XV CHRONIC LYMPHOID LEUKEMIAS AND PLASMA CELL DISORDERS

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The chronic lymphoid leukemias are a group of generally indolent B cell malignancies that include chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HCL), and large granular lymphocyte (LGL) leukemia. The plasma cell disorders are a group of disorders generally characterized by the presence of circulating paraproteins and/or accumulation of clonal plasma cells in the bone marrow, bones, or soft tissues. Plasma cell disorders include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, solitary extramedullary plasmacytoma, Waldenström macroglobulinemia (WM), and amyloidosis.

Chronic Lymphocytic Leukemia

EPIDEMIOLOGY

CLL is the most common form of leukemia in most Western countries.[1,2] CLL affects approximately three to five individuals per 100,000, with 10,000 to 15,000 newly diagnosed cases each year in the United States.[2,3] The male-to-female ratio is approximately 2:1, and the median age at the time of diagnosis is approximately 63.[4] Roughly 20 to 30% of patients are under the age of 60 and 10% are under the age of 50. The disease appears to occur with equal frequency in blacks and whites but is uncommon in individuals of Asian decent.

ETIOLOGY AND GENETICS

The etiology of CLL is unknown. To date, studies have failed to identify a specific genetic or environmental factor (chemical exposure, radiation) that increases disease risk. Nonetheless, approximately 10% of patients with CLL have a family history of lymphoid malignancy, with one or more first-degree relatives affected by CLL or another B cell lymphoproliferative disorder (i.e., non-Hodgkin lymphoma, Hodgkin disease). This observation implies a genetic basis for CLL in at least some cases, and large-scale genetic analysis of individuals with familial CLL is ongoing (patients with a family history should be directed to the National Cancer Institute [NCI] familial CLL telephone referral line: 800-518-8474).

Recent studies have suggested that CLL may also have a precursor state. In the late 1990s, investigators from the Centers for Disease Control and Prevention (CDC) found a B cell clone phenotypically similar to CLL in approximately 1% of individuals in population studies.[5] The presence of such a clone has been termed monoclonal B cell lymphocytosis (MBL). More recent work using highly sensitive assessment techniques suggests that MBL may be present in up to 3.5% of individuals over the age of 40 and 13.5% of first-degree relatives of patients with CLL.[6,7] Although all individuals who develop CLL appear to have preexisting MBL,[8] the majority of patients with MBL will not develop a B cell malignancy. Among individuals with MBL who come to clinical attention as a result of slight elevations in the lymphocyte count, approximately 1% per year will progress to require treatment for CLL.[9,10] Consensus recommendations for the evaluation and management of patients with MBL have been published.[11,12]

PATHOGENESIS

CLL is characterized by a clonal expansion of B lymphocytes, which accumulate in the bone marrow, lymph nodes, and circulatory system. These cells are morphologically similar to mature lymphocytes, with clumped chromatin and scant cytoplasm; however, unlike normal B cells, they express CD5. CLL B cells accumulate as a result of both defects in their ability to undergo apoptotic cell death[13] and increased leukemic cell proliferation,[14] abnormalities likely, in part, perpetuated through interactions between the leukemic cell and its microenvironment.[15]

DIAGNOSIS

Clinical Presentations

Prior to the advent of automated blood counters, CLL was typically diagnosed at a more advanced disease stage when patients presented with lymphadenopathy, hepatosplenomegaly, cytopenias (anemia, thrombocytopenia), or B symptoms (fatigue, drenching night sweats, unintentional weight loss). In the modern era, 70 to 80% of patients with CLL are diagnosed incidentally when a complete blood count (CBC) obtained for other purposes demonstrates an elevation in the absolute lymphocyte count (ALC). Although such patients should undergo thorough examination of the lymphatic system (cervical, supraclavicular, axillary, and inguinal nodes) and be assessed for hepatosplenomegaly, the overwhelming majority of such patients have no abnormalities on physical examination. Rarely, patients present with other disease-related complications, such as recurrent infections or autoimmune cytopenias (discussed below).

LABORATORY TESTS

The diagnosis of CLL is considered when the B cell count is 5×10^9/L or greater.[16] It is critical to note that lymphocytosis is not always attributable to CLL. One study of 280 consecutive patients with an ALC over 5,000/μL on at least two occasions found that 51.4% experienced a spontaneous resolution, 30.4% had CLL, 7.5% had another malignant lymphoid disorder, 1.1% had hepatitis C, 0.4% had MGUS, and 9.3% had no specific diagnosis.[2]

Lymphocyte immunophenotyping by flow cytometry can distinguish between malignant (clonal) and nonmalignant (nonclonal) causes of lymphocytosis and eliminates the need to rely on the duration or magnitude of the lymphocyte count elevation to differentiate CLL and other lymphoproliferative disorders from reactive causes lymphocytosis. The diagnosis of CLL is made when the B cell count is 5×10^9/L

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or greater and a monoclonal B cell population with the characteristic phenotype (membrane coexpression of CD19, CD20[dim], CD23, CD5, and dim surface immunoglobulin) is present.[16] Patients with a B cell count less than 5×10^9/L and without evidence of lymphadenopathy or hepatosplenomegaly should be classified as MBL. Those with a B cell count less than 5×10^9/L but who do have lymphadenopathy or hepatosplenomegaly should be considered to have the small lymphocytic lymphoma (SLL) variant of CLL.[13] Although previous classification systems distinguished between CLL and SLL, they are now considered a single entity in the current World Health Organization (WHO) classification system and should be managed in the same fashion.[17] Immunophenotyping can also distinguish between CLL and many other lymphoproliferative disorders [*see Table 1*].

Although a bone marrow biopsy is recommended prior to initiating treatment and can be helpful in evaluating the cause of anemia or thrombocytopenia in patients with CLL, it is not necessary for diagnostic purposes. No routine imaging (i.e., computed tomographic [CT] scans) is recommended at the time of CLL diagnosis.

STAGING AND PROGNOSTIC FEATURES

Staging

It has long been recognized that some patients with newly diagnosed CLL require immediate treatment and have a survival of only 1 to 2 years, whereas others live for decades without requiring therapy. Prognostic tools help predict patient outcomes, identify individuals who may benefit from different management strategies, and provide patients with useful information to help plan their lives. For over three decades, clinical staging systems based on physical examination findings and the results of a CBC have proved to be powerful prognostic tools that stratify individuals with widely different treatment-free and overall survival. The Rai staging system has been the most widely used clinical staging system in North America and predicts both time to treatment and overall survival. The original five-stage Rai system (0 to IV) was later revised to a three-tier system that classifies patients into low (isolated lymphocytosis), intermediate (lymphocytosis with presence of lymphadenopathy and/or splenomegaly), or high (lymphocytosis with the presence of anemia [hemoglobin < 11 g/dL] or thrombocytopenia [platelet count < 100×10^9/L]) risk categories.[18] The treatmentfree and overall survival for the 1,474 patients in the Mayo Clinic CLL database diagnosed with CLL since January 1, 1995, are shown in Figure 1.

