Draft PMB definition guideline: Chronic Lymphocytic Leukaemia (CLL)/ CLL like

Published date: 31 July 2020

Comments due on: 30 November 2020

Disclaimer:

The chronic lymphocytic 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 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 available here.

CMS is cognisant of the criteria for bone marrow transplantation as stipulated in the 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.*

Acknowledgements

The Council for Medical Schemes (CMS) would like to acknowledge all stakeholders who assisted in drafting this document, including participant haematologists, oncologists, pathologists, patient advocacy groups, funders, and administrators.

Specifically, the CMS acknowledges the following clinical experts for their insights during the drafting of this document:

Dr Estelle Verburgh	Dr Leonard Mutema	Dr Theo Gerderner
Dr Hannes Koorhof	Dr Lucile Singh	Dr Yasmin Goga
Dr H-T Wu	Dr Nokwanda Zuma	Professor Mariana Kruger
Dr Jacqueline Thompson	Dr Pelisa Ford	Professor Moosa Patel
Dr Johani Vermuelen	Dr Sheynaz Bassa	Professor Paul Ruff
Dr Justine du Toit		

The contributions of the following individuals from professional bodies, patient advocacy groups, different medical scheme funders, and administrators who were also members of the clinical advisory committee set up to discuss member entitlements for mature b-cell neoplasms were immensely valuable in drafting this document:

Dr Eric Hefer	Ms Caroline Rich
Dr Jo Samsononwicz	Ms Edelweiss Potgieter
Dr Lindiwe Mbekeni	Ms Kim Cardwell
Dr Morwesi Mahlangu	Ms Lauren Pretorius
Dr Samukeliso Dube	Ms Shelley McGee

Dr Mohlamme John Mathabathe is also acknowledged by the CMS for his assistance in the drafting of this document.

Table of Contents

Abbreviations

PMBs	Prescribed Minimum Benefits
DTPs	Diagnosis Treatment Pairs
CLL	Chronic lymphocytic leukaemia
NHL	Non-Hodgkin lymphoma
HIV	Human immunodeficiency virus
LDH	Lactate dehydrogenase
CT	Computed tomography
FDG-PET	Fluoro-deoxy-glucose positron emission tomography
OS	Overall survival
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
BR	Bendamustine-rituximab
MRD	Minimal residual disease
IGHV	Immunoglobulin heavy chain variable
CLL-IPI	Chronic lymphocytic leukaemia International Prognostic Index
iwCLL	International workshop on chronic lymphocytic leukaemia
FCR	Fludarabine, cyclophosphamide and rituximab
FC	Fludarabine and cyclophosphamide
EBMT	European Group for Blood and Marrow Transplantation
ECOG PS	Eastern Cooperative Oncology Group Performance Status
IVIG	Intravenous immunoglobulins
CIRS	Cumulative illness rating scale
CrCl	Creatinine clearance

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. 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 is a recommendation for the diagnosis, treatment and care of individuals with chronic lymphocytic lymphoma (CLL) in any clinically appropriate setting as outlined in the Act.

2.2. The management of CLL variants (including small lymphocytic lymphoma (SLL)) is also included in this guideline.

2.3. The purpose is to provide a detailed clarification in respect of benefit and entitlements to members and beneficiaries of medical schemes.

Table 1: Possible ICD10 codes for identifying CLL

DTP code	ICD 10 code	WHO description
901 S Acute leukaemias, lymphomas	C91.1	Chronic lymphocytic leukemia of B -cell type

2.4. When the treatment intent is palliative, DTP 260S, may be applied depending on the clinical case.

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

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

3.1. Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia in Western populations. Approximately 20,980 new cases were reported in 2016 in the USA (Teras *et al.*, 2016).

3.2. The prevalence of CLL increases with age and the median age at the time of diagnosis is between 65 and 70 years (Shanafelt *et al.*, 2010).

3.3. The incidence of CLL is highest among Caucasians, intermediate among Africans/African Americans, and low among Asian/Pacific Islanders. The incidence of CLL is almost twice as high among men than women (Shenoy *et al.*, 2011; Diehl, Karnell and Menck, 1999; Yang *et al.*, 2015).

3.4. The aetiology of CLL is poorly understood. A family history of haematologic malignancy is an established risk factor (Wang *et al.*, 2007).

3.5. South African incidence and prevalence data are lacking due to available data not distinguishing between CLL and other types of leukaemia. The 2016 National Cancer registry reported a crude incidence of leukaemia in South Africa of 0.97/100 00 and 0.79/100 000 for males and females, respectively.

4. Pathology

4.1. The most common form of CLL originates in B lymphocytes and CLL is characterised by the clonal expansion of leukaemic ($CD5^{+}CD23^{+}$) B -cells in blood, marrow, and secondary lymphoid tissues (Zhang and Kipps, 2014).

