CancerCare Manitoba
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Practice Guideline: Disease Management

Consensus Recommendations for the Management of Chronic Lymphocytic Leukemia

Effective Date: November 2015

CancerCare Manitoba Guideline

Disease Management – Chronic Lymphocytic Leukemia

Developed by: Chronic Lymphocytic Leukemia Clinic

Preface

At CancerCare Manitoba (CCMB) the Clinical Practice Guidelines Initiative (CPGI) seeks to improve patient outcomes through the development, dissemination, implementation and evaluation of guidelines for the management of common clinical scenarios encountered by cancer patients throughout the province.

This practice guideline was created through the efforts of an interdisciplinary working group, comprised of members of the Chronic Lymphocytic Leukemia (CLL) Clinic, which includes the Department of Nursing and the Department of Pharmacy.

Purpose

This document is intended as a guide to facilitate a common approach to the clinical management of CLL, monoclonal B cell lymphocytosis (MBL) and small lymphocytic lymphoma (SLL).

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology caregivers, and dieticians at CCMB, and Community Oncology Program sites (Community Cancer Programs Network (CCPN) sites, Uniting Primary Care and Oncology (UPCON) clinics and WRHA Community Oncology Program sites).

Disclaimer

This guideline document should be viewed as an evidence-based practice tool, and as such, it does not represent an exhaustive text on the subject of CLL. Clinicians are advised to use it in their practice concomitantly with information from other evidence-based sources.

Use of this guideline in the clinical setting should not preclude use of the practitioner's independent clinical judgment, nor should it replace consultation with the appropriate oncology specialist when indicated (e.g., medical oncologist, radiation oncologist, family practitioner in oncology (FPO), hematologist, nurse practitioner/clinical nurse specialist, pharmacist, psychosocial oncology professional and dietician).

It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under his/her care and ideally this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

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I. Introduction

In Manitoba, approximately 100 new cases of CLL are diagnosed each year with the median age being 72 years. However, one-third of patients are < 65 years and 10% are < 50 years.[1] There is a slight male predominance, with the male:female ratio being 1.3:1. Males are diagnosed at a younger age than women (70 versus 73 years) and have a worse prognosis, particularly in the elderly. The median age at diagnosis in the CLL clinic is 68 years, younger than that seen in the general population, indicating a referral bias. The incidence of CLL has increased over the past 20 years, perhaps due to improved diagnostics.[1] Relative survival (survival of CLL patients as compared to an age- and sex-matched population) has also improved in this time, except for those > 80 years of age.[2] Similarly, the relative survival of patients in the clinic has also improved since the introduction of fludarabine, with the primary beneficiaries being younger patients with advanced disease (i.e., 2a). The only known predisposing factor to CLL is a genetic predisposition, with 10% of patients with CLL having a first-degree relative with CLL or another hematological malignancy.[3]

CLL is not an entirely benign disorder and many patients with this leukemia die prematurely from progressive disease (including Richter's transformation) or the complications of CLL, such as infections and second malignancies. A recent study from the Mayo Clinic has confirmed the importance of specialized clinics for the management of CLL patients, since patients managed by CLL specialists have a better median overall survival (OS) compared to patients managed by non-CLL specialists (10.5 versus 8.4 years, respectively).[4] The difference was related to the use of prognostic markers, timing and type of chemotherapy, and awareness and management of the infectious or immune complications seen in CLL. Therefore, all patients with CLL (and the related disorders (MBL and SLL) (*See Section IV: Diagnosis*) should be referred to the CLL clinic at CancerCare Manitoba.[4]

A CLL clinic is run twice weekly at the MacCharles site of CancerCare Manitoba and is managed by a group of clinicians who have a specific interest in this disease. The purpose of this clinic is to ensure that all patients with CLL/SLL and MBL in Manitoba receive optimum care that promotes health and wellbeing and focuses on patient outcomes. In addition, it gives patients the opportunity to participate in research activities and clinical trials. Participating in clinical trials allows access to novel agents or drug combinations that would be unavailable in standard practice. Also, participating in other research activities can improve the patient's understanding of their disease and minimize uncertainty and anxiety. To this end, an educational evening on CLL is held for patients and their caregivers by the CLL clinic each fall at CancerCare Manitoba, at which time an overview of CLL is provided with an update on new therapies. This session is telelinked across the province to rural oncology sites and is attended by approximately 110 patients and their relatives. The CLL clinic's

approach to patient care is unique in that patients are followed long-term in the clinic or by the Community Cancer Program (CCP) clinicians. This is for prevention, assessment and early intervention of disease progression, and disease-related complications or development of second malignancies.

For over a decade, Winnipeg has hosted the annual Canadian CLL Research Meeting bringing experts from across Canada and North America together to share the results of their recent biomedical and clinical research in CLL. Eminent keynote speakers from internationally renowned institutes also participate to ensure that Canadian CLL researchers are kept abreast of the most recent advances in this disease.

Key Points

CLL should not be considered a benign disorder as many patients with this leukemia die prematurely from progressive disease or the complications of CLL.

References

1. Seftel MD, Demers AA, Banerji V et al. High incidence of chronic lymphocytic leukemia (CLL) diagnosed by immunophenotyping: a population based Canadian cohort. *Leuk Res* 2009;33(11):1463-8.
2. Brenner H, Gondos A, Pulte D. Trends in long-term survival of patients with chronic lymphocytic leukemia from the 1980s to the early 21st century. *Blood* 2008;111(10):4916-21.
3. Brown JR. Inherited predisposition to chronic lymphocytic leukemia. *Exp Rev Hematol* 2008;1(1):51-61.
4. Shanafelt TD, Kay NE, Rabe KG, et al. Hematologist/oncologist disease-specific expertise and survival: lessons from chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). *Cancer* 2012;118(7):1827-37.

II. Scope of Guideline

Aim and Purpose

Development of this guideline was undertaken for the purpose of knowledge translation of the current standards in practice for treatment of CLL in Manitoba. The overall aim of the developers is to improve the standard of care received by this patient population, through application of evidence-based interventions and promotion of best practices.

Clinical Questions
What are the main diagnostic and clinical features for patients with CLL?
How do you diagnose CLL, MBL and SLL?
What are the key components of a routine clinical assessment for these disorders?
What are the main staging features used for patients with CLL?
Which prognostic markers are most useful in CLL/SLL?
What are the recommended treatments for patients with CLL/SLL? What are the recommended follow-up and supportive care options for patients with CLL?
What are common complications of CLL/SLL?

Development Panel

Development Panel	
Oncology Subspecialties CancerCare Manitoba/University of Manitoba	3 Hematologists 2 Bone Marrow Transplant Specialists
Nursing CancerCare Manitoba	1 Clinical Nurse Specialist/Lymphoma Nurse
Pharmacy CancerCare Manitoba	1 Pharmacist

Development Process

A multidisciplinary group of medical professionals participated in the development of this guideline. Recommendations were based on the best available evidence.

Patient Population and Healthcare Setting

The recommendations in this guideline are applicable to the care of patients diagnosed with CLL, MBL and SLL, and are intended for use in both inpatient and outpatient settings.

CLL Clinic

The CLL clinic is a multidisciplinary team with experience in medical oncology/hematology, bone marrow transplantation, dermatology, pharmacy and nursing.

End-Users

This guideline is written for use by clinicians providing care for the above mentioned patient population. Intended primarily for use by medical clinicians, the guideline may be of interest to trainees, physician extenders, allied healthcare staff, healthcare administrators, policy-makers and possibly members of the general public.

III. Guideline Methodology

Literature Search

An initial literature search was conducted in January 2011 and later updated in November 2014. PubMed, EMBASE, and www.guidelines.gov were systematically searched for clinical practice guidelines. The following search strategy was used to search for clinical practice guidelines in PubMed with humans and English as a limit, yielding 15 results:

> *("Practice Guidelines as Topic"[Mesh] OR "Guideline"[Publication Type]) AND (Chronic Lymphocytic Leukemia[Mesh] OR (Chronic Lymphocytic Leukemia[Title/Abstract])*

Guidelines were also searched environmentally by guideline developers, including Cancer Care Ontario, Alberta Health Services, BC Cancer Agency, Saskatchewan Cancer Agency, National Comprehensive Cancer Network (NCCN), New Zealand Guidelines Group, Scottish Intercollegiate Guideline Network (SIGN), Cancer Australia and National Institute for Health and Care Excellence (NICE).

Primary evidence was searched *via* PubMed. Literature searches were limited to human studies and English. Each contributor conducted their own literature search for primary evidence.

Working Group Meetings

Each guideline section was drafted by the working group members based on the best available evidence. The sections were reviewed by the working group and revised according to consensus decisions (*See Section XII for working group members*).

Internal and External Review

Internal and external peer reviews were pursued, the results of which are appended to this guideline. The internal review process was consensus-based and completed by the working group. An external review was conducted by a hematologist from the Mayo Clinic (Minnesota), a hematologist from CCMB, and a senior scientist/medical biophysicist from the University of Toronto (Ontario) (*See Section XII*). All participants completed a full review of the guideline document and submitted a standardized practitioner feedback survey (adapted from Brouwers and colleagues).[1] Feedback was considered and discussed by the working group. Decisions to incorporate any changes into the guideline were consensus-based (acceptance, rejection or acceptance with modifications).

Maintenance

At CancerCare Manitoba clinical practice guidelines are considered 'living' documents which require ongoing evaluation, review and update. Re-evaluation of this guideline is planned for 2016. The working group will revise and update the document as needed, with any critical new evidence brought forward before this scheduled review.

References

1. Brouwers MC, Graham ID, Hanna SE, et al. Clinicians' assessments of practice guidelines in oncology: the CAPGO survey. *Int J Technol Assess Health Care* 2004;20(4):421-6.

IV. Diagnosis and Clinical Features

A. Diagnosis

The abnormal cells in MBL, SLL and CLL are mature appearing lymphocytes, which have a typical monoclonal pattern and markers on flow cytometry (Table 1 and 2).[1,2] Atypical CLL is when one of these markers is atypical (e.g., strong CD20 or weak CD5).

In MBL, the B cell count is $< 5 \times 10^9$/L and the lymphocyte count may be normal or slightly increased, but the complete blood count (CBC) is otherwise normal (i.e., platelet count, hemoglobin and neutrophils) and there is no lymphadenopathy or splenomegaly. Our current practice to confirm MBL includes a review of biochemistry, immunoglobulin levels and CT scans to rule out lymphadenopathy and splenomegaly. If either lymphadenopathy or splenomegaly is present, further work-up is required.

In SLL, the B cell count is $< 5 \times 10^9$/L and there is lymphadenopathy and/or splenomegaly (by physical examination or CT scans).[1,2] The diagnosis of SLL is based on lymph node histology and immunophenotyping.

In CLL, the B cell count is $\geq 5 \times 10^9$/L with typical morphology and immunophenotype on flow cytometry and there may or may not be lymphadenopathy and splenomegaly.[1]

Key Points

CT scans or ultrasounds should not be performed for routine staging.

Table 1. Immunophenotypes of CLL and Related Conditions

	CD19	CD20	CD5	CD23	CD10	CD25	CD79b	FMC7	CD103
CLL/SLL	**++**	**+ (Dim)**	**++**	**++**	**-**	**+/-**	**-**	**-/+**	**-**
Prolymphocytic Leukemia (PLL)	++	++	-/+	++	-/+	-/+	++	+	-
Mantle Cell Lymphoma	++	++	++	-	-/+	-	++	++	-
Marginal Zone Lymphoma	++	++	-	+/-	-	-	++	+	-
Follicular Lymphoma	++	++	-/+	-/+	++	-	++	++	-
Lymphoplasmacytoid Lymphoma	++	++	-	-	-	-/+	+	+	-
Hairy Cell Leukemia	+++	+++	-	-	-	+++	+	+++	+++

As long as there are ≤ 10% prolymphocytes in the blood the diagnosis is CLL; 11-54% prolymphocytes indicates CLL/prolymphocytic leukemia (PLL) and ≥ 55% prolymphocytes indicates PLL. If the immunophenotypic parameters are slightly abnormal (e.g., CD23 staining is weak or CD20 staining is strong) diagnosis is classified as Atypical CLL.