Prognostic Parameters

Despite the continued value of clinical staging, several changes in the natural history of CLL over the last several decades have created a need for additional prognostic tools.[19] As discussed above, 70 to 80% of patients who are now diagnosed with CLL are discovered incidentally and fall into the Rai low-risk category. It has been recognized that, patients with Rai low-risk disease have widely different experiences, with 40 to 50% of patients having an aggressive disease course with early clinical progression and the remaining 50 to 60% of patients experiencing a much more indolent disease course.[20]

Recognition of these facts has led to intense efforts to identify additional prognostic parameters that are able to substratify patients in the Rai low-risk category. A number of molecular characteristics of the leukemic cells have been found to predict the rapidity of disease progression, need for treatment, and overall survival. To date, the best established factors to predict progression among Rai low-risk patients include immunoglobulin variable region heavy chain (*IGHV*) gene mutation status, cytogenetic abnormalities as assessed by fluorescence in situ hybridization (FISH), and leukemic cell expression of CD38 and ZAP-70.[19] Although there is some correlation between *IGHV* gene mutation, CD38, and ZAP-70 status, it is not absolute. Whereas *IGHV* mutation status is not yet widely available in clinical practice, the remaining tests can be obtained through most clinical or reference laboratories. Despite the availability of the ZAP-70 assay, the interlaboratory reproducibility of this assay has been poor. Only ZAP-70 assays performed at laboratories that perform rigorous external standardization and, preferably, those that can demonstrate results correlate with actual clinical outcomes can be interpreted. Very few of the clinical laboratories performing ZAP-70 assays at the present time fulfill these criteria. How to optimally integrate multiple independent parameters into a

Table 1 Distinguishing Between CLL and Other B Cell Lymphoproliferative Disorders Using Immunophenotyping

Lymphoproliferative Disorder	*CD5*	*CD19*	*CD20*	*CD23*	*CD10*	*CD103*	*CD11c/22*	*Surface Immunoglobulin*
CLL	+	+	+ (dim)	+	–	–	–	+ (dim)
Mantle cell lymphoma	+	+	+ (bright)	– (or dim)	–	–	–	+ (bright)
Lymphoplasmacytic lymphoma	– (rare +)	+	+	+/–	–	–	–	+ (dim)
Marginal zone lymphoma (nodal or splenic)	–	+	+ (bright)	–	–	–	–	+
Hairy cell leukemia	–	+ (bright)	+ (bright)	–	–	+	Bright	
B-PLL	– (most)	+	+	–	–	–	–	+ (bright)
Follicular lymphoma	–	+	+	+/–	+/–	–	–	+

B-PLL = B cell prolymphocytic leukemia; CLL = chronic lymphocytic leukemia.

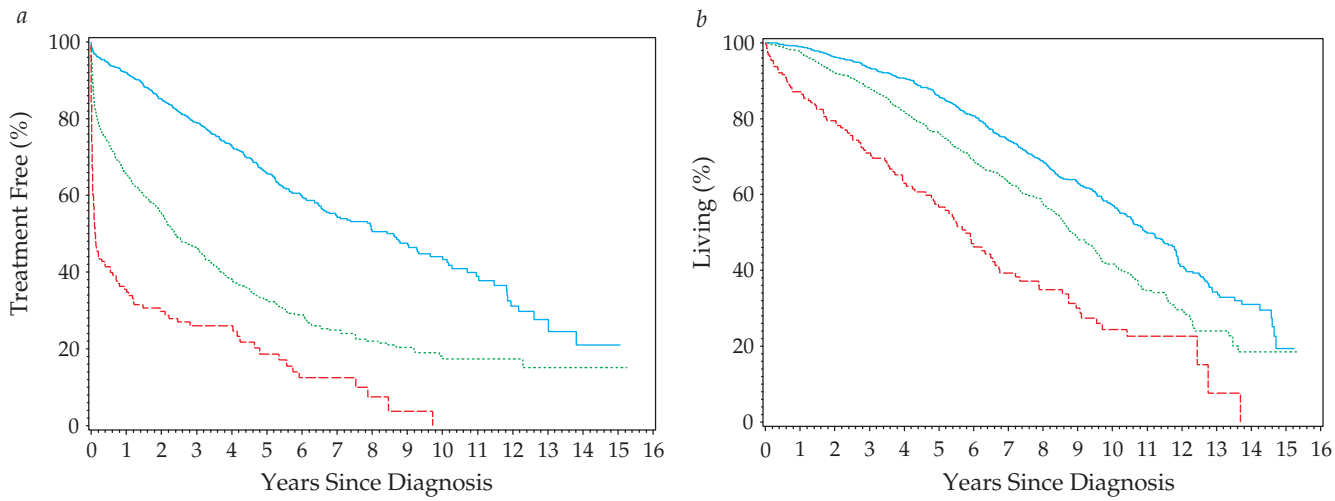

Figure 1 **Curves show the (*a*) treatment-free (n = 2,746) and (*b*) overall survival (n = 2,760) for patients in the Mayo Clinic chronic lymphocytic leukemia database diagnosed since January 1, 1995. p value < .001. Blue line = low Rai risk; green line = intermediate Rai risk; red line = high Rai risk.**

unified prognostic index is not yet established.[19] The time from diagnosis to disease progression requiring treatment for CLL patients in the Mayo Clinic CLL database based on *IGHV* mutation, ZAP-70, and CD38 status is shown in Figure 2. Overall survival for CLL patients based on these factors is shown in Figure 3. The utility of prognostic tools is influenced by patient age at diagnosis.[21]

Chromosome analysis by FISH also predicts patient survival. In a retrospective analysis of a heterogeneous patient population, many of whom had advanced-stage disease and were previously treated, Dohner and colleagues developed a hierarchical system that assigns patients to one of five categories with widely different median survival[22]:

- 17p$^-$ plus or minus any other abnormalities (median survival 2 to 5 years[22,23])
- 11q$^-$ plus or minus any other abnormalities except 17p$^-$ (median survival 7 to 9 years[22,23])
- Trisomy 12 plus or minus any other abnormalities except 17p$^-$ or 11q$^-$ (median survival 9 to 10 years[22,23])
- Normal karyotype (median survival > 9 years[22,23])
- 13q$^-$ as the only abnormality present (median survival > 11 years[22,23])

A subsequent prospective series of 159 untreated patients evaluated by FISH shortly after diagnosis (median 3 months) and then prospectively followed (median follow-up 10 years) confirmed the ability of the Dohner system to predict survival in newly diagnosed, early-stage patients.[23] In addition to its value as a prognostic factor, assessment of cytogenetic abnormalities by FISH has also been shown to be a predictive factor for progression-free survival (PFS) after fludarabine-based treatment regimens where the presence of 17p$^-$ or 11q$^-$ predicted shorter PFS (< 2 years).[19,24,25]

MANAGEMENT

Indications for Treatment

At the present time, CLL is an incurable illness with the possible exception of allogeneic stem cell transplantation. Accordingly, the goals of therapy are alleviation of disease-related symptoms, prolongation of life, and improvement in quality of life. Two randomized phase III trials conducted in the 1980s evaluated the effects of early treatment with alkylator-based chemotherapy (i.e., chlorambucil) compared with observation until the development of symptoms for asymptomatic, early-stage patients with CLL.[26] These trials found that early treatment had no effect on overall survival and one third of patients randomized to the observation group never required treatment. These trials established observation until the development of cytopenias or disease-related symptoms (often termed "watchful waiting") as the standard of care for patients who are asymptomatic or who have Rai low- and intermediate-risk CLL.