4.2. Morphologically, these leukaemic cells appear as small, mature lymphocytes that may be found mixed with occasional larger, or atypical cells, or prolymphocytes (Oscier *et al.*, 2016).

4.3. CLL originates from antigen-stimulated mature B lymphocytes, which either avoid death through the intercession of external signals or die by apoptosis, only to be replenished by proliferating precursor cells (Cheson and Meyer, 2009).

4.4. Approximately half of the cases of CLL carry unmutated Ig variable region (IgV) genes (uCLL), and the remaining cases have somatically mutated IgV genes (mCLL) (Seifert *et al.*, 2012; Damle *et al.*, 1999).

4.5. This distinction has clinical relevance as uCLL is more aggressive with a significantly shorter time from diagnosis to initial treatment compared to mCLL (Rassenti *et al.*, 2008).

5. Diagnosis

5.1. Consultations

Essential workup includes a complete history and physical examination, with particular attention to node bearing areas and the size of the spleen, liver, symptoms present, performance status, laboratory and imaging radiology.

Table 3: Recommended consultations for the diagnosis of CLL

Treating provider	Comment
Specialist physician Radiologist Pathologist Haematologist Oncologist	Number of consultations cannot be stipulated as this may vary by discipline, disease subtype and other patient factors

5.2. Histopathology and laboratory work up

5.2.1. If there is peripheral blood lymphocytosis, a flow cytometry for full CLL panel should be done and this can be diagnostic for CLL.

5.2.2. The diagnosis of CLL is based on the presence in blood of more than 5,000 monoclonal B cells/µl (>5 × 10^9/L) , with a distinctive immunophenotype (CD5+, SmIg, CD20+, CD19+, CD23+), which persists for more than 3 months (Delgado *et al.*, 2013).

5.2.3. Newer monoclonal antibodies, such as anti-CD43, anti-CD200 or anti-ROR1, may provide further information in differentiating CLL from other chronic lymphoproliferative disorders (Delgado *et al.*, 2013).

5.2.4. A bone marrow aspirate and trephine for flow cytometry, immunohistochemistry, cytogenetics (and karyotyping) is typically performed at diagnosis as part of the patient's staging evaluation and is recommended as PMB level of care.

5.2.5. Lymph node biopsy may be performed if clinically indicated (e.g. lymph nodes enlarged and there is a clinical suspicion of small lymphocytic lymphoma and/or Richter's transformation).This is rarely indicated, is not routine and hence motivation is required.

5.2.6. FISH panel for chromosomes 11q, trisomy12,13q, 17p and TP53 mutation analysis; molecular studies e.g. Next generation sequencing (NGS) and polymerase chain reaction (PCR); B Cell receptor IgHV (immunoglobulin heavy chain) testing are all recommended as PMB level of care (Rosenquist *et al.*, 2017).

5.2.7. Other essential workup that is recommended as PMB level of care incudes (Dreyling, 2016; Hallek *et al.*, 2018a):

- Full blood count with differential count, smear and reticulocyte count
- Glucose
- Calcium, magnesium and phosphate
- Haematinics
- International normalised ratio (INR) and partial thromboplastin time (PTT)
- Haemolytic screen: Coombs, haptoglobin

- Biochemistry, including renal (urea and creatinine), and liver function tests (LFTs)
- Tissue typing as appropriate for allogenic transplants
- Protein electrophoresis and immunoglobulins
- Lactate dehydrogenase (LDH) and uric acid
- Beta -2 microglobulin
- Serology for hepatitis B, C and HIV, Epstein-Barr virus (EBV), Cytomegalovirus (CMV)

5.3. Imaging

5.3.1. The following imaging is recommended as PMB level of care:

- Chest x-rays
- MRI/CT brain where indicated
- Contrasted CT neck to pelvis (if no renal impairment), where indicated
- Abdominal ultrasound
- ECG/echocardiogram – when clinically indicated.
- PET/CT – it is not recommended for diagnosis. Only after confirmed diagnosis a PET/CT may confirm localized stage 1 or 2 before involved field radiotherapy.

6. Staging and Risk Assessment

This section will provide a description of the different approaches to staging and stratifying patients with CLL.

6.1. An important aspect of disease assessment is determining the anatomical stage of disease as this has direct implication on treatment selection and prognosis.

6.2. Patients with newly diagnosed CLL should undergo a comprehensive clinical, laboratory and imaging assessment to characterise the stage of disease.

6.3. The most common staging systems for CLL are the Rai (Table 4) and Binet (Table 5) systems (Hallek *et al.*, 2018a; Binet *et al.*, 1981; Rai KR, 1975).