Table 2. Variants of CLL

	MBL	CLL	SLL
B cell count*	$< 5 \times 10^9$/L	$\geq 5 \times 10^9$/L	$< 5 \times 10^9$/L
Enlarged Lymph Nodes or Spleen	No	Maybe	Yes

*The number of B cells is calculated from the flow cytometry report (which gives the percentage of B cells in the lymphocyte population) and the lymphocyte count obtained from the CBC. Use the manual lymphocyte count, if available.

Abbreviations: CLL, chronic lymphocytic leukemia; MBL, monoclonal B cell lymphocytosis; SLL, small lymphocytic lymphoma

B. Referrals

Essential and useful tests to order *before* referral to CancerCare Manitoba when a patient has a high lymphocyte count (> 5 x 10^9/L):

Essential diagnostic tests:

- CBC with differential
- Review of peripheral blood smear to look for smudge cells
- Flow cytometry
    - CLL patients have ≥ 5 x 10^9 B cells with typical molecular markers (i.e., positive for CD19, CD5 and CD23)
    - Testing for ZAP-70 and CD38, which are associated with worse prognosis if positive, can only be performed on a fresh blood sample

Useful tests: reticulocyte count, immunoglobulin levels, serum protein electrophoresis (SPEP) biochemistry (electrolytes, creatinine, glucose, lactate dehydrogenase (LDH), liver function tests (LFT)), viral hepatitis screen, HIV screen, direct antiglobulin test (DAT) and β2-microglobulin.

CT scans, lymph node biopsy or bone marrow aspirate/biopsy are **not** routinely required for CLL, however may be necessary for MBL and SLL.

C. Clinical Features

MBL is defined as the persistent presence of small numbers of monoclonal B cells in the peripheral blood and most usually the immunophenotype is that of CLL/SLL.[3] The rationale for defining this follows the change in the definition of CLL in 2008; prior to that date the definition of CLL was a peripheral blood lymphocyte count of > 5 x 10^9/L. In epidemiological studies, using highly sensitive techniques, MBL can be detected in 12% of individuals over the age of 40 years, with the incidence increasing with age.[4] However, the number of monoclonal cells detected is often very small and in most cases it is only a curiosity with no evidence of disease progression in follow-up studies.[5] Where patients have 'clinical MBL' with an increase in lymphocyte count but a B cell count that is usually 3-5 x 10^9/L, approximately 1-2% of patients each year will require chemotherapy due to progression to CLL.[6] In contrast, CLL patients with a B cell count of 5-10 x 10^9/L or a B cell count of ≥ 10 x 10^9/L, required treatment at a rate of 3% and 5% per year, respectively.[7] In addition, while the 10-year survival of the MBL patients does not differ from age- and sex-matched controls, the survival of patients with CLL was significantly shortened. These data confirm the value of defining patients with MBL (as opposed to CLL). Approximately 40% of patients who were previously diagnosed as having CLL are now diagnosed as MBL.[8] Although MBL is not designated as a malignancy, these patients still require monitoring for immune deficiency, infectious complications and to promote healthy living and age-appropriate cancer screening practices. Cancer screening and routine immunization (except for Shingles vaccination (Zostavax)) should be encouraged for prevention, early detection and intervention of other malignancies (*See Section IX: Complications*).

References

1. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008;111(12):5446-56.
2. Johnston JB, Seftel M, Gibson SB. Chronic Lymphocytic Leukemia. *In:* Greer JP, Arber DA, Glader B, et al. (eds), Wintrobe's Clinical Hematology, 13th edition, pp. 1888-1928, Baltimore, MD: Lippincott, Williams and Wilkins, 2013. *(Last updated for online version October, 2014)*
3. Shanafelt TD, Ghia P, Lanasa MC, et al. Monoclonal B-cell lymphocytosis (MBL): biology, natural history and clinical management. *Leukemia* 2010;24(3):512-20.
4. Nieto WG, Almeida J, Romero A, et al. Increased frequency (12%) of circulating chronic lymphocytic leukemia-like B-cell clones in healthy subjects using a highly sensitive multicolour flow cytometery approach. *Blood* 2009;114(1):33-7.
5. Fazi C, Scarfò L, Pecciarini L, et al. General population low-count CLL-like MBL persist over time without clinical progression, though carrying the same cytogenic abnormalities of CLL. *Blood* 2011;118(25):6618-25.
6. Rawstron A, Bennet FL, O'Connor SJM, et al. Monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia. *N Engl J Med* 2008;359(6):575-83.
7. Shanafelt TD, Kay NE, Rabe KG, et al. Survival of patients with clinically identified monoclonal B-cell lymphocytosis (MBL) relative to the age- and sex-matched general population. *Leukemia* 2012;2012(26): 373-6.
8. Shanafelt TD, Kay NE, Jenkins G, et al. B-cell count and survival: differentiating chronic lymphocytic leukemia from monoclonal B-cell lymphocytosis based on clinical outcome. *Blood* 2009;113(18):4188-96.

V. Clinical Assessment

A. History

- Clinical presentation, e.g., was it incidental or symptomatic (did the patient go to the physician with a specific complaint, such as fatigue or enlarged lymph nodes). Functional status is measured using the Eastern Cooperative Oncology Group (ECOG) scale (*See Appendix I*)
- Social history related to physical activities, social supports, smoking and alcohol use
- Detailed history of other co-morbidities (e.g., diabetes, hypertension, cardiac, hepatic or lung dysfunction). Patients are requested to bring a complete list of all medications, vitamins, herbal remedies, recent immunizations and allergies to their initial appointment. The severity of co-morbidities is ranked using the Cumulative Illness Rating Scale (CIRS) (*See Appendix II*)
- Detailed family history of other medical conditions, especially of CLL and other hematological malignancies
- History of other malignancies and screening practices the patient has had performed (e.g., colonoscopy, mammogram, skin check by dermatologist and details of prior surgery)
- Significant infections, hospitalizations, transfusion history and immunizations
- Previous treatment(s) of CLL should be documented, noting the timing and duration of therapy, response, duration of response and major toxicities

B. Physical Examination

- Height, weight and baseline vital signs
- Assessment of lymphadenopathy and splenomegaly. The sites of lymphadenopathy are documented with the variation in lymph node size at each location measured. Spleen size is measured by the distance (in centimeters) from the spleen tip to the costal margin – the line connecting the two is not vertical but at right angles to the costal margin
- Presence and size of palpable abdominal masses
- As second cancers are so common, a careful skin examination should be carried out for all patients at least once per year. Screening for other second malignancies should also be performed, as indicated
- Cardiac, respiratory and neurological or other abnormalities should be noted

C. Laboratory Assessment

Baseline and follow-up laboratory studies are shown in Table 3. A marrow is not required for diagnosis but may be useful in the following scenarios:

- For patients with Rai stages III/IV disease to ascertain the cause of the anemia and/or thrombocytopenia
- In patients on a clinical trial as per protocol, particularly after chemotherapy to ascertain the response and

determine the presence of minimal residual disease

- In atypical cases of CLL, to assess marrow morphology/cellularity and immunohistochemistry (e.g., cyclin D1 expression is increased in mantle cell lymphoma)
- To rule out autoimmune causes for anemia, thrombocytopenia and/or neutropenia

Table 3. Laboratory Assessment

Test	Initial Visit	At Each Visit	Annual Visit
CBC	x	x	x
Reticulocyte count	x	x	x
Examination of peripheral blood smear	x	x	
Complete biochemistry (including creatinine, glucose, LDH, and liver function tests)	x	x	x
Flow cytometry of peripheral blood (including measurement of ZAP-70 and CD38 levels; Zap-70+ or CD38+ is defined as ≥ 20% of the CLL cells staining positively)	x		
Immunoglobulin levels	x		x
Serum electrophoresis	x		x
Coombs Test (direct antiglobulin test (DAT))	x		x
β2-microglobulin test	x		x
Vitamin D	x		

Note: Other tests such as FISH are essential prior to treatment for symptomatic or relapsed disease

VI. Staging

Background

The standard staging system in North America is Rai staging, while the Binet staging system is still used in Europe.[1,2] At CCMB, Rai staging is most commonly used except if Binet staging is required as part of a research protocol (Table 4).

Key Points

There are several points regarding Rai staging that should be noted:

- Most patients are diagnosed with CLL through routine annual blood work, with 85% of patients presenting to the clinic with Rai stages 0/I disease.
- The median survival for patients with stages III/IV disease is now 5 years while it was 2 years in the original description. This may be partly due to improved treatment and diagnostics with immunophenotyping.
- Patients with Rai stages III/IV disease have anemia or thrombocytopenia due to marrow failure, and usually both the hemoglobin and platelet count fall together. Marrow failure accounts for half the cases of anemia (hemoglobin 110 g/L) or thrombocytopenia (platelets < 100 x 10^9/L).[3,4] Approximately 25% of patients will have immune cytopenias and another 25% of cytopenias are due to other causes, such as renal failure, hypersplenism or blood loss. The prognosis will thus differ according to the cause and frequency that bone marrow aspiration/biopsy is performed on these patients to ascertain the cause of the cytopenia. Patients with thrombocytopenia related to hypersplenism have Rai stage II disease with thrombocytopenia. Patients with autoimmune hemolytic anemia (AIHA) and lymphadenopathy should be diagnosed as having Rai stage I disease with AIHA. However, others might define these patients having Rai stage III disease with "immune hemolytic anemia".[5] SLL is not staged using the Rai classification rather, as with other lymphomas, the Ann Arbor staging system is utilized.[6]

Table 4. Rai Staging for Chronic Lymphocytic Leukemia†

Rai Stage	Characteristic	Description	Median survival: Original Report, 1975 (Years [months])	Median Survival: Mayo Clinic, 2009 (Years [months])
0	Low Risk	Lymphocytosis only (B cells ≥ 5 x 10^9/L)	12.5 (150)	> 10 (120)
I	Intermediate Risk	Lymphocytosis + Lymphadenopathy*	8.4 (101)	9 (108)
II	Intermediate Risk	Lymphocytosis + Splenomegaly	5.9 (71)	7 (89)
III	High Risk	Lymphocytosis + Hemoglobin < 110 g/L	1.6 (19)	2-5 (24-60)[1,2]
IV	High Risk	Lymphocytosis + Platelets < 100 x 10^9/L	1.6 (19)	2-5 (24-60)[1,2]

*The presence of lymphadenopathy and splenomegaly is based on physical examination and not on CT scans or ultrasound.

† Modified from Shanafelt TD, 2009.

References

1. Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. *Blood* 1975;46(2): 219-34.
2. Dighiero G, Binet J. When and how to treat chronic lymphocytic leukemia. *N Engl J Med* 2000;343(24): 1799-1801.
3. Zent CS, Ding W, Schwager SM, et al. The prognostic significance of cytopenia in chronic lymphocytic leukemia/small lymphocytic lymphoma. *Br J Haematol* 2008;141(5):615-21.
4. Moreno C, Hodgson K, Ferrer G, et al. Autoimmune cytopenia in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance. *Blood* 2010;116(23):4771-6.
5. Visco C, Barcellini W, Maura F, et al. Autoimmune cytopenias in chronic lymphocytic leukemia. *Am J Hematol* 2014;89(11):1055-62.
6. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging. *Cancer Res* 1971;31:1860-1.
7. Shanafelt TD. Predicting clinical outcome in CLL: how and why. ASH Education Book 2009;2009(1):421-9.