Consistent with this strategy, the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) and the NCI CLL Working Group established criteria specifying when therapy should be initiated for patients with CLL.[16,27] These criteria have been widely adopted and should be considered standard of care. According to these criteria, accepted indications for the initiation of therapy include

- Anemia (hemoglobin < 11 g/dL) attributable to CLL-induced marrow failure
- Thrombocytopenia (platelet count < 100 × 10^9/L) attributable to CLL-induced marrow failure
- Progressive or massive lymphadenopathy or splenomegaly
- B symptoms attributable to CLL
  - Fever higher than 38ºC (100.5ºF) for 2 weeks without infection
  - Unintended weight loss of 10% body weight or greater in the preceding 6 months
  - Drenching night sweats
  - Extreme fatigue (unable to work or perform usual activities because of CLL)
- Lymphocyte doubling time less than 6 months (or 50% increase in 2 months)

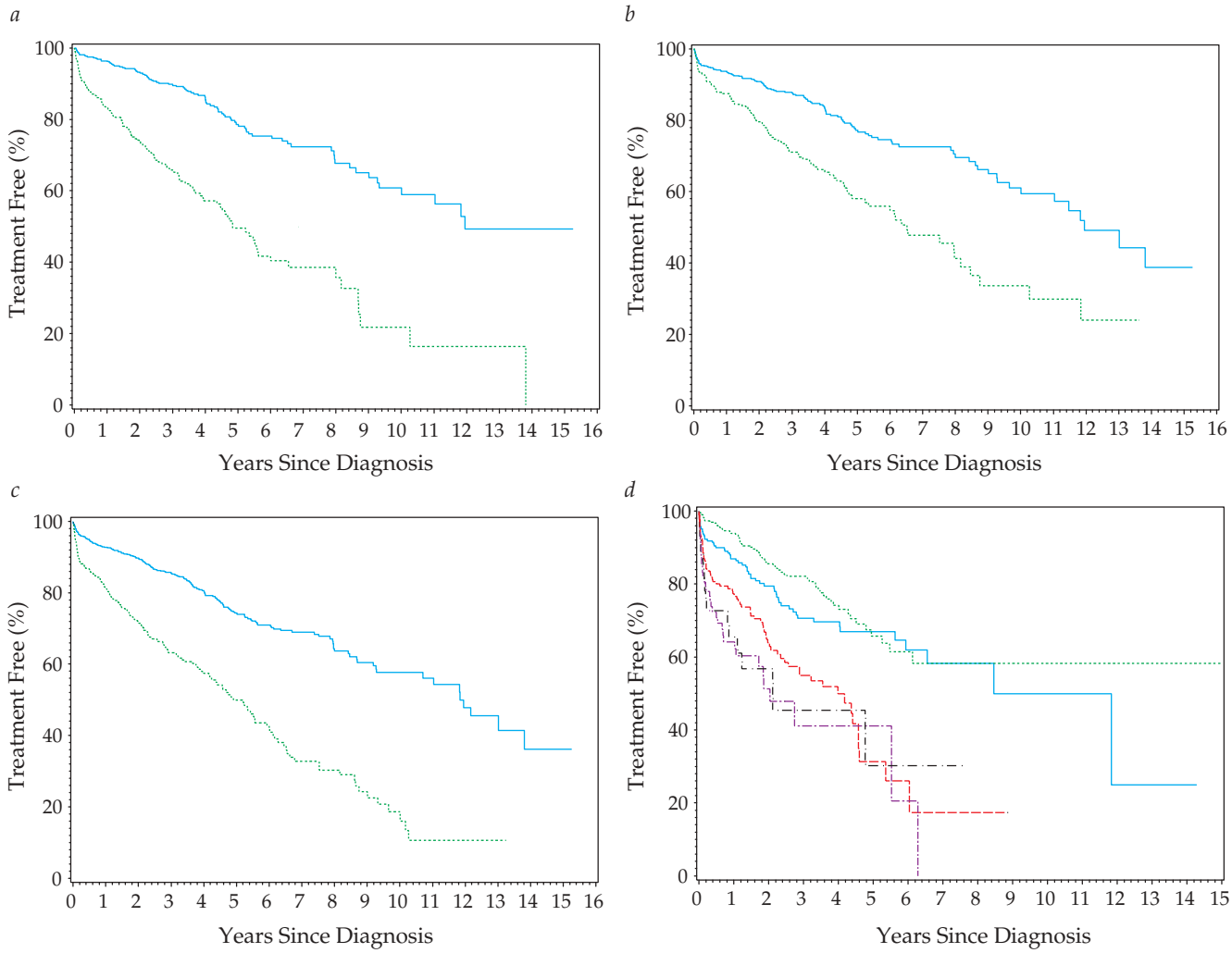

Figure 2 **Curves show the overall survival for patients in the Mayo Clinic chronic lymphocytic leukemia (CLL) database diagnosed since January 1, 1995, based on the results of (*a*) immunoglobulin variable region heavy chain (*IGHV*) gene mutation status (p value < .001; blue line = mutated; green line = unmutated); (*b*) ZAP-70 (p value < .001; blue line = negative; green line = positive); (*c*) CD38 (p value < .001; blue line = negative; green line = positive); and (*d*) chromosome analysis by fluorescence in situ hybridization (FISH) analysis (p value < .001; blue line = normal; green line = $13q^-$; red line = trisomy 12; purple line = 11q; black line = $17p^-$).**

No ALC or B cell count threshold in and of itself dictates that patients start treatment in the absence of the above findings. Other causes of fatigue (depression, comorbid illness, medication effects) and weight loss (other malignancy, gastrointestinal disease) should be excluded prior to initiating treatment based on these symptoms alone.

With the advent of more precise methods of risk stratification (FISH, *IGHV* mutation status, ZAP-70, CD38) and the development of more efficacious therapies (discussed below), there is renewed interest in evaluating the role of early treatment for selected, high–risk, early-stage patients. Randomized phase III trials testing this approach are currently under way in both Europe and North America. Until the results of these trials are available, treatment of asymptomatic and Rai low- or intermediate-risk patients based on the results of prognostic tests cannot be recommended.

First-Line Therapy

Historically, single–agent, alkylator-based therapy with oral chlorambucil was the treatment of choice for patients with CLL. Using the NCI criteria to evaluate response to treatment, this approach achieves a response in 30 to 40% of patients, although fewer than 5% achieve a complete response.[28] In the late 1980s, purine nucleoside analogues (PNAs; fludarabine, pentostatin, cladribine) demonstrated significant single-agent activity in patients with CLL refractory to alkylating agents. This led to three randomized phase III trials comparing single-agent fludarabine with a variety of alkylating agent–based treatment strategies, including single-agent chlorambucil, CAP (cyclophosphamide, Adriamycin [doxorubicin], prednisone), and CHOP (cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], prednisone).[28–30] All three trials found