Table 4: Rai System

Stage	Description	Modified Risk Status
0	Lymphocytosis, lymphocytes in blood > 5 x 10^9 /L clonal B cells and 40 % lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node (s)	Intermediate
II	Stage 0 -1 with splenomegaly, hepatomegaly, or both.	Intermediate

III[c]	Stage 0-II with haemoglobin < 11.0 g/dL, or haematocrit < 33 %	High
IV[c]	Stage 0-III with platelets < 100,000 mcL	High

[c]: Immune-mediated cytopenias are not the basis for these stage definitions.

Table 5: Binet System

Stage	Description
A	Haemoglobin ≥ 10 g/dL, and platelets ≥ 100,000/ mm^3, and <3 enlarged areas.
B	Haemoglobin ≥ 10 g/dL and platelets ≥ 100,000/ mm^3 and ≥ 3 enlarged areas
C	Haemoglobin < 10 g/dL and /or platelets < 100,000/ mm^3, and any number of enlarged areas

The most relevant prognostic score is the CLL International Prognostic Index (CLL-IPI) (Table 6). The CLL-IPI uses a weighted grading of five independent prognostic factors (International CLL Working Group, 2016):

- TP53 deletion and/or mutation (collectively called TP53 dysfunction)
- IGHV mutational status
- Serum β2-microglobulin
- Clinical stage
- Age

6.4. The value of CLL-IPI is that it separates four groups of CLL with different overall survival (OS) at 5 years (Table 7). It also identifies more accurately the treatment approach for CLL patients (Hallek, 2019).

Table 6: CLL International Prognostic Index (CLL-IPI)

Independent Predictors of OS	Weighted Scoring
Age > 65 years	1 point
Clinical stage > 0	1 point
17p deletion and/or TP53 mutation	4 points
IGHV mutation status	2 points
Serum β2-microglobulin > 3.5 mg/L	2 points

Table 7: The different CLL-IPI categories and potential clinical consequences

CLL-IPI category (risk groups)	Risk factors (weighted scoring)	5-year OS, %	Potential clinical consequence
Low	0-1	93.3	Do not treat
Intermediate	2-3	79.2	Do not treat except if the disease is symptomatic

High	4-6	63.3	Treatment indicated except if the disease is asymptomatic
Very high	7-10	23.3	If you need to treat, do not use chemotherapy but rather novel agents or treatment in clinical trials

6.5. Assessment of functional status and comorbidity is important as CLL is diagnosed in older patients, with a median age of 72 years at diagnosis. Cumulative Illness Rating Scale (CIRS) in combination with creatinine clearance (CrCl) has been used by the German Chronic Lymphocytic Leukemia Study Group (GCLLSG) trials to assess the overall fitness of patients enrolled in clinical trials. Patients are stratified into three groups based on their functional status and presence or absence of comorbidities:

- Frail patients with significant comorbidities
- Patients ≥ 65 years or younger with significant comorbidities (CrCl < 70 mL/min)
- Patients < 65 years without significant comorbidities (Goede *et al.*, 2014).

7. Management of CLL

Previous studies have shown that treatment of early-stage CLL with chemotherapeutic agents does not translate into survival advantage (Dighiero *et al.*, 1998).

The International Workshop on Chronic Lymphocytic Leukaemia (iwCLL) guidelines recommend that when patients progress or present with progressive or symptomatic/active disease treatment should be initiated (Hallek, 2019).

The iwCLL guidelines define symptomatic or active disease (at least one of the following criteria should be met):

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia. Cut- off levels of Hb < 10 g/dL or platelet counts of <100 000/µL are generally regarded as an indication for treatment. However, it should be pointed out that in some patients with platelet counts of <100 000/ µL, may remain stable over a long period of time; this situation does not always require therapeutic intervention.
- Massive (i.e., ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
- Massive nodes (i.e., ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
- Progressive lymphocytosis with an increase of ≥50% over a two- month period, or lymphocyte doubling time (LDT) of less than 6 months. The LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts (ALC) obtained at intervals of 2 weeks over an observation period of 2 to 3 months. Patients with initial blood lymphocyte counts of <30 000/µL may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (e.g., infections, steroid administration) should be excluded.
- Autoimmune complications including anaemia or thrombocytopenia poorly responsive to corticosteroids.

- Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).
- Disease-related symptoms as defined by any of the following:
    - Unintentional weight loss ≥10% within the previous 6 months.
    - Significant fatigue (i.e., ECOG PS 2 or worse; cannot work or unable to perform usual activities).
    - Fevers ≥100.5°F or 38.0 °C for 2 or more weeks without evidence of infection.
    - Night sweats for ≥1 month without evidence of infection.

7.1. First-line treatment for CLL

7.1.1. Chlorambucil was the therapeutic "gold standard" used as initial front-line therapy for CLL for several decades. The advantages of chlorambucil are its relatively low cost and it is convenient as an oral drug. Its major disadvantages are its low to non-existent complete response (CR) rate and some side effects that occur after extended use (prolonged cytopenia, myelodysplasia and secondary acute leukemia) (CLL Trialists' Collaborative Group., 1999). Chlorambucil monotherapy is currently used as an option to achieve palliation in elderly or unfit patients (Hallek, 2019).

