Draft PMB definition guidelines: Best supportive care for haematology oncology

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Disclaimer:

The draft benefit definition on best supportive care has been developed for the majority of standard patients. All interventions described only apply if the patient has been diagnosed with a haematology oncology condition. Regulation 15(h) and 15(I) may be applied for patients who are inadequately managed by the stated benefits.

Once the registration status of some pharmaceuticals that are not currently registered in South Africa changes or the essential medicine list (EML) listing changes, these products may become eligible as PMB level of care.

A referral pathway should be followed for the management of some of the interventions detailed in this document.

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Abbreviations

CMS - Council for Medical Schemes

PMB - Prescribed Minimum Benefits

Hb – Haemoglobin

RBC - Red Blood Cell

CRA – Cancer related anaemia

CIA – Chemotherapy induced anaemia

CKO – Chronic Kidney Disease

ECAS - European Cancer Anaemia Survey

ESA - Erythropoiesis stimulating agents

PRBC - Packed red blood cell

CIA - Cancer induced anaemia

DA - Darbepoetin alfa

AHRQ - Agency for Healthcare Research and Quality

FFTF - Freedom from treatment failure

OS - Overall survival

TIBC - Total iron binding capacity

HL - Hodgkin's lymphoma

NHL - Indolent non-Hodgkin's lymphoma

CLL - Chronic lymphocytic leukaemia

MM - Multiple myeloma

FCM - Ferric carboxymaltose

FN - Febrile neutropenia

MASCC - Multinational Association of Supportive Care in Cancer

CSFs - Colony-stimulating factors

G-CSF - Granulocyte colony-stimulating factor

GM-CSF - Granulocyte-macrophage colony-stimulating factor

VTE - Venous thromboembolism

UFH - Unfractionated Heparin

LMWH - Low Molecular Weight Heparins

PE - Pulmonary embolism

HSCT - Hematopoietic stem cell transplantation

TLS - Tumour lysis syndrome

PFS - Progression-free survival

BPs – Bisphosphonates

IUI - Inter Uterine Insemination

IVF - Vitro Fertilization

CMV – Cytomegalovirus

AML -Acute myeloid leukaemia

MDS - Myelodysplastic syndrome

HSCT - Allogeneic hematopoietic stem cell transplant

IVIG - Intravenous immune globulin

PCP - Prophylaxis for Pneumocystis pneumonia

1. Introduction

1.1. A diagnosis of cancer and its subsequent treatment can have a devastating impact on the quality of a person's life. Patients face new fears and uncertainties and may have to undergo unpleasant and debilitating treatments.

1.2. It is internationally accepted that the essential components of cancer care should include the relief of suffering and support of physical and psychological wellbeing (Kaasa et al., 2018).

1.3. Medical schemes interpret best supportive care benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.4. The benefit definition project is coordinated by the Council for Medical Schemes (CMS) and aims to define the prescribed minimum benefits (PMB) package for the best supportive care, whilst guiding the interpretation of the PMB provisions by relevant stakeholders.

2. Scope and purpose

2.1. The purpose of this document is to improve clarity in respect of funding decisions by medical schemes in the context of haematology oncology, taking into consideration evidence-based medicine, affordability and in some instances cost-effectiveness. It is important to note that schemes may apply formularies where there are therapeutic equivalents.

2.2. The National Institute of Cancer at the National Institutes of Health (US) defines supportive care as care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal of supportive care is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment (National Cancer Institute, 2020).

2.3. Supportive care for common disease and/or treatment-related morbidities, and challenges encountered by patients with hematologic malignancies, listed below, will be discussed.

- Anaemia
- Neutropenia
- Thrombocytopenia
- Bleeding
- Thrombo-embolic disease
- Iron overload
- Metabolic disorders, including hyperuricemia, hypercalcemia and tumour lysis syndrome

- Bone disease
- Peripheral neuropathy – please refer to relevant section in pain document available here
- Fertility issues
- Infections
- Dental issues
- Orthopedic complications
- Frailty and mobility challenges
- Psychosocial challenges – mental health should be managed as per the corresponding DTP.

3. Anaemia

3.1. Description

3.1.1. Anaemia is characterized by a decrease in haemoglobin (Hb) concentration, red blood cell (RBC) concentration and/or haematocrit to subnormal levels.

3.1.2. Pathophysiological origins of anaemia can be grouped into the following three categories:

- Decreased production of functional RBC
- Increased destruction of RBC
- Blood loss (Griffiths et al., 2020).

3.1.3. Anaemia in cancer patients is multifactorial and may occur as a direct effect of the cancer, as a result of the cancer treatment itself, or due to chemical factors produced by the cancer (Mercadante and Gebbia, 2000).

3.1.4. The immune system of cancer patients is usually activated by the tumour cells, leading to the production of several cytokines. This inflammatory response affects the production of erythropoietin, suppresses the burst-forming unit-erythroid as well as the colony-forming unit-erythroid, and disrupts the utilization of iron.

3.1.5. Erythrocyte survival may also be affected by the tumour cells either via tumour necrosis factor or by causing erythrophagocytosis (Buck et al., 2009).

3.1.6. Figure 1 below show types of cancer-related anaemia and their pathophysiology in patients with cancer (Gilreath, Stenehjem and Rodgers, 2014).

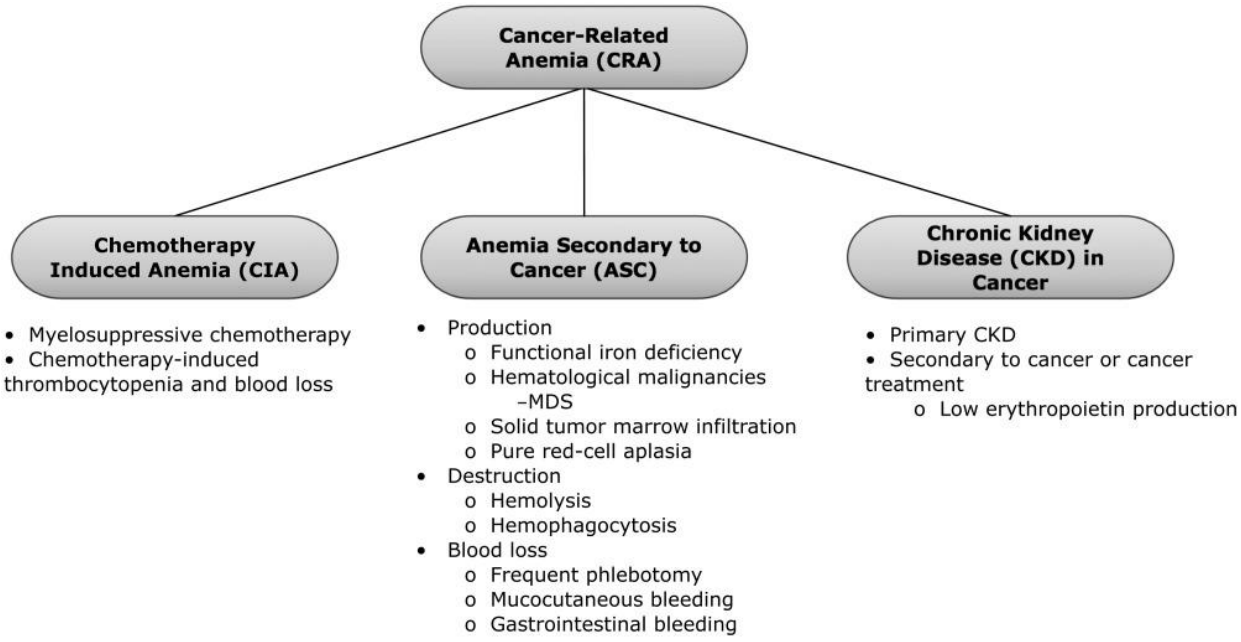

Figure 1 Types of Cancer-Related Anaemia (Gilreath, Stenehjem and Rodgers, 2014).

3.1.7. Anaemia prevalence in patients with cancer vary widely and is affected strongly by the definition of anaemia (<9 g/dL vs. <11 g/dL). 7% of patients with Hodgkin lymphoma had anaemia when the condition was defined as a haemoglobin level <9 g/dL; and as many as 86% of patients had anaemia when it was defined as a haemoglobin value <11 g/dL (Knight, Wade and Balducci, 2004).