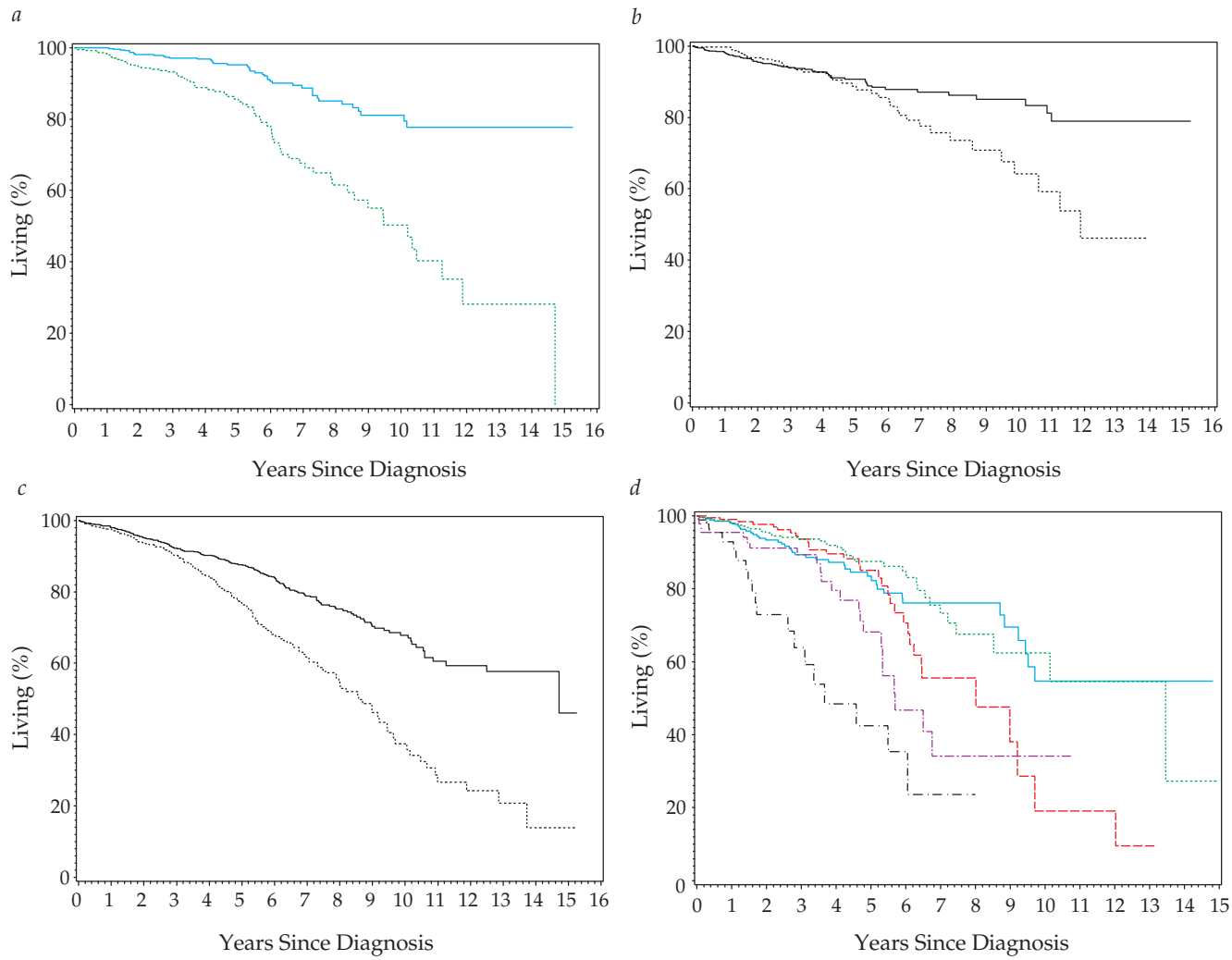

Figure 3 **Curves show the treatment–free survival for patients in the Mayo Clinic chronic lymphocytic leukemia (CLL) database diagnosed since January 1, 1995, based on the results of (*a*) immunoglobulin variable region heavy chain (*IGHV*) gene mutation status (p value < .001; blue line = mutated; green line = unmutated); (*b*) ZAP-70 (p value < .037; solid line = negative; dashed line = positive); (*c*) CD38 (p value < .001; solid line = negative; dashed line = positive); and (*d*) chromosome analysis by fluorescence in situ hybridization (FISH) analysis (p value < .001; blue line = normal; green line = 13q$^-$; red line = trisomy 12; purple line = 11q; black line = 17p$^-$).**

higher response rates and PFS for fludarabine-based treatment. Long-term follow-up from one of these trials also demonstrated that PNA-based treatment prolongs overall survival. A study of patient quality of life accompanying one of these trials found higher quality of life for fludarabine-treated patients.[24] Collectively, these data have made PNA-based treatment the preferred first-line treatment for CLL patients. The overall and complete response rates with single-agent fludarabine are approximately 70% and 10%, respectively.[28–32]

Three subsequent phase III trials compared single-agent fludarabine with combination therapy with fludarabine and cyclophosphamide (FC).[31–33] All three trials found higher overall and complete responses rates for combination therapy in addition to improved PFS. No improvement in overall survival has been observed to date, although long-term follow-up for these trials is not yet available. The FC combination achieves a response in approximately 80% of patients and a complete response in approximately 25%.[31–33]

Another recent advance in the treatment of CLL is the development of monoclonal antibodies targeting specific proteins on the surface of CLL B cells. Several trials have evaluated the efficacy of combining these immunologic therapies with chemotherapy (termed "chemoimmunotherapy"). To evaluate the benefit of adding the anti-CD20 monoclonal antibody rituximab to PNAs and alkylating agents, the German CLL Study Group conducted a randomized phase III trial comparing FC with fludarabine and cyclophosphamide plus rituximab (FCR). This study found higher overall (95% versus 88%) and complete remission (44% versus 22%) rates for the FCR combination as well as better PFS and overall survival.[34] These data confirmed the results of previous phase II studies[35] and established PNA- and

rituximab-based chemoimmunotherapy as the standard of care for patients with CLL requiring treatment. Multiple different PNA- and rituximab-based chemoimmunotherapy regimens have been developed, and the optimal approach for a given patient may depend on age and performance status.[36–40] Age, comorbidities, and life expectancy unrelated to CLL must all be taken into account when selecting the most appropriate therapy for an individual patient.[41] Our approach to selecting first-line therapy for patients with CLL is shown in Figure 4a.

Finally, although patients with 17p⁻ on FISH testing may respond to FCR or other chemoimmunotherapy regimens, the durability of response is short, with a median PFS of less than 12 months.[25] Because there is insufficient evidence that a specific alternative treatment strategy leads to superior survival for these individuals, patients with 17p⁻ should be referred for participation in clinical trials and considered for allogeneic stem cell transplantation if they are appropriate candidates (discussed below). Although less effective in individuals with bulky lymph nodes, the anti-CD52 monoclonal antibody alemtuzumab appears to be as efficacious in patients with 17p⁻ as those without this cytogenetic defect and may be an appropriate first-line treatment for patients with 17p⁻ who are unable or unwilling to participate in clinical trials.[42–44] High-dose methylprednisolone-based regimens also appear to be active for patients with 17p⁻.[45,46]

Treatment of Relapsed or Refractory Disease

Most patients treated for CLL eventually relapse and/or experience disease progression. Patients with an asymptomatic relapse (i.e., rising ALC) do not necessarily require therapy. Most experts favor using the same criteria for initiating salvage therapy as those used to initiate first-line treatment,[27] although salvage treatment should be instituted before the development of bulky lymph nodes (> 5 cm).

The type of first-line treatment received and the duration of benefit influence the choice of second-line therapy. Patients initially treated with a fludarabine or alkylating agent monotherapy should typically be salvaged with either an FCR or pentostatin, cyclophosphamide, and rituximab (PCR)-based combination regimen.[47,48] Additionally, patients who have a long disease-free interval (> 24 months) after first-line PCR or FCR may be retreated with the same regimen.

A variety of other agents, including bendamustine, alemtuzumab, ofatumumab, and high-dose methylprednisolone, have clinical efficacy in relapsed CLL.[45,46,49–52] Alemtuzumab is also an effective and approved salvage therapy for individuals with relapsed disease. Phase II studies suggest a 35 to 40% response rate with single-agent alemtuzumab in relapsed or refractory CLL patients.[49,50] This agent causes profound and prolonged T cell immunosuppression and places patients at high risk for opportunistic infections, including cytomegalovirus reactivation. Trials combining alemtuzumab with rituximab also support use of this combination.[53] Phase II studies suggest that single-agent bendamustine has a response rate of 56%, whereas the combination of bendamustine with rituximab may have even higher response rates.[54] The anti-CD20 monoclonal antibody ofatumumab has single-agent activity in patients who are refractory to PNA and alemtuzumab and represents another salvage option.[51] Lenalidomide, flavopiridol, and a variety of other agents have also shown promise as a salvage therapy for relapsed patients in phase II trials.[55,56] Our approach to selecting first-line therapy for patients with CLL is shown in Figure 4b.

Highly selected individuals with CLL who are under the age of 70 and have good performance status are candidates for allogeneic stem cell transplantation. Consensus recommendations[57] suggest considering allogeneic transplantation (myeloablative or nonmyeloablative) for relapsed individuals with poor-risk CLL defined as those who

- Fail to respond to first-line therapy with a PNA
- Relapse within 12 months of a PNA-based treatment or within 24 months of a PNA-based combination regimen
- Require therapy and have a 17p⁻ abnormality on FISH testing

Such individuals should be referred to a transplant center for evaluation. Allogeneic transplantation remains an effective therapy for patients with 17p⁻; however, it is less effective for patients who have bulky nodes at the time of transplantation.[58] At the present time, there is no role for autologous transplantation in the treatment of CLL outside clinical trials.