7.1.2. Purine analogue Fludarabine is also used in CLL. Fludarabine monotherapy produces superior overall response (OR) rates compared with other treatment regimens containing alkylating agents or corticosteroids. Fludarabine induced more remissions and more CR (7%-40%) than other conventional chemotherapies, including CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), CAP (cyclophosphamide, doxorubicin, prednisone), or chlorambucil. However, fludarabine did not improve overall survival when used as a single agent (Rai *et al.*, 2000; Steurer *et al.*, 2006; Johnson *et al.*, 1996; Leporrier *et al.*, 2001).

7.1.3. Bendamustine (4-[5-[Bis(2-Chloroethyl) amino]-1-methylbenzimid- azol-2-yl] butanoic acid) is a potent single agent for the treatment of CLL. Bendamustine was compared to chlorambucil in a randomized trial and produced improved responses but greater toxicity and no OS benefit. The overall response (OR) and median progression free survival (PFS) rates were 67% and 22 months respectively for bendamustine vs 30% and 8 months for chlorambucil (both $P < .0001$)(Knauf *et al.*, 2009). Another trial compared bendamustine to fludarabine in 96 patients with relapsed CLL requiring treatment after one previous systemic regimen. Overall response rates were 76% on bendamustine and 62% on fludarabine, with clinical complete response rates of 27% and 9%, respectively. Median PFS was 20.1 and 14.8 months, median overall survival 43.8 and 41.0 months (Niederle *et al.*, 2013). Bendamustine is not currently listed on the NEML, and is recommended based on scheme rules, however, it is worth noting the efficacy compared to other therapeutic options.

7.1.4. Rituximab (anti-CD20 monoclonal antibodies) in CLL is less active as a single agent than in follicular lymphoma, unless very high doses are used (Huhn *et al.*, 2001; O'Brien *et al.*, 2001). In contrast, combinations of rituximab with chemotherapy have proven to be very efficacious therapies

for CLL. The CALGB 9712 protocol combined rituximab with fludarabine in either a sequential or concurrent regimen in a randomised study. Patients (n=104) with previously untreated CLL received six cycles of fludarabine, with or without rituximab, followed by four once-weekly doses of rituximab. Overall and complete response rates were higher in the concurrent group (90% and 47% vs 77% and 28% (Byrd *et al.*, 2003).

7.1.5. Bendamustine plus rituximab (BR) has demonstrated activity in patients with previously untreated CLL resulting in an ORR of 81 % (35 % CR) to 95 % (43 % CR) (Michallet *et al.*, 2018).

7.1.6. The CLL10 study confirmed the superiority of the combination of fludarabine, cyclophosphamide and rituximab (FCR) over BR as first-line therapy for CLL without the del(17p) in fit patients (n=567); CIRS (Cumulative Illness Rating Scale) score ≤ 6; CrCl (Creatinine Clearance) > 70 mL/min). The FCR resulted in higher CR rate (40 % vs. 31 %), more minimal residual disease (MRD) negativity (59 % vs. 26 % at 12 months; p < 0.0001; 55 % at vs. 27 % at 18 months; p = 0.002), and longer median PFS (55 months vs. 42 months; p0.0003) compared to BR. The PFS benefit of PCR was significant in physically fit patients < 65 years and in patients with mutated IGHV (Eichhorst *et al.*, 2016). From the CLL10 study, BR is associated with decreased risk of secondary acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). After a median follow-up of 58 months, the incidence of secondary AML and MDS were 3 % and 1 % in FCR and BR arms, respectively (Eichhorst *et al.*, 2016).

7.1.7. The CLL8 study in which 817 physically fit patients with previously untreated CLL (median age 61 years) were randomised to receive up to six courses of either FCR (N=408) or FC (n=409) regimen. The FCR resulted in higher ORR (90 % vs. 80 %; p < 0.001) and CR rate (44 % vs. 22 %; p <0.001) compared to FC. After median follow-up of 6 years, the median PFS was 57 months and 33 months, respectively, for FCR and FC (p < 0.001). Median overall survival (OS) was not reached for the FCR group and was 86.0 months for the FC group (HR, 0.68; 95% CI, 0.54-0.89, P= .001). In patients with mutated IGHV (IGHV MUT), FCR improved PFS and OS compared with FC (PFS: HR, 0.47; 95% CI, 0.33-0.68, P < .001; OS: HR, 0.62; 95% CI, 0.34-1.11, P= .1). This improvement remained applicable for all cytogenetic subgroups other than del(17p). Long-term safety analyses showed that FCR had a higher rate of prolonged neutropenia during the first year after treatment (16.6% vs 8.8%; P= .007). Secondary malignancies including Richter's transformation occurred in 13.1% in the FCR group and in 17.4% in the FC group (P= .1) (Fischer *et al.*, 2016).

