CHRONIC LYMPHOCYTIC LEUKEMIA: A REVIEW FOR
PRIMARY CARE PRACTITIONERS

By

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Abstract

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Chronic lymphocytic leukemia (B-CLL) is the most common leukemia encountered and co-managed by primary care. It is characterized by clonal B cell accumulation in the blood, marrow, lymph nodes, spleen and liver resulting in lymphocytosis, marrow failure, lymphadenopathy and organomegaly. The disease results in progressive immune dysfunction leading to the common complications of infections, autoimmune hematological disorders, and secondary malignancies that can present at any stage of disease. The use of new diagnostic markers enables improved individual prognostic and treatment decision making. Improved therapies are changing the “watchful waiting” and palliative strategies of the past to earlier or more aggressive treatment for some high risk patients. This review aids the primary care provider in the understanding of the pathophysiology, clinical presentation, and diagnostic testing for B-CLL, as well as, provides a general overview of treatment and management strategies employed by specialty care. Primary care familiarity with current management strategy helps optimize outcomes for patients with B-CLL.
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Dedication

This clinical project is dedicated to my dear friend Tom, whose ongoing battle with chronic lymphocytic leukemia inspired my investigation of this disease.
Chronic Lymphocytic Leukemia: A Review for Primary Care Practitioners

Introduction

Chronic lymphocytic leukemia (B-CLL) is a lymphoproliferative disorder clinically classified as one of the indolent disseminated non-Hodgkin’s lymphomas (Shipp, Mauch, & Harris, 1997). It is characterized by clonal B cell accumulation in the peripheral blood, bone marrow, lymph nodes, spleen, and liver, resulting in organomegaly, marrow failure, and immune dysfunction (Deisseroth et al., 1997). Typically the disease is detected by primary care when lymphocytosis is noted during routine or diagnostic workup for other conditions. Collaboration with the hematologist/oncologist is essential to establish staging and develop therapy recommendations. This is particularly important as new diagnostic indicators are being recognized that may help predict the course of the disease, revising previous “watchful waiting” strategies in early disease for some groups of patients.

Unlike most other leukemias, which generally have a more rapid course and are treated and managed at diagnosis by oncologists, B-CLL often has an indolent course with asymptomatic or early stage patients often seen more frequently by primary care. These providers are likely to detect important complications, particularly those of autoimmune and infectious origin, and second primary malignancies that patients with B-CLL are predisposed regardless of the stage of disease. Primary care providers are therefore pivotal to the initial detection, workup and ongoing management in the care of patients with B-CLL. This is particularly true with managed care where primary care providers are increasingly required to make decisions regarding referral visits and diagnostic procedures. To optimize this co-management, this review is intended to familiarize the primary care provider with the pathophysiology, clinical presentation, and diagnostic testing for B-CLL, as well as provide a
general overview of current treatment and management strategies employed by specialty and primary care. It will also present oncology and pathology terms to acquaint the non-specialist with those commonly encountered in laboratory reports and specialty care chart notes of patients with B-CLL.

Incidence and Etiology

B-CLL is the most common leukemia in Western countries comprising one third of all leukemias. The expected new cases and deaths in the United States (US) for 2003 are estimated at 7,300 and 4,400 respectively (Jemal et al., 2003). It is predicted that the number of asymptomatic cases detected, particularly in those less than 55 years, will continue to grow due to increased pre-surgical screening procedures and from routine physicals (de Lima, O’Brien, Lerner, & Keating, 1998). B-CLL is a disease of the elderly with the median age at diagnosis of 64 years. Only 10-15% of patients are diagnosed less than 50 years, it is rare under 30 years (Diehl, Karna, & Menck, 1999). The incidence is highest in Caucasians, much less common in Asian populations including US immigrants, intermediate in those of Hispanic origin and is twice as common in men as women (Diehl et al., 1999; Jemal et al., 2003; Yanagihara, Blaisdell, Hayashi, & Lukes, 1989). The incidence in men is further increased in those diagnosed less than 55 years (Mauro et al., 1999). The etiology of B-CLL is as yet unknown. There is no evidence for retroviral causality and no increase in incidence with exposure to ionizing radiation. First degree relatives have a two-fold to four fold increased risk for B-CLL as well as other lymphoid neoplasms as compared to the general population (Cuttner, 1992; Shah, Maeda, Deegan, Roth, & Schnitzer, 1992).
Diagnostic Features

Morphological characteristics.

The diagnostic features of B-CLL are peripheral blood lymphocytosis of greater than 5.0 \( \times 10^9 \) per liter, marrow lymphocytosis greater than 30%, and characteristic immunophenotyping pattern (Cheson et al., 1996). There is no diagnostic cytological feature for B-CLL as it usually presents morphologically with nearly normal appearing mature lymphocytes by light microscopy on the peripheral smear and bone marrow biopsy. The cells are most often medium sized, with a small to moderate amount of agranular pale blue cytoplasm, frequently showing exaggerated nuclear chromatin clumping (Dick, 1994). Striking cellular homogeneity is the rule with little cellular variability seen. Usually there is less than 5% prolymphocytes or cells with cleaved or folded nuclei present, except in advanced or transformed disease. If there is greater than 55% or 15.0\( \times 10^9 \) per liter of prolymphocytes present, the diagnosis of prolymphocytic leukemia (PLL) or mixed B-CLL/PLL must be considered (Cheson et al., 1996; Dick, 1994). In the presence of high numbers of cleaved cells careful phenotyping is needed to exclude leukemic phase small cleaved cell lymphoma. Other neoplastic lymphocytic disorders are distinguished morphologically by immaturity and other cellular characteristics that aid in differentiation from B-CLL.