COMPLICATIONS

Richter Transformation

During the course of their disease, 5 to 10% of patients with CLL develop transformation to an aggressive Hodgkin or non-Hodgkin lymphoma (Richter transformation). Richter transformation should be suspected when a patient develops fever, night sweats, weight loss, a sudden increase in lactate dehydrogenase (LDH), or rapid enlargement of a single lymph node region. Although such symptoms can occasionally be attributable to CLL, patients with rapid enlargement of a single lymph node region should undergo excisional lymph node biopsy. Those with Richter transformation should receive aggressive chemotherapy regimens used to treat Hodgkin or non-Hodgkin lymphoma or should be referred for participation in a clinical trial. Stem cell transplantation may be appropriate for some patients.[59]

Autoimmune Complications

Approximately 5 to 10% of patients with CLL will develop autoimmune hemolytic anemia (AIHA), 5% will develop idiopathic thrombocytopenic purpura (ITP), and 1% will develop pure red blood cell aplasia (PRBCA).[60,61] Given the frequency of these autoimmune complications, it is important to evaluate the cause of cytopenias before assuming that they are attributable to marrow replacement by CLL and initiating chemotherapy. AIHA is readily distinguished from bone marrow failure by an increased reticulocyte count, indirect bilirubin, and LDH in conjunction with a positive Coombs test. PRBCA as the etiology of anemia and ITP as the cause of thrombocytopenia can be distinguished from marrow failure attributable to CLL only by bone marrow biopsy. For this reason, marrow biopsy is recommended prior to the initiation of chemotherapy in all patients with CLL for whom anemia is the primary indication for treatment. These autoimmune complications can often be arrested with immunosuppressive therapy (steroids, cyclosporine), rituximab, or splenectomy. If such

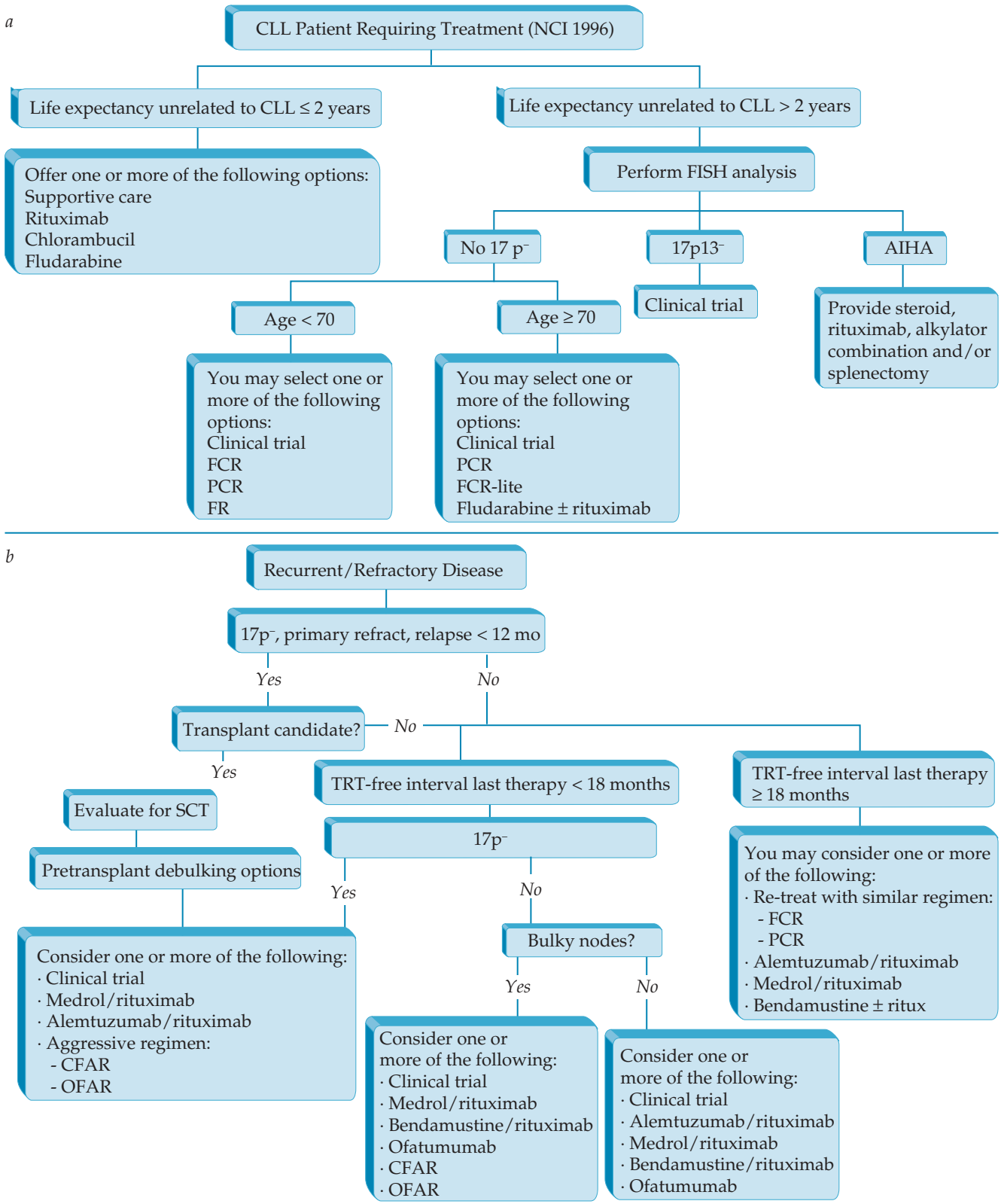

Figure 4 **(*a*) An approach to selecting first-line therapy for patients with chronic lymphocytic leukemia (CLL) based on age, comorbidities, and disease characteristics. (*b*) An approach to selecting salvage therapy for patients with CLL initially treated with chemoimmunotherapy (CIT) based on response to first-line treatment and disease characteristics. CFAR= cytoclophosphamide, fludarabine, alemtuzumab, and rituximab; FCR = fludarabine and cyclophosphamide plus rituximab; FISH = fluorescence in situ hybridization; FR = fludarabine and rituximab; NCI = National Cancer Institute; OFAR = oxaliplatin, fludarabine, cytarabine, and rituximab; PCR = pentostatin, cyclophosphamide, and rituximab; SCT = stem cell transplantation; TRT = treatment.**

therapies are ineffective, patients should receive chemotherapeutic treatment for CLL. In the event that chemotherapy is required for treatment of AIHA, PNAs should be avoided because they can lead to life-threatening exacerbation of hemolytic anemia,[62] whereas alkylator-, rituximab-, and steroid-based combinations appear to be effective options.[63,64]

Second Malignancy

A number of studies demonstrate that patients with CLL are at increased risk for developing a second malignant disorder. One study found that CLL patients had a threefold increased risk of nonlymphoid second malignant disease other than nonmelanoma skin cancer.[65] These observations underscore the importance of encouraging smoking cessation and keeping CLL patients up to date with age-appropriate cancer screening.

Infectious Complications

Patients with CLL are also at increased risk for infection attributable to defects in cell-mediated and humoral immunity. Patients with frequent, recurrent bacterial infections should be evaluated for hypogammaglobulinemia. A randomized, double-blind, placebo-controlled trial demonstrated that gammaglobulin replacement (400 mg/kg every 3 weeks) decreased the risk of bacterial infection by 50% in CLL patients with hypogammaglobulinemia and a history of infection.[66]

A number of CLL therapies, including PNA and alemtuzumab, cause profound and prolonged ($\geq$ 12 months) T cell depletion, placing patients at risk for opportunistic infections such as *Pneumocystis*, *Aspergillus*, and *Cryptococcus*, as well as varicella-zoster reactivation.[67] Cytomegalovirus infection is a frequent occurrence during or after treatment with alemtuzumab, and most experts recommend active surveillance for CMV reactivation during alemtuzumab-based treatment.