7.1.8. In a CALGB 9712 multicentre trial, 104 previously untreated CLL patients were randomized to receive either 6 monthly courses of fludarabine concurrently (n=51) with rituximab followed 2 months later by 4 weekly doses of rituximab for consolidation therapy, or sequential (n=53) fludarabine alone followed 2 months later by rituximab consolidation therapy. The overall response rate with the concurrent regimen was 90% (47% complete response [CR], 43% partial response [PR]; 95% confidence interval [CI], 0.82-0.98) compared with 77% (28% CR, 49% PR; 95% CI, 0.66-0.99) with the sequential regimen. After a median follow-up of 117 months (range, 66 to 131

months), the median OS was 85 months, and 71% of patients were alive at 5 years. The median PFS was 42 months, and 27% were progression free at 5 years (Byrd *et al.*, 2003; Woyach *et al.*, 2011).

7.1.9. High-dose methylprednisolone (HDMP) and rituximab (R) were evaluated as first-line therapy in a single centre, observational study. Twenty-eight patients with a median age of 65 years were enrolled. Patients received HDMP at 1 g/m^2 each day for three days during each of the three four-week cycles together with rituximab and prophylactic anti-microbial therapy. The treatment was well tolerated with few adverse events of grade III or higher. The overall response rate was 96% (n=27). Nine patients (32%) achieved a complete remission (CR), two of which were without detectable minimal residual disease (MRD). This study demonstrates that HDMP and rituximab is an effective non-myelosuppressive treatment combination for patients with CLL that warrants consideration particularly for patients with limited myeloid reserve that might not tolerate standard treatment regimens (Castro *et al.*, 2009).

7.1.10. The French Cooperative Group on Chronic Lymphocytic Leukemia initiated a randomized clinical trial in 1980 in which intermediate prognosis patients (stage B) received either an indefinite course of chlorambucil (0.1 mg/kg/d) or 12 cycles of the COP regimen (vincristine, cyclophosphamide, and prednisone). There was no improvement in overall survival with the COP regimen (P= .44) even after adjusting for both prognostic and imbalanced factors (P= .24). The 3-year and 5-year overall survival rates were, respectively, 69% and 44% in the chlorambucil group as compared with 73% and 43% in the COP group. The median survival times were 58 months in the chlorambucil group and 57 months in the COP group. Moreover, no significant difference was observed between the two treatment groups in terms of either treatment response, 9-month status, time to disease progression to stage C, or causes of death (Binet *et al.*, 1990).

7.1.11. NCCN guidelines version 4.2020 consider bendamustine plus rituximab as a reasonable alternative for older patients otherwise eligible for chemoimmunotherapy and as an option for patients ≥ 65 years or younger patients with significant comorbidities and for patients < 65 years without significant comorbidities (NCCN guidelines).

7.1.12. NCCN guidelines version 4.2020 recommend fludarabine plus rituximab (FR) as an option for patients < 65 years without significant comorbidities. These guidelines do not recommend FR for CLL with del(17p) as these patients do better on chemoimmunotherapy containing an alkylating agent.

7.1.13. The NCCN guidelines version 4.2020 recommends high-dose methylprednisolone plus rituximab for all patients, regardless of patient's age and comorbidities.

7.1.14. The 2015 ESMO guidelines recommend FCR as a standard first-line therapy in physically fit patients (physically active, with no major health problems, normal renal function) without TP53 deletion/mutation. In fit but elderly patients, the 2015 ESMO guidelines states that BR should be considered, as FCR is associated with higher rates of severe infections when compared to BR.

7.1.15. In patients with relevant comorbidity, who are usually older, but without the TP53 deletion/mutation, the combination of chlorambucil plus anti-CD20 antibody (e.g. rituximab) is a recommended standard approach in the 2015 ESMO guidelines.

Table 8: Summary of PMB recommendations for chemotherapy agents used as monotherapy and/ or in combination in CLL/ CLL like

TP53/del 17p negative		TP53/del 17p positive:	
Fit patients	Unfit patients	Fit patients	Unfit patients
- Fludarabine - Cyclophosphamide - Rituximab - Prednisone	- Rituximab - Chlorambucil - Cyclophosphamide - Vincristine - Prednisone	- Fludarabine - Cyclophosphamide - Rituximab - Methylprednisolone	- Rituximab - Chlorambucil - Cyclophosphamide - Vincristine - Prednisone