VII. Prognosis

Key Evidence and Recommendations

Rai stage is the most important clinical prognostic marker, and it is important to ensure that the staging is accurate, as discussed in Section VI: Staging. At the time of referral, 85% of patients have Rai stages 0/I disease and 30-50% of these patients will require therapy in 1-4 years with a median survival of 7-8 years.[1] As patients are only treated if there is clear evidence of disease progression, many patients experience considerable anxiety because of the uncertainty of their future.[2] Indeed, the majority of patients will worry about their disease on a daily basis and reassurance that they have a 'good leukemia' is unhelpful.[2] Great effort has been put into developing reliable prognostic markers to provide patients with a more accurate prognosis when first seen and to determine the frequency of monitoring. The standard prognostic markers are provided in Table 5 and are reviewed in the articles published by Shanafelt et al and Johnston et al.[3,4]

The lymphocyte doubling time is the second most important clinical prognostic marker, with a doubling time of < 12 months predicting early treatment and short survival.

Other important clinical prognostic features are the patient's sex and age. Females have a better relative survival than males and younger patients (< 70 years) have a better relative survival than older patients.[3-6] Relative survival reflects deaths directly related to CLL, and is calculated by comparing the death rate in an age- and sex-matched population without CLL.

Patients with low vitamin D levels at diagnosis have more aggressive disease, with a shorter time to treatment and survival.[7,8] Whether repleting vitamin D stores is clinically beneficial in CLL is unknown, but we recommend all patients be maintained on vitamin D 2000 units/day.

In addition to the above clinical markers, there are a variety of cellular and biochemical markers that are primarily of use in patients with Rai stages 0/I disease. It should be emphasized that these markers may predict time to treatment, progression-free survival (PFS), likelihood of response to treatment or OS, but not necessarily predict all of these disease characteristics. In addition, prognostic markers are often assessed for patients going onto clinical trials, where the average age is approximately 60 years. Thus, the results of these studies may not be relevant to the elderly or when assessed at the time of diagnosis.

1. There are innumerable prognostic markers but only those that are routinely measured or have significant potential in the future will be discussed. A simple and very useful prognostic marker is the plasma β2-microglobulin level with increased levels being predictive of time to treatment, PFS and OS.[3,4,9-11] This may be related to the fact that β2-microglobulin levels reflect tumour burden, renal function and the plasma concentrations of the inflammatory cytokines, interleukin 6 (IL-6) and interleukin 8 (IL-8).[5,12] In addition, increased β2-microglobulin levels predict the development of second malignancies.[13]

2. The most rational prognostic marker is detecting the presence or absence of mutations of the immunoglobulin heavy chain variable region (IgV_H) in CLL cells, as this reflects the cell origin of the two types of CLL and does not change over time.[14] Mutations occur in 60% of patients with CLL (M-CLL) and these patients generally have a more benign disease than those without mutations (U-CLL), respond

better to chemotherapy, have a prolonged remission after chemotherapy and better survival.[11] IgV_H measurements are time-consuming and not yet routinely available in Manitoba.

3. Surrogate markers for IgV_H mutational status are ZAP-70 and CD38, which are measured by flow cytometry.[15,16] ZAP-70 is an intracellular tyrosine kinase that is involved in signaling from the T cell receptor and from the B cell receptor in a small percentage of B cells, whereas CD38 is a surface enzyme involved in the formation of cyclic ADP-hydrolase. Most M-CLL cases are ZAP-70 and CD38 negative (< 20% cells stained positively), while the reverse is true for U-CLL. ZAP-70 and CD38 are generally associated with a shorter time to treatment and survival.[15,16] Both CD38 and ZAP-70 measurements can vary during the disease course.

4. The results of fluorescence in situ hybridization (FISH) studies are important for prognosis and can provide information as to appropriate therapy. In Manitoba, FISH is carried out prior to each planned course of treatment or hematopoietic stem cell transplant (HSCT). The most common abnormalities in patients requiring therapy are del13q14 (del 13), trisomy 12, del 11q22-23 (del 11) and del 17p13 (del 17), with frequencies of 55%, 16%, 18% and 7%, respectively.[17] Patients with del 13 usually have a good prognosis while patients with trisomy 12 have an increased risk of a Richter's transformation. Patients with del 11 are younger, have bulky lymph nodes, more advanced disease, early relapse from chemotherapy and poor prognosis; however, prognosis can be improved with FCR (fludarabine, chlorambucil, rituximab) (*See Section VIII: Treatment*).[11,18] For patients on therapy, the likelihood of developing del 17 increases over time and is present in half the patients who are fludarabine-resistant. These patients are resistant to standard chemoimmunotherapy and their management is discussed in Section VIII: Treatment.

5. The measurement of minimal residual disease (MRD) in marrow following therapy has become an important prognostic marker for measuring PFS and OS.[19,20] The measurement of MRD by flow cytometry has become standardized and may be used to decide if a patient should be considered for marrow transplant following FCR. In addition, it may be carried out on patients after 3 cycles of FCR chemotherapy if they have achieved a complete clinical remission (usually patients with mutated IgV_H). Recent studies have demonstrated that the long-term outcome of patients is similar after either 3 or 6 cycles of FCR, as long as their marrow shows no MRD.[21]

6. A number of novel markers have been recently elucidated in CLL, including mutations of *p53*, *NOTCH1, SF3B1* and *BIRC3*.[22-24] These are measured by DNA sequencing and while not yet routinely measured, they will likely become standard in the future allowing the development of a molecular 'prognostic index'. In addition, they may assist in predicting the likelihood of a Richter's transformation and response to chemotherapy.

Table 5. Prognostic Markers in CLL

Prognostic Marker	Better Prognosis	Worse Prognosis
Sex	Female	Male
Age	< 70 years	≥ 70 years
Plasma vitamin D level	Sufficient	Insufficient
Rai Stage	0, I and II	III and IV
Lymphocyte count	< 12 x 10^9/L	≥ 12 x 10^9/L
Lymphocyte doubling time	< 12 months	> 12 months
Number of smudge cells	≥ 30%	< 30%
β2-microglobulin level	Low	High
Flow cytometry • B cell count • CD38 • ZAP-70	 < 11 x 10^9/L < 20% cells positive < 20% cells positive	 ≥ 11 x 10^9/L ≥ 20% cells positive ≥ 20% cells positive
FISH	Del 13	Del 11* or Del 17*
IgV_H gene	Mutated	Unmutated

*Loss of chromosome 11q22-23 is usually associated with bulky lymph nodes, younger age group and poorer prognosis. Loss of 17p13 usually indicates loss of the p53 protein and this is associated with drug-resistance and aggressive disease.

References

1. Shanafelt TD, Byrd JC, Call TG, et al. Narrative review: Initial management of newly diagnosed, early-stage chronic lymphocytic leukemia. *Annals Int Med* 2006;145(6):435-47.
2. Shanafelt TD, Bowen DA, Venkat C, et al. The physician-patient relationship and quality of life: lessons from chronic lymphocytic leukemia. *Leuk Res* 2009;33(2):263-70.
3. Shanafelt TD. Predicting clinical outcome in CLL: how and why. *Hematol Am Soc Hematol Educ Program* 2009, 421-9.
4. Johnston JB, Seftel M, Gibson SB. Chronic Lymphocytic Leukemia. *In*: Greer JP, Arber DA, Glader B, et al. (eds), Wintrobe's Clinical Hematology, 13th Edition, pp. 1888-1928, Baltimore, MD: Lippincott, Williams and Wilkins,

2013. *(Last updated for online version October, 2014)*

5. Yoon JY, Lafarge S, Dawe D, et al. Association of interleukin-6 and interleukin-8 with poor prognosis in elderly chronic lymphocytic leukemia patients. *Leuk Lymph* 2012;53(9):1735-42.
6. Baumann T, Delgado J, Santacruz R, et al. Chronic lymphocytic leukemia in the elderly: clinico-biological features, outcomes, and proposal of a prognostic model. *Haematologica* 2014;99(10):1599-1604.
7. Molica S, Digiesi G, Antenucci A, et al. Vitamin D insufficiency predicts time to first treatment (TFT) in early chronic lymphocytic leukemia (CLL). *Leuk Res* 2011;36(4):443-7.
8. Shanafelt TD, Drake MT, Maurer MJ, et al. Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia. *Blood* 2011;117(5):1492-8.
9. Keating MI, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol* 2005;23(18):4079-88.
10. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood* 2008;112(4):975-80.
11. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomized, open-labeled, phase 3 trial. *Lancet* 2010;376(9747):1164-74.
12. Gentile M, Cutrona G, Neri A, et al. Predictive value of β2-microglobulin (β2-m) levels in chronic lymphocytic leukemia in Binet A stages. *Haematologica* 2009;94(6):887-8.
13. Tsimberidou A-M, Wen S, McLaughlin P, et al. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol* 2009;27(6):904-10.
14. Hamblin TJ, Davis Z, Gardiner A, et al. Unmutated IgVH genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood* 1999;94(6):1848-54.
15. Rassenti LZ, Jain S, Keating M, et al. Relative value of ZAP-70, CD38, and immunoglobulin mutation status in predicting aggressive disease in chronic lymphocytic leukemia. *Blood* 2008;112(5):1923-30.
16. Pepper C, Majid A, Lin T-T, et al. Defining the prognosis of early stage chronic lymphocytic leukemia patients. *Br J Hematol* 2011;156(4):499-507.
17. Döhmer H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med* 2000;343:1910-6.
18. Tsimberidou A-M, Tam C, Abruzzo LV, et al. Chemoimmunotherapy may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with chronic lymphocytic leukemia. *Cancer* 2009;115:373-89.
19. Rawstron AC, Villamor N, Rigen M, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lmyphocytic leukemia. *Leukemia* 2007;21:956-64.
20. Böttcher S, Ritgen M, Fischer K, et al. Minimal residual disease quantification is an independent predictor of

progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized CGLLSC CLL8 trial. *J Clin Oncol* 2012;30:980-8.

21. Strati P, Keating J, O'Brien SM, et al. Eradication of bone marrow minimal residual disease may prompt early treatment discontinuation in CLL. *Blood* 2014;123(24):3727-32.
22. Baliakas P, Hadzidimitriou A, Sutton L-A, et al. Recurrent mutations refine prognosis in chronic lymphocytic leukemia. *Leukemia* 2015;29(2):329-36.
23. Stigenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood* 2014;123(L21):3247-54.
24. Chigrinova E, Rinaldi A, Kwee L, et al. Two main genetic pathways lead to the transformation of chronic lymphocytic leukemia to Richter syndrome. *Blood* 2013;122(15):2673-82.

VIII. Treatment

A. Indications for Treatment

These are guidelines, and clinical judgment is also required to assess the need for treatment. For a patient who is asymptomatic and has borderline indications for therapy, a period of observation is justified. Indications to treat are as follows:

- Rai stages III/IV disease due to marrow infiltration
- Lymphocyte or lymph node/spleen doubling within 6 months or a > 50% increase in 2 months
- Progressive anemia, neutropenia and/or thrombocytopenia
- Symptomatic lymphadenopathy or splenomegaly
- Significant symptoms, such as night sweats, weight loss or fatigue
- Immune cytopenias

ALL patients should be offered a clinical trial when available.

Key Points

All patients requiring treatment should be reassessed by the CCMB CLL Clinic to ensure access to clinical trials and up to date therapies.