3.1.8. Prevalence also varied by cancer type, disease stage, and cancer treatment status (Knight, Wade and Balducci, 2004)(Birgegård et al., 2005).

3.1.9. The prevalence of anaemia at the time of diagnosis is around 30 to 40% of patients with non-Hodgkin's lymphoma or Hodgkin's lymphoma, and usually about 70% in patients with multiple myeloma. Less than 50% of patients with solid cancers or lymphomas develop anaemia after chemotherapy (Bennett et al., 2010).

3.1.10. The European Cancer Anaemia Survey (anaemicfound that of the patients who were not anemic at enrollment and started cancer treatment during the survey and those patients undergoing chemotherapy – either alone or in combination with radiotherapy – had the highest incidence of anaemia (63% and 42%, respectively) (Birgegård et al., 2005).

3.1.11. Anaemia is a regular cause of morbidity and mortality (Caro et al., 2001). CMS recommends that a haemoglobin level ≤11 g/dl in cancer patients should be investigated and treated accordingly.

3.2. Treatment options for anaemia

Anaemia can be corrected by:

- Treating the underlying etiology
- Packed red blood cell transfusions
- Erythropoiesis stimulating agents (ESA)
- Iron preparations
- Folate supplementation e.g. in Primary Myelofibrosis

Any cause of anaemia that is not caused by cancer or chemotherapy should be treated as indicated (Griffiths et al., 2020).

3.2.1. Packed red blood cell transfusion

3.2.1.1. If the haemoglobin level decreases after chemotherapy, then transfusion may be appropriate even in the absence of symptoms or significant comorbidity (Saslow et al., 2012).

3.2.1.2. Packed red blood cell (PRBC) transfusion is the only option for treating patients that require immediate correction of anaemia.

3.2.1.3. Certain risks such as transfusion-related reactions, congestive heart failure, bacterial contamination, viral infections, iron overload, and an increase in thrombotic events are usually associated with PRBC (Spivak, Gascón and Ludwig, 2009).

3.2.1.4. PRBC are recommended as a PMB benefit in patients who require immediate correction of anaemia at the discretion of the treating clinician.

3.2.2. Erythropoiesis stimulating agents (ESA)

3.2.2.1. Erythropoiesis stimulating agents (ESA) stimulate erythropoiesis in patients with low RBC levels, although not all patients respond to them. ESA can take weeks to elicit an Hb response but are effective at maintaining a target Hb level with repeated administration (Griffiths et al., 2020).

3.2.2.2. In a retrospective pharmacoepidemiologic study of 2,192 patients treated with erythropoiesis-stimulating agents (ESAs) from 307 centres, a Hb increase of equal or greater than 1 g/dl was attained in 65 % of the patients over 8 weeks (Ludwig, Aapro, et al., 2009).

3.2.2.3. There is a debate regarding the association between increased morbidity and/or mortality and ESA therapy. The first Cochrane Database meta-analysis on ESA treatment outcomes in cancer patients (2004) reported a reduction in the need for blood transfusions with ESA use and a reduction in the number of units transfused (Bohlius et al., 2004).

3.2.2.4. In the recent update of 2004 Cochrane review, the authors concluded that ESAs reduce the need for red blood cell transfusions but increase the risk for thromboembolic events and deaths (Tonia et al., 2012).

3.2.2.5. In a pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials in 2,122 patients with cancer induced anaemia (CIA) receiving darbepoetin alfa (DA; n = 1,200) or placebo (n = 912) to assess the benefits and risks of ESAs in CIA, no association between darbepoetin alfa and risk of death or disease progression was found (Ludwig, Crawford, et al., 2009).

3.2.2.6. A systematic review by the Agency for Healthcare Research and Quality (AHRQ) showed that delaying ESA treatment until the Hb is less than 10 g/dl resulted in fewer thromboembolic events and a reduced mortality (Grant MD, Piper M, Bohlius J, 2013).

3.2.2.7. Pharmacovigilance data have reported no adverse effects on survival in patients with CIA receiving ESA. The prospectively randomized HD15EPO study performed by the German Hodgkin Study Group showed that there was no difference between patients treated with epoetin alfa or placebo with respect to freedom from treatment failure (FFTF) and overall survival (OS) in patients with advanced-stage Hodgkin's lymphoma (HL) (Engert et al., 2010).

3.2.2.8. The 2018 ESMO Clinical Practice Guidelines recommend that ESA should be considered for treatment of anaemia in patients under chemotherapy after correction of iron deficiency and other underlying causes other than the cancer or its treatment (Aapro et al., 2018).

3.2.2.9. In South Africa the ESA are currently only approved on the EML in the renal setting (for treatment of anaemia of chronic disorder in patients with chronic kidney disease).

3.2.2.10. CMS recommends that the choice of the ESA be at the discretion of the treating provider and that schemes may apply formularies. The ESAs that are currently available in South Africa at the time of publishing include:

- Human EPO
- Epoetin alfa
- Epoetin beta
- Darbepoetin alfa
- Methoxy polyethylene glycol-epoetin beta

3.2.3. Iron deficiency and iron preparations

3.2.3.1. Iron deficiency can be classified as absolute (when iron reserves are depleted) or functional (when iron reserves are normal or even increased). In both cases, there is a reduction in the iron available for erythropoiesis, leading to anaemia (Naoum, 2016).

3.2.3.2. In absolute iron deficiency, the lack of iron in reserves is the main triggering event of anaemia. In the case of functional iron deficiency, although the reserves are satisfactory, the presence of an inflammatory process causes the iron to become 'trapped' in macrophages and enterocytes, limiting its availability to the bone marrow, triggering anaemia (Naoum, 2016).

3.2.3.3. Iron deficiency is reported in 32% to 60 % of patients with cancer, most of whom are also anemic (Aapro et al., 2012). Iron deficiency should be ruled out by iron studies (serum iron, total iron binding capacity (TIBC) and serum ferritin) as it may respond to oral or IV iron monotherapy (Griffiths et al., 2020).

3.2.3.4. Although oral iron is appropriate for most iron-deficiency anaemia patients, many patients do not respond to or may be intolerant of oral iron, or may experience bleeding of sufficient magnitude to require higher iron doses than that are achievable with oral iron (Silverstein, Gilreath and Rodgers, 2008).

3.2.3.5. A systematic review and meta-analysis of randomised controlled trials comparing IV iron with no iron or oral iron for treatment of chemotherapy induced anaemia found that IV iron added to ESA results in an increase in hematopoietic response and reduction in the need for RBC transfusions (Gafter-Gvili et al., 2013).

3.2.3.6. Iron can be administered orally or intravenously and both formulations are recommended as PMB level of care. The dosage and duration of this therapy will be at the discretion of the treating clinician.

3.2.4. Low Molecular Weight Iron Dextran

3.2.4.1. A prospective, multicentre, open-label, randomized trial enrolled 157 patients with chemotherapy-related anaemia on epoetin alfa to receive (1) no-iron; (2) oral iron; (3) iron dextran repeated IV bolus; or (4) iron dextran total dose infusion (TDI). Mean Hb increases for both IV iron groups were greater ($P < .02$) than for no-iron and oral iron groups. There was no statistically significant difference between the IV iron groups, suggesting that lower, intermittent doses of IV iron dextran are equally as efficacious as TDI (Auerbach et al., 2004).

3.2.4.2. Severe reactions to IV iron dextran test dose may occur. Pre-medication of the patient prior to the test dose is recommended. Anaphylaxis-like reactions occur within minutes of the test dose but respond readily to IV adrenaline, diphenhydramine and corticosteroids (Griffiths et al., 2020).

3.2.5. Ferric Hydroxide Sucrose Complex (Iron Sucrose)

3.2.5.1. A prospective, open-label, multicentre study randomised 67 patients with clinically stable lymphoproliferative malignancy (indolent non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) or multiple myeloma (MM)) not requiring chemotherapy or blood transfusions to receive ESA with no iron or intravenous iron. In this study, Hb increase and response rate were significantly greater with the addition of intravenous iron to epoetin treatment in iron-replete patients and a lower dose of epoetin was required (Hedenus et al., 2007).

