malignancies in recent years, include monoclonal antibodies, antibody-drug conjugates, small molecule tyrosine kinase inhibitors, immunomodulatory agents, proteasome inhibitors, and histone deacetylase inhibitors. The optimal application for many of these agents remains under investigation even in resource-rich settings, and they are prohibitively expensive for use in SSA at present.

3. There is an urgent need to increase global funding for cancer and rigorously assess cost-effectiveness of cancer control measures: Sub-Saharan Africa accounted for 5.4% of new global cancer cases in 2009 but only 0.2% of global cancer spending, with South Africa by itself accounting for 51% of the total \$581 million (US) in regional cancer expenditures (Beaulieu *et al.*, 2012). By comparison, \$2.8 billion (US) was spent on HIV in sub-Saharan Africa in 2009. (UNAIDS, 2012).
4. There is need for increased human capital investments for cancer management: Although non oncologist providers can deliver cancer treatment safely and effectively (Farmer *et al.*, 2010), critical health worker shortages, enabling environment and optimum infrastructure need to be addressed.
5. There is need to optimize the delivery of effective (adequate and safe) blood transfusion supportive care for patients with haematologic malignancies that may need specialized blood products (antigen negative products for those with alloantibodies, CMV negative, gamma irradiated products, HLA and HPA matched platelet.

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