PROLYMPHOCYTIC LEUKEMIA

PLLs are rare lymphoid leukemias of either T or B cell origin (T-PLL and B-PLL) characterized by marked elevations in the ALC with a high percentage of prolymphocytes.[68] Both diseases have a median age at onset in the mid- to late 60s. These disorders can be readily distinguished from CLL based on peripheral blood immunophenotyping. The immunophenotype of T-PLL includes lymphocyte expression of CD2, CD3 (60%), and CD7 with variable CD4 and CD8 expression (60% $CD4^+/CD8^-$, 25% $CD4^+/CD8^+$, 15% $CD4^-/CD8^+$).[68] T-PLL typically presents with lymphadenopathy, hepatosplenomegaly (65%), cytopenias (50%), skin involvement (20%), and marked peripheral blood lymphocytosis (often > 100×10^9/L).[68,69] The clinical course is typically aggressive, with a median survival of less than 1 year. Treatments include alemtuzumab[70,71] and PNAs.[72] Responding patients should be evaluated for allogeneic transplantation. [73,74]

B-PLL can arise as a transformation from CLL or de novo. The immunophenotype of de novo B-PLL includes surface expression CD19, CD20, CD22, CD79b, FMC7, and strong IgM typically in the absence of CD23 and CD5 (present in one third of cases).[68,69] With proper immunophenotyping, genetic, and tissue evaluation, the diagnosis of de novo B-PLL is vanishingly rare, with many historic cases now recognized to be leukemic forms of mantle cell or marginal zone lymphoma.[75] De novo B-PLL typically presents with massive splenomegaly, cytopenias (50%), and marked peripheral blood lymphocytosis (often > 100×10^9/L; > 55% prolymphocytes), often in the absence of significant lymphadenopathy.[68,69] The clinical course is aggressive with a median survival approximately 3 years. PNA-based regimens are the cornerstone of treatment.[76]

HAIRY CELL LEUKEMIA

HCL is another rare B cell malignancy characterized by infiltration of the bone marrow and spleen with small to medium-size lymphocytes with irregular cytoplasmic projections. Immunophenotyping classically demonstrates expression of CD19, CD20, CD11c, and CD103 [*see Table 1*], and tartrate-resistant acid phosphatase staining of leukemic cells is positive in most cases.[68] Clinically, HCL typically presents as pancytopenia, splenomegaly, and opportunistic infection. The median age at onset is approximately 55. The clinical course is indolent, with a 10-year survival of less than 80%.[77–79] Indications for treatment include neutropenia (antineutrophil count [ANC] < 1.0×10^9/L) with recurrent infections, symptomatic anemia (Hg < 11 g/dL), bleeding attributable to thrombocytopenia (with platelets < 100×10^9/L), symptomatic splenomegaly, or constitutional symptoms (fever, weight loss, night sweats, fatigue). Treatment with PNAs (cladribine[77,78] or pentostatin[79,80]) leads to a response in nearly 100% of patients, with a complete response in 80 to 90%. Median PFS after PNA-based therapy is more than 10 years.[77–79] Pentostatin and cladribine appear to be equally efficacious. Recurrent disease can often be effectively managed by repeat PNA-based therapy. HCL cells express CD20 and respond to rituximab alone or in combination with PNA.[81] Although effective,[82] splenectomy for treatment of cytopenias and/or symptomatic splenomegaly is not typically needed in the PNA era. Some studies suggest that patients with HCL may be at increased risk for second malignancies and patients should receive age-appropriate cancer screening.

LARGE GRANULAR LYMPHOCYTE LEUKEMIA

T cell LGL leukemia is a rare chronic leukemia characterized by an increased number of mature LGLs in the peripheral blood, bone marrow, liver, and spleen.[68] Clinically, LGL leukemia typically presents with mild lymphocytosis (ALC < 10×10^9) associated with neutropenia, thrombocytopenia, or anemia attributable to PRBCA or AIHA. Not infrequently, the increase in the number of LGLs in peripheral blood and bone marrow is subtle, and the diagnosis requires specialized T cell clonality and immunophenotypical studies. An association with rheumatoid arthritis and Felty syndrome is well documented.[83] The clinical course of LGL leukemia is varied, with most patients experiencing an indolent disease course.[83] Staging systems that predict clinical outcome based on the presence or absence of anemia (hemoglobin < 12 g/dL), lymphopenia (ALC < 1×10^9/L), and severe neutropenia (ANC < 0.1×10^9/L) have been developed and appear to stratify patients with widely different survivals.[84] Observation until development of symptoms is the standard management approach. Treatment is indicated for patients with symptomatic cytopenias (recurrent

infection attributable to neutropenia, symptomatic anemia, bleeding attributable to thrombocytopenia) or constitutional symptoms (fever, weight loss, night sweats, fatigue).[83] Treatment options include alkylating agents, methotrexate, cyclosporine, and corticosteroids.[83]

Multiple Myeloma

EPIDEMIOLOGY

Multiple myeloma is an uncommon malignancy. In 2010, 20,180 new diagnoses and 10,650 deaths are projected. The male-to-female ratio is 55:45. Myeloma comprises 1.2% of all cancer diagnoses, 0.8% of all cancer deaths, and 15% of hematologic malignancies. The median age at diagnosis is 71. In men, the incidence rate is 4.5 in 100,000 for whites and 9.2 in 100,000 for African Americans. The incidence of multiple myeloma increases with each successive decade of life. The disease is uncommon below the age of 40 at less than 1 in 100,000,[85] 2.5 in 100,000 between the ages of 40 and 44, and 20 in 100,000 at ages 65 to 69. The 5-year survival is 36%.

Myeloma is characterized by the proliferation of clonal plasma cells in the bone marrow. Myeloma cells express surface CD38 and CD138. Interleukin-6 (IL-6) is an essential growth factor in multiple myeloma and appears to be important in mediating myeloma-related bone resorption. The diagnosis should be considered in any patient with a normocytic or slightly macrocytic anemia. Unexplained rib fractures or spinal compression fractures and severe osteoporosis should result in screening for myeloma. Renal insufficiency with proteinuria and unexplained hypercalcemia should lead to serum and urine protein electrophoretic studies.

Using conventional metaphase cytogenetics, the most important abnormalities are hypodiploidy and deletion of chromosome 13. By FISH, the most important abnormalities are t(4;14), t(14;16), $17p^-$, and t(14;20). A high gene expression–based centrosome index is associated with poor prognostic, genetic, and clinical subtypes. Centrosome amplification is integral to early chromosome instability in the pathogenesis of multiple myeloma.[86]

IMMUNOLOGY

Myeloma is characterized by the production of a monoclonal immunoglobulin IgG in 52%, IgA in 21%, IgD in 2%, light chain myeloma in 16%, and biclonal immunoglobulin in 2%. Only 7% of patients have no detectable monoclonal immunoglobulin in the serum. Urine immunofixation will demonstrate a kappa monoclonal protein in 49% and a lambda monoclonal protein in 29%.[87] Only 1% of myeloma patients actually have no detectable monoclonal protein by immunofixation of serum or urine, and with the introduction of the new immunoglobulin-free light chain assay, less than 1% have no detectable immunoglobulin abnormality. Depression of the uninvolved immunoglobulins is frequently seen but has no impact on the disease.[88]

DIAGNOSIS

Myeloma

Myeloma is diagnosed on a routine examination in 25% of patients, 30% present with bone pain, 15% present as part of the evaluation of an elevated serum or urine protein, 15% present with anemia, 3% with infection, 2% with renal dysfunction, and 10% with other causes.