This is particularly important for novel agents that are expensive and require close monitoring and on-going evaluation (e.g., ibrutinib and obinutuzumab).

- A high white blood cell count per se is no longer an indication for treatment.
- Patients should not receive chemotherapy intermittently 'to keep the counts down'.
- The indefinite use of low-dose chlorambucil is not appropriate as therapy. It likely increases the risk of transformation, second malignancies and prolonged bone marrow suppression.

B. Principles of Therapy

a) **Decisions regarding the type of therapy depend on the patient's fitness, rather than on age**. Fitness is assessed by the performance status (ECOG), number of co-morbidities (CIRS) and renal function (creatinine clearance). For patients who have had prior therapy, treatment will also be influenced by marrow reserve, which may be impaired by prior therapy.

b) Improved progression free survival (PFS) and overall survival (OS) with more intense first-line therapy have changed the goal of therapy to obtain the best possible initial response. Treatment duration is typically 6 cycles, except for those on chlorambucil alone, where therapy may continue for a maximum of 12 cycles if the patient is continuing to respond at 6 cycles.

c) FISH can provide useful information regarding treatment options and should be carried out prior to each

course of therapy.

d) If the patient is responding poorly to therapy (i.e., < 50% decrease in lymphocyte count or reduction in spleen/lymph node size after 2 months of therapy) the treatment plan should be re-evaluated.

e) CLL patients are often immunocompromised at diagnosis and this may worsen with treatment. Thus, they should receive prophylaxis for infection (*See Section IX: Complications - Supportive Therapy*).

C. First-Line Therapy

CD20 Antibody Containing Regimens (FCR, FR, PCR and RCD)

The addition of rituximab to fludarabine (FR) or to fludarabine and cyclophosphamide (FCR) markedly increases the response rates compared to conventional chemotherapy alone.[1-6] In addition, FCR produces a higher complete remission and overall response rate than FR, although at the expense of greater myelosuppression. Table 6 defines response and Table 7 demonstrates the response rates with different standard regimens.

In the German CLL8 prospective study, FCR, compared to fludarabine and cyclphosphamide (FC), was shown to increase the response rate, duration of response and OS.[2] As a result, FCR has become the standard first-line therapy for CLL across Canada for 'fit patients'. Fit patients must have a good performance status (ECOG score < 2), low number of co-morbidities (CIRS score ≤ 6) and normal creatinine clearance. Appendix I and II demonstrates criteria to calculate the ECOG and CIRS scores. At CCMB CLL clinic, we estimate that one-third of patients receive FCR first-line. Several points should be made about FCR:

- FCR produces significant myelosuppression, which increases with the duration of therapy. Dose-reductions are required in half the patients and only 75% will complete 6 cycles. If the patients develop an infection with therapy or if the neutrophils and platelets have not returned to baseline by week 5, the dosages of cyclophosphamide and fludarabine should be reduced by 20-40% but the dosage of rituximab remains unaltered.
- While the addition of granulocyte colony-stimulating factor (G-CSF) may improve progression-free survival with FCR, it may also increase the risk of myelodysplasia/AML.[7,8] Acute myeloid leukemia (AML)/myelodysplasia appear to be more common with FCR than with FR, and the risk may be increased with G-CSF. Thus, patients developing significant cytopenias with FCR should not receive G-CSF in an attempt to complete planned therapy; instead, alternative therapy should be considered. **Therefore, we do not recommend G-CSF for patients receiving a fludarabine-based regimen.**
- FCR has the capacity to overcome the poor prognosis associated with del 11 with the OS at 3 years with FCR being 94%. Comparatively, the 3 year survival with FC is significantly lower at 83%.
- FCR does not overcome the poor prognosis associated with del 17.
- The FR regimen is used in approximately half of our patients and is generally well tolerated and produces less myelosuppression and AML/myelodisplasia than FCR; however, FR may not overcome the poor risk associated with del 11.

Monitoring

Patients are seen pre-cycle with CBC and full biochemistry to look for neutropenia and tumour lysis. Due to increased risk of myelodysplasia, a delay in treatment is preferred to G-CSF use. Immune mediated neutropenia, hemolytic anemia and aplastic anemia can be induced by fludarabine.

Variants of FCR have been developed to either enhance efficacy or reduce toxicity. To enhance the potency of FCR, alemtuzumab has been added to produce CFAR (cyclophosphamide, fludarabine, alemtuzumab, rituximab).[9] To reduce the myelosuppression seen with fludarabine, pentostatin has been substituted for fludarabine in FR and FCR regimens. These regimens, although well tolerated, continue to demonstrate myelosuppression, with PCR (pentostatin, cyclophosphamide, rituximab) being more effective than PR (pentostatin, rituximab).[10,11]

RCD (rituximab, cyclophosphamide, dexamethasone) is a highly effective treatment for immune cytopenias, but it is also effective for the treatment of CLL.[12] An advantage of this regimen is that it produces transient and mild myelopsuppression and is thus also useful for treatment of patients with a history of immune cytopenias or impaired bone marrow reserve.

Bendamustine[13]

Bendamustine single-agent was studied by Knauf and colleagues for the first-line treatment of CLL. First-line treatment with single-agent bendamustine was compared to single-agent chlorambucil in patients who were ineligible for fludarabine-based therapy. The median PFS was 21.2 months for the patients treated with bendamustine versus 8.8 months for those treated with chlorambucil.

Standard Dose

- First-line: 90 mg/m^2
- Second-line: 70 mg/m^2

Obinutuzumab and Chlorambucil

The recommended treatment for previously untreated, unfit patients is obinutuzumab/chlorambucil based on the results of the German CLL11 study.[14] This phase III study evaluated obinutuzumab (a monoclonal antibody directed against CD20 antigen) with chlorambucil compared to rituximab in combination with chlorambucil or chlorambucil alone.[14] Patients enrolled in this trial had a CIRS score > 6, creatinine clearance between 30 and 69 mL/minute and were untreated. The results indicated that obinutuzumab-chlorambucil treatment led to a better PFS when compared to rituximab-chlorambucil and chlorambucil alone. .

The main adverse event with obinutuzumab was an infusion-related reaction. Twenty percent (20%) of the patients experienced a Grade 3 or higher infusion-related reaction to the first obinutuzumab dose administered. There were no Grade 3 or 4 infusion-related reactions with subsequent infusions during the clinical trial. The infusion-related reactions are due to the high affinity of obinutuzumab against the CD20 antigen expressed on the CLL cells.

For cycle 1, the dose of chlorambucil may be dose-reduced from 0.5 mg/kg to 0.25 mg/kg orally on Days 1 and 15. Reassessment of dose will occur prior to each cycle.

For cycle 1, the dose of obinutuzumab is 1000 mg on Days 1, 8 and 15, and on Day 1 of cycles 2 to 6.

Monitoring

Obinutuzumab may cause a severe infusion-related reaction in 20% of patients during the first treatment and must be administered with caution. Premedication with 40 mg of dexamethasone IV is recommended. Reactions include chest pressure and hypotension, and are more common with increased lymphocyte counts. In addition clinical trials show that> 50% of patients had neutropenia, therefore G-CSF is recommended for support.

Chlorambucil and Cyclophosphamide

For patients who are ineligible to receive FCR, PCR or FR, treatment options are a 6 month to a maximum of 12 month course of chlorambucil (CLB) or cyclophosphamide. The best results for chlorambucil are seen by increasing the dose-intensity.[15-22] We recommend using either the British (10 mg/m^2/day x 7, repeated every 28 days) or the German (0.5 mg/kg on Days 1 and 15, repeated every 28 days) regimens, which appear to be equivalent to fludarabine.[18,20] If patients cannot tolerate bolus chlorambucil, alternate dosing schedules may be determined in consultation with the attending oncologist. **Treatment is for 6 months, or a maximum of 12 months if patients are still responding at 6 months. Indefinite therapy is not recommended.**

For patients who have significant pancytopenia, a history of immune cytopenias, or a positive direct antiglobulin test (DAT), oral cyclophosphamide is a good alternative to chlorambucil. Cyclophosphamide is less marrow toxic than chlorambucil, and due to its immunosuppressive effects, is actually a treatment for autoimmune cytopenias whereas chlorambucil induces autoimmune cytopenias in 10% of cases. The usual starting dose for cyclophosphamide is 150 mg orally/day, continuously **for a maximum of 12 months.**

Monitoring

Monthly CBC and full biochemistry is recommended to monitor for cytopenia and bone marrow suppression, hemolysis due to chlorambucil, and tumour lysis. **If the neutrophils fall to < 1 x 10^9/L, platelets to < 100 x 10^9/L or hemoglobin to < 100 g/L, the chlorambucil or cyclophosphamide therapy is stopped until the counts have recovered, and then restarted at a reduced dose.**

While prednisone is often added to chlorambucil, there is no evidence that it increases the effectiveness of chlorambucil and should be avoided if possible. However, prednisone 25-50 mg/day for 2-3 weeks may clear the bone marrow and improve the blood counts prior to chlorambucil initiation.[20]

D. Second-Line and Subsequent Therapy for Relapsed Disease

When a patient relapses, it is important to decide whether they have relapsed with drug-sensitive disease and can be treated with standard therapy, or whether they have developed drug-resistance.

Drug-Sensitive

For patients who relapse 2 years or longer after FCR, or 1 year after other regimens, it is likely that they will remain sensitive to standard chemotherapy and can be treated with first-line therapy. FCR and CFAR have been evaluated in the second-line setting and may be considered for carefully selected patients. Both drugs retain activity in the relapsed setting, while CFAR produces more myelosuppression and infections.[23,24]

Drug-Refractory/Drug-Resistant

Patients with initial response who relapse within 2 years of FCR or within 1 year of other regimens are considered drug-refractory.[25] Those who do not respond to treatment within 2 months of primary therapy are also considered drug-refractory. Forty percent (40%) of patients who are resistant to a fludarabine-containing regimen will have a del 17 and require an alemtuzumab-containing regimen or high-dose steroid combination therapy followed, if possible, by allogenic HSCT. Fludarabine-resistant patients without a del 17 should receive ofatumumab, bendamustine or lenalidomide. Chlorambucil-resistant patients should be offered alternate therapy, according to clinical status and physician/patient preferences.

Alemtuzumab and Alemtuzumab-Containing Regimens

Alemtuzumab alone is indicated for patients who are refractory to fludarabine-containing regimens where lymph nodes are < 5 cm in diameter. [26] Alemtuzumab is a humanized monoclonal antibody directed against CD52, which is present on the surface of both B and T lymphocytes, monocytes and natural killer cells. Due to better tolerance, the subcutaneous route is generally used in CLL. The alemtuzumab dose is 30 mg subcutaneously given 3 times a week for a minimum of 12 weeks. With this regimen, side effects are generally seen in the first 2 weeks due to the release of cytokines from monocytes and natural killer cells. Side effects are limited to local skin reactions which can be easily controlled using ice packs to the injection sites. In addition, to minimize cytokine release syndrome, methylprednisolone 125 mg IV is administered for the first two weeks prior to alemtuzumab. Responses are very rapid, but tumour lysis is seldom seen. The main problems are with infection, particularly with reactivation of cytomegalovirus (CMV).

CFAR may be used in patients < 70 years who have a del 17 and are being aggressively treated for a HSCT. FluCam (fludarabine, alemtuzumab) is well tolerated and may be used in elderly patients with a del 17.

Monitoring

Any alemtuzumab containing regimen requires weekly monitoring for CMV reactivation or infection (*See Section IX: Complications - Supportive Care*).

Ibrutinib[27]

Ibrutinib is an oral agent that belongs to a pharmacological class called Bruton's tyrosine kinase inhibitor.