The presence of “smudge” or “basket” cells is a feature commonly noted on the differential of B-CLL patients although rare in other leukemias or conditions. These are disintegrating lymphocyte nuclei, an artifact created by mechanically rupturing fragile B-CLL cells during the slide preparation process (Fischbach, 1996; Ryan, 2001). The significance is a relative percent increase in neutrophils on the manual differential due to under counting of lymphocytes. The automated differential fortunately is unaffected.
In contrast to the monotonous appearance of lymphocytes typically seen in a clonal neoplastic disease such as B-CLL, reactive lymphocytosis is characterized by morphologic variability from polyclonal expansions of T and/or B lymphocytes. Reactive lymphocytes are generally larger than the normal small mature lymphocyte, have a slightly finer nuclear chromatin with a distinct nucleus and abundant cytoplasm frequently with a blue plasmacytoid appearance. These cells are often associated with acute viral infection and are also termed Downey cells (Hanson, 1994). The lymphocytosis of Bordetella pertussis can appear as clefted cells, mimicking the cells of peripheralized small cleaved cell lymphoma. Of note the "atypical lymphs" associated with mononucleosis are typically reactive T-cells rather than B-cells (Bagby, 1996).

**Immunophenotyping.**

Immunophenotyping is performed to determine the definitive diagnosis of B-CLL. It can also be used as a prognostic indicator and for assessing response to treatment. Some antigens are also treatment targets. Immunophenotyping, specifically for CD20, is required before certain treatments are reimbursed by Medicare and other providers.

Surface immunophenotyping by flow cytometry (FCM) is indicated when persistent lymphocytosis is present that cannot be attributed to other causes. While B-CLL is morphologically mature, it is immunologically less mature, and is distinguished from infectious and other neoplastic causes of lymphocytosis by its characteristic immunophenotyping pattern (DiGiuseppe & Borowitz, 1998). FCM enables enumeration and identification of cell populations through light scattering and/or fluorescence from fluorochrome conjugated monoclonal antibodies to specific cell surface markers (Jacobs, Oxley, & DeMott, 2002). Clusters of antibodies that bind a known antigen (human leukocyte cell surface marker) are
termed “clusters of differentiation” or CD. Antigens are catalogued by CD designation resulting in a schema for identifying cellular lineage and maturation based on immunophenotype expression. Normal B and T-cells have a specific CD pattern of expression, which is predictably altered in lymphoid malignancies. CD antigen panels have been developed for lymphoma/leukemia evaluation utilizing specific markers to delineate the various lymphoid disease phenotypes as shown in Table 1.

B-CLL lymphocytes express some normal B-cell markers, lose expression of other markers, and also express markers associated with T lymphocytes. The National Cancer Institute (NCI) sponsored Working Group (NCI-WG) guidelines for diagnosis of chronic lymphocytic leukemia specify one or more B-cell marker (CD19, CD20, CD 23) plus CD5 (T-cell) be present for diagnosis (Cheson et al., 1996). The accepted characteristic B-CLL phenotype as codified by the Royal Marsden group (Moreau et al., 1997), consists of strong expression of CD5, CD19, and CD23 markers, sparse but monoclonal expression of immunoglobulin (Ig) of one light chain type (kappa or gamma) and weak expression of CD20, CD22 and CD79b. Conformational disposition of CD20 detected by FMC7 monoclonal antibody is usually absent (positive in other lymphomas), as well as CD3 and CD10.

Refinements in flow cytometry have lead to sensitive assays designed to detect minimal residual disease after chemotherapy treatment. Using these assays to screen normal individuals, researchers found small clonal B-CLL phenotypical populations of lymphocytes in 3.5% of normal individuals over 40 years (Rawstron, Green, et al., 2002). In familial B-CLL a 13.5% incidence of a clonal population was found in seemingly unaffected family members (Rawstron, Yuille, et al., 2002). NCI guidelines are set with the certain knowledge that malignancy exists before diagnostic threshold is met. However, mere demonstration of clonality especially in light
of the low level of lymphocytosis needed for diagnosis, demands careful consideration before a diagnosis of B-CLL is given to asymptomatic patients with small monoclonal populations. There is an emerging recognition of a monoclonal lymphocytosis of undetermined significance akin to monoclonal gammopathy of unknown significance (Hamblin, 2002). Future study will hopefully more fully define this condition.

**Differential Diagnosis**

The differential diagnosis of lymphocytosis includes a variety of infectious as well as neoplastic disorders as outlined in Table 2 (Bagby, 1996). Patients with B-CLL generally present with lymphocytosis greater than $15.0 \times 10^9$ per liter with a median white blood cell count (WBC) of $30-40 \times 10^9$ per liter and some well over $100 \times 10^9$ per liter. Moderate lymphocytosis with a count less than $15.0 \times 10^9$ per liter can be from a host of viral and other infectious diseases, Graves' disease, drug reactions, and some neoplastic diseases including early B-CLL. High lymphocytosis with counts greater than $15.0 \times 10^9$ per liter, are generally limited to mononucleosis, pertussis, acute infectious lymphocytosis, and neoplastic lymphocytic disorders most frequently B-CLL. Less common lymphoproliferative disorders that present with lymphocytosis are the acute lymphocytic leukemias, mantle cell lymphoma, splenic marginal zone lymphoma (also known as splenic lymphoma with villous lymphocytes), B-prolymphocytic leukemia (B-PLL), mixed B-CLL/PLL, and T-prolymphocytic leukemia (T-PLL) (Hamblin, 2003). Most patients presenting with lymphocytosis from non-neoplastic causes generally have overt signs of an underlying illness involving sites other than the hematopoietic system.
**Clinical Presentation**

Eighty to ninety percent of patients with B-CLL initially present asymptptomatically or with minor symptoms (Byrd, Farag, Lucas, & Lin, 2002). Constitutional symptoms of fatigue and malaise are common, with fever and night sweats the so-called B symptoms (name taken from “B” lymphocytes), weight loss, recurrent infections, and bleeding more frequent in advanced disease. Fatigue can be present even without anemia or clinical evidence of organ involvement. Lymphocytosis usually ranges from 40-150 x 10^9 per liter but can be dramatic with some counts over a million. Hyperviscosity symptoms, which may include hypervolemia from a reactive expansion of the plasma volume, impaired microcirculation, headache, confusion and other neurologic findings, can occur with counts over 500 x 10^9 per liter. High numbers of B-CLL cells however, are less apt to form circulatory aggregates compared with other leukemias (Kipps, 2001). Leukostasis can be found in counts over 800 x 10^9 per liter. Marrow involvement can be of the interstitial, nodular, mixed or diffuse type, with the diffuse pattern associated with aggressive or advanced disease.