3.2.6. Ferric Carboxymaltose

3.2.6.1. An observational study evaluating the use of ferric carboxymaltose with or without ESA in patients with cancer found that the median Hb increase was comparable in patients receiving ferric carboxymaltose (FCM alone (1.4 g/dl [0.2–2.3 g/dl; N = 233]) or FCM + ESA, suggesting a role for IV iron alone in anaemia correction in cancer patients (Steinmetz et al., 2013). Another observational, prospective study of patients with a solid tumour or a haematological malignancy treated with FCM alone or additional ESA achieved similar median Hb increase (1.3 [0.4, 2.1] g/dL and 1.4 [0.4, 2.5] g/dL, respectively)(Toledano et al., 2016).

4. Neutropenia

4.1. Description

4.1.1. Febrile neutropenia (FN) is defined as an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 hours and an absolute neutrophil count of < 0.5 x 10^9 /L or expected to fall below 0.5 x 10^9 /L (J Klastersky et al., 2016).

4.1.2. Febrile neutropenia (FN) can occur at any time during the course of a hematologic malignancy, from diagnosis to end-stage disease.

4.1.3. Most FN episodes are typically confined to the period of initial diagnosis and active treatment.

4.1.4. The only sign of infection the patient has is fever as the inflammatory responses are suppressed (Keng and Sekeres, 2013).

4.1.5. The risk of FN and its complications increases when one or several co-morbidities are present in the patient. These considerations will be instrumental in deciding whether a chemotherapy-treated patient should receive primary prophylaxis to decrease the potential risk of FN.

4.1.6. Mortality varies according to the Multinational Association of Supportive Care in Cancer (MASCC) prognostic index, as seen below in Table 1: lower than 5% if the MASCC score is ≥21, but possibly as high as 40% if the MASCC score is <15 (J Klastersky et al., 2016). The MASCC index was developed in 2000 by a multinational study including patients from Belgium, Canada, Copenhagen, South Africa and the USA. It is now widely used in assessing the risk associated with febrile neutropenia.

Table 1: Components of the Multinational Association for Supportive Care in Cancer Index

Clinical characteristic	Score
Burden of illness (1 of the 3 options only):	
No or mild symptoms	5
Moderate symptoms	3
Severe symptoms	0
No hypotension (systolic BP > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour or no prior fungal infection in patient with hematologic neoplasm	4
No dehydration (hydration with IV fluids not required)	3
Outpatient at onset of fever	3
Age < 60 years	2

4.1.7. Febrile neutropenia (FN) occurs with common chemotherapy regimens in 25% to 40% of treatment-naive patients, and its severity depends on the dose intensity of the chemotherapy regimen, the patient's prior history of either radiation therapy or use of cytotoxic treatment, and comorbidities (Dale, 2002).

4.2. Management of neutropenia

4.2.1. The occurrence of FN subsequently leads to delays in chemotherapy or reductions in the dose of chemotherapy. It may also increase the length of monitoring and hospital stay, the costs of treatment and diagnosis and reduction in the quality of patient's life (Rosa and Goldani, 2014).

4.2.2. A significant part of preventing life threatening FN is the introduction of colony-stimulating factors (CSFs) such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF)

4.2.3. These adjunctive agents hasten the development of neutrophils from committed progenitors, hence reducing the extent and severity of neutropenia.

4.2.4. The CSFs are significantly used in oncology for the prevention of FN after chemotherapy, treatment of febrile neutropenic episodes and support following bone marrow transplantation, as well as collection of CSF-mobilized peripheral blood progenitor cells. G-CSF is used more frequently than GM-CSF for all of these indications as there are fewer associated adverse effects (Dale, 2002).

4.2.5. In a meta-analysis of 13 studies involving a total of 1,518 patients, found that the overall mortality was not influenced significantly by the use of CSF (odds ratio [OR] = 0.68; 95% CI, 0.43 to 1.08; P = 0.1). A marginally significant result was obtained for the use of CSF in reducing infection-related mortality (OR = 0.51; 95% CI, 0.26 to 1.00; P = 0 0.05). Patients treated with CSFs had a shorter length of hospitalization (hazard ratio [HR] = 0.63; 95% CI, 0.49 to 0.82; P = 0.0006) and a shorter time to neutrophil recovery (HR = 0.32; 95% CI, 0.23 to 0.46; P < 0.00001)(Clark et al., 2005).

4.2.6. Another meta-analysis evaluating the safety and efficacy of adding G-CSF or GM-CSF to standard treatment (antibiotics) when treating chemotherapy-induced febrile neutropenia in individuals diagnosed with cancer found that although the overall mortality was not improved by the use of CSF plus antibiotics versus antibiotics alone (hazard ratio (HR) 0.74 (95% confidence interval (CI) 0.47 to 1.16) P = 0.19; 13 RCTs; 1335 participants; low quality evidence), the amount of time participants spent in hospital and improved their ability to achieve neutrophil recovery (Mhaskar et al., 2014).

4.2.7. A meta-analysis of 17 RCTs involving 3,493 patients with solid tumour and lymphoma, primary prophylaxis with G-CSF (defined as G-CSF administration within 5 days of beginning chemotherapy) reduced the risk of FN (RR, 0.54; CI 0.43 – 0.67; p < 0.001) (Kuderer et al., 2007).

4.2.8. An algorithm for the decisions about primary prophylactic G-CSF use is shown in Figure 2 below.

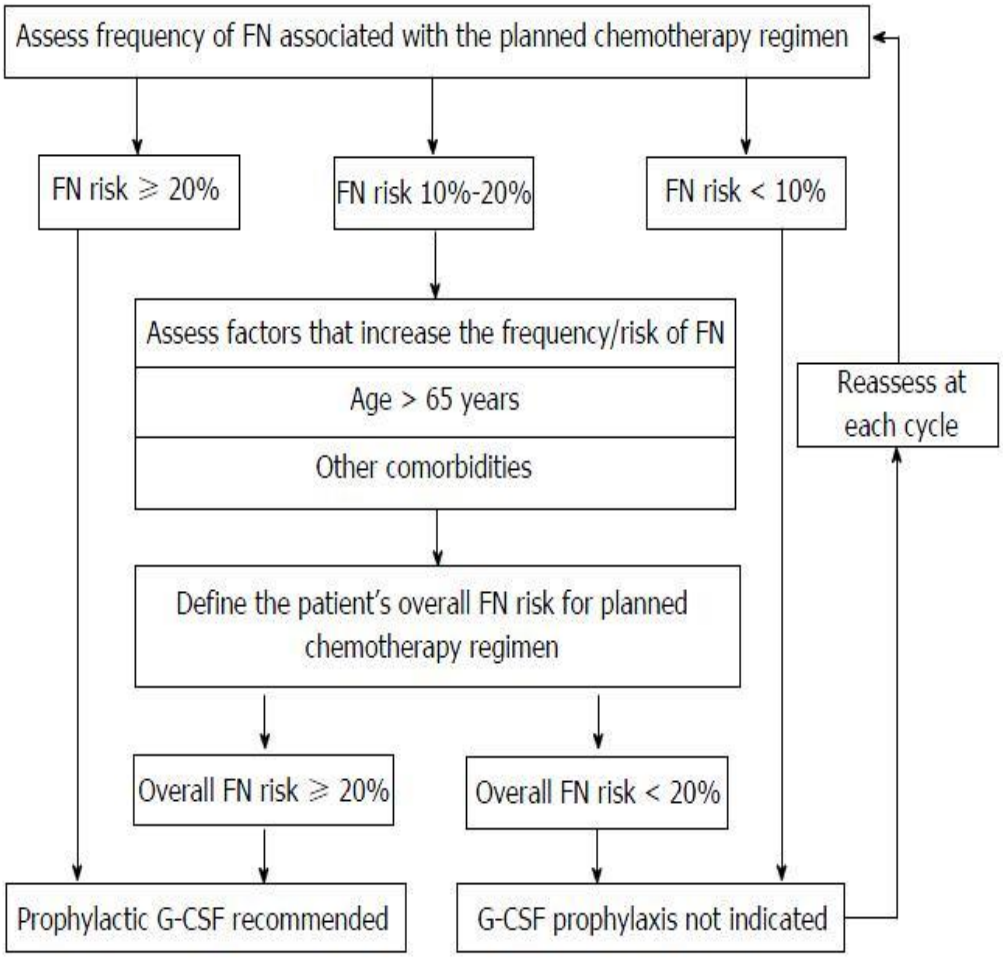

Figure 2 Algorithm to decide primary prophylactic granulocyte colony-stimulating factor usage. (Jean Klastersky et al., 2016).