The RESONATE phase III trial results compared ibrutinib to ofatumumab in patients with previously treated CLL.[28] At a follow-up of 9.4 months, ibrutinib significantly improved PFS with the median PFS not being reached compared to a median of 8.1 months in the ofatumumab arm. In addition, ibrutinib showed activity in patients with 17p del CLL, as the median PFS was not reached while it was only 5.8 months in patients treated with ofatumumab. *An initial increase in lymphocytes is usually seen in patients treated with ibrutinib for their CLL. It can take several months for the lymphocytes to normalize. It is important that the patient be reassured that an initial lymphocyte increase does not necessarily indicate relapsed disease.*

Ibrutinib is an oral agent administered at 420 mg once daily (3 x 140 mg tablets) until progression or unacceptable toxicity. Due to unique side effects and complex drug and food interactions, this medication requires close specialized monitoring:

- Lymphocytosis: This is a class effect and indicates response. It is not a sign of disease progression and treatment should not be stopped if this occurs. Lymphocytosis does not alter PFS or OS compared with patients with no lymphocytosis.[29]
- Bleeding: Ibrutinib can interfere with platelet function. Signs and symptoms of bleeding should be reported to the clinic. Caution should be exercised on warfarin and other anticoagulants such as Aspirin®. Supplements that interfere with platelet function
(i.e., fish oil, flaxseed oil and vitamin E) must be discontinued or avoided while patients are on ibrutinib.
- Diarrhea: This usually develops after 2-3 months of treatment and must be reported to the attending physician to determine if the drug should be discontinued. Late onset diarrhea may also occur after 6 months of therapy and should be reported to the attending physician.
- Cardiovascular: Atrial fibrillation has been reported in 5% of patients taking ibrutinib. Cardic arrythmias can occur at any time in patients on ibrutinib and this toxicity may be exacerbated by concomitant drugs (e.g., valacyclovir).
- Arthralgias: 22% of patients may have arthralgias. Topical NSAIDs or steroids may be used; however, systemic NSAIDs are not advised due to platelet dysfunction.
- Drug-drug and drug-food interactions: As many drugs interact with CYP3A4, a thorough medication history will need to be taken prior to initiation of ibrutinib. Grapefruit and Seville oranges (citrus juices and fruits) must not be consumed during ibrutinib treatment as they contain inhibitors of CYP3A.

Monitoring

Baseline EKG (due to risk of cardiac arrhythmias) and CT scans should be done; lymphocytosis occurs with treatment and cannot be used as a response measurement. Weekly CBC and full biochemistry should be done for 8 weeks at which time CT scans should be done to assess response. Reduction in lymph nodes and lymphocytosis occurs first, followed by reduction in spleen size and an improvement in hemoglobin and platelets. Petechiae are common despite no evidence of thrombocytopenia, as ibrutinib can interfere with platelet function.

Current Evidence to Predict Relapse on Ibrutinib[29]

Recent data suggests that patients who are multiply treated, or have cytogenic abnormalities (11q or 17p deletions) have shorter PFS at 30 months. Patients with neither of these cytogenic abnormalities had a PFS of 87% versus 74% and 54% in patients with an 11q del and a 17p del, respectively. Similarly, OS at 30 months in patients with no cytogenic abnormalities was 90% compared to 85% and 65% in those with an 11q del and a 17p del, respectively. In addition, resistance may occur to the drug itself due to mutations in the kinase domain or downstream kinases leading to drug resistance.

High-Dose Steroid Combination Therapy

High-dose methylprednisolone (1 g/m^2 once daily, for five days q28 days) combined with rituximab (375 mg/m^2 IV on Day 1) or alemtuzumab (30 mg, subcutaneous three times a week) have produced responses in two-thirds of patients with del 17.[30,31] However, the high doses of steroids can induce diabetes, alter mood and increase the risk of infection.

Hematopoietic Stem Cell Transplantation (HSCT)

The only curative treatment for CLL is an allogeneic HSCT, but due to its toxicity, it is only offered for relapsed or refractory disease in fit and relatively young patients. The indications for HSCT are as follows[32]:

- Non-response to a fludarabine-containing regimen
- Relapse (within 3 years) after a fludarabine or pentostatin combination therapy or treatment of similar efficacy
- Patients with del 17 requiring treatment

At present, transplant is offered to suitable patients up to the age of 70 years. The 5-year OS is approximately 50-60%, disease-free survival is 35-45% and early transplant related mortality (within 100 days) is less than 5%; however non-relapse mortality increases to 15-30% within the first 2 years of transplant.[33] The transplants are reduced-intensity conditioning (RIC) transplants, as myeloablative conditioning has a very high treatment-related mortality and offers no survival advantage.[34] Autologous transplantation is no longer offered to CLL patients, as it has no advantage over chemotherapy.[35] These indications may evolve over time and eligible patients for transplant should be referred promptly to the Manitoba Bone Marrow Transplant (BMT) Program for review and assessment. With the availability of novel agents, transplant may be deferred in those who respond. The decision to proceed to transplant should be based on the risk of disease relative to the risk of transplant.[33]

E. New Agents

Three new agents are being used occasionally at the CCMB CLL clinic but will likely become standard in the future. Ofatumumab is given intravenously and is a humanized monoclonal antibody directed against CD20.[36] It is effective in 50% of patients who have become resistant to rituximab and fludarabine. It is licensed to be used for patients who are resistant to alemtuzumab.

Bendamustine-a, combination alkylating agent and nucleoside analogue, is also given intravenously and can be used in patients who have moderately impaired renal or liver disease. In the first-line setting it demonstrated significantly greater activity than chlorambucil.[19]

Other agents that may be used in the context of a clinical trial or through third party insurance are lenalidomide and idelasilib.

F. Supportive Therapy

Cytomegalovirus (CMV) Monitoring in Patients on Alemtuzumab Therapy

The estimated incidence of CMV in patients on alemtuzumab is 4-29% based on data from seven clinical trials evaluating single-agent alemtuzumab.[26]

CMV testing is done by polymerase chain reaction. The test should be drawn prior to treatment initiation (baseline) once weekly while on alemtuzumab therapy, and then every two weeks for 6 weeks after discontinuation.[37] Alemtuzumab should not proceed if baseline CMV polymerase chain reaction value is ≥ 500 copies/mL (Cadham laboratory will report this as 5 x 10e2 copies/mL).

The CMV by polymerase chain reaction testing should be drawn early in the week (preferably Mondays or Tuesdays) at a consistent date and time. This will prevent sample rejection and a missed test.

Valganciclovir should be administered for treatment of CMV infection if any of the following occur:

- A CMV polymerase chain reaction value level ≥ 500 copies/mL (Cadham laboratory will report this as 5 x 10e2 copies/mL).
- A patient with clinical symptomatic CMV infection (e.g., fever, diarrhea or pneumonia), with positive CMV polymerase chain reaction. If clinical suspicion of CMV infection is high, start valganciclovir while awaiting CMV polymerase chain reaction.
- Two consecutive weekly CMV values that are > 275 copies/mL (Cadham laboratory will report this as 2.75 x 10e2 copies/mL) and rising (e.g., an increasing CMV titre).

Please contact the primary clinic if there are questions about the reports issued by Cadham laboratory.

Dosing

Valganciclovir 900 mg (2 x 450 mg capsules) twice daily for 21 days. If CMV polymerase chain reaction is positive at 21 days, continue with valganciclovir 900 mg once daily until the CMV polymerase chain reaction is negative.[37]

Dosing of valganciclovir depends on kidney function.

Infection Prophylaxis

Due to the nature of this disease, patients with CLL are immunosuppressed and the situation is worsened when they receive chemotherapy or steroids, with the likelihood of infections increasing with the duration of disease and the number of treatments.[38] During chemotherapy with purine analogues or alemtuzumab, patients should be protected from *Pneumocystis jiroveci* with cotrimoxazole 800/160 mg, one tablet twice daily on Saturdays and Sundays (alternatives for patients who have allergies or intolerance to sulfa include dapsone or pentamidine) and this should be continued for 6 months after stopping chemotherapy.

Prophylaxis with valacyclovir 500 mg/day (or an equivalent agent) for herpes infection is required with purine analogues or alemtuzumab, if a patient has a history of shingles or recurrent cold sores. Prophylaxis may also be considered for patients receiving second-line or beyond therapy, particularly if they are elderly. Prophylactic antibiotics should be considered during chemotherapy for patients with a past history of bacterial infections; although their role is not established.[36] These practices are consistent with those in clinical trials.

Irradiated Blood Products

Patients who have received alemtuzumab- or fludarabine-based regimens should receive irradiated blood products to prevent transfusion related graft-versus-host disease.

Bisphosphonates

Patients on long-term steroids are at high risk of developing osteoporosis. Thus, if patients are on prednisone for longer than 2 weeks they should be maintained on (in addition to vitamin D 2000 units/day), calcium carbonate 500 mg orally three times a day. Patients should be considered for bisphosphonate therapy (zoledronic acid, single 5 mg infusion ***OR*** pamidronate, 30 mg IV every 3 months) while on steroids.

Granulocyte Colony-Stimulating Factor (G-CSF)

G-CSF in fludarabine-based regimens should be used with caution due to a possible increased risk of prolonged pancytopenia and myelodysplasia. It should **not** be used prophylactically to maintain counts to allow continuation of therapy; however, it may be considered for the treatment of febrile neutropenia.

Table 6. Definitions of Response

Remission	Features
Complete Remission (CR)	No symptoms
	No hepatosplenomegaly/lymphadenopathy (by physical and CT)
	Normal CBC (hemoglobin 110, neutrophils > 1.5 and platelets > 100)
	• Above should be maintained for 2 months after which a marrow should show < 30% lymphocytes and no lymphoid nodules. If marrow hypocellular, repeat in 4 weeks. If lymphoid nodules, then patient has a nodular PR • If patient remains anemic or thrombocytopenic but is otherwise in CR, patient has a PR
Partial Remission (PR)	> 50% decrease in peripheral blood lymphocyte count and > 50% decrease in lymphadenopathy and/or splenomegaly (or hepatomegaly)
	The above should be maintained for 2 months in conjunction with one or more of the features below: • Hemoglobin > 100 or > 50% improvement from baseline • Neutrophils > 1.5 or > 50% improvement from baseline • Platelets > 100 or > 50% improvement from baseline • With lymphocytosis: systemic response and improvement in hemoglobin and platelets (e.g., ibrutinib and idelalisib)
Persistent Disease (PD)	> 50% increase in the sum of the products of > 2 nodes on at least 2 determinations carried out 2 weeks apart, and/or • > 50% in liver and/or spleen size, and/or • > 50% increase in lymphocyte count to at least 5 x 10^9/L, and/or • Transformation to a more aggressive histology
Stable Disease	Patients who do not fit the criteria for CR, PR or PD

Table 7. Response Rates for Standard Regimens

Reference	Treatment[a]	Patient Number	Previously Treated	CR(%)	nPR(%)	PR(%)
Tam et al (2008)[2]	FCR	224	No	72	10	13
Badoux et al (2011)[24]	FCR	284	Yes	30	14	30
Hallek et al (2010)[5,b]	FCR	388	No	44		51[c]
	FC	371	No	22		67[c]
Parikh et al (2011)[9,d]	CFAR	60	No	70	3	18
Badoux et al (2011)[23]	CFAR	80	Yes	29	4	33
Byrd et al (2005)[6]	FR	104	No	38		46[b]
Byrd et al (2014)[28]	Ibrutinib	391	Yes			43[g]
Goede et al (2014)[14]	OC	781	No	22		55[c]
Kay et al (2007)[10]	PCR[e]	64	No	41	22	28
Kay et al (2010)[11]	PR[f]	33	No	27	15	33