Lymphadenopathy is the most common presenting symptom, present in two-thirds to eighty percent of patients at diagnosis (Keating, 1996; Kipps, 2001). Enlarged nodes are initially non-tender, discrete, rubbery, and mobile, becoming matted and bulky over time. Usually initially presenting in the cervical chain, nodal dissemination to the supraclavicular, axillary and inguinofermal regions occurs with progression. Even with extensive lymphadenopathy, lymphedema and superior vena cava syndrome is uncommon, although some may develop symptoms of upper airway obstruction with extensive oral-pharyngeal lymphadenopathy (Waldeyer ring). Bulky retroperitoneal lymphadenopathy can result in ureteral obstruction or hydronephrosis and rarely partial bowel obstruction. New acute tenderness at a previously non-
tender chronically enlarged node requires evaluation for a secondary lymphadenitis, which may be due to herpes simplex infection (Higgins & Warnke, 1999).

At diagnosis, splenomegaly and hepatomegaly is seen in 40% and 10% of patients respectively, representing more advanced disease, and may cause symptoms of early satiety and abdominal fullness (Keating, 1996; Kipps, 2001). Hypersplenism can contribute to anemia and thrombocytopenia although this is more often due to marrow infiltration or autoantibodies. Less commonly occurring is lymphoid infiltration of other sites including the eyelids/retro-orbit region, heart, lungs, pleura, and gastrointestinal tract, which may result in proptosis, pericarditis, pulmonary infiltrates (nodular or miliary), pleural effusions, gastrointestinal mucosa thickening, bleeding and malabsorption (Kipps, 2001). Central nervous system involvement is rare with symptoms more apt to be from an infectious source. Cases have been reported of nasal involvement manifesting as chronic rhinitis refractory to standard treatment (Amir, Dowdy, & Goldberg, 1999). Exaggerated response to insect bites, particularly mosquitoes, and insect bite-like skin reactions have also been reported (Barzilai et al., 1999; Weed, 1965). The cause is unknown and the condition is difficult to treat other than with systemic corticosteroids.

Other pertinent lab abnormalities seen are elevated serum lactate dehydrogenase (LDH) as well as beta-2-microglobulin particularly in advanced or aggressive disease. Hypogammaglobinemia is often present on serum protein electrophoresis or quantitative immunoglobulin analysis. A monoclonal paraprotein is detectable in 5% of patients (Kipps, 2001).
Immune Dysregulation

Immune dysfunction and resulting immunodeficiency.

Transformation of a B lymphocyte to a malignant clone is the principle defect in B-CLL. However, a mere excess of these cells is not the extent of the disorder as it is now known there are numerous other immune system defects present that play a role in the immune dysfunction and progression of this disease. The most profound and life threatening consequence of this dysfunction is the resulting immunodeficiency. Hypogammaglobinemia, myelosuppression, T-cell immunodeficiency as well as immunosuppressive cytokine production by B-CLL cells themselves, contribute to the immunodeficiency. Severe hypogammaglobinemia develops in three-fourths of patients at some time during their disease, loosely correlating with stage of disease (Kipps, 2001).

The defects affect many cellular components of the immune system including regulation of T-cells, natural killer (NK) cells, and dendritic cells which have been found to be deficient in function (Bartik, Welker, & Kay, 1998; Orsini, Guarini, Chiaretti, Mauro, & Foa, 2003; Stadelmeyer, Grube, Chraust, Linkesch, & Strunk, 2001). NK cells play an integral part in the first line of defense against malignancy, while dendritic cells are important in the induction of cytotoxic T-cell response to tumor cells. This dysfunction may play a role in B-CLL progression. Expansion of polyclonal T-cells is found in early disease especially T-helper (CD4+) cells in nodes and marrow, however B-CLL cells have a defective antigen presenting capability and can render the T-cell anergic. With disease progression the CD4/CD8+ T cell ratio declines and can invert with an absolute increase in CD8+ (suppressor) cells (as is seen in human immunodeficiency virus (HIV) infection). B-CLL cells down-modulate expression of CD40-ligand on CD4+ T cells, which is integral in immunoglobulin response and regulation, adding to
the immunodeficiency and may play a role in the development of hypogammaglobulinemia (Cantwell, Hua, Pappas, & Kipps, 1997). Myelosuppression from marrow infiltration by B-CLL cells result in neutropenia (as well as anemia and thrombocytopenia) further adding to the immunodeficiency.

Infection is the leading cause of death in B-CLL patients. Mucosal infections are most cited, with increased risk positively correlated with immunoglobulin level decline (Morrison, Hibbs, & Janoff, 1996). The combined acquired immunodeficiency results in an increased risk for infection, especially with encapsulated organisms, herpes zoster and opportunistic pathogens (Keating, 1996; Molica, 1994). Sinopulmonary infections predominate early in the disease with gram negative bacterial, fungal and viral infections increasing with progression. While aspects of the immunodeficiency in B-CLL is similar to that seen in HIV infection and patients may contract similar opportunistic infections particularly while on treatment for, and in advanced disease, a direct infectious disease management correlation cannot be made. Primary care usually readily manages most common infections with close follow up, particularly in the earlier stages of disease when opportunistic pathogens are rare. Vaccines may have a suboptimal response especially late in the disease due to impaired immune response (Molica, 1994).

Faulty immune surveillance.

