PMB definition guideline for acute myeloid leukaemia
Version 1

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Disclaimer:

The acute myeloid leukaemia benefit definition guideline has been developed for majority of standard patients and is aligned with best practice. These benefits may not be sufficient for outlier patients. Therefore, regulation 15h may be applied for patients who are inadequately managed by the stated benefits. The benefit definition does not describe specific in-hospital management. However, these interventions form part of care and are prescribed minimum benefits. Supportive medication for all haematology oncology conditions is detailed in a separate guideline available here.

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Abbreviations

CMS	Council for Medical Schemes
PMBs	Prescribed Minimum Benefits
DTPs	Diagnosis Treatment Pairs
AML	Acute Myeloid Leukaemia
WHO	World Health Organization
ALL	Acute Lymphocytic Leukemia
MRC	Myelodysplasia-Related Changes
TAML	Therapy-related Acute Myeloid Leukaemia
FBC	Full blood Count
U&E	Urea and Electrolytes
LFT	Liver Function Test
LDH	Lactate Dehydrogenase
CRP	C-reactive protein
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
INR	International Normalized Ratio
PCT	Procalcitonin
HIV	Human Immunodeficiency Virus
TSH	Thyroid Stimulating Hormone
HLA	Human Leukocyte Antigen
HSCT	Haemopoietic Stem Cell Transplantation
MUGA	Multigated Acquisition
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
CNS	Central Nervous System
CBF	Core Binding Factor
DFS	Disease-Free Survival
ATRA	All-Trans Retinoic Acid
CR	Complete Remission

1. Introduction

1.1. The legislation governing the provision of the Prescribed Minimum Benefits (PMBs) is contained in the Regulations enacted under the Medical Schemes Act, No. 131 of 1998 (the Act). With regards to some of the Diagnosis Treatment Pairs (DTPs), medical scheme beneficiaries find it difficult to be fully aware of their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements.

1.2. The benefit definition project is undertaken by the CMS with the aim of defining the PMB package, as well as to guide the interpretation of the PMB provisions by relevant stakeholders.

2. Scope and purpose

2.1. This is a recommendation for the diagnosis, treatment and care of individuals with acute myeloid leukaemia (AML) in any clinically appropriate setting as outlined in the Medical Schemes Act.

2.2. The purpose is to provide detailed clarification in respect of benefits and entitlements to members and beneficiaries of medical schemes.

Table 1: Possible ICD10 codes for patients with AML in curative and palliative setting

DTP code	ICD 10 code	ICD10 code description
901S	C92.0	Acute myeloblastic leukaemia
	C92.6	Acute myeloid leukaemia with 11q23-abnormality
	C92.8	Acute myeloid leukaemia with multilineage dysplasia
260S - # Imminent death regardless of diagnosis	Z51.5	Palliative care

3. Classification

3.1. Evaluation of acute leukaemia can result in any of the below diagnoses as classified by WHO, 2016:

- Acute promyelocytic leukaemia
- Acute myeloid leukaemia
- Myelodysplastic syndrome
- B or T lymphoblastic leukaemia/lymphoma

3.2. In accordance with the 2016 World Health Organization (WHO) classification, a diagnosis of AML is made based on the presence of $\geq$20% blasts in the marrow or peripheral blood.

3.3. In an appropriate clinical setting, a diagnosis of AML may be made with <20% blasts in patients with recurrent cytogenetic abnormalities including:

- t(15;17),

- t(8;21),
- t(16;16),
- inv(16)

3.4. As evidenced by the ICD-10 classification shown earlier, AML is primarily categorised by recurrent genetic abnormalities, with morphological classification reserved for patients not otherwise classifiable.

4. Epidemiology

4.1. Leukaemia is the most common cancer diagnosis in children who are younger than 15 years. In this age group, however, acute lymphocytic leukemia (ALL) is about five times more common than AML. On the contrary AML accounts for 25% of leukemias in children (Deschler & Lübbert, 2008; Kiem Hao et al., 2020).

4.2. The incidence of AML is age dependent and increases progressively with age. Patients newly diagnosed with AML have a median age of 65 years.

4.3. With advanced age, the relative incidence of AML with recurrent genetic abnormalities decreases, while the relative incidence of other AML categories [such as AML with myelodysplasia-related changes (MRC-AML) or therapy related AML (tAML)] increases with age, comprising about 19% and 7% of AML cases, respectively.