Monoclonal Gammopathy of Undetermined Significance

MGUS is defined by the finding of a monoclonal protein in the serum of less than 3 g/dL, bone marrow clonal plasma cells that are less than 10%, and a low level of plasma cell infiltration in a trephine biopsy,[89] with no evidence of other B cell proliferative disorders and no related organ or tissue impairment, including elevation of the creatinine, anemia, or bone lesions. Patients with amyloidosis, cryoglobulinemia, cold agglutinin disease, or an IgM-associated neuropathy would not be considered to have MGUS. The prevalence of monoclonal gammopathy rises with each decade and is 1.7% between the ages of 50 and 59, rising to 6.6% in those over the age of 80; the overall prevalence is 3.2%. Patients need to be followed indefinitely because the probability of progression over time is constant at 1% per year; that is, at 20 years, 21% of patients will have developed myeloma, amyloidosis, or a lymphoproliferative disorder. The risk of progression is predicted by (a) the concentration of the monoclonal protein greater than or less than 1.5 g/dL, (b) whether it is an IgG or non-IgG, and (c) whether the immunoglobulin-free light chain ratio is abnormal. The actuarial risk at 20 years for transformation with all three factors favorable is 5% and for all three factors unfavorable is 50%. Studies have shown that virtually all myeloma patients have an antecedent MGUS.[90]

Myeloma requires an M protein in the serum of 3 g/dL or greater and/or a bone marrow plasma cell infiltration of less than 10%. Patients who have no related organ impairment or symptoms are classified as smoldering myeloma. Patients who have hypercalcemia, renal insufficiency, a hemoglobin less than 2 g below the lower limit of normal, or bone lesions—either lytic lesions or compression fractures—are considered symptomatic and are therefore classified as overt multiple myeloma in need of therapy.

Plasmacytoma

A solitary plasmacytoma of bone is associated with no or a small monoclonal protein in the serum or urine, a single area of bone destruction attributable to clonal plasma cell infiltration, and a bone marrow inconsistent with multiple myeloma to differentiate patients with multiple myeloma presenting with a solitary bone lesion. A skeletal survey and magnetic resonance imaging (MRI) of the spine, if done, should otherwise be negative, with no end-organ damage. An extramedullary plasmacytoma is similarly defined, but the single lesion is in a nonbony site, that is, the nasopharynx, intestinal tract, etc. The majority of patients with solitary plasmacytoma of bone will progress to overt multiple myeloma. Progression can be predicted by one of three features: (1) abnormal marrow signal by MRI, (2) abnormal immunoglobulin-free light chain ratio, or (3) failure of the M component to disappear following the completion of radiation therapy,[91,92] the preferred first-line treatment.

CLINICAL PRESENTATIONS

Bone Disease

The radiographic findings in newly diagnosed myeloma include lytic lesions in two thirds of patients [*see Figure 5*],

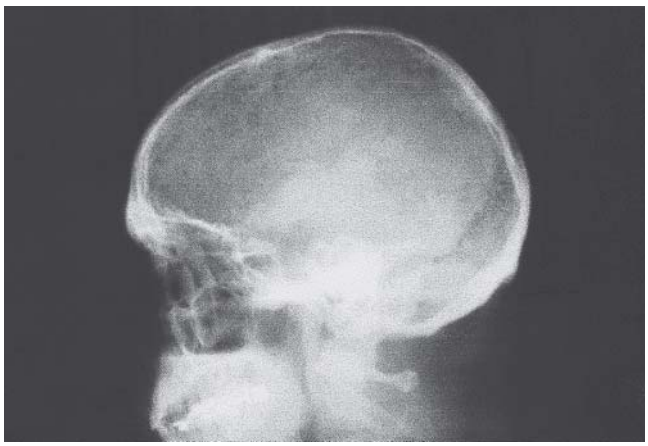

Figure 5 **Radiograph showing lytic bone lesions of the calvarium.**

pathologic fractures in 25%, compression fractures in 22%, and osteoporosis in 24%. Only 21% of patients have normal bone radiographic studies. Bone disease is mediated by both direct tumor infiltration into cortical bone and increased osteoclast activity. Seventy percent of patients with myeloma have elevated levels of macrophage inflammatory protein in their marrow plasma. Myeloma cells also produce receptor activator of nuclear factor κB (RANK). Marrow stromal cells produce IL-6, which induces osteoclast formation, all of which tend to promote the destruction of bone. Myelomatous lesions not visible by plain radiographic techniques are visible using CT and MRI. Myeloma is a positron emission tomography–avid malignancy, and this test is extremely useful in detecting metabolically active disease.[93]

Radiation therapy in multiple myeloma is required only for the prevention of pathologic fractures and neurologic and spinal cord compromise.[94] Most patients who have pain as a major manifestation will respond to systemic chemotherapy without radiation. Vertebral compression fractures generally do not require radiation therapy because these lesions result from bone mineral loss and may not be related to direct tumor infiltration. For pain palliation, vertebroplasty can be an effective technique.[95]

Bisphosphonate therapy is now routinely given to all patients with myeloma bone disease. Mayo Clinic consensus guidelines prefer the use of pamidronate over zoledronic acid until more data become available on jaw osteonecrosis.[96] The Mayo Clinic consensus guidelines recommend cessation of bisphosphonate use after 2 years of therapy for patients who have achieved a complete response or a plateau. For patients whose disease is not in plateau, bisphosphonate therapy is reduced to every 3 months.[97]

Anemia

At presentation, the hemoglobin level is below 8 g in 6% of patients, between 8.1 and 10 g in 27%, between 10.1 and 12 g in 36%, and more than 12 g in 27% of patients. Anemia is a consequence of marrow infiltration and renal failure. Erythropoietin use will reduce red cell dependency in half of patients. There are no data as to the quality of life benefits of erythropoietic stimulating agents in multiple myeloma.[98] There is, however, an increased risk of thrombosis that has been reported when erythropoietin therapy is combined with thalidomide.[99]

Hypercalcemia

Calcium ranging between 10.2 and 10.9 mg/dL is seen in 15% of patients, and an additional 12% will present with a calcium of 11 mg/dL or more. Saline hydration and diuresis are standard because these patients are frequently hyperosmolar. Previously untreated patients will usually respond to the first dose of bisphosphonates followed by the initiation of systemic therapy. Resistant hypercalcemia is unusual. The hypercalcemia of multiple myeloma is highly sensitive to the therapeutic effects of corticosteroids.

Renal Insufficiency

At presentation, the serum creatinine value will be abnormal in 22% of patients. Renal insufficiency is related to volume depletion, hypercalcemia, contrast exposure, and nonsteroidal antiinflammatory drugs. The differential diagnosis of renal insufficiency associated with light chain proteinuria includes amyloidosis, Fanconi syndrome, crystalline nephropathy, cryoglobulinemia, and Randall-type light chain deposition disease.[100] There is a strong association between high levels of urinary light chains and renal insufficiency. The most common finding on renal biopsy is cast nephropathy. Filtered immunoglobulin light chains bind to a common site on Tamm-Horsfall protein produced by cells of the thick ascending limb of the loop of Henle. Of patients in the United States on dialysis, 0.88% have multiple myeloma. The 2-year all-cause mortality rate in myeloma nephropathy is 58%.[101] Patients on dialysis have a shorter survival following high-dose therapy and stem cell transplantation. Transplant-related mortality in patients with renal insufficiency can reach 17%. A prospective randomized study of plasma exchange failed to demonstrate a benefit using the end points of dialysis dependency or creatinine clearance less than 30 mg/min. The study did not quantify immunoglobulin-free light chains, so the possibility that subgroups might benefit from plasma exchange cannot be excluded. Following induction therapy, only 5% of patients have impaired renal function.

Neurologic Symptoms

Vertebral plasmacytomas can extend from the body of the vertebra posteriorly and cause anterior compression of the spinal cord. This is one of the few true emergencies in myeloma management because emergency radiation therapy and high-dose corticosteroid therapy can prevent permanent functional loss. Peripheral neuropathy in a patient with a monoclonal protein should raise the possibility of amyloid neuropathy, osteosclerotic myeloma (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes [POEMS] syndrome), cryoglobulinemia, and MGUS neuropathy.