Faulty immune surveillance is another consequence of the immune dysregulation associated with B-CLL. A predisposition for autoimmune hematological complications occurs despite the profound immunodeficiency. Interestingly the pathologic autoantibody is typically produced by not by the malignant B cell clone, but from polyclonal bystander B cells (Kipps & Carson, 1993). As this complication can occur independently from direct progression of B-CLL,
it usually is managed separately by oncologists and the underlying B-CLL is not necessarily treated. An increased incidence of other types of autoimmune disorders has not been found.

Autoimmune hemolytic anemia (AIHA) is the most common disorder seen, with 37% of patients developing it at some time in the course of their disease (Byrd, Lucas, et al., 2003; Mauro et al., 2000). Patients are also predisposed to idiopathic thrombocytopenia purpura (ITP) (2-3%), and to a lesser degree pure red-cell aplasia (0.5 %) although this likely is under recognized (Diehl & Ketchum, 1998; Rozman & Montserrat, 1995). AIHA and ITP occur together 10% of the time (Evans’s disease) (Linker, 2003).

There is also an increased risk for second malignancies (10-20%) which either precedes or follows the diagnosis of B-CLL (Mauro et al., 1999; Travis, Curtis, Hankey, & Fraumeni, Jr., 1992). The causative factors are unclear but the role of impaired immune surveillance is implicated and may be related to the NK and dendritic dysfunction previously discussed. An increase in the incidence of skin cancers (including melanoma), colorectal cancer, sarcomas, and lung cancers is found compared to age matched controls. Disease transformation can also occur and carries a poor prognosis. Conversion to PLL is most common, occurring in 10% of patients, high grade large cell lymphoma (Richter’s transformation) occurs in 3-5%, while conversion to acute leukemia is rare, less than 1% (Rozman & Montserrat, 1995).

*Apoptotic resistance and angiogenic pathways.*

The immune dysregulation also creates a favorable microenvironment for the longevity of leukemic cells and for disease progression through apoptotic resistance and angiogenic pathways. B-CLL is a disease of cellular accumulation with only a small pool of proliferating cells identified in sites such as the white pulp of the spleen (Lampert, Wotherspoon, Van Noorden, & Hasserjian, 1999). Circulating and most nodal B-CLL cells are found to be in the G0
phase of the cell cycle, accumulating due to an acquired resistance to normal apoptotic mechanisms. Numerous resistance mechanisms have been described including B-CLL production of anti-apoptotic proteins such as bcl-2, mcl-1, bag-1 and others (McConkey et al., 1996; Robertson, Plunkett, McConnell, Keating, & McDonnell, 1996). There is increased T-cell production of anti-apoptosis cytokines such as IL-4, interferon alpha and gamma (Granziero et al., 2001; Kay, Han, Bone, & Williams, 2001).

Abnormal angiogenesis with marrow and nodal neovascularization is also seen in B-CLL and has been positively associated with increased stage of disease by some workers (Kay, Jelinek, & Dewald, 2002; Kini, Kay, & Peterson, 2000). Increased vascular endothelial growth factor (VEGF) levels of 7.4 times normal have been measured and shown to be utilized by B-CLL cells for apoptosis resistance (Aguayo et al., 2000; Chen et al., 2000). B-CLL cells also secrete VEGF and may use an autocrine pathway to increase resistance.

Current evidence suggests an accrual of these immune defects with increasing stage of disease (Bartik et al., 1998). Progress in the understanding of the complex nature of the immune system dysregulation in B-CLL is leading researchers to new strategies in management and treatment therapies.

**Staging Systems**

Unlike most other leukemias, B-CLL has been long known to be a heterogeneous disorder with some patients having a long indolent course ("smoldering" B-CLL) and others with an aggressive rapidly progressive one. One third of patients never require treatment and die of other causes, another third has an indolent phase that then becomes progressive requiring treatment; and the remaining third has aggressive disease at the outset requiring treatment. This heterogeneity has lead to the development of two staging systems to classify patients into groups
to determine those that may benefit from immediate treatment. Patients are typically staged by oncologists upon initial diagnosis then restaged with progression.

The most frequently used staging system by oncologists in the US is by Rai et al. (1975) and defines five stages, whereas the system by Binet et al. (1981) is generally used in Europe and has three stages, see Table 3 for comparison. Both systems have been prospectively validated and are straightforward to use. Rai reorganized his system in 1987 into three categories, low risk (stage 0), intermediate risk (stage I and II) and high risk (stage III and IV). Use of this revised system is advocated by the NCI-WG, however the original system still predominates in general practice in the US today.

The systems reliably identify progressive disease, which is used in determining initiation of treatment and prognosis. However, neither system enables physicians to predict which patients in the early stages will likely progress. They fail to consider indicators such as age or newer genetic or molecular markers as prognostic features. These newer indicators may change treatment decisions for patients with early disease but with poor prognostic factors. Without consideration of these newer factors patients with more indolent disease may be over treated based on staging while those with early disease but with aggressive characteristics may be delayed or under treated (Guarini et al., 2003).

Newer Prognostic Markers

Research utilizing molecular testing and cytogenetic techniques has enabled oncologists to identify sub-types of B-CLL each with a different clinical course (Dohner et al., 2000; Juliusson & Merup, 1998). Through this genetic research, specialty tests have been developed to aid oncologists in determining those patients who have poor prognostic indicators that may benefit from closer monitoring or more aggressive treatment.
Through complex processes of gene splicing on the Ig light and heavy chains (IgV_H genes) during normal B lymphocyte maturation in the lymph node a unique B cell signature is created. Additional B cell somatic hypermutation takes place in the presence of T cells and antigen presenting cells in the germinal center to better refine antibody structure before the cell leaves to circulate as a B-memory cell or to mature to a plasma cell. B-CLL subtypes that lack somatic mutation (unmutated type) have been associated with a poorer prognosis and a median survival of 8 years as compared to the mutated type who have acquired somatic mutations and have a median survival of 25 years (Hamblin, Davis, Gardiner, Oscie, & Stevenson, 1999; Naylor & Capra, 1999). In most decades of life the more indolent mutated type is twice as common as the unmutated type except in the over 80 years age group perhaps because incidental blood tests are less common (Hamblin, 2003).