[a]F, fludarabine; C, cyclophosphamide; R, rituximab; FluCam, fludarabine/alemtuzumab; OC, obinutuzumab and chlorambucil
[b]Progression-free survival 32.8 months with FC and 51.8 months with FCR ($p<0.001$). Overall survival at 37.7 months was 84.1% with FCR and 79.0% with FC ($p=0.01$). Patients with Rai stages 0-II primarily benefit from the addition of rituximab
[c]nPR and PR were combined
[d]High risk patients with a β2-microglobulin of ≥ 4 mg/L and aged < 70 years
[e]Dose of pentostatin, 2 mg/m^2
[f]Dose of pentostatin, 4 mg/m^2
[g]An additional 20% of patients had a PR with lymphocytosis

Table 8. Response According to Chlorambucil Dose-Intensity

Reference	Chlorambucil Schedule	Chlorambucil per month (mg)*	CR (%)	PR (%)	PFS (months)
Rai et al (2000)[16]	40 mg/m^2 every 28 days (6-12 months)	68	4	33	14
Hillmen et al (2007)[17]	40 mg/m^2 every 28 days (6-12 months)	68	2	53	11.7
Eichhorst et al (2009)[18]	0.4-0.8 (median 0.5) mg/kg days 1 and 15 (12 months)	70	0	51	18
Knauf et al (2009)[19]	0.8 mg/kg, Days 1 and 15 (6 months)	112	2	29	8.3
Catovsky et al (2007)[20]	10 mg/m^2, Days 1-7, every 28 days (6-12 months)	119	7	65[a]	23
Robak et al (2000)[21]	12 mg/m^2/day, Days 1-7, every 28 days	204	12	45	18
Jaksic et al (1997)[22]	15 mg/day, continuously	420	60	28	

*Assuming a weight of 70 kg and surface area 1.7 m^2

[a]nPR and PR were combined

Table 9. Infection Prophylaxis

Regimen	Varicella zoster virus (herpes zoster) prophylaxis	*Pneumocystiis jirovecii* prophylaxis
FCR	Yes – start at initiation of treatment and for 12 months post completion	Yes – start at initiation of treatment and for 12 months post completion
FR	Yes – start at initiation of treatment and continue for 6 months post completion	Yes – start at initiation of treatment and continue for 6 months post completion
Obinutuzumab-chlorambucil	No*	No*
Alemtuzumab	Yes – start at initiation of treatment and continue for 6 months post completion	Yes – start at initiation of treatment and continue for 6 months post completion
R-CD	No	Yes – start at initiation of treatment and continue for 3 months post completion
Bendamustine and rituximab	Yes – start at initiation of treatment and continue for 6 months	Yes – start at initiation of treatment and continue for 6 months post completion

*= case by case basis

Doses for Pneumocystiis jirovecii prophylaxis:

- Septra DS: 1 tablet orally twice daily on Saturdays and Sundays only
- Dapsone 100mg tablet: 1 tablet once daily
- Pentamidine 300mg via inhalation once monthly

Doses for varicella zoster prophylaxis:

- Valacyclovir 500mg orally once daily

References

1. Keating MJ, O'Brien S, Albitar M, et al. Early results of chemoimmunothearpy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol* 2005;23(18):4079-88.
2. Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. *Blood* 2008;112(4):975-80.
3. Tsimberidou AM, Tam C, Abruzzo LV, et al. Chemoimmunotherapy may overcome the adverse prognostic significance of 11q deletion in previously untreated patients with chronic lymphocytic leukemia. *Cancer* 2009;115(2):373-89.
4. Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. *Blood* 2004;103(9):3278-81.
5. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomised, open-labeled, phase 3 trial. *Lancet* 2010;376(9747):1164-74.
6. Byrd JC, Peterson BL, Morrison VA, et al. Addition of rituximab to fludarabine may prolong progression-free survival and overall survival in patients with previously untreated chronic lymphocytic leukemia: an updated retrospective comparative analysis of CALGB 9712 and CALGB 9011. *Blood* 2005;105(1):49-53.
7. Gruber M, Fleiss K, Porpaczy E, et al. Prolonged progression-free survival in patients with chronic lymphocytic leukemia receiving granulocyte colony-stimulating factor during treatment with fludarabine, cyclophosphamide, and rituximab. Ann Hematol 2011;90(10):1131-6.
8. Zhou Y, Tang G, Medeiros LJ, et al. Therapy-related myeloid neoplasms following fludarabine, cyclophosphamide, and rituximab (FCR) treatment in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. Mod Pathol 2012;25(2):237-45.
9. Parikh SA, Keating MJ, O'Brien S, et al. Frontline chemoimmunotherapy with fludarabine, cyclophosphamide, alemtuzumab, and rituximab for high-risk chronic lymphocytic leukemia. *Blood* 2011;118(8):2062-8.
10. Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. *Blood* 2007;109(2):405-11.
11. Kay NE, Wu, W, Kabat B, et al. Pentostatin and rituximab therapy for previously untreated patients with B-cell chronic lymphocytic leukemia. *Cancer* 2010;116(9):2180-7.
12. Rossignol J, Michallet A-S, Oberic L, et al. Rituximab-cyclophosphamide-dexamthasone combination in the management of autoimmune cytopenias associated with chronic lymphocytic leukemia. *Leukemia* 2011;25(3):473-8.
13. Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia: updated results of a randomized phase III trial. *Br J Haematol*

2012;159(1):67-77.

14. GoedeV, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* 2014;370(12):1101-10.
15. Rai K, Peterson BL, Appelbaum FR, et al. Long-term survival analysis of the North American Intergroup Study c9011 comparing fludarabine (F) and chlorambucil (C) in previously untreated patients with chronic lymphocytic leukemia (CLL). *Blood* 2009;114(22):A-536.
16. Rai KR, Pererson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med* 2000;343(24):1750-7.
17. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol* 2007:25(35):5616-23.
18. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood* 2009;114(16):3382-91.
19. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol* 2009;27(26):4378-84.
20. Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomized controlled trial. *Lancet* 2007;370(9583):230-9.
21. Robak T, Bloñski JZ, Kasznicki M, et al. Cladribine with prednisone versus chlorambucil with prednisone as first-line therapy in chronic lymphocytic leukemia: report of a prospective, randomized, multicenter trial. *Blood* 2000;96(8):2723–9.
22. Jaksic B, Brugiatelli M, Krc I, et al. High dose chlorambucil versus Binet's modified cyclophosphamide, doxorubicin, vincristine, and prednisone regimen in the treatment of patients with advanced B-cell chronic lymphocytic leukemia: results of an international multicenter randomized trial. International Society for Chemo-Immunotherapy, Vienna. *Cancer* 1997;79(11):2107–14.
23. Badoux XC, Keating MJ, Wang X, et al. Cyclophosphamide, fludarabine, alemtuzumab, and rituximab as salvage therapy for heavily pretreated patients with chronic lymphocytic leukemia. *Blood* 2011;118(8): 2085-93.
24. Badoux XC, Keating MJ, Wang X, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. *Blood* 2011;117(111):3016-24.
25. Tam CS, O'Brien S, Plunkett W, et al. Long-term results of first salvage treatment in CLL patients treated initially with FCR (fludarabine, cyclophosphamide, rituximab). *Blood* 2014;124(20):3059-64.
26. Osterborg A, Foà R, Bezares RF, et al. Management guidelines for the use of alemtuzumab in chronic lymphocytic leukemia. *Leukemia* 2009;23(11):1980-8.
27. Janssen Inc. Product Monograph Imbruvica™. Updated 14 November 2014. www.janssen.ca [Accessed

January 2015].

28. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* 2014;371(3):213-23.
29. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naive and previously treated patients wtih CLL and SLL receiving single-agent ibrutinib. *Blood* 2015;125(16):2497-506.
30. Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol* 2009;27(24):3994-4001.
31. Pettitt AR, Jackson R, Carruthers S, et al. Alemtuzumab in combination with methylprednisolone is a highly effective induction regimen for patients with chronic lymphocytic leukemia and deletion of TP53: final results of the National Cancer Research Institute CLL206 trial. *J Clin Oncol* 2012;30(14):1647-55.
32. Dreger P, Corradini P, Kimby E, et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. *Leukemia* 2007;21(1):12-7.
33. Dreger P, Schetelig J, Andersen N, et al. Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents. *Blood* 2014;124(26):3841-9.
34. Gribben JG. Stem Cell Transplantation in Chronic Lymphocytic Leukemia. *Biol Blood Marrow Transpl* 2009;15(1 Suppl):53-8.
35. Sutton L, Chevret S, Tournilhac O, et al. Autologous stem cell transplantation as a first-line treatment strategy for chronic lymphocytic leukemia: a multicenter, randomized, controlled trial from the SFGM-TC and GFLLC. *Blood* 2011;117(23):6109-19.
36. Nightingale G. Ofatumumab: a novel anti-CD20 monoclonal antibody for treatment of refractory chronic lymphocytic leukemia. *Annals Pharmacotherapy* 2011;45(10):1248-55.
37. Corona-Nakamura AL and Arias-Merino MJ. Management of CMV-associated diseases in immunocompromised patients. In Price P, Makwana N, Brunt S, eds.: Manifestations of cytomegalovirus infection. InTech, 2013. Available from: http://www.intechopen.com/books/manifestations-of-cytomegalovirus-infection/management-of-cmv-associated-diseases-in-immunocompromised-patients.
38. Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. *Best Practice Res Clinical Haematol* 2010:145-53.

IX. Complications of CLL/SLL

A. Autoimmune Complications

Autoimmune complications can occur in CLL and are most usually immune cytopenias, although rarely paraneoplastic pemphigoid, polyneuropathies and other disorders may occur.[1,2] Immune cytopenias occur in about 10% of CLL patients, and is most commonly Autoimmune Hemolytic Anemia (AIHA) followed by immune thrombocytopenia (ITP), immune neutropenia and red cell aplasia. The immune cytopenias are caused by antibodies produced by normal B cells and can be triggered by chemotherapy. Both fludarabine and chlorambucil can cause this problem in 10% of patients, and it is less likely if rituximab is part of the regimen. If a patient develops a decrease in any of the blood lines following chemotherapy, this may be related to immune cytopenia or marrow suppression.

Approximately 10-20% of patients will have a positive direct antiglobulin test (DAT) at some point in their disease; however this may be transient and does not necessarily result in AIHA. If AIHA is suspected, the patient requires a reticulocyte count, bilirubin, LDH, haptoglobin and a DAT. Normally in AIHA, the reticulocyte count, indirect bilirubin and LDH will be high and the haptoglobin low. However, the picture may be atypical in CLL due to marrow suppression by CLL infiltration or chemotherapy. To diagnose red cell aplasia, ITP or immune neutropenia, a bone marrow examination is required.

For therapy of isolated AIHA, the initial treatment is prednisone 1 mg/kg/day. Folic acid 5 mg/day is added if there is ongoing hemolysis. If a patient has AIHA, the prednisone dosage should be tapered once the hemoglobin, LDH, bilirubin and reticulocyte count have normalized, and discontinued in 4-6 weeks. The CBC, LDH and reticulocyte count should be measured each week while the prednisone is being tapered and if the hemolytic anemia recurs then the prednisone dosage should be increased. Patients should be monitored carefully for steroid-related complications such as gastric irritation, diabetes mellitus, insomnia, increased risk of opportunistic infections and osteoporosis. If the underlying CLL does not require chemotherapy, the patient should receive cyclosporine. Alternatives to cyclosporine are cyclophosphamide, mycophenolate mofetil (MMF) or single-agent rituximab. If there is progressive CLL and an immune cytopenia, we recommend RCD chemotherapy for 4-6 cycles.