STAGING AND PROGNOSIS

For over 30 years, the staging system of Durie and Salmon served well, but limitations of the Durie-Salmon system have been identified. Durie-Salmon stage I patients are often

not candidates for treatment, and assessment of bone lesions is subjective. Patients are disproportionately assigned (80%) to stage III. The new International Staging System for multiple myeloma should be used for all patients. The system was validated in over 10,000 patients across continents and is independent of conventional or high-dose therapy. An evaluation of five different staging systems reflected the superiority of the International Staging System.[102]

The International Staging System is given in Table 2. Serum β_2-microglobulin is shed from the surface of the myeloma cell, an indirect reflection of tumor mass. Albumin is a negative acute-phase reactant, and its level is depressed as IL-6 levels rise, exerting growth effects on the myeloma population. The staging system divides patients into groups of equal size and distinct differences in median survival. Given that the validation data set required that all variables be performed in virtually all patients, it was incapable of assessing the value of conventional cytogenetics, FISH, and MRI for their ability to predict adverse outcomes. The median survival of stage I patients is 62 months, of stage II patients is 44 months, and of stage III patients is 29 months. For patients treated with standard chemotherapy, the survivals in stages I, II, and III were 55, 40, and 25 months, respectively. For patients treated with high-dose therapy and stem cell transplantation, median survivals were 111, 66, and 45 months, respectively. Table 3 lists recommended initial testing for myeloma patients.

Deletion of chromosome 13 has been associated with a median survival as short as 10 months. The incidence of chromosomal abnormality detected by FISH is much higher than that detected by metaphase analysis. With FISH, deletion 13 is detected in 45% of patients, deletion 17p13 is noted in 25%, and 11q abnormalities are noted in 16%. Chromosome 13 deletion and p53 deletions are associated with a median overall survival of 24 months. In a cohort of 1,000 patients, translocation t(11;14) had no effect on event-free or overall survival, and hyperdiploidy was only marginally significant. There were significant associations between chromosome 13 deletion and t(4;14). Three factors were identified in multivariate analysis: t(4;14), p53, and β_2-microglobulin level greater than 3 mg/dL.[103] It has been questioned whether patients with t(4;14) benefit sufficiently from high-dose therapy and stem cell transplantation to justify its use. Although important, FISH changes, including t(4;14), t(14;16), and $17p^-$, have not been fully integrated into an international staging system. Gene expression profiling has the ability to refine current prognostic models.[104]

Table 2 International Staging System for Multiple Myeloma

Stage	*Test*	*Test Result*
Stage 1	β_2M	< 3.5
	Alb	≥ 3.5
Stage 2	Alb	< 3.5
		and/or
	β_2M	3.5–5.5
Stage 3	β_2M	> 5.5

Alb = albumin g/dL; β_2M = serum β_2 microglobulin mg/dL.
Age is the only other factor that significantly impacts outcome.
Cytogenetics influences outcome; however, chromosome 13 deletion and complex cytogenetic abnormalities do not add to the impact of age, β_2M, and albumin.

Table 3 Recommended Initial Testing for Myeloma

- CBC, WBC differential, chemistry panel to include creatinine, calcium, and LDH
- Serum protein electrophoresis + immunofixation
- Quantitative immunoglobulins, nephelometric
- Immunoglobulin-free light chain quantitation
- 24-Hour urine, total protein, electrophoresis, immunofixation
- Marrow aspiration and trephine biopsy, immunophenotyping and conventional cytogenetics
- Radiologic skeletal bone survey—all bones; selected patients require CT, MRI, and/or PET scanning
- Serum β_2-macroglobulinemia

CBC = complete blood count; CT = computed tomography; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; WBC = white blood count.

THERAPY FOR MULTIPLE MYELOMA

Indications for Treatment

Given that multiple myeloma is not curable with conventional therapy, patients who are asymptomatic do not require intervention. These patients fulfill the criteria for smoldering multiple myeloma and lack anemia, renal insufficiency, or bone disease. Bisphosphonate therapy is not routinely indicated. Indications for therapy are progressive anemia, threatening or symptomatic bone disease, or myeloma cast nephropathy. Research into lenalidomide treatment of high-risk smoldering multiple myeloma is under way.

The key therapeutic decision is determining whether the patient is a candidate for high-dose chemotherapy. High-dose therapy has been demonstrated to provide survival benefit when compared with traditional conventional chemotherapy.[105,106] In patients who are not felt to be candidates for stem cell mobilization, melphalan can be used safely because its stem cell toxic effect is not a relevant consideration. Traditionally, the use of oral melphalan and prednisone has been the standard of care for nontransplant patients, but recent studies have suggested that the introduction of the novel agents thalidomide, lenalidomide, and bortezomib, as well as combinations of the three agents, can result in higher response rates.[107]

The use of melphalan and prednisone combined with thalidomide was compared with melphalan and prednisone in patients between the ages of 65 and 85. The addition of thalidomide improved the rate of response from 47 to 76% and the 2-year event-free survival from 27 to 54%. The toxicities of thalidomide include skin rash, somnolence, constipation, and deep vein thrombosis. The frequency of deep vein thrombosis requires that all patients receive prophylaxis when thalidomide is used in conjunction with a corticosteroid, an anthracycline, or erythropoietin. The use of aspirin, low-molecular-weight heparin, and warfarin has been reported to reduce the thrombosis rates.[108] The dose-limiting toxicity of thalidomide is peripheral neuropathy, which can

be progressive and irreversible and in many patients limits the duration of exposure. Given that lenalidomide is not neurotoxic to the same extent as thalidomide, induction using melphalan and prednisone with lenalidomide has been piloted.[109] Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma also results in higher response rates that have been reported with melphalan and prednisone alone. An overall response rate of 89%, including 32% immunofixation-negative complete responses, was seen. The combination appeared to overcome the poor prognosis conferred by $17q^-$ and translocations at chromosome 14. The event-free survival was 83% and overall survival was 90% at 16 months. The toxicities included myelosuppression and peripheral neuropathy, which tends to be reversible with bortezomib.[110] A phase III trial validated significantly longer survival.[111] Complete response predicts superior outcomes.[112]

High-Dose Therapy and Stem Cell Transplant

Induction High-dose therapy is typically preceded by 4 months of cytoreductive therapy. For more than 20 years, infusional vincristine, doxorubicin, and dexamethasone (VAD) therapy has been the standard pretransplantation induction therapy. Most centers report response rates in the 50 to 60% range. This regimen has no impact on stem cell mobilization or subsequent engraftment. The VAD regimen is currently infrequently used because the Intergroupe Francophone du Myelome (IFM) myeloma 2005 trial showed it to be inferior to bortezomib and dexamethasone.[113] Use of novel agents to improve response rates have resulted in the introduction of thalidomide-dexamethasone for newly diagnosed myeloma. When thalidomide plus dexamethasone was directly compared with single-agent dexamethasone, responses rate rose from 41 to 63%. However, grade III or greater toxicity was 45 versus 21%.[114] When lenalidomide was demonstrated to be effective in the treatment of patients with relapsed or refractory multiple myeloma,[115] it was combined with dexamethasone in induction therapy, with an overall objective response rate of 91%.[116] The combination of lenalidomide and dexamethasone is currently the subject of a national phase III trial for induction therapy in multiple myeloma. Bortezomib plus dexamethasone as induction prior to autologous stem cell transplantation has also been reported.[117] The overall response rate was 66%, including 21% complete responses and 10% very good partial responses. Grade 2 to 3 neuropathy was seen in 14%. There was no impact on stem cell mobilization.[118] Bortezomib was used with dexamethasone for previously untreated myeloma with a complete plus partial response rate of 88% without affecting stem cell mobