Prescribed Minimum Benefit definition guideline: Adult T-cell leukaemia / lymphoma (ATLL)

Version 1: 30 September 2021

Disclaimer:

The Adult T-cell Leukemia/ Lymphoma benefit definition guideline has been developed for the 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 such as theatre, anaesthetists, anaesthetist drugs and supportive medication. 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.

Council for Medical Schemes (CMS) is cognisant of the criteria for bone marrow transplantation as stipulated in the Prescribed Minimum Benefits (PMB) regulations, however clinical evidence has changed, and clinical best practice should prevail. The following should be noted:

- Related or unrelated donors on local registry should be considered as there is no difference in outcome data for patients transplanted from a matched family donor or a matched unrelated donor.
- There should not be any age restrictions.

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Abbreviations

ATLL: Adult T cell Leukaemia/Lymphoma

CHOP: Cyclophosphamide, doxorubin, vincristibe and prednisone

CMV: Cytomegalovirus

CNS: Central nervous system

CR: Complete remission

DTPs: Diagnosis Treatment Pairs (dtps)

EBV: Epstein-Barr virus

EML: Essential medicines list

FBC: Full blood count

GP: General practitioner

HIV: Human immuno deficiency virus

HSCT: Haemopoietic stem cell transplant

HTLV-1: Human T-lymphotropic virus type 1

IgG: Immunoglobulin G

IgM: Immunoglobulin M

INR: International normalized ratio

LFT: Liver function test

LDH: Lactate dehydrogenase

NCCN: National comprehensive cancer network

NEML: National essential medicines list

ORR: Overall response rate

PHC: Primary health care

PMBs: Prescribed minimum benefits

PTT: Partial thromboplastin time

U&E: Urea and electrolytes

WHO: World health organisation

1. Introduction

1.1 The legislation governing the provision of the PMBs is contained in the Regulations enacted under the Medical Schemes Act, No. 31 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 guideline is a recommendation for the diagnosis, treatment and care of individuals with adult T cell leukaemia/lymphoma (ATLL) in any clinically appropriate setting as outlined in the Act.

2.2 It aims to provide detailed clarification in respect of benefit and entitlements to members and beneficiaries of medical schemes.

Table 1: Possible ICD10 codes for identifying adult T cell leukaemia/lymphoma

ICD 10 code	WHO description
C77.0	Secondary and unspecified malignant neoplasm, lymph nodes of head, face and neck
C77.1	Secondary and unspecified malignant neoplasm, intrathoracic lymph nodes
C77.2	Secondary and unspecified malignant neoplasm, intra-abdominal lymph nodes
C77.3	Secondary and unspecified malignant neoplasm, axillary and upper limb lymph nodes
C77.4	Secondary and unspecified malignant neoplasm, inguinal and lower limb lymph nodes
C77.5	Secondary and unspecified malignant neoplasm, intrapelvic lymph nodes
C77.8	Secondary and unspecified malignant neoplasm, lymph nodes of multiple regions
C77.9	Secondary and unspecified malignant neoplasm, lymph node, unspecified
C81.0	Lymphocytic predominance
C81.3	Lymphocytic depletion
C84.5	Other and unspecified T-cell lymphomas
C84.9	Mature T/NK-cell lymphoma, unspecified
C85.7	Other specified types of non-Hodgkin's lymphoma
C85.9	Non-Hodgkin's lymphoma, unspecified type
C91.5	Adult T-cell lymphoma/leukaemia [HTLV-1-associated]
C91.9	Lymphoid leukaemia, unspecified
C94.7	Other specified leukaemias
C95.0	Acute leukaemia of unspecified cell type

2.3 The above ICD10 codes are classified under acute leukaemias, lymphomas (DTP901S).

2.4 The CMS acknowledges that some patients will not qualify for PMB entitlements under the definition of treatable cancers as outlined in explanatory note 3, annexure A of the Act. In these instances, when the treatment intent is no longer curative, DTP 260S, may be applied depending on the clinical case.

Table 2: Applicable PMB code for a non-curative setting in ATLL

PMB Code	PMB Description		ICD10 Code	ICD10 Description
260S	# Imminent death regardless of diagnosis	# Comfort care; pain relief; hydration	Z51.5	Palliative care

3. Epidemiology and burden of the disease

3.1 Adult T-cell leukaemia/lymphoma (ATLL) is a rare and often aggressive type of T-cell lymphoma – a lymphoma that develops from white blood cells called T cells (Lymphoma action, 2019).

3.2 It is estimated that at least 5–10 million individuals worldwide are infected with HTLV-1, with most affected people remaining asymptomatic carriers and having an estimated lifetime risk of developing ATLL of 3-5% (Hermine et al, 2018).

3.3 Although there are many reports regarding the HTLV-I seroprevalence rates in African countries, only a few epidemiological studies of ATLL were available. In South Africa the estimated seroprevalence of HTLV-1 is between 0.5% - 3% of the population (Gessain and Cassar, 2012), and there is no data for the ATLL prevalence.

3.4 There is no gender prevalence for ATLL, but it mostly develops at 50 years of age (Hermine et al, 2018). HTLV-1 infection is prevalent in certain parts of world including southern Japan, the Caribbean islands, Central and South America, Iran, Romania and parts of Africa (Iwanga et al, 2012).

3.5 The three modes of HTLV-1 transmission are mother to child, sexual transmission, and transmission with contaminated blood products (Gessain and Cassar, 2012).

3.6 ATLL is classified into four clinical subtypes which are an important factor for predicting prognosis and deciding on appropriate treatment strategies (NCCN Guidelines, 2021). The subtypes are:

- Acute
- Lymphoma-type
- Chronic
- Smouldering

3.7 Acute (leukaemic) ATL

This is an aggressive high-grade cancer that accounts for about 3 in every 20 cases of ATLL. It is called ‘leukaemic’ because it leads to the production of lots of abnormal white blood cells (‘leukocytes’) in the blood.

3.8 The Lymphoma-type ATL

This is also an aggressive high-grade lymphoma that accounts for about 13 in every 20 cases of ATLL. It is called ‘lymphoma-type’ because it leads to the production of abnormal white blood cells in the lymphatic system rather than in the blood.

3.9 Chronic ATL

This is a slow growing (low-grade) lymphoma that accounts for about 3 in every 20 cases of ATLL. It is called ‘chronic’ because it develops slowly over a long time.

3.10 Smouldering ATL

This is a low-grade lymphoma that accounts for about 1 in every 20 cases of ATLL. It is called ‘smouldering’ because it can go on for a long time without causing many problems.

3.11 Acute and lymphoma subtypes

Typically require immediate treatment, while smouldering and chronic subtypes are considered indolent and thus managed similarly to indolent non-hodgkin lymphoma with watchful waiting until symptomatic disease (NCCN Guidelines, 2021).

4. Diagnosis

4.1. Consultations

Table 3: Recommended consultations for the diagnosis of ATLL

Treating provider	Frequency	Comment
- Specialist physician / Paediatrician Radiologist - Haematologist - Oncologist - Histopathologist	6	The stipulated frequency is for the diagnosis of ATLL. Regular assessment of disease status and toxicity during observation and therapy is essential and will vary according to disease subtype.

4.2. Laboratory investigations

Laboratory evaluation includes blood count and serum biochemistry (Tse and Kwong, 2017). Lactate dehydrogenase (LDH) and calcium levels may be elevated in acute and lymphoma subtypes (Matutes, 2007). A defining feature of all types of NK/T-cell lymphoma is the invariable infection of lymphoma cells with Epstein-Barr virus (EBV). Although EBV is required, it is not conclusive for diagnosis (Tse and Kwong, 2017). Hepatitis C is associated with some low-grade lymphoproliferative disorders.

The following laboratory investigations are recommended as PMB level of care:

- For peripheral blood lymphocytosis: morphology & flowcytometry
- FBC & differential count
- U&E, full LFT
- INR & PTT – ATLL can manifest in various ways which may manifest as bleeding, hence INR and PTT are recommended as part of the diagnostic workup .
- LDH
- Calcium, Magnesium and Phosphate – The exclusion of hypercalcemia is important in the work up of ATLL. However, in order to correctly interpret the calcium levels, magnesium and phosphate levels are also checked, as these electrolytes are closely related with regard to bone and renal disease. Moreover, the phosphate may be increased and the calcium decreased if tumour lysis complicates the disease. All three electrolytes should be measured, rather than the calcium in isolation.
- Hemolytic screen: A basic haemolytic screen includes the reticulocyte count, peripheral blood smear review, bilirubin levels and an LDH. Where indicated a Coomb's test should be performed
- Immunoglobulins (IgG, IgM,IgA) – This is not routine for all ATLL patients. It is indicated for patients with chronic leukemic variety and in patients with recurrent infections.
- Hepatitis BsAg/core antibody
- Hepatitis C serology
- CMV IgG and IgM
- EBV

- HIV
- HTLV-1

4.3 Histopathology

The diagnosis of ATLL can be established by integrating the clinical and laboratory features. The morphology of the circulating neoplastic lymphocytes and the immunophenotype are very characteristic of the disease (Matutes, 2007).

The following histopathology is recommended as PMB level of care for ATLL.

- Histology (tissue biopsy) – Immunohistochemistry for peripheral blood lymphocytosis for enlarged lymph nodes or tissue masses (e.g. Leukaemia cutis). Minimum required markers are CD3, CD20 and TdTt. Often more markers are done as part of an investigative panel if lymphoblastic lymphoma is not suspected initially.
- Bone marrow aspirate and trephine biopsy - The aspirate may show infiltration by lymphocytes with the same morphological features to those in the blood. The trephine biopsy may or may not show lymphoid infiltration, with the degree of involvement being variable (Matutes, 2007).

5. Treatment options

5.1 In patients with ATLL, combination chemotherapy with CHOP (cyclophosphamide, doxorubin, vincristine and prednisone) has resulted in overall response rate (ORR) of 64-88% and complete remission (CR) rates of 18-25% (Tsukasaki et al., 2007, Bazarbachi et al., 2010).

5.2 Those with lymphoma subtype appeared to benefit more from first line therapy with CHOP or CHOP-like chemotherapy (with or without maintenance antivirals) than with antivirals alone (Bazarbachi et al., 2010).

5.3 The following drugs in different combinations are recommended as PMB level of care for ATLL.

- Carboplatin
- Cyclophosphamide
- Gemcitabine
- Doxorubicin
- Corticosteroids
- Etoposide
- Cytarabine
- Vincristine
- Methotrexate
- Ifosfamide
- Cisplatin
- Gemcitabine
- Oxaliplatin
- Vinorelbine
- Bendamustine – on motivation on a case by case basis.

5.4 Symptomatic smouldering (skin lesions, opportunistic infections etc.) And favourable chronic:

- Zidovudine with or without topical therapies/phototherapy. A combination of zidovudine and interferon alpha has shown high efficacy, with limited research on the efficacy of zidovudine only (Bazarbachi et al., 2010). Interferon alpha is however not currently available in South Africa.
- Where zidovudine is not available and non-tumorous skin lesions (patches, plaques) are present, consider skin-directed therapies as clinically indicated (NCCN, 2021).
- If no response to first line therapy (zidovudine or skin-directed therapies) at two months, then chemotherapy agents as listed above with or without topical therapies/phototherapy followed by allogeneic haemopoietic stem cell transplant (HSCT) can be considered (NCCN , 2021).
- If progressive disease with tumorous skin lesions is present or patient experiences transformation into acute-lymphoma type during active monitoring or zidovudine, a switch to treatment strategy for aggressive acute-lymphoma subtype may be considered.
- Radiation therapy in selected cases with localized, symptomatic disease is recommended. The dose, duration and frequency varies widely and cannot be stipulated in this guideline.

5.5 Unfavourable chronic:

- Zidovudine is continued indefinitely unless there is progressive disease (NCCN, 2021).
- If no response to zidovudine at 2 months (initial response), then chemotherapy options as discussed above may be considered (NCCN, 2021).
- Where zidovudine is unavailable or if the patient experiences progressive disease on zidovudine chemotherapy followed by allogeneic HSCT may be considered (NCCN, 2021).

5.6 Acute

- Clinical trial or zidovudine (Hermine et al., 2002, Hodson et al., 2010) or first line chemotherapy as outlined above. Scheme rules will apply when patients are enrolled in clinical trials.
- Follow up for initial response after two cycles of chemotherapy or zidovudine (NCCN, 2021).
- If a favourable response is observed, initial therapy may be continued or allogenic HSCT may be considered.
- Efficacy of long-term treatment is limited and transplant may be beneficial on a case by case assessment (Tsukasaki et al., 2009).

5.7 Lymphoma-type

- Chemotherapy and zidovudine should be used.
- First line chemotherapy as outlined above followed by early allogeneic HSCT in first remission (NCCN, 2019).
- For older patients or patients not fit for transplant the chemotherapy dose may be reduced at the discretion of the treating provider.
- If initial response if favourable after two cycles, chemotherapy may be continued as maintenance or zidovudine or an allogeneic HSCT(Hodson et al., 2010, Hermine et al., 2002).
- If unfavourable response, other chemotherapy options that have not been used may be explored and an allogeneic HSCT.

5.8 Refractory / Progressive disease

- In cases of persistent and progressive disease at two months from start of treatment (non-responders to initial therapy), then options for additional therapy include participation in clinical trials, where available or second line chemotherapy or best supportive care (radiation therapy) (Ishida et al., 2017). Clinical trials are not PMB level of care.
- Allogeneic HSCT (if donor is available) should be considered for patients with acute or lymphoma subtype. If there is no sibling match, the donor registry (local or international) may be utilised to find a matched-unrelated donor.
- All patients with lymphoma subtype should receive central nervous system (CNS) prophylaxis with intrathecal methotrexate, dexamethasone and cytarabine (NCCN,2021).

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