Determination of mutation status of IgV_H genes is not currently widely available by routine testing methods. However, it has been shown that testing for CD38 co-expression on B-CLL cells using FCM can be another good prognostic indicator of the disease and is routinely used (Ibrahim et al., 2001). Three subsets of expression of CD38 have been identified as homogenously CD38+, homogenously CD38-, and a bimodal group that show concomitant presence of two populations of cells some with CD38 positivity and some without. The CD38-subset show the best survival advantage of more than 15 years while the CD38+ and bimodal group having a median survival of 183 months and 156 months respectively (Ghia et al., 2003).

There is no specific cytogenetic karyotype abnormality associated with B-CLL and patients can have a variety of deletions. Survival is generally longer in those with normal karyotype (> 15 years) as compared with those with abnormal cytogenetics (clonal abnormalities 7.7 years), and those with diploid karyotypes showing improved survival over those with clonal
abnormalities (Dohner et al., 2000; Hamblin, 2003). Thirty to fifty percent of patients have detectable abnormalities, most on chromosomes 12 and 14. Deletion 13q14 is the most common deletion and is associated with the mutated subset, carrying a better prognosis. Deletions at 11q23, 17p12 and trisomy 12 are generally associated with the unmutated subset and carry a poorer prognosis. The 17p12 have a median survival of less than 2 years (Hamlin, 2003; Juliusson & Merup, 1998). In addition to traditional cytogenetics, fluorescence in situ hybridization (FISH) techniques have been developed to detect B-CLL associated cytogenetic abnormalities (i.e. CLL by FISH). While traditional cytogenetics is usually performed on bone marrow, FISH can be performed on peripheral blood and is generally available.

**Younger Patients**

Younger patients with B-CLL (less than 55 years) have not been found to have more aggressive disease and survival is the same as older age groups. However they are more likely to die of their disease (98%) compared with old patients (72%) who are more likely to die of comorbidities. The proportion of deaths due to direct progression of disease is reported as larger in younger patients than old (85% vs. 49% respectively) in one Italian study (Mauro et al., 1999) and again is most likely related to more comorbidity in the elderly. There was no significant age-matched difference in second primary cancers between the groups but there was a significant difference in the incidence of Richter's syndrome between younger and older patients of 5.9% vs. 1.2% respectively in the same Italian study (Mauro et al., 1999).

These statistics are important when developing treatment strategies in the younger patient. Testing with newer prognostic indicators may be of greater importance particularly in the initial workup in this patient group who are more likely to die as a direct result of their disease.
Treatment Strategies

Though oncologists prescribe and manage treatment therapies, primary care providers may see patients for management of other conditions during or between treatments courses. A basic overview of treatment modalities currently in use as well as their associated risks and issues, will provide primary care providers with additional insight for co-management of these patients.

Strategies of when and how to treat B-CLL, currently is undergoing change. Therapy has consisted principally of systemic chemotherapy although radiation, surgery and immunotherapy all can play role in the management of B-CLL. The previous focus has been on palliative therapy as cure was rarely achieved (Deisseroth et al., 1997). Older studies showing no survival benefit to early treatment with alkylator based therapies has shaped current practice, which is to treat patients only with symptomatic progression or when presenting in advanced stages (CLL Trialists' Collaborative Group, 1999). Newer therapy modalities may now shift the focus to attaining more enduring remissions or even cure. The NCI-WG has established guidelines defining progression for initiation of treatment as presented in Table 4 (Cheson et al., 1996).

Oncological practice and studies utilize specific terminology to describe response to treatment. Further, oncology groups define these responses using disease specific standardized parameters, thus enhancing study comparability. Terms typically used to describe a response to treatment are: complete response (CR), usually defined as complete resolution of the disease for a minimum specified amount of time; partial response (PR), partial resolution of disease; and overall response (OR), the number of partial and complete responses combined in a study. The NCI-WG has defined the parameters for response to treatment for use in B-CLL studies and clinical practice (Cheson et al., 1996).
Numerous systemic therapies are used in the treatment of B-CLL. Chlorambucil is a well-tolerated, long used, alkylator based oral medication whose efficacy was validated by the pivotal French Cooperative Group on Chronic Lymphocytic Leukemia study (1990). Chlorambucil is the least expensive therapy used and is administered as a pulse or continuous therapy. It is effective at achieving cytoreduction and its emetogenic potential is low, but myelosuppression is the principle dose limiting side effect. Use continues in the elderly population, particularly in those who have significant comorbidities that may preclude the use of other systemic chemotherapy. Purine analogs principally fludarabine are used when there is a failure to respond to alkylator therapy and may now be the best first line therapy. Several studies have shown a higher CR rate of 10-30% and prolongation of progression-free survival with fludarabine as compared with chlorambucil or older combination therapy with cyclophosphamide, doxorubicin, prednisone (Johnson et al., 1996; Pott & Hiddemann, 1997; Rai et al., 2000). Although an overall survival advantage has not yet been demonstrated with fludarabine, a quality of life advantage has been shown by the French CLL Cooperative Group (Levy et al., 2001). Fludarabine is an intravenous therapy, also with low emetogenic potential, however myelosuppression and infection again remain the primary risks to therapy with an increased incidence of herpesvirus infections.