4.2.9. Besides this approach, G-CSF can be considered in patients with reduced bone marrow reserve due to extensive radiotherapy or patients who are neutropenic in the context of HIV infection (J Klastersky et al., 2016).

4.2.10. Recent meta-analysis of randomised, controlled trials and experience in real-world settings confirm the that there is a more than 50% success of primary prophylaxis with filgrastim or pegfilgrastim (Wang et al., 2015); however the

4.2.11. Systematic review of real-world comparative effectiveness studies showed that the risks of FN and FN-related complications were generally lower for prophylaxis with pegfilgrastim versus prophylaxis with filgrastim (Mitchell et al., 2016) .

4.2.12. CSF are recommended as PMB level of care in patients with chemotherapy induced febrile neutropenia who meet the following criteria:

- If the risk of FN is greater or equal to 20 % with the planned chemotherapy regimen (treatment with myelosuppressive chemotherapy)
- If there are other factors that increase the risk of FN such as:
    - Age greater than 65
    - Other comorbidities (renal disease, cardiovascular disease)
    - Poor performance status
    - Low body surface area/ body mass index
    - Advanced disease
    - Low baseline blood cell counts (Lyman, Abella and Pettengell, 2014).

4.2.13. Schemes may develop formularies for the different CSF that are available for chemotherapy induced neutropenia.

4.2.14. There are currently no GM-CSF available in South Africa hence not currently recommended as PMB level of care.

4.2.15. Although only filgrastim is currently listed on the EML, CMS recommends the therapeutic class of G-CSF (including pegfilgrastim).

5. Thrombocytopenia

5.1. Description

5.1.1. Thrombocytopenia is defined as a platelet count of less than 150 X 10^9 per L (Gauer and Braun, 2012). However, clinical thrombocytopenia refers to a platelet count of less than 100 X 10^9 per L. Thrombocytopenia is a frequent complication of cancer and its treatment (Liebman, 2014).

5.1.2. The causes of thrombocytopenia in cancer patients can be diverse and multifactorial (Liebman, 2014).

5.1.3. In lymphoproliferative malignancies, thrombocytopenia can result from:

- splenic sequestration of platelets in patients with splenomegaly,
- decreased production due to bone marrow replacement and/or systemic chemotherapy, and
- immune-mediated platelet destruction (Kuznetsov et al., 1992) .

5.1.4. The degree and duration of thrombocytopenia depend upon whether the chemotherapeutic treatment is myeloablative, as used in stem cell transplants or non-myeloablative (Liebman, 2014).

5.1.5. Additional causes of significant thrombocytopenia include tumour involvement of bone marrow and spleen; microangiopathic disorders such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura or hemolytic uremia syndrome.

5.1.6. Lymphoproliferative malignancies can also be associated with secondary immune thrombocytopenia (Liebman, 2014).

5.1.7. In haematological malignancies, a threshold level of 10,000 platelets/μL is widely accepted as the minimal level prompting prophylactic platelet transfusion (Castaman and Pieri, 2018).

5.2. Management of thrombocytopenia

5.2.1. The primary goal of thrombocytopenic management following myeloablative chemotherapy is the prevention of major bleeding with the minimal use of platelet transfusions.

5.2.2. Platelet transfusion is the elective procedure to prevent or treat bleeding in patients with hypo-proliferative thrombocytopenia due to haematological disorders, bone marrow infiltration, chemotherapy or hematopoietic stem cell transplantation(Castaman and Pieri, 2018).

5.2.3. For active bleeding in patients with cancer related thrombocytopenia, platelet transfusion is the first line of therapy if bleeding is considered related to thrombocytopenia (Castaman and Pieri, 2018).

5.2.4. A systematic review of 17 randomised controlled trials showed a beneficial effect of prophylactic compared with therapeutic transfusion for the prevention of significant bleeding in patients with hematologic disorders undergoing chemotherapy or stem cell transplantation (Kumar et al., 2015).

5.2.5. Two randomized clinical trials have demonstrated that prophylaxis with platelet transfusions reduced the incidence of WHO grade 2 - 4 bleeding events in patients with cancer related hypo-proliferative thrombocytopenia (Stanworth et al., 2013)(Wandt et al., 2012).

5.2.6. Platelet transfusion is recommended as PMB level of care for treatment and/or prophylaxis of thrombocytopenia in patients with haematological malignancies. The threshold or timing of the treatment will be at the discretion of the treating clinician.

6. Bleeding

6.1. Description

6.1.1. Patients with hematologic malignancies bleed for a variety of reasons, including:

- alterations in platelet function and numbers (thrombocytopenia),
- clotting factor deficiencies,
- circulating anticoagulants,
- defects in vascular integrity (Green, 2007)

6.1.2. Patients with Ph-negative myeloproliferative neoplasms (MPN), such as polycythemia Vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are at increased risk for major bleeding. The MPN registry of the Study Alliance Leukaemia non-interventional prospective study reported that significant odds for major bleeding were previous thromboembolic events (OR = 2.71; 95% CI = 1.36-5.40), splenomegaly (OR = 2.22; 95% CI 1.01-4.89), and the administration of heparin (OR = 5.64; 95% CI = 1.84-17.34). The study also found that major bleeding episodes were significantly less frequent in ET patients compared to other MPN subgroups (Kaifie et al., 2016).

6.1.3. Patients with advanced haematological malignancies may experience many troublesome haemorrhagic complications requiring hospitalisation during palliative home care (Cartoni et al., 2009).

6.1.4. Patients with a platelet count lower than 20×10^9/L ($P < 0.00005$) or with a diagnosis of acute leukaemia or in blast crisis of myeloproliferative disorders ($P < 0.00005$) showed a significant higher incidence of haemorrhages than other patients (Cartoni et al., 2009).

6.1.5. Bleeding may present as bruising, petechiae, epistaxis, haemoptysis, haematochezia, haematochezia, melena, haematuria, or vaginal bleeding (Johnstone and Rich, 2017).

6.2. Management of bleeding

6.2.1. Tranexamic acid can be used prophylactically to decrease the bleeding risk in patients with haematologic malignancies. It has also been used in patients who are refractory to platelet transfusions or in cases where platelet transfusions did not clinically work (Kalmadi et al., 2004; Antun et al., 2013; Estcourt et al., 2016). Tranexamic acid is recommended for prevention and/ or management of bleeding in patient's refractory to platelet transfusions or when platelet transfusions did not clinically work.

6.2.2. Although there is currently no reported RCT data on the use of tranexamic acid for bleeding in patients with haematologic malignancies, there is some experience with its use in acute severe bleeding. A meta-analysis of individual patient-level data from 40,138 bleeding patients showed that tranexamic acid significantly increased overall survival from bleeding (odds ratio [OR] 1·20,

95% CI 1·08–1·33; p=0·001), with no heterogeneity by site of bleeding (interaction p=0·7243)(Gayet-Ageron et al., 2018).

6.2.3. An ongoing TREATT Trial (TRial to EvaluAte Tranexamic acid therapy in Thrombocytopenia), multinational (UK and Australia), randomised, double-blind, placebo-controlled, parallel, superiority trial randomizing patients to receive either tranexamic acid (given intravenously or orally) or a matching placebo aiming to test whether giving tranexamic acid to patients receiving treatment for haematological malignancies reduces the risk of bleeding or death and the need for platelet transfusions, will shed more information in due course (Estcourt et al., 2019).

7. Thrombo-embolic disease

7.1. Description

7.1.1. Thrombo-embolic disease is usually due to Venous thromboembolism (VTE). VTE includes deep vein thrombosis and pulmonary embolism, is an important cause of morbidity and mortality among patients with cancer (Falanga and Marchetti, 2009). The incidence of VTE is variable and is influenced by many factors, including the type of disease, the type of chemotherapy, and the use of a central venous device (Falanga and Marchetti, 2009)(Kekre and Connors, 2019).

7.1.2. Biologic properties of the tumour cells can influence the hypercoagulable state of patients with these malignancies by several mechanisms. Oncogenes responsible for neoplastic transformation in leukaemia may also be involved in clotting activation. The contribution of chemotherapy on the incidence of thrombosis is particularly evident in acute leukaemia as it causes the exacerbation of the clotting/bleeding syndrome typical of this disease. The effect of chemotherapy on thrombosis is also relevant in lymphoma, and in multiple myeloma, in which the use of immunomodulating agents, in combination with chemotherapy and steroids significantly increases the risk of VTE (Falanga, Marchetti and Russo, 2012).