4.4. AML is the most common type of leukaemia in adults, accounting for approximately 25% of all leukemias in the Western countries (Deschler & Lübbert, 2008; De Kouchkovsky et al., 2016).

4.5. Globally, 606 000 people had leukemia in 2015, and of those 190 00 had AML. When compared with other cancers, AML ranks 22nd by incidence. In South Africa, AML was ranked 19th.

4.6. The 2016 South African National Cancer registry reported an age standardised incidence of leukaemia in South Africa of 0.82 /100 00 and 1.52/100 000 for females and males, respectively. The male: female distribution is consistent with the global male predominance that is seen in AML.

5. Diagnostics and risk stratification work up.

5.1. Laboratory tests

The evaluation and initial workup for suspected AML consists of a comprehensive medical history and physical examination and a comprehensive range of laboratory investigations (Ferrara & Mirto, 1996; Yamauchi et al. 2013). The following laboratory work-up is PMB level of care.

- Full blood count (FBC) including differential count, peripheral blood smear and platelet count.
- Urea and Electrolytes (U&E)
- Full liver function tests (LFT) including lactate dehydrogenase (LDH). LDH can be used to determine the prognosis.
- C-reactive protein (CRP)
- Clotting profile including partial thromboplastin time (PTT), international normalized ratio (INR)/ prothrombin time (PT), Fibrinogen and disseminated intravascular coagulation (DIC) where indicated.
- Procalcitonin (PCT) as clinically indicated.
- Human immunodeficiency virus (HIV)
- Hepatitis B & C

- Glucose
- Calcium, magnesium, phosphate
- Uric acid
- Pregnancy test - where appropriate
- Haematinics - iron studies, vitamin B12, folate.
- Thyroid stimulating hormone (TSH), T4
- Lumbar puncture – as clinically indicated.

5.2. **Haematology and Histopathology**

The following are PMB level of care:

- Human leukocyte antigen (HLA) typing for patient with potential haemopoietic stem cell transplantation (HSCT).
- Bone marrow aspirate and trephine biopsy- including immunophenotyping and cytochemistry and cytogenetic analyses (karyotype with fluorescence in situ hybridization) are necessary for risk stratification and to guide therapy of AML (NCCN, 2019).
- Soft tissue biopsy – when indicated (to exclude myeloid sarcoma).
- Flow cytometry.
- Next generation screening

5.3. **Imaging radiology**

The following imaging radiology are PMB level of care:

- Chest x-ray
- Echocardiogram or multiple-gated acquisition (MUGA) scan to evaluate myocardial function in patients with history or symptomatic of cardiac disease, or when treatment with cardiotoxic medicine is planned.
- Brain CT without contrast – if CNS haemorrhage is suspected.
- Brain MRI with contrast - if leukemic meningitis is suspected.

6. Treatment options for AML

6.1. Management of AML is divided into induction chemotherapy and post-remission therapy. The induction strategy is influenced by individual patient characteristics such as age (younger or older than age 60), cytogenetics, molecular genetics, presence of comorbid conditions affecting performance status, pre-existing hematologic disorder (MDS, myeloproliferative disorder), prior cytotoxic or radiation therapy (NCCN, 2019).

6.2. Although the age may influence the treatment options, for patients aged ≥60 years with AML, decisions should not only be determined by the chronological age but also patient performance status, in addition to

adverse features (e.g. de novo AML without favourable cytogenetics or molecular markers; t-AML; antecedent hematologic disorder) and comorbid conditions, are used to select treatment options. .

Induction therapy

6.3. Standard induction regimens used are based on a backbone of cytarabine plus an anthracycline (e.g. daunorubicin, idarubicin). In a systematic review and meta-analysis of 29 randomized controlled trials (RCTs) comparing idarubicin to daunorubicin, idarubicin had a lower remission failure rate compared with daunorubicin (relative risk [RR], 0.81; 95% CI, 0.66–0.99; P5.04), but no difference was observed in early death or overall mortality (Teuffel et al., 2013).

6.4. As the risk for neurotoxicity and renal insufficiency are increased with the high-dose cytarabine-containing regimen (HiDAC); both renal and neurologic function should be closely monitored in these patients (Willemze et al., 2014).