For therapy of CLL-associated ITP, the initial treatment is prednisone, as described above. If there is no response within 7 to 10 days, intravenous immunoglobulin 1 g/kg/day x 2 days may be added. This can produce a rapid response, but the response is transient. Steroid-dependent or resistant patients can be treated with cyclosporine or alternatives, as indicated above for AIHA.[3] (*See Appendix IV*)

Splenic irradiation or splenectomy, although rarely required, may be considered for patients unresponsive to the above therapy. However, there is significant morbidity and mortality with splenectomy. To minimize morbidity, splenectomy should be carried out by laparoscopy. Patients should be immunized for pneumococcus, meningococcus and Hemophilus influenza 3-4 weeks before the procedure.

Key Points

Immune cytopenias in CLL are caused by increased activity of normal B or T cells. They are treated by immunosuppressives and NOT chlorambucil or fludarabine.

B. Immunodeficiency

Even at diagnosis, the immune system is compromised in CLL with abnormalities in both T and B cell function; thus the benefit with immunizations is questionable.[4] Regardless, a yearly influenza vaccine is recommended for all patients and Pneumovax at diagnosis and every 5 years. The shingles vaccine is **not** recommended in these patients as it is a live vaccine. Patients with hypogammaglobulinemia and recurrent bacterial infections should be treated with replacement intravenous immunoglobulin (IVIG) therapy although there is no evidence that this is cost-effective.[4] High-dose IVIG, administered as 400 mg/kg IV every 3 weeks, reduces the incidence of bacterial infections by 50%, particularly those caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, but the total number of severe bacterial infections and nonbacterial infections is not reduced, and this treatment does not prolong survival.[5] Lower doses of IVIG may be as effective (i.e., 10 g every 3-4 weeks) and this dosing schedule has been our standard treatment at CCMB.

Subcutaneous immunoglobulin (SCIG) therapy is now being offered as a more convenient alternative to IVIG and can be self-administered by patients or caregivers in the home without the need for venous access. Subcutaneous infusion has been shown to achieve higher trough immunoglobin (Ig) levels than IVIG therapy and is associated with fewer systemic adverse reactions and higher patient reported health related quality of life parameters.[6,7]

C. Richter's Transformation

Approximately 10% of patients will develop a Richter's transformation, indicating that the CLL has transformed to a more aggressive disease.[8] Richter's transformation is a transformation of CLL usually to diffuse large B cell lymphoma (DLBCL), although multiple myeloma, Hodgkin's disease or acute leukemia can also develop. Patients in transformation are usually symptomatic with fevers, weight loss, rapidly enlarging lymph node(s) and an elevated LDH. A positron emission tomography (PET) scan should be performed to identify which nodes are highly hypermetabolic or transformed (SUV > 5) and thus most amenable to biopsy. Excisional biopsy should be performed whenever possible. A bone marrow biopsy should also be performed to complete staging. Clonality of the transformed cell is important in determining patient outcomes, but is presently not available in Manitoba. In general, the prognosis for Richter's transformation is poor, although patients with clonally unrelated transformation (20%) may respond to therapy and have a prognosis similar to *de novo* DLBCL.

Evolution to prolymphocytic leukemia (PLL) is associated with an increase in the number of prolymphocytes in the peripheral blood. The patient has PLL if they have > 55% prolymphocytes in peripheral blood.

D. Second Malignancies

Patients with CLL have a two-fold increase in second malignancies when compared with age- and sex-matched

controls.[9-11] The increased rate is likely related to the immunosuppression, which progressively worsens with disease progression. At the initial visit, a family and personal history of cancer is conducted as well as a history of the patient's cancer screening practices. Both males and females of all ages are affected, and in particular skin cancer is common and tends to be aggressive. Patients are advised to avoid the sun, use sunscreen and wear protective clothing and eyewear. Patients with actinic keratosis and skin cancers are referred for dermatological review (*See Section XII for consulting dermatologist*) and may require skin monitoring every 6-12 months. In females, breast cancer is frequent and a common cause of death, while prostate cancer is common in men, but is less likely to cause death. Smoking cessation is strongly advised as patients are particularly susceptible to all malignancies. All CLL patients who smoke should be referred to the CCMB Quit Smoking Program. Patients are also encouraged to make lifestyle changes to minimize their risk of second malignancy and to continue with standard, age/gender appropriate cancer screening practices (e.g., mammography) to facilitate early detection and prompt intervention. CLL patients with anemia should be evaluated for iron deficiency. If present, or in the presence of a strong family history, patients should be evaluated for an occult gastrointestinal malignancy.

Key Points

Three key areas for patient monitoring at every clinic visit:

- CLL disease status
- Development of new infection
- Development of second malignancies

Referrals to the MacCharles CancerCare Manitoba Quit Smoking Clinic can be made by:

- Calling the self-referral hotline at 204-787-1202 or toll-free 1-888-775-9899
- Contacting the Referrals office by fax at 204-786-0621

References

1. Hodgson K, Ferrer G, Montserrat E, et al. Chronic lymphocytic leukemia and autoimmunity: a systematic review. *Haematologica* 2011;96(5):752-61.
2. Dearden C. Disease-specific complications of chronic lymphocytic leukemia. *Hematolology Am Soc Hematol Educ Program* 2008:450-6.
3. Cortes J, O'Brien S, Loscertales J, et al. Cyclosporin A for for the treatment of cytopenia associated with chronic lymphocytic leukemia. *Cancer* 2001;92(8):2016-22.
4. Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. *Best Practice Res Clinical Haematol* 2010;23(1):145-53.
5. Cooperative Group for the study of immunoglobulin in chronic lymphocytic leukemia: intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized control trial. *N Engl J Med* 1988;319(14):902–7.

6. Compagno N, Cinetto F, Semezato G, et al. Subcutaneous immunoglobulin in lymphoproliferative disorders and rituximab-related secondary hypogammaglobulinemia: a single-center experience in 61 patients. *Haematologica* 2014;99(6):1101-6.

7. Gardulf A, Borte M, Ochs HD, et al. Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. *Clin Immunol* 2008;126(1):81-8.

8. Johnston JB, Seftel M, Gibson SB. Chronic Lymphocytic Leukemia. *In*: Greer JP, Foerster J, Lukens J, et al (eds), Wintrobe's Clinical Hematology, 12th Edition, pp 2256-2275, Baltimore, MD: Williams and Wilkins, 2013. (*Last Updated for online version October, 2014)*.

9. Tsimberidou A-M, Wen S, McLaughlin P, et al. Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. *J Clin Oncol* 2009;27(6):904-10.

10. Royle JA, Baade PD, Joske D, et al. Second cancer incidence and cancer mortality among chronic lymphocytic leukaemia patients: a population-based study. *Br J Cancer* 2011;105(7):1076-81.

11. Beiggi S, Lambert PJ, Pitz MW, et al. Risk of second malignancies in patients with chronic lymphocytic leukemia: a population based Canadian study. *American Assoc Cancer Res* 2012;Abstract #5505.

X. Research Activities

Manitoba CLL Tumour Bank

All patients attending the CLL clinic have the opportunity to provide tissue samples to the Manitoba CLL Tumour Bank for research purposes. Following consent, peripheral blood and a buccal smear are obtained at the time of diagnosis for banking. Thereafter, blood samples are obtained every 2 years if the disease is stable, each year if there is disease progression and at the time of treatment. If a patient fails to respond to therapy, a blood sample is taken 1 month post treatment.

XI. Implementation and Dissemination

The value of guidelines truly lies in their implementation and use. For that purpose, consideration was given to implementation during the drafting of this guideline document.

CancerCare Resources

It was recognized that resources would be needed to distribute these guidelines to the community. For that purpose, the guideline will be accessible online through the CancerCare Manitoba website. Online availability will be preceded by an e-blast notification with the website embedded. Announcement of the guideline and updates will be through established provincial communication channels; the Community Oncology Program to CCPN rural sites, UPCON clinics and WRHA Community Oncology Program sites. This guideline will also be provided to partner organizations and guideline reviewers in other provinces. Use of the guideline in clinics will be through the online version.

Educational Events

Presentation of the guideline's recommendations will be made at rounds and conferences; Lymphoproliferative Disorders DSG rounds, CCMB Hematology/Oncology Regional Grand rounds, Allied Health rounds (Patient Services rounds), CCPN Community Cancer Care annual educational conference and at UPCON education and training events. The CCMB CLL guideline will also be presented at the annual Canadian CLL Research Meeting held in Winnipeg.

Training

The members of the CLL working group will utilize the guideline for the purpose of staff training (physicians, allied health) at CancerCare Manitoba.

XII. Contact Physicians and Contributors

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XIII. Appendices

Appendix 1

Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Criteria
0	Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)
1	Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about greater than or equal to 50% of walking hours (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair greater than or equal to 50% of walking hours (Karnofsky 30-40)
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10-20)

Oken MM, Creech RH, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55. Eastern Cooperative Oncology Group, Robert Comis B.D., Group Chair.

Appendix 2

The Lymphoproliferative Disorders DSG encourages healthcare professionals to use the comprehensive cumulative illness rating scale (CIRS) cited here when determining a patients' CIRS score.

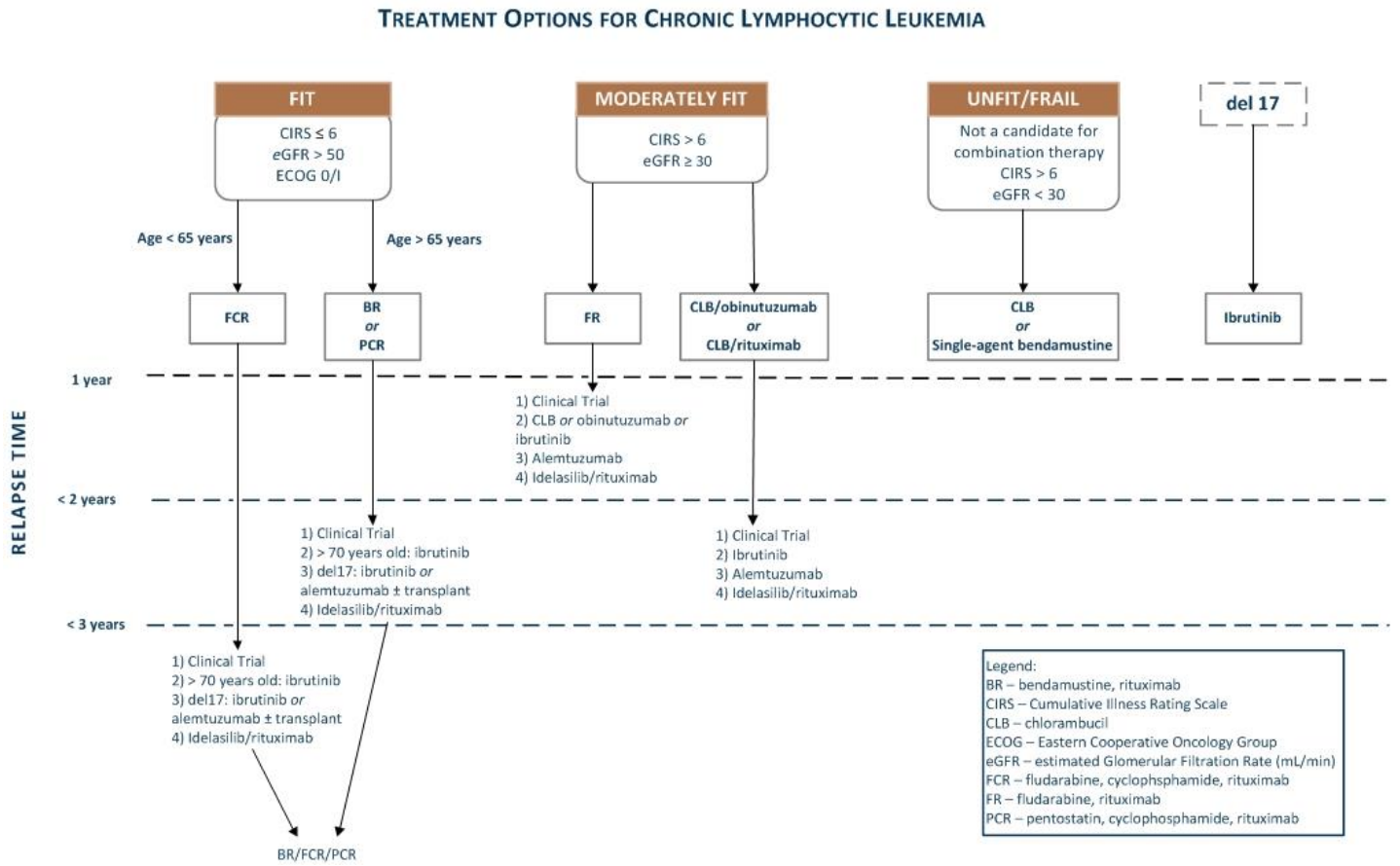
The tool can be accessed at Wiley Online Library, Journal of American Geriatrics Society: http://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2008.01935.x/suppinfo and the filename is JGS_1935_sm_Appendix.doc.