FDA approval of the use of monoclonal antibody therapies alone or in combination with other therapies has expanded the treatment options for B-CLL. Humanized anti-CD52 antibody, alemtuzumab (Campath), has shown effectiveness in eliminating mature B and T lymphocytes from the blood, marrow and spleen in patients with fludarabine refractory disease. Nodal sites are less responsive. A pivotal trial showed a 33% response although only 2% achieved a CR (Keating et al., 2002). Common toxicities are a self-limited cytokine release syndrome (febrile reactions and chills, often including rigors), prolonged immunosuppression and neutropenia,
resulting in opportunistic infections and cytomegalovirus reactivation. Antibiotic prophylaxis is generally included with therapy. More recent trials have administered alemtuzumab subcutaneously rather than intravenous with marked reduction in febrile reactions and showing an overall response (OR) rate of 75% and CR of 20% in previously untreated patients (Lundin et al., 2002). However local skin reactions are seen in 90% of patients.

Rituximab (Rituxan) is a chimeric CD 20 antibody, which has shown effectiveness in cytoreduction but has a low complete response rate as a single agent. As B-CLL has weak expression of CD 20, some trials have employed higher or more frequent dosing of rituximab than has been traditionally used with non-Hodgkin’s lymphoma with some increase in overall response. It is generally well tolerated with minimal side effects and minor myelosuppression. Occasionally a hypersensitivity reaction can occur with the initial intravenous infusion that is managed with diphenhydramine (Benadryl) and dexamethasone. Testing for CD 20 must be performed prior to rituximab therapy as it may block detection for a prolonged period (sometimes months). Rituximab has been shown in vivo to down-regulate the anti-apoptotic proteins mcl-1 and XIAP expression in B-CLL cells perhaps enhancing response to fludarabine based therapy (Byrd, Kitada, et al., 2002).

Newer strategies with combination therapies hold new promise for sustained remission in B-CLL. Two recent phase II trials combining fludarabine, cyclophosphamide (intravenous), with concurrent rituximab in previously untreated patients have found significantly higher OR rates (90-95%) and CR rates (47-70%) than have been seen for treatments in the past (Byrd, Lucas, Farag, & Lin, 2003; Byrd, Peterson, et al., 2003). Interestingly, fifty percent of the CR patients had no detectable residual disease, becoming negative for the IgV\textsubscript{H} gene rearrangement, using sensitive polymerase chain reaction techniques. Also most achieved a complete remission as
determined by FCM with CD5 + CD 19 coexpression < 1% (Keating, 2003). Grade 3 and 4
neutropenia in 74% of patients is the main toxicity to be managed, and there is increased
emetogenic potential and alopecia with this regime. Although long term studies are needed to
establish improvement in survival, the current trend is for use of this treatment particularly in
younger patients with poor prognostic factors and for salvage therapy as it has shown promise
with a 25% CR and 80% OR.

Other newer agents are also under investigation that may make a curative approach more
attainable in the future. New purine and guanosine analogues, Bcl 2 antisense, proteasome
inhibitors, and new monoclonal antibodies are but a few under study. All, like previous
treatments, are associated with an increase risk of infection particularly herpesvirus,
cytomegalovirus and Pneumocystis carinii pneumonia (PCP) (Keating, 2003).

Allogeneic and autologous transplantation have shown good response rates in B-CLL
(Dreger et al., 1998; van Besien, Keralavarma, Devine, & Stock, 2001). Conventional and
nonablative (so called minitransplant) allogeneic approaches have shown the best responses of
70-90% in selected patients although studies are few and small (Esteve, Villamor, & Colomer,
2001). As B-CLL is primarily a disease of the elderly and can have a long indolent course, few
are candidates for this approach due to age or comorbidities. Also, the one year morbidity
remains high at 10-15% even for the allogeneic minitransplants. Consequently, those primarily
targeted are younger patients with genetic abnormalities at high risk for rapid relapse and is
recommended by some investigators to be performed during the first remission (Byrd, Lucas, et
al., 2003).
Supportive Care

Medical management.

Supportive medical care for patients with B-CLL involves management of bulky lymphadenopathy, organomegaly, chemotherapy side effects, cytopenias, infections, and autoimmune complications. Leukapheresis is used infrequently to manage high lymphocytosis but may be useful to reduce organomegaly and improve hemoglobin and platelet counts temporarily in those with refractory disease (Marti, Folks, Longo, & Klein, 1983). Splenectomy may be performed for pain reduction, and can improve cytopenias in advanced disease and in refractory autoimmune complications (Coad, Matutes, & Catovsky, 1993). Localized radiation therapy is generally reserved for reduction of nodal masses associated with organ compromise, nerve impingement, disfigurement, or painful bone lesions. Occasionally the spleen is irradiated for palliative pain reduction.

Hydration and short term allopurinol prophylaxis is often used with any of the systemic treatments to minimize uricemia resulting from tumor lysis syndrome, particularly in those patients with high white counts and bulky disease. Anemia can develop or be further exacerbated with chemotherapy treatment causing fatigue and dyspnea, greatly impacting patient quality of life and social function. Use of the recombinant erythropoietins, epoetin alpha and the newer darbepoetin alpha, both have shown utility in managing anemia in B-CLL patients with improved hematocrit and quality of life, reducing the need and associated risk of transfusion (Osterborg et al., 2002; Pangalis, Poziopoulos, Angelopoulou, Siakantaris, & Panayiotidis, 1995). Granulocyte colony stimulating factor or filgrastim (Neupogen) is also sometimes used in the treatment setting to decrease the time of chemotherapy induced neutropenia.
Infection control is imperative in the management of B-CLL. However, antibiotic prophylaxis is generally limited to targeting PCP or herpesvirus during and up to six months post myelosuppressive therapy. Trimethoprim/sulfamethoxazole or equivalent and acyclovir or equivalent, respectively are used. Evidence for the use of prophylactic antibiotics outside the treatment setting is lacking (Byrd, Lucas, et al., 2003). Patients in advanced stage disease often respond poorly to routine antibiotic therapy needing longer duration of treatment. Nonviable vaccines such as pneumococcal and influenza can be given and may carry some benefit particularly if given in earlier stage disease and are therefore usually recommended.