7.2. Maintenance Therapy

7.2.1. There is currently lack of sufficient randomised data on maintenance therapy.

7.2.2. In a randomised, double-blind, phase 3 study (CLLM1; CLL Maintenance 1 of the German CLL Study Group), patients older than 18 years and diagnosed with immunophenotypically confirmed chronic lymphocytic leukaemia with active disease, who responded to chemoimmunotherapy 2-5 months after completion of first-line therapy and who were assessed as having a high risk for an early progression with at least a partial response after four or more cycles of first-line chemoimmunotherapy, were eligible if they had high minimal residual disease levels or intermediate levels combined with an unmutated IGHV gene status or TP53 alterations. Patients were randomly assigned (2:1) to receive either lenalidomide (5 mg) or placebo. Maintenance was started with 5 mg daily, and was escalated to the target dose of 15 mg. If tolerated, medication was administered until disease progression. Recruitment was closed prematurely due to poor accrual after 89 of 200 planned patients were randomly assigned: 60 (67%) enrolled patients were assigned to the lenalidomide group and 29 (33%) to the placebo group, of whom 56 (63%) received lenalidomide and 29 (33%) placebo, with a median of 11·0 (IQR 4·5-20·5) treatment cycles at data cut-off. After a median observation time of 17·9 months (IQR 9·1-28·1), the hazard ratio for progression-free survival assessed by an independent review was 0·168 (95% CI 0·074-0·379). Median progression-free survival was 13·3 months (95% CI 9·9-19·7) in the placebo group and not reached (95% CI 32·3-not evaluable) in the lenalidomide group (Fink *et al.*, 2017).

7.2.3. The NCCN guidelines version 4.2020 includes lenalidomide maintenance after first-line chemoimmunotherapy under other recommended regimens for CLL without del(17p)/TP53 mutation in high risk patients (MRD ≥ 10^{-2} or ≥ 10^{-4} and < 10^{-2} with unmutated IGHV) based on the CLLM1 study.

7.2.4. The 2015 ESMO guidelines states that the maintenance therapy in CLL patients with higher risk of relapse may have some benefit but cannot be generally recommended. These guidelines do not make any reference to the agent/regimen for maintenance therapy (Eichhorst *et al.*, 2015).

7.2.5. There are currently no medicines recommended as PMB level of care for maintenance in patients with CLL.

7.3. Treating Relapsed or Refractory Disease

7.3.1. First-line therapy mentioned above may be repeated if relapse or progression occurs at least 24 to 36 months after chemoimmunotherapy (Eichhorst *et al.*, 2015).

7.3.2. The combination of fludarabine and cyclophosphamide cannot be repeated. An anthracycline (e.g. doxorubicin, epirubicin) and mitoxantrone can be added.

7.3.3. No rituximab should be given in refractory disease unless given as first line. Transplant can also be considered in relapsed disease

7.4. Stem cell transplantation (SCT)

Allogeneic Stem Cell Transplantation (Allo-SCT) has the potential for durable remissions for CLL lasting over 5 years. The efficacy of allo-SCT is primarily due to the graft-*versus*-leukemia effect in CLL (Mewawalla and Nathan, 2014).

Table 9: Selected Reduced Intensity Conditioning allogeneic transplantation in chronic lymphocytic leukemia (Mewawalla and Nathan, 2014).

	(Dreger *et al.*, 2010)	(Sorror *et al.*, 2008)	(Brown *et al.*, 2013)	(Khouri *et al.*, 2011)
N	90	82	76	86
Conditioning chemotherapy	Nonmyeloablative (FluCy ± ATG)	Nonmyeloablative (FluTBI)	Reduced intensity (FluBu)	Nonmyeloablative (FluCyRit)
Alternative donors* (%)	59	37	63	50
Relapse incidence (%)	40 (4 years)	38 (5 years)	40 (5 years)	NR
PFS (%)	42 (4 years)	39 (5 years)	43 (5 years)	36 (5 years)
OS (%)	70 (4 years)	50 (5 years)	63 (5 years)	51 (5 years)
100-day mortality (%)	2	<10	<3	3
NRM (%)	23 (4 years)	23 (5 years)	16 (5 years)	17 (1 year)
Follow up (years)	3.8 (0.6–8.5)	5 (0.9–7.3)	5.1	3.1 (0.9–10.9)

**Donors other than HLA-matched siblings. FluCy, Fludarabine and Cyclophosphamide; ATG, Anti-thymocyte globulin; FluTBI, Fludarabine and Total Body Irradiation; FluBu, Fludarabine and Busulfan; FluCyRit, Fludarabine, Cyclophosphamide and Rituxan; RIC, Reduced Intensity Conditioning.*
HLA, human leucocyte antigen; NR, not reached; NRM, nonrelapse mortality; OS, overall survival; PFS, progression-free survival.