7.2. Management of thrombo-embolic disease

7.2.1. Unfractionated Heparin [(UFH) – e.g. heparin sodium], Low Molecular Weight Heparins [(LMWH) e.g. enoxaparin and dalteparin], warfarin and aspirin are recommended for prophylaxis and/or treatment of thromboembolic disease in patients with hematologic malignancy. The choice, timing

and duration of therapy will be at the discretion of the treating clinician, considering the contraindications and risk of each therapy.

7.2.2. A meta-analysis of the efficacy and safety of enoxaparin vs UFH in patients with proximal DVT with/without symptomatic pulmonary embolism (PE) found demonstrated safety and efficacy of enoxaparin. The observed RR (enoxaparin/UFH) of VTE was 0.81 (95% CI, 0.52 to 1.26) for the intention-to-treat population (RR, 0.70; 95% CI, 0.43 to 1.13; for per-protocol analysis). Results did not differ for patients with clinical PE (235 patients; RR, 0.84) and without clinical PE (1,268 patients; RR, 0.71), with a nonsignificant heterogeneity test between groups (p = 0.76). A trend in favor of enoxaparin was observed for reduced mortality and major bleeding (Mismetti et al., 2005).

7.2.3. There seems to be no difference between UFH and LMWH with regard to VTE-related and all-cause mortality. A meta-analysis assessing the effects of subcutaneous UFH versus intravenous UFH, subcutaneous LMWH or any other anticoagulant drug for the initial treatment of venous thromboembolism, found no evidence of a difference between subcutaneous versus intravenous UFH for preventing VTE recurrence, VTE-related or all-cause mortality, and major bleeding. There is also no evidence of a difference between subcutaneous UFH and LMWH for preventing VTE recurrence, VTE-related or all-cause mortality or major bleeding (Robertson and Strachan, 2017)

7.2.4. There is moderate-quality evidence that fixed dose LMWH reduced the incidence of recurrent thrombotic complications and occurrence of major haemorrhage during initial treatment. A recent revision of the Cochrane review which included 29 studies showed that the incidence of recurrent venous thromboembolic events was lower in participants treated with LMWH than in participants treated with UFH (Peto odds ratio (OR) 0.69, 95% confidence intervals (CI) 0.49 to 0.98). Major haemorrhages occurred less frequently in participants treated with LMWH than in those treated with UFH (Peto OR 0.69, 95% CI 0.50 to 0.95; 8,780 participants; 25 studies; P = 0.02; moderate-quality evidence). There was no difference in overall mortality between participants treated with LMWH and those treated with UFH (Peto OR 0.84, 95% CI 0.70 to 1.01; 9,663 participants; 24 studies; P = 0.07; moderate-quality evidence) (Robertson and Jones, 2017).

7.2.5. A meta-analysis of efficacy and safety of oral anticoagulants in ambulatory people with cancer undergoing chemotherapy, hormonal therapy, immunotherapy or radiotherapy, but otherwise have no standard therapeutic or prophylactic indication for anticoagulation showed no mortality benefit from oral anticoagulation (warfarin used in six of these RCTs) in people with cancer but suggests an increased risk for bleeding (Kahale *et al.*, 2017).

7.2.6. A prospective, multicentre Phase III trial, involving newly diagnosed multiple myeloma patients randomized to receive aspirin (100 mg/day), warfarin (1.25 mg/day) or enoxaparin (40 mg/day) for

the duration of the induction therapy found no significant difference in the incidence of thromboembolic events between the three groups, with an incidence of 3.2, 5.9 and 8.2% in the LMWH, aspirin and warfarin groups, respectively (Palumbo *et al.*, 2011).

7.2.7. Another study involving 342 multiple myeloma patients that received four cycles of lenalidomide–dexamethasone as induction and were randomized to either aspirin (100 mg/day) or enoxaparin (40 mg/day) found that the incidence of VTE was not statistically different between the arms, being 2.3% in the aspirin group and 1.2% in the LMWH group. No major haemorrhagic complications were reported (Larocca *et al.*, 2012).

7.2.8. The NCCN Guidelines on Cancer-associated Venous Thromboembolic Disease (Version 1, 2019) , American College of Chest Physicians (ACCP) guidelines (7th Edition), and the latest International Union of Angioplasty (IUA) guidelines (Number 2, April 2013), all categorize hospitalized cancer patients as a group at high or highest risk for VTE who should be considered for pharmacological thromboprophylaxis, provided no contraindications to anticoagulant therapy exist (Khorana, 2007).

7.2.9. Aspirin is considered an option in only a select group of myeloma patients with one or fewer individual or multiple myeloma-specific risk factors (NCCN, 2018).

8. Iron overload

8.1. Description

8.1.1. Patients who receive repeated transfusions with red cells may accumulate excess iron (Koreth and Antin, 2010). In MDS patients, Iron overload may start to develop even before they become transfusion-dependent because of ineffective erythropoiesis (Gattermann, 2018). The risks of iron overload may be further increased in the context of hematopoietic stem cell transplantation (HSCT)(Koreth and Antin, 2010).

8.1.2. A retrospective study of patients who have undergone allogeneic HSCT have shown that pre-transplant red blood cell (RBC) transfusion-dependence and/or elevated serum ferritin levels (surrogate measures of iron overload) are associated with poorer post-transplant survival among patients with MDS and acute leukaemias (Alessandrino *et al.*, 2010).

8.2. Management of iron overload

8.2.1. Deferoxamine (also known as Desferrioxamine) is one of the most widely used iron chelators (Fisher *et al.*, 2013). Deferoxamine is a non-toxic iron chelator which is clinically approved and

effective for long-term iron chelation therapy in beta-thalassemia and other iron overload cases (Mobarra *et al.*, 2016)

8.2.2. Although Deferoxamine has oral absorption ability, pharmacokinetics of oral forms of chelators is not optimal. The intramuscular injection also has been shown to be ineffective. Therefore, continuous intravenous or subcutaneous infusion is recommended (Kuo and Mrkobrada, 2014).

8.2.3. Deferoxamine is typically administered through subcutaneous infusion with deferasirox as a once-daily oral iron chelator (Al-Kuraishy and Al-Gareeb, 2017).

8.2.4. A randomized trial of deferasirox versus placebo in lower risk MDS patients with red cell transfusion dependence and a serum ferritin greater than 1000 ng/mL (TELESTO; NCT00940602) has completed accrual and results are eagerly awaited (Steensma, 2018).

8.2.5. Iron chelation therapy improves mortality in patients with myelodysplastic syndrome. A meta-analysis involving 7,242 participants with MDS showed that iron chelation therapy (ICT) resulted in a lower risk of mortality compared to those with no ICT (HR 0.57; 95% CI 0.44–0.70; $P < 0.001$); what is more, ICT led to a lower risk of leukaemia transformation (HR 0.70; 95% CI 0.52–0.93; $P = 0.016$)(Liu *et al.*, 2019).

8.2.6. Iron chelation agents deferoxamine and deferasirox are recommended as PMB level of care for the management of iron overload in hematologic malignancies.

8.2.7. Deferasirox is currently recommended on the EML as an oral alternative for patients who need deferoxamine.

9. Metabolic disorders

9.1. Description

9.1.1. Metabolic alterations are possible complications in patients with hematologic malignancies (Carella *et al.*, 2015). Endocrine manifestations of cancer are usually para-neoplastic syndromes, including hypercalcemia, Cushing's syndrome and syndrome of inappropriate antidiuretic hormone secretion. These may be the presenting feature of an underlying malignancy (Yousaf and Popat, 2017).

9.1.2. Hematologic malignancies that frequently cause hypercalcemia include lymphoma, multiple myeloma, and adult T cell leukaemia. Extensive bone destruction is common in multiple myeloma, and over 30% of patients develop hypercalcemia (John P. Bilezikian, Robert Marcus, 2001).

9.1.3. Hyperuricemia is a common metabolic disorder in patients with haematological malignant diseases. Uric acid is the final oxidation product of purine metabolism. Increases in the uric acid plasma level may be evident in these patients by increase in neoplastic cell turnover and apoptosis, blast crisis and breakdown of malignant cells following chemotherapy. An increased serum uric acid level may also be caused by insufficient urinary excretion.