Immunoglobulin (IVIG) replacement therapy is occasionally employed in patients with severe hypogammaglobulinemia with recurrent life-threatening infections. It is usually administered at 250-400 mg/kg every three to four weeks. Studies using prophylactic IVIG therapy have shown a reduction in the number of moderate infections but no reduction in life-threatening infections, consequently it is not routinely used especially in light of its high cost (Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia, 1988).

Management of autoimmune complications begins with early detection. New fatigue or bleeding, splenomegaly, jaundice, rapidly declining hemoglobin or platelet counts, generally without signs of B-CLL progression is suspicious of a new or recurrent autoimmune disorder. Increased reticulocyte count, positive direct antiglobulin test (Coombs), elevated LDH, indirect bilirubin and haptoglobin along with microspherocytosis and polychromasia on the peripheral smear are the hallmarks of AIHA. The antierythrocyte autoantibody is most often an IgG warm antibody although can be an IgM with a frequency of 87% and 13% respectively in one study (Mauro et al., 2000). Mauro et al. (2000) also showed an increased frequency of AIHA at diagnosis in males, those over 65 years, and those with a lymphocyte count greater than $60 \times 10^9$
per liter. With ITP, giant platelets are seen on the peripheral smear, and there are adequate
marrow megakaryocytes on biopsy. Frequently there is minimal bleeding or petechiae present
for the degree of thrombocytopenia, although severe or chronic thrombocytopenia can result in
melena and secondary iron deficiency anemia.

Initial therapy for either AIHA or ITP consists of prednisone usually at 1 mg/kg/d which
is then tapered slowly upon response, sometimes requiring a maintenance dose (Diehl &
Ketchum, 1998). There is a 90% OR and 65% CR with most patients responding in 3-5 days.
There is however a 60% relapse rate with treatment cessation. Red cell transfusions for AIHA
are avoided and must be managed by the hematologist/oncologist. They are only advised when
the anemia is very severe and or the patient has significant cardiac risk factors, as these patients
are difficult to cross-match and incompatible blood may have to be given. Also, transfused blood
will survive similarly to the patient’s own cells and may exacerbate complications (Linker,
2003). Patients refractory to or intolerant of corticosteroid therapy are offered IVIG,
cyclosporine, danazol (more effective in ITP), and more recently rituximab therapy with varying
but sometimes good result (Byrd, Lucas, et al., 2003; Grupta et al., 2002). Splenectomy is often
effective but generally used as a last resort, as symptoms can recur as with other treatments
(Coad et al., 1993). The NCI-WG guidelines for treatment include uncontrolled autoimmune
complication as an indication for treatment of B-CLL and this is approach is effective in some
patients’ refractory to other treatments.

Psychological issues.

The psychosocial issues for patients and their families living with a diagnosis of leukemia
can be profound. Depression, feelings of uncertainty or loss, dependency, or disfigurement,
coupled with financial issues related to disability, employability, or treatment can impact quality
of life particularly in younger patients (Hays & McCartney, 1998). Cancer patients continue to struggle with issues of insurability, discrimination in the workplace and can suffer from feelings of “job lock.” Family members also encounter many stressors, in balancing work and family roles with the additional caregiver role particularly during treatment and at end of life. A multidisciplinary approach is necessary to address the complexity of problems that often accompany a chronic illness such as this. Providing patient education, referral for individual or family counseling, social work, as well as pharmacological support and hospice may be needed at different junctures in the disease process (Hardwick & Lawson, 1995). Linking patients and families to local chapters of the Leukemia & Lymphoma Society and the American Cancer Society as well as hospital based support groups and websites, can provide peer and caregiver support as well as access to services. Assessment of family adaptation and coping to chronic disease as well as frank discussions by providers is necessary to help families make treatment decisions that best meet their quality of life goals (Bertero, Eriksson, & Ek, 1997; Stetz, Lewis, & Houck, 1994).

Summary and Implications for Primary Care

The role of primary care in the management of patients with B-CLL is not only in the initial detection but also in the awareness of and ongoing surveillance for complications specific to this disease. Initial laboratory work up for persistent lymphocytosis should include complete blood count (CBC) with manual differential, chemistry panel and flow cytometry to make the presumptive diagnosis of B-CLL. Referral to a hematologist/oncologist is needed for confirmation of diagnosis, staging (may include bone marrow biopsy), and treatment planning. Early stage asymptomatic or minimally symptomatic patients are then usually followed with periodic CBCs and physical examinations every three to six months until signs of progression or
complications are evident. Progression includes a lymphocyte count doubling time of less than one year; new or symptomatic lymphadenopathy or organomegaly; or new non-immune based anemia or thrombocytopenia.

The majority of management during the “watchful waiting” period including emotional support and surveillance for complications/progression is performed by primary care. Primary care providers should promote primary and secondary prevention strategies with this population to reduce the incidence of and morbidity from secondary complications. This can be accomplished by screening for up to date tetanus/diphtheria toxoid immunization status, promoting vaccination to pneumococcus and influenza, as well as for providing general cancer prevention education (i.e. sunscreen use, smoking cessation, etc.). It is important to encourage patients, particularly those with smoldering or early stage B-CLL not regularly seen by an oncologist, to adhere to routine cancer screening guidelines and recommendations (e.g. occult blood testing, colonoscopy, mammograms, skin examination, etc) for early detection of secondary malignancies. Ongoing mental health screening is vital to determine individual and family coping with the difficult issues often associated with living with cancer. Reinforcement of good nutrition and hygiene practices as well as thoughtful management of concurrent medical conditions is also needed. Aggressive therapeutic management and follow up of infectious and other complications is often necessary once they occur, and may require co-management by other specialties such as infectious disease, oncology, dermatology, surgical services, and mental health, among others.