7.4.1. SCT should only be considered if the patient is fit, well informed and willing, and a donor available. The entry criteria for allogenic SCT should be aligned with current guidelines. This includes:

- Co-morbidity score < 3
- EBMT score >5
- Chemosensitive disease after 1st line therapy in TP53 / del17p positive patients.
- Patients failing several lines of therapy i.e. more than 2; but there should be a response even though they failed

7.4.2. Autologous stem cell transplant is not recommended in CLL.

7.5. Radiotherapy

7.5.1. Low-dose RT (4 Gy in 2 fractions) is a highly effective palliative treatment of localized lymph node masses in patients with CLL. In a Phase II study of palliative low-dose local radiotherapy in disseminated indolent non-Hodgkin's lymphoma and chronic lymphocytic leukemia, twenty-two patients (11 men, 11 women, median age 62 years, range 30-89) with disseminated INHL (n= 15) or CLL (n= 7) were treated with local low-dose RT (2 Gy x 2 within 3 days), with the aim of achieving palliation from localized lymphoma masses.

7.5.2. Of the 22 patients, the following was observed:

- 18 responded to the treatment, corresponding to an overall response rate (RR) of 82%.
- 12 patients (55%) achieved a complete response (CR)
- 5 patients (22%) a partial response (PR)
- 1 patient had a CR at three sites and a PR at one site.

7.5.3. Of the 31 irradiated sites:

- 27 responded to treatment, corresponding to an overall RR of 87%
- For 20 sites (65%) a CR was achieved
- For 7 sites (22%) a PR.

7.5.4. Patients with disseminated INHL had an overall RR of 87% (74% CR, 13% PR); patients with CLL had an overall RR of 71% (29% CR, 42% PR). The median duration of response was estimated at 22 months. None of the patients had significant side effects from the treatment (Jóhannsson *et al.*, 2002).

7.5.5. Involved-field radiation therapy (IFRT) is recommended as PMB level of care.

7.5.6. 3-15# of CD conformal radiation in the palliative setting is also recommended as PMB level of care.

8. Response evaluation and Follow Up:

8.1. CLL is an incurable disease with life-long observation and follow-up being recommended.

8.2. Asymptomatic patients should be reviewed every 3-12 months with FBC and clinical examination (palpate lymph nodes, liver and spleen).

8.3. If CLL proves more aggressive, more regular follow up will be required (for example: once every two weeks to once a month or more frequently when clinically indicated based on the discretion of the attending clinical haematologist).

8.4. The following imaging is recommended based on the clinical symptoms and/or signs:

- CT scan if indicated
- Chest x-ray with abdominal ultrasound
- Depending on the nature of the disease a PET/CT might be required – if Richter's transformation is suspected to guide biopsy
- Contrasted CT neck to pelvis

8.5. A CD4 count at 3 monthly intervals for patients receiving Fludarabine chemotherapy.

8.6. Repeat bone marrow with flow cytometry and molecular studies as clinically indicated.

8.7. If Richter's transformation suspected, repeat lymph node biopsy indicated.

8.8. If recurrent infections and receiving IVIG – repeat immunoglobulin tests.

8.9. Response to treatment involves both physical examination and evaluation of blood parameters. The iwCLL guidelines provide recommendations for the evaluations and response assessments appropriate for general clinical practice setting versus for clinical trial. To define the response to therapy, 2 groups of parameters need to be assessed and documented: parameters of group A assess the lymphoid tumor load and constitutional symptoms; parameters of group B assess the hematopoietic system (figure 1) (Hallek *et al.*, 2018b).

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Hemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

Figure 1: Response definition after treatment of CLL patients

8.10. The assessment of minimal residual disease (MRD), although not always part of the routine practice, is an additional and increasingly important category of response assessment, resulting in four different response categories (Hallek, 2019):

- CR, MRD+
- CR, MRD-
- PR, MRD+
- PR, MRD-

References

Advani, R., Rosenberg, S.A., Horning, S.J. (2004) Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. *J Clin Oncol 2004*; 22(8):1454-1459.

Alexander, D.D., Mink, P.J., Adami, H.O., et al. (2007) The non-Hodgkin lymphomas: a review of the epidemiologic literature. International Journal of Cancer, 120, 1– 39.

Ansell, S.M. (2013) Malignant B cells at the helm in follicular lymphoma. *J Clin Oncol*, 31: 2641- 2642.

Ardeshna, K.M., Smith, P., Norton, A., et al. (2003) Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. *Lancet*, 362:516–522.

Bachy, E., Houot, R., Morschhauser, F., et al. (2013) Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. *Haematologica*, 98: 1107–1114.

Barrington, S.F., Mikhaeel, N.G., Kostakoglu, L., et al. (2014) Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol*, 32(27):3048–58.

Cheson, B.D., Fisher, R.I., Barrington S.F., et al. (2014) Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol*, 32(27):3059–68.