Reference

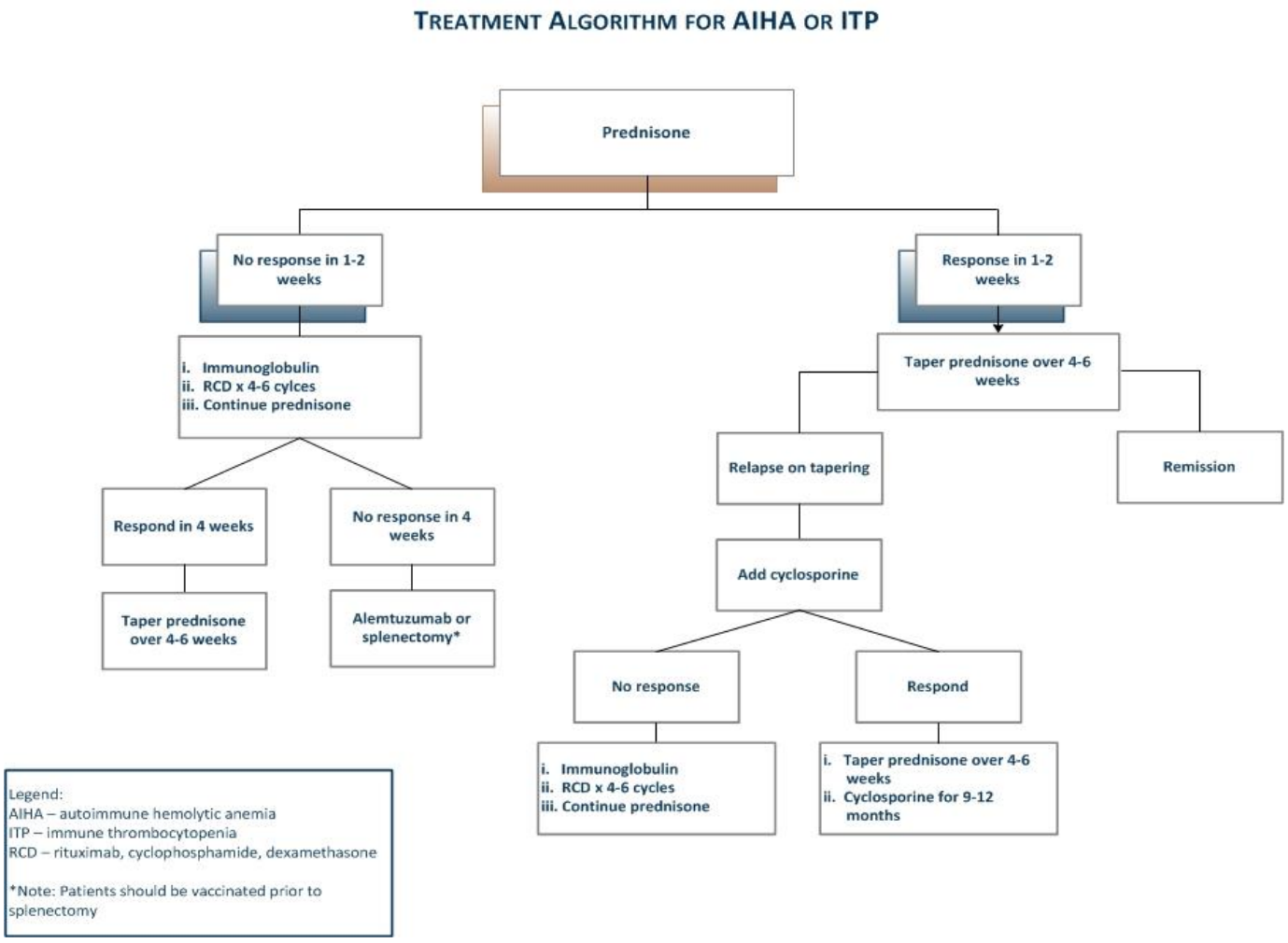
1. Salvi F, Miller MD, Towers A, et al. A Manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients supplementary material: *J Am Geriatr Soc* 56;10:1926-31.

   Appendix S1. Guidelines for scoring the modified cumulative illness rating scale (CIRS).

Appendix 3


TREATMENT OPTIONS FOR CHRONIC LYMPHOCYTIC LEUKEMIA
FIT
CIRS ≤ 6
eGFR > 50
ECOG 0/I
MODERATELY FIT
CIRS > 6
eGFR ≥ 30
UNFIT/FRAIL
Not a candidate for combination therapy
CIRS > 6
eGFR < 30
del 17
Age < 65 years
Age > 65 years
FCR
BR or PCR
FR
CLB/obinutuzumab or CLB/rituximab
CLB or Single-agent bendamustine
Ibrutinib
RELAPSE TIME
1 year
< 2 years
< 3 years
1) Clinical Trial
2) CLB or obinutuzumab or ibrutinib
3) Alemtuzumab
4) Idelasilib/rituximab
1) Clinical Trial
2) > 70 years old: ibrutinib
3) del17: ibrutinib or alemtuzumab ± transplant
4) Idelasilib/rituximab
1) Clinical Trial
2) Ibrutinib
3) Alemtuzumab
4) Idelasilib/rituximab
1) Clinical Trial
2) > 70 years old: ibrutinib
3) del17: ibrutinib or alemtuzumab ± transplant
4) Idelasilib/rituximab
BR/FCR/PCR
Legend:
BR – bendamustine, rituximab
CIRS – Cumulative Illness Rating Scale
CLB – chlorambucil
ECOG – Eastern Cooperative Oncology Group
eGFR – estimated Glomerular Filtration Rate (mL/min)
FCR – fludarabine, cyclophsphamide, rituximab
FR – fludarabine, rituximab
PCR – pentostatin, cyclophosphamide, rituximab

Appendix 4


TREATMENT ALGORITHM FOR AIHA OR ITP
Prednisone
No response in 1-2 weeks
Response in 1-2 weeks
i. Immunoglobulin
ii. RCD x 4-6 cylces
iii. Continue prednisone
Taper prednisone over 4-6 weeks
Relapse on tapering
Remission
Respond in 4 weeks
No response in 4 weeks
Add cyclosporine
Taper prednisone over 4-6 weeks
Alemtuzumab or splenectomy*
No response
Respond
i. Immunoglobulin
ii. RCD x 4-6 cycles
iii. Continue prednisone
i. Taper prednisone over 4-6 weeks
ii. Cyclosporine for 9-12 months
Legend:
AIHA – autoimmune hemolytic anemia
ITP – immune thrombocytopenia
RCD – rituximab, cyclophosphamide, dexamethasone
*Note: Patients should be vaccinated prior to splenectomy

Appendix 5

CLL Primary Care Guideline

This document was developed to guide primary care providers in the diagnosis and management of patients with CLL/SLL and is intended to supplement the Consensus Recommendations for the Management of Chronic Lymphocytic Leukemia.

Essential and Useful Tests to Order before Referral to CancerCare Manitoba When a Patient Has a High Lymphocyte Count (> 5 x 10^9/L)

Essential diagnostic tests:

- CBC with differential
- Review of peripheral smear to look for smudge cells
- Flow cytometry
    - CLL patients have > 5 x 10^9 B cells with typical molecular markers (positive for CD19, CD5 and CD23)
    - Testing for ZAP-70 and CD38, which are associated with worse prognosis if positive, can only be performed on a fresh blood sample

Useful tests: reticulocyte count, immunoglobulin levels, SPEP biochemistry (electrolytes, creatinine, glucose, LDH, LFT), viral hepatitis screen, HIV screen, direct antiglobulin test (DAT) and β2-microglobulin.

CT scans, lymph node biopsy or bone marrow aspirate/biopsy are **not** routinely required for CLL however, may be necessary for MBL and SLL.

Co-Management of Patients with the Hematologist or the CancerCare Manitoba CLL Clinic

Annual testing (to be performed by the CLL clinic at the first appointment of the calendar year):

- CBC, complete biochemistry, immunoglobulin levels, Coombs (direct antiglobulin) test, serum electrophoresis, and
  β2-microglobulin

Common complications of CLL to be aware of:

- Autoimmune cytopenias
    - Especially autoimmune hemolytic anemia (AIHA) – if suspected, check LDH, bilirubin, haptoglobin and Coombs (direct antiglobulin) test
    - Patients may also develop immune thrombocytopenia (ITP), immune neutropenia and red cell aplasia
- Immunodeficiency
    - Watch for recurrent sinus/respiratory infections
    - Administer pneumococcal vaccine at diagnosis (a single re-immunization is recommended after 5 years)

  - Administer annual influenza vaccine
  - **Do not** administer live virus vaccines (e.g., shingles vaccine)

- Development of second malignancies
  - Two-fold increase in CLL patients; especially skin, lung, breast, colon, prostate and lymphoma
  - Patients need:
    - Aggressive screening (e.g., regular full skin exam; strict adherence to usual breast, prostate and colorectal cancer screening guidelines)
    - Education regarding cancer risk reduction (e.g., smoking cessation, sun protection, eating healthy and staying active)
    - Early detection and intervention of suspicious findings (e.g., endoscopy if iron-deficiency anemia discovered; referral to dermatology for suspicious skin lesions)

Indications to call the CancerCare Manitoba Hematologist:

- Significant interval progression of CLL:
  - Lymphocyte or lymph node/spleen doubling within 6 months or a > 50% increase in 2 months
  - Progressive anemia, neutropenia and/or thrombocytopenia
  - Symptomatic lymphadenopathy or splenomegaly
  - Significant symptoms, such as night sweats, weight loss or fatigue
- Significant delays in treatment
- Suspected development of an immune cytopenia
- Suspected transformation to more aggressive disease (e.g., prolymphocytic leukemia, diffuse large B cell lymphoma, multiple myeloma, Hodgkin's disease or acute leukemia). Patients in transformation are usually symptomatic with rapidly enlarging lymph nodes, fevers, weight loss and an elevated LDH
- Multiple recurrent bacterial infections. Patients may be a candidate for replacement immunoglobulin therapy (IVIG or SCIG)

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CCMB Clinical Practice Guideline: Disease Management
Chronic Lymphocytic Leukemia
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