A diagnosis of B-CLL frequently results in emotional anxiety for patients and their families. As most patients do not present with emergent issues requiring immediate specialty referral as with other leukemias, it may be weeks before an evaluation is performed by an
oncologist and links to support provided. In the interim families often turn to their primary care provider, whom they already have an established relationship and trust, to provide that initial support and obtain general information. Primary care has a vital role in providing this support initially and throughout the disease process as they frequently have more patient contact than specialty care over its long course particularly when diagnosed at an early stage. Comprehensive joint management of B-CLL by primary care and specialty care is crucial to providing the best quality of life and overall outcomes for these patients.
References


Table 1. Lymphocyte Markers in B-CLL and Similar Diseases.

<table>
<thead>
<tr>
<th>Marker</th>
<th>B-CLL</th>
<th>MCL</th>
<th>SMZL</th>
<th>B-CLL/PLL</th>
<th>B-PLL</th>
<th>T-PLL</th>
<th>Follicular Lymphoma</th>
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</thead>
<tbody>
<tr>
<td>CD3</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>CD5</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>80% negative</td>
<td>20% positive</td>
<td>Positive</td>
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<tr>
<td>CD 10</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>CD19</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>CD20</td>
<td>Weak</td>
<td>Positive</td>
<td>Positive</td>
<td>Weak</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>CD 22</td>
<td>Weak or negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Weak or positive</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>CD23</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>CD79b</td>
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<td>Positive</td>
<td>Weak or negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>FMC7</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>Surface Ig</td>
<td>Weak</td>
<td>Positive</td>
<td>Positive</td>
<td>Weak</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Note. B-CLL = B-chronic lymphocytic leukemia; MCL = mantle cell lymphoma; SMZL = splenic marginal zone lymphoma; B-CLL/PLL = B chronic lymphocytic leukemia/prolymphocytic leukemia; B-PLL = B prolymphocytic leukemia; T-PLL = T prolymphocytic leukemia.
### Table 2. Causes of Lymphocytosis.

#### I. High lymphocytosis (>\(15 \times 10^9\) per liter)

- **Infectious**
  - Infectious mononucleosis
  - Pertussis
  - Acute infectious lymphocytosis

- **Neoplastic**
  - **Most common**
    - B-chronic lymphocytic leukemia (B-CLL)
    - Acute lymphocytic leukemias (ALL)
  - **Less common**
    - Mantle cell lymphoma (MCL)
    - Splenic marginal zone lymphoma (SMZL)
    - B-prolymphocytic leukemia (B-PLL)
    - T-prolymphocytic leukemia (T-PLL) or Sézary syndrome
    - Mixed B-CLL/PLL

#### II. Moderate lymphocytosis (<\(15 \times 10^9\) per liter)

- **Viral infections**
  - Infectious mononucleosis: Measles
  - Varicella: Hepatitis
  - Coxsackie: Adenovirus
  - Mumps: Cytomegalovirus
  - HTLV-1 (adult T cell lymphoma/leukemia)
Other infectious diseases

Toxoplasmosis
Tuberculosis
Syphilis (secondary)

Other disorders

Graves’ disease
Drug reactions (i.e., phenytoin, para-aminosalicylic acid)

Inflammatory disorders

Autoimmune syndromes

Neoplastic disorders

B-CLL (early phase) as well as the other neoplastic disorders listed in section I.
Follicular lymphoma, leukemic phase
Carcinoma
Hodgkin’s disease
Plasma cell leukemias

Table 3. Comparison of Binet and Rai Staging Systems.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Disease Parameters</th>
<th>[Lymphocytosis (blood and marrow)]</th>
<th>[Lymphadenopathy]</th>
<th>[Hepatomegaly or Splenomegaly]</th>
<th>[Hemoglobin (g/dL)]</th>
<th>[Platelets (x 10^9/L)]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rai System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>≥11</td>
<td>≥100</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>≥11</td>
<td>≥100</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Positive</td>
<td>Positive or negative</td>
<td>Positive</td>
<td>≥11</td>
<td>≥100</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Positive</td>
<td>Positive or negative</td>
<td>Positive or Negative</td>
<td>&lt;11</td>
<td>≥100</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Positive</td>
<td>Positive or negative</td>
<td>Positive or Negative</td>
<td>Any</td>
<td>≤100</td>
<td></td>
</tr>
<tr>
<td><strong>Binet System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Positive</td>
<td>&lt;3 areas enlarged*</td>
<td>Positive or Negative</td>
<td>≥10</td>
<td>≥100</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Positive</td>
<td>≥3 areas enlarged*</td>
<td>Positive or Negative</td>
<td>≥10</td>
<td>≥100</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Positive</td>
<td>Positive or negative</td>
<td>Positive or Negative</td>
<td>&lt;10</td>
<td>&lt;100</td>
<td></td>
</tr>
</tbody>
</table>

* Adenopathy > 1 cm in diameter palpable enlargement. Each considered one area whether unilateral or bilateral: head and neck; axillary; inguino-femoral; palpable spleen; palpable liver (clinically enlarged).

Table 4. NCI-WG Guidelines for Initiation of Treatment.

1. Any one of the following disease-related symptoms must be present.
   a. Weight loss ≥ 10% within the previous 6 months.
   b. Extreme fatigue (i.e., Eastern Cooperative Oncology Group Performance Standard (ECOG PS) of 2 or worse; unable to work or perform usual activities)
   c. Fevers of > than 100.5°F for ≥ 2 weeks without evidence of infection.
   d. Night sweats without evidence of infection.

2. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia.

3. Autoimmune anemia and/or thrombocytopenia poorly responsive to corticosteroid therapy.

4. Massive (i.e., > 6 cm below the left costal margin) or progressive splenomegaly.

5. Massive nodes or clusters (i.e., > 10 cm in longest diameter) or progressive lymphadenopathy.

6. Progressive lymphocytosis with an increase of > 50% over a 2-month period, or an anticipated doubling time of less than 6 months.

7. Marked hypogammaglobulinemia or the development of a monoclonal protein in the absence of any of the above criteria for active disease is not sufficient for protocol therapy.