Chiu, B.C. & Hou, N. (2015) Epidemiology and etiology of non-Hodgkin lymphoma. *Cancer Treatment and Research*, 165, 1– 25.

Dreyling, M., Ghielmini, M., Rule, S., et al. (2016). Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, Volume 27, v83 - v90

Ekström-Smedby, K. (2006) Epidemiology and etiology of non-Hodgkin lymphoma–a review. *Acta Oncol,* 45(3):258-271.

Freedman, A. (2018) Follicular lymphoma: 2018 update on diagnosis and management. *Am J Hematol,* 93(2):296-305.

Friedberg, J.W., Byrtek, M., Link, B.K., et al. (2012) Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the National LymphoCare Study. *J Clin Oncol*, 30: 3368–3375
Friedberg, J.W., Taylor, M.D, Cerhan, J.R., et al. (2009) Follicular lymphoma in the United States: first report of the national LymphoCare study. *J Clin Oncol,* 27(8):1202-1208.

Goodlad, J.R., Batstone, P.J., Hamilton, D., et al. (2003) Follicular lymphoma with marginal zone differentiation: cytogenetic findings in support of a high-risk variant of follicular lymphoma. *Histopathology*, 42 (3): 292– 298

Guadagnolo, B.A., Li, S., Neuberg, D., et al. (2006) Long-term outcome and mortality trends in early-stage, Grade 1–2 follicular lymphoma treated with radiation therapy. *Int J Radiat Oncol Biol Phys*, 64:928–934.

Herold, M., Haas, A., Srock, S., et al. (2007) Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology Study. *J Clin Oncol*, 25: 1986–1992.

Hiddemann, W., Kneba, M., Dreyling, M., et al. (2005) Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* ;106(12):3725-3732

Hoskin, P.J., Kirkwood, A.A., Popova, B., et al. (2014) 4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial. Lancet Oncol. An important study on the limits of further lowering the RT dose for indolent lymphoma.

Huet, S., Sujobert, P and Salles, G. From genetics to the clinic: a translational perspective on follicular lymphoma. *Nat Rev Cancer.* 2018; 18(4):224-239.

Kridel, R., Sehn, L.H. and Gascoyne, R.D. (2012) Pathogenesis of follicular lymphoma. *J Clin Invest,* 122(10):3424-3431.

Kuruvilla, J., Assouline, S., Hodgson, D., et al. (2015) A Canadian evidence-based guideline for the first-line treatment of follicular lymphoma: joint consensus of the Lymphoma Canada Scientific Advisory Board. *Clin Lymphoma Myeloma Leuk*,15:59–74.

Marcus, R., Imrie, K., Solal-Celigny, P., et al. (2008) Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*, 26(28):4579-4586.

Monga, N., Nastoupil, L., Garside J., et al. Burden of illness of follicular lymphoma and marginal zone lymphoma. *Ann Hematol.* 2019; 98(1):175-183.

Montoto, S., Davies, A.J., Matthews, J., et al. (2007) Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. *J Clin Oncol*, 25: 2426- 2433.

Morton, L.M., Wang, S..S., Devesa, S.S., et al. (2006) Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. *Blood*, 107, 265– 276.

Muller, A.M., Ihorst, G., Mertelsmann, R., et al. (2005) Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution and etiology. *Ann Hematol,* 84:1-12.

Nabhan, C, Zhou, X., Day, B.M., et al. (2016) Disease, treatment, and outcome differences between men and women with follicular lymphoma in the United States. *Am J Hematol* 91:770-775.

Nicd.ac.za. (2020). [online] Available at: http://www.nicd.ac.za/wp-content/uploads/2019/12/2014-NCR-tables.pdf [Accessed 3 Mar. 2020].

Rummel, M., Niederle, N., Maschmeyer, G., et al. (2013) Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet,* 381: 1203–1210

Salles, G., Seymour, J.F., Feugier, P., et al. (2013) Updated 6 year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immunochemotherapy. *Blood*, 122: abstr. 509.

Swerdlow S.H., Campo, E., Pileri, S.A., et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016; 127:2375–2390.

Tan, D.E., Foo, J.N., Bei, J.X., et al. (2013) Genome-wide association study of B-cell non-Hodgkin's lymphoma identifies 3q27 as a susceptibility locus in the Chinese population. *Nat Genet*, 4:804-7.

Taverna, C.J., Martinell, G., Hitz, F., et al. (2013) Rituximab maintenance treatment for a maximum of 5 years in follicular lymphoma: results of the randomized phase III trial SAKK 35/03. *Blood,* 122: abstr. 508.

Vidal, L., Gafter-Gvili, A., Salles, G., et al. (2011) Rituximab maintenance for the treatment of patients with follicular lymphoma: an updated systematic review and meta-analysis of randomized trials. *J Natl Cancer Inst,* 103: 1799–1806.