6.5. Cytarabine and anthracyclines (e.g.idarubicin, daunorubicin, and doxorubicin) are PMB level of care.

Post-induction therapy

6.6. Post induction, purine analogues (cladribine, fludarabine), anthracyclines, cytarabine and allogeneic Hematopoietic stem-cell transplantation (HSCT) are PMB level care when clinically appropriate.

6.7. To assess the efficacy of the induction therapy, a bone marrow aspirate and biopsy may be performed 14 to 21 days after start of therapy (NCCN, 2019).

6.8. In patients who have received standard-dose cytarabine induction and have significant residual disease without hypoplasia (defined as cellularity less than 20% of which the residual blasts are less than 5%), additional therapy with standard dose cytarabine and anthracycline or escalation to HiDAC may be considered for reinduction (Stone et al., 2017)

6.9. For patients who have residual blasts after induction with standard-dose cytarabine combined with daunorubicin and cladribine, a second cycle of the same induction regimen may be administered if >50% cytoreduction is observed (Stone et al., 2017).

6.10. If hypoplasia status is unclear, a repeat bone marrow biopsy should be considered before proceeding with post induction therapy.

6.11. For patients who achieve complete response (CR) with the additional postinduction therapy, consolidation therapy can be started.

6.12. Patients who have persistent disease after 2 courses of therapy are considered to have primary induction failure. Treatment options include a clinical trial or use of salvage chemotherapy regimens used for relapsed/refractory (R/R) disease (NCCN, 2019).

6.13. Patients initially treated with HiDAC and who have significant residual disease without a hypocellular marrow 21 to 28 days after start of therapy are considered to have experienced induction failure.

6.14. If an HLA-matched sibling or alternative donor has been identified, an allogeneic HSCT may be effective in 25%–30% of patients with induction failure (Dohner et al., 2017).

Post-Remission or Consolidation Therapy

6.15. Post-remission therapy is also based on risk status defined by cytogenetics and molecular abnormalities.
6.16. For those with core binding factor (CBF) cytogenetic translocations without KIT mutation, the following options are for consolidation therapy (Burnette et al., 2011).
- HiDAC
- Participation in a clinical trial. Participation in clinical trials is not PMB level of care.
- Intermediate-dose cytarabine plus daunorubicin and gemtuzumab ozogamicin (for patients with CD33-positive AML). Gemtuzumab ozogamicin is not PMB level of care.

6.17. Allogeneic HSCT or the use of HiDAC demonstrated a lower risk of relapse and a higher disease-free survival (DFS) when given as consolidation for patients with intermediate-risk cytogenetics (Farag et al., 2005; Stone et al., 2015).
6.18. The role of autologous HSCT in the intermediate-risk group outside of clinical trials is diminishing due to improvements in allogeneic transplants.
6.19. The following are PMB level of care for AML:

- Cytarabine
- Anthracyclines (Idarubicin, Daunorubicin, Doxorubicin)
- Etoposide
- Mitoxantrone
- Fludarabine
- Cladribine – as an alternative to Fludarabine
- Methotrexate
- 6- Mercaptopurine
- Thioguanine
- Hydroxyurea
- Hypomethylating agents – only in the elderly
- All-trans retinoic acid (ATRA) for suspected or confirmed acute promyelocytic leukemia (APML).

7. Transplant for AML

7.1. Allogeneic and autologous HSCT are PMB level of care for AML when clinically appropriate.
7.2. CMS is cognisant of the criteria provided for SCT, however clinical evidence has evolved, and clinical best practice should prevail.
7.3. For allogeneic SCT there should be a first complete remission (CR1) / second complete remission (CR2) </=5% blast in bone marrow and:
– related donor or
- matched unrelated donor or
– Haploidentical transplant (HAPLO) identical

7.4. Autologous SCT for CR1 with low – intermediate risk disease; CR2 for APML as salvage.

7.5. Antifungal prophylaxis is PMB level of care.
7.6. For transplant candidates, total body radiation is PMB level of care.
7.7. The following medicines are PMB level of care for transplant.

- Fludarabine
- Busulphan
- Cyclophosphamide
- ATG
- Melphalan
- Cyclosporin
- Tacrolimus
- Methotrexate
- Etoposide
- Thalidomide
- Imatinib

8. Supportive treatment

8.1. Supportive treatment for AML is PMB level of care when clinically indicated.
8.2. Guidance on supportive treatment is available here.

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