9.1.4. Tumour lysis syndrome (TLS) is an oncologic emergency characterised by hyperuricaemia (> 8 mg/dL), hyperkalaemia (> 6 mEq/dL), hyperphosphataemia (> 4,5 mg/dL) and hypocalcaemia (< 7 mg/dL) (Carella *et al.*, 2015).

9.1.5. Hypokalaemia may occur in patients with vomiting, diarrhoea due to drugs such as corticosteroids and amphotericin and also accompanied lysozymuria in AML

9.2. Management of metabolic disorders

9.2.1. Bisphosphonates (e.g. zoledronic acid, ibandronic acid, pamidronate) are indicated for management of lytic bone lesions in patients with multiple myeloma (MM), treatment and prevention of osteoporosis, treatment of moderate to severe hypercalcemia. Bisphosphonates are resistant to hydrolysis by phosphatases found in the blood. Bisphosphonates inhibit bone resorption by suppressing osteoclast activity (Berenson, 2020).

9.2.2. A meta-analysis to determine whether adding bisphosphonates to standard therapy in multiple myeloma improves OS and progression-free survival (PFS), and decreases skeletal-related morbidity found that bisphosphonates in participants with MM reduces pathological vertebral fractures, skeletal-related events and pain (Mhaskar *et al.*, 2017).

9.2.3. Allopurinol (xanthine oxidase inhibitor) is a commonly used antihyperuricemic agent (Alakel *et al.*, 2017) and is recommended as PMB level of care. A meta-analysis evaluating effectiveness and safety of different treatments for hyperuricemia found that allopurinol and other agents were all highly effective at reducing the risk of hyperuricemia compared to placebo (Li *et al.*, 2016).

9.2.4. The British Committee for Standards in Haematology recommend that symptomatic hypocalcaemia be treated with a short infusion of calcium gluconate at a dose applicable to the age/weight of the patient and close monitoring of calcium levels, phosphate levels and renal function (Jones *et al.*, 2015).

9.2.5. Patients with hematologic malignancies should be evaluated for possible metabolic derangements and the abnormalities corrected as per treatment protocol.

9.2.6. Patients with hematologic malignancies should also be evaluated by an endocrinologist for support and appropriate management of the underlying metabolic disorders.

10. Bone disease

10.1. Description of bone disease

10.1.1. Hematologic malignancies can have multiple direct and indirect effects on bone including pathologic fractures, bone pain, and hypercalcemia (Silbermann and David Roodman, 2013).Multiple myeloma (MM) has the highest incidence of bone involvement among malignant diseases. Up to 80% of patients present with osteolytic bone lesions at diagnosis. The basis of the pathogenesis of myeloma-related bone disease is the uncoupling of the bone-remodelling process. The interaction between myeloma cells and the bone microenvironment ultimately leads to the activation of osteoclasts and suppression of osteoblasts, resulting in bone loss (Terpos *et al.*, 2018).

10.1.2. Although bone involvement is rare in lymphomas, it is seen more frequently in HIV associated NHL and in patients with adult T-cell leukaemia/lymphoma associated with HTLVI. It is usually characterised by lytic bone lesions located in the metaphysis of long bones or in the axial skeleton (Roux and Mariette, 2000). In primary lymphomas of bone presenting with an isolated bone lesion, local treatment with radiation therapy and/or surgical ablation is required, and adjuvant chemotherapy may improve the prognosis of these located lymphomas (Roux and Mariette, 2000).

10.1.3. International Myeloma Working Group recommend that bisphosphonates (BPs) should be considered in all patients with multiple myeloma receiving first-line antimyeloma therapy, regardless of presence of osteolytic bone lesions on conventional radiography (Terpos *et al.*, 2013).

10.2. Management of bone disease

Bisphosphonates (e.g. zoledronic acid, ibandronic acid, pamidronate) are recommended PMB benefit for patients with multiple myeloma for prevention and/or management of bone disease.

11. Fertility Management

11.1. The significant increase in long-term survival of patients with cancer have generated worldwide interest in preserving fertility in patients to exposed to gonadotoxic chemo- and radiotherapy (Lambertini *et al.*, 2016).

11.2. The gonadotoxic effect of various chemotherapeutic agents is diverse, may involve a variety of pathophysiologic mechanisms not yet fully understood (Blumenfeld, 2012).

11.3. Proliferating cells, such as in tissues with high turnover, including growing ovarian follicles, are more vulnerable to the toxic effect of alkylating agents. These agents may also be cytotoxic to cells at rest, as they are not cell-cycle specific (Blumenfeld, 2012).

11.4. Alkylating agents, the most gonadotoxic chemotherapeutic medications, cause dose-dependent, direct destruction of oocytes and follicular depletion, and may bring about cortical fibrosis and ovarian blood-vessel damage (Blumenfeld, 2012).

11.5. The testis is extremely susceptible to the toxic effects of radiation and chemotherapy at all stages of life (Jahnukainen *et al.*, 2011).Testicular damage can affect the somatic cells of the testis (Sertoli and Leydig cells) or the germ cells (Skaznik-Wikiel *et al.*, 2016).

11.6. Infertility represents one of the main long-term consequences of combination chemotherapy given for lymphoma, leukaemia and other malignancies in young women (Blumenfeld, 2012)

11.7. Infertility is an important survivorship issue that should be addressed at diagnosis and in follow-up to ensure optimal decision-making, including consideration of pursuing fertility preservation (Poorvu *et al.*, 2019). Standard fertility preservation options include embryo or oocyte cryopreservation for women and sperm banking for men. All options for pre-pubertal children are experimental (Loren, 2015).

11.8. Tables 2 and 3 below summaries fertility preservation options available.

Table 2: Fertility Preservation Options for Boys and Men(Skaznik-Wikiel et al., 2016).

Method	Description	Special Considerations
Sperm cryopreservation	Cryopreservation of ejaculated sperm	Must be post pubertal; can be used for Inter Uterine Insemination (IUI) or In Vitro Fertilization (IVF)
Surgical sperm extraction	Percutaneous puncture and aspiration of sperm from the testis or epididymis	Outpatient surgical procedure; can be used for IVF with intracytoplasmic sperm injection
Immature testicular tissue cryopreservation	Surgical biopsy of testicular tissue from prepubertal boys	Experimental; only option for prepubertal boys

Table 3: Fertility Preservation Options for Girls and Women(Skaznik-Wikiel et al., 2016).

Method	Description	Special Considerations

Embryo cryopreservation	Hormonal stimulation of ovaries and collection of oocytes to create embryos using IVF methods; resulting embryos are cryopreserved	Must be postpubertal; need partner or donor sperm; established technique with thousands of live births
Oocyte cryopreservation (Cobo and Diaz, 2011)	Hormonal stimulation of ovaries and collection of oocytes with cryopreservation of unfertilized oocytes; can be fertilized in future to create embryos for transfer	Must be postpubertal; do not need sperm source; IVF required upon thawing; several studies demonstrating live birth rates similar to procedures using fresh embryos
Ovarian tissue cryopreservation (Cobo and Diaz, 2011; Donnez *et al.*, 2012)	Removal and cryopreservation of outer layer of the ovary (cortex), which contains immature oocytes	Experimental; can be pre- or postpubertal; outpatient surgical procedure; future uses include transplantation of thawed tissue or in vitro maturation of follicles and fertilization of oocytes; currently only option for prepubertal girls; 20 human live births from transplantation reported; none reported from in vitro maturation of follicles
In vitro maturation (Fadini *et al.*, 2012; Grynberg *et al.*, 2013)	Collection of immature oocytes without hormonal stimulation	Must be postpubertal; case reports demonstrating viable embryos; one live birth reported

11.9. Fertility management in patients with hematologic malignancies is a recommended as PMB level of care in line with the Medical Schemes Act, No. 31 of 1998.

12. Infections

12.1. Description

12.1.1. Patients with haematological malignancies are at increased risk of infections, not only because of the malignancy itself, but also because of neutropenia induced by intensive chemotherapy and its

cytotoxic effect on the cells that line the gastrointestinal tract (Crawford, Dale and Lyman, 2004; Gedik *et al.*, 2014).

12.1.2. Neutropenia and defects in adaptive B-cell–mediated immunity and/or lack of splenic function predispose patients to a host of diverse and often serious infections (Safdar and Armstrong, 2011).

12.1.3. Some malignancies are inherently associated with immune deficits. Patients with haematologic malignancies such as chronic and acute leukaemias, non-Hodgkin lymphoma, and myelodysplastic syndromes may be leukopaenic due to marrow infiltration by malignant cell, or by marrow dysfunction (NCCN, 2020)(Griffiths *et al.*, 2008).

12.1.4. Patients with multiple myeloma often have a functional hypogammaglobulinemia. The total level of immunoglobulin production may be elevated, but the repertoire of antibody production is restricted (NCCN, 2020).

12.1.5. Patients with chronic lymphocytic leukaemia (CLL) often have hypogammaglobulinemia which increases susceptibility to encapsulated bacteria, especially *streptococcus pneumoniae* (NCCN, 2020) (Nosari, 2012).

12.1.6. Patients with CLL are predisposed to infections because of both the humoral immunodepression related to stage and duration of CLL, and to a further immunosuppression related to therapy with steroids, cytotoxic drugs and monoclonal antibodies (Nosari, 2012).

12.1.7. Hematologic oncology patients are commonly malnourished and malnutrition impairs immune function and increases the susceptibility to infection (Bourke, Berkley and Prendergast, 2016; Yilmaz *et al.*, 2020).

12.2. Prophylactic antibiotics

12.2.1. In a meta-analysis of neutropenic patients (18 trials, N = 1,408) with solid tumours and haematological malignancies, fluoroquinolone prophylaxis (ciprofloxacin, norfloxacin, enoxacin, and ofloxacin) reduced the occurrence of gram-negative infections significantly by 80 % (RR, 0.21; 95 % CI 0.12–0.37) when compared with placebo and by 70 % when compared with trimethoprim-sulfamethoxazole. Quinolone prophylaxis did not change the incidence of gram-positive bacterial and fungal infections or infection-related mortalities (Engels, Lau and Barza, 1998).

12.2.2. In another meta-analysis of afebrile neutropenic patients (109 trials, N = 13,579) with hematologic malignancies, antibiotic prophylaxis significantly decreased all-cause mortality (RR 0.66, 95 % CI 0.55–0.79) and infection-related mortality (RR 0.61, 95 % CI 0.48–0.77) compared to placebo or no intervention. Quinolone prophylaxis was associated with the most significant reduction in mortality (Gafter-Gvili *et al.*, 2012).

12.2.3. A single-centre, observational cohort study of patients with newly diagnosed ALL, comparing prospectively collected infection-related outcomes in patients who received no prophylaxis, levofloxacin prophylaxis, or other prophylaxis during induction therapy, found that prophylaxis prevented febrile neutropenia and systemic infection. Levofloxacin prophylaxis also minimized the use of treatment antibiotics and drastically reduced *C. difficile* infection (Wolf *et al.*, 2017).

12.2.4. The use of fluroquinolones is recommended; however, the risk vs benefit should be assessed considering the recent warnings of the serious adverse effects associated with their use.

12.2.5. Trimethoprim-sulfamethoxazole is useful in patients with a low CD4 counts (<200 x 10^6/ l). The requested dose is 960mg/ day three times a week (Monday, Wednesday and Friday).

12.3. Influenza virus

In the case of influenza virus, inactivated influenza vaccine is administered annually to patients undergoing chemotherapy (Eliakim-Raz *et al.*, 2013). Vaccination should be administered at least two weeks prior to receiving immunosuppressive therapy. Patients should be considered unprotected if they were vaccinated less than 2 weeks before the start of immunosuppressive therapy. These patients should be revaccinated at least three months after the cytotoxic therapy is discontinued (Rubin *et al.*, 2014). Patients with acute leukaemia should be vaccinated after completion of chemotherapy (Patel *et al.*, 2007).

12.4. Cytomegalovirus (CMV)

12.4.1. Because of a higher degree of immunosuppression, haploidentical (allogeneic) transplant recipients may be at an increased risk of viral infections, particularly CMV (Gagelmann *et al.*, 2018).

12.4.2. Alemtuzumab may also be associated with CMV reactivation.

12.4.3. The safety and efficacy of valacyclovir in patients receiving allogeneic stem transplant has been demonstrated. A retrospective single centre study to evaluate the safety and efficacy of valacyclovir for prevention of cytomegalovirus (CMV) infection (reactivation) after allogeneic stem cell transplantation (SCT) found that prophylaxis with valacyclovir appears to be safe and efficacious in preventing both primary and secondary CMV reactivation in at-risk patients after allogeneic SCT (Vusirikala *et al.*, 2001).

12.4.4. In a randomized, double-blind, acyclovir-controlled, multicentre clinical trial in recipients of allogeneic BMT who were CMV seropositive (or donor positive) before transplantation, valacyclovir was found to be more effective than acyclovir in preventing CMV reactivation in BMT recipients and showed a similar safety profile (Ljungman *et al.*, 2002).

12.4.5. The EML has listed valganciclovir and for patients who cannot tolerate oral therapy, ganciclovir is recommended.

12.4.6. Schemes may also apply formularies and ensure that there is adequate treatment for CMV when required.

12.5. Varicella-Zoster Virus

12.5.1. Impaired cellular immunity is the main risk factor for Varicella-Zoster Virus (Boeckh *et al.*, 2006).

12.5.2. In allogeneic HCT recipients with a history of VZV infection, about 30 % have reactivation of VZV disease without prophylaxis (Boeckh *et al.*, 2006).

12.5.3. In patients with history of chicken pox, oral acyclovir administered from 1 to 2 months until 1 year after allogeneic HCT reduces the incidence of VZV disease compared to placebo (5 % vs 26 %, respectively) (Boeckh *et al.*, 2006).

12.5.4. Patients receiving T-cell-depleting agents (proteasome inhibitors, purine analogs, and prednisone ≥ 1 mg/kg/day) are also at risk for VZV infection. Antiviral prophylaxis is continued until the immunosuppressive therapy is completed (Tomblyn *et al.*, 2009).

12.5.5. Antiviral prophylaxis with acyclovir or valacyclovir for one year post transplant significantly reduces reactivation compared to no therapy (9 % vs. 25 %, $p < 0.001$) (Erard *et al.*, 2007).

12.6. Prophylactic antifungals

12.6.1. Patients with acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) and allogeneic hematopoietic stem cell transplant (HSCT) recipients are at increased risk for life-threatening infections with yeasts or moulds. *Candida* and *Aspergillus* species are the most common pathogens(Bhatt, Viola and Ferrajoli, 2011).

12.6.2. Studies have shown that fluconazole as an antifungal prophylaxis is more effective than placebo when preventing invasive candidiasis in patients undergoing induction chemotherapy for AML (Rotstein *et al.*, 1999), and also as effective as amphotericin B (Koh *et al.*, 2002) even though it lacks activity against moulds.

12.6.3. Itraconazole is active against both *Candida* and *Aspergillus* species and greatly reduces invasive fungal disease compared to fluconazole, but produces higher toxicity (Ethier *et al.*, 2012). Voriconazole is as effective as itraconazole and is better tolerated (Wingard *et al.*, 2010). Fluconazole reduces invasive candidiasis and invasive fungal disease (IFD) related mortality (Nucci, 2012)

12.6.4. Posaconazole has wider antifungal range including *Candida* spp., *Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., and *Mucorales*. As a matter of fact, it is the only antifungal that has exhibited survival advantage in prophylaxis against mycosis during AML induction therapy (Cornely *et al.*, 2007).

12.6.5. Caspofungin shows activity against both *Candida* and *Aspergillus* spp. It has similar efficacy as itraconazole and is better tolerated (Mattiuzzi *et al.*, 2006). It can be administered to patients that cannot take oral posaconazole during antifungal prophylaxis.

12.6.6. In patients undergoing HSCT, antifungal prophylaxis is more complex due to concerns for poor oral absorption due to mucositis and drug interactions with antineoplastic and immunosuppressive medications.

12.6.7. Micafungin is as efficacious as itraconazole with less toxicity (Huang *et al.*, 2012).

12.6.8. When indicated, antifungals are PMB level of care and funding might be subject to results of sensitivity tests.

12.7. TB prophylaxis

Patients with immunodeficiencies, such as those suffering from haematological malignancies, have a greater risk of progressing to TB disease once infected. It is estimated that the relative risk of TB disease in patients with hematologic malignancies is 2 – 40 times that of the general population (Anibarro and Pena, 2014). The treatment of latent TB infection that has been most studied and has a proven efficacy is that with isoniazid. This treatment regimen should last between 6 and 9 months, while having the prolonged treatment offer the greatest preventive efficacy. The 9 months regimen reaches a protective efficacy against TB reactivation of 90% and is probably the best duration for LTBI treatment with isoniazid (Snider, Caras and Koplan, 1986; Comstock, 1999; American Thoracic Society., 2000). Management of TB is PMB level of care as per the applicable ICD10 code.

12.8. Pneumocystis Jirovecii prophylaxis

12.8.1. Trimethoprim-Sulfamethoxazole prophylaxis for pneumocystis jirovecii is highly effective. In systematic review and meta-analysis of randomized controlled trials to assess the efficacy of prophylaxis for Pneumocystis pneumonia (PCP), caused by Pneumocystis jirovecii for immunocompromised non-HIV-infected patients, when trimethoprim-sulfamethoxazole was administered, a 91% reduction was observed in the occurrence of PCP (RR, 0.09; 95% CI, 0.02-0.32); the number needed to treat was 15 (95% CI, 13-20) patients, with no heterogeneity.

Pneumocystis pneumonia-related mortality was significantly reduced (RR, 0.17; 95% CI, 0.03-0.94)(Green *et al.*, 2007). Trimethoprim-sulfamethoxazole is therefore recommended in patients with a low CD4 counts (<200 x 10^6/ l). The requested dose is 960mg/ day three times a week (Monday, Wednesday and Friday).

13. Immune support
    13.1. One of the main defects predisposing patients with hematologic malignancies is a reduction in the level of immunoglobulins (Raanani *et al.*, 2008).
    13.2. In patients with hypogammaglobulinemia secondary to chronic lymphocytic leukaemia (CLL) or multiple myeloma (MM), intravenous immune globulin (IVIG) may be administered to reduce the risk of infection (Ammann *et al.*, 2016)
    13.3. A systematic review assessing the role of administration of immunoglobulins from healthy donors as prophylaxis in patients with haematological malignancies, showed that in the context of bone marrow transplantation the administration of immunoglobulins did not have an effect on survival or other outcomes. On the other hand, in patients with lymphoproliferative disorders like chronic lymphocytic leukaemia or multiple myeloma, it reduced the rate of infections substantially (Raanani *et al.*, 2008).

14. Dental issues
    14.1. Patients with hematologic malignancies may have oral manifestations due to the disease itself or as a complication of treatment (Gomes *et al.*, 2018). Chemotherapy and hematopoietic stem cell transplantation (HSCT), as the treatment for hematologic malignancy, result in myelosuppression and increase the susceptibility of patients to severe infections, including that of the oral cavity (Akashi *et al.*, 2013).
    14.2. Some of the common oral conditions in patients with hematologic malignancy are dry lips, mucositis , petechiae, and candidiasis (Gomes *et al.*, 2018).
    14.3. In acute leukaemias, gingival hyperplasia is generally observed, localized or generalized. Leukemic infiltration may also occur (Caroline Zimmermann, Liliane Janete Grando and Inês Beatriz da Silva Rath, 2015).
    14.4. A retrospective study involving 161 cases of patients with haematological malignancies (multiple myeloma, acute myeloid/ lymphoid leukaemia and myelodysplastic syndrome) to define and evaluate oral health conditions highlighted the importance of removal of infection focus in oral cavity as much as

possible is important to prevent the complications after chemotherapy (Shimada *et al.*, 2015)(Shimada *et al.*, 2017).

14.5. Tooth extraction is a common surgical procedure performed to eliminate dental focal infection, and it carries a risk of perioperative surgical site infection. The study by Shimada et al did not find a significant relationship between tooth extraction before the first chemotherapy cycle and oral adverse events thereafter(Shimada *et al.*, 2017).

14.6. A retrospective study to evaluate sequelae and complications after dental extractions and to analyse their impact on medical treatment in patients with myelodysplastic syndrome, acute and chronic leukaemia, and multiple myeloma during a 3-year period found that dental extraction intervention provided in the prechemotherapy and pre-BMT time frame did not have a negative bearing on medical outcome (Raut *et al.*, 2001).

14.7. On referral, dentists, oral hygienists and oral and maxillofacial surgeons should form part of the multidisciplinary team managing the patient with hematologic malignancies. Dental care for patients with hematologic malignancy will be reimbursed as PMB benefit on motivation, as clinically indicated.

15. Orthopedic complications

15.1. Patients with haematological malignancies frequently encounter spine-related symptoms, which are caused by disease itself or process of treatment (Kim *et al.*, 2017).

15.2. The epidural space is an uncommon site for involvement by haematolymphoid malignancies, and may present unexpectedly with neurological symptoms related to spinal cord compression (Pandey *et al.*, 2019).

15.3. A retrospective analysis of 195 patients (98 males and 97 females) suffering from haematological malignancies combined with spinal problems found that major presenting symptoms were mechanical axial pain (132, 67.7%) resulting from pathologic fractures, and followed by radiating pain (49, 25.1%). Progressive neurologic deficits were noted in 15 patients (7.7%), which revealed as cord compression by epidural mass or compressive myelopathy combined with pathologic fractures (Kim *et al.*, 2017).

15.4. The most common location of bone changes in multiple myeloma is the thoracic spine, where it causes osteolytic changes with consequent compressive fractures. Paraplegia may be the associated sequela (Basić-kes *et al.*, 2002).

15.5. A systematic review (3,391 citations, of which 111 clinical reports (4,235 patients) evaluated the effectiveness of vertebroplasty (78 reports, 2,545 patients) or kyphoplasty (33 reports, 1,690 patients)

on vertebral augmentation of cancer-related vertebral compression fractures for patients with mixed primary spinal metastatic cancers, multiple myeloma, or haemangiomas found that both vertebroplasty and kyphoplasty significantly and rapidly reduced pain intensity in cancer patients with vertebral compression fractures. These procedures also significantly decreased the need for opioid pain medication, and functional disabilities related to back and neck pain (Ontario, 2016).

15.6. Timely surgical interventions should be considered for the cases of pathologic fractures with progressive neurologic compromise (Kim *et al.*, 2017).

15.7. Orthopaedic surgeons should form part of the team managing patients with haematological malignancies prone to involvement of bones and/ or spine.

15.8. The surgical intervention for managing the pathologic fractures and/ or involvement of the spine will be reimbursed as PMB benefit on motivation, as clinically indicated.

16. Frailty and Mobility challenges

16.1. People with haematological malignancies must endure long phases of therapy and immobility which is known to diminish their physical performance level (Knips *et al.*, 2019). An assessment for frailty increasingly important for patients with hematologic malignancy, as most of the blood cancers occur in the elderly. Frailty is defined as ‘’a vulnerable state that arises from “decreased reserves in multiple organ systems, which are initiated by disease, lack of activity, inadequate nutritional intake, stress, and/or the physiologic changes of aging’’ (Abel and Klepin, 2018).

16.2. Physical frailty is an important medical syndrome. Physical frailty as "a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death’’ (Abel and Klepin, 2018)

16.3. Physical frailty can potentially be prevented or treated with specific modalities, such as exercise, protein-calorie supplementation, vitamin D, and reduction of polypharmacy (Abel and Klepin, 2018).

16.4. A recent systematic review of 31 studies of frailty in persons 65 years or older found a prevalence of from 4.0% to 17.0% (mean 9.9%) of physical frailty (Collard *et al.*, 2012).

16.5. A recent Cochrane review found that physical exercise added to standard care might improve fatigue and depression (Knips *et al.*, 2019)

16.6. A systematic review, found that 45 to 60 minutes of exercise 3 times a week seemed to have positive effects on frail older adults and may be used for the management of frailty (Theou *et al.*, 2011).

16.7. A Physiotherapist plays an important role in the assessment, prevention and/ or treatment of patients with physical frailty. The use of rehabilitative approaches to care for the frail older adult population with hematologic malignancy has a potential to improve functional status and QOL, while concurrently reducing rates of disability, rehospitalisation, institutionalization, and healthcare costs (Gustavson *et al.*, 2017).

16.8. The assessment, prevention and/ or treatment of physical frailty and management of mobility issues by a physiotherapist as clinically indicated, will be reimbursed as PMB benefit on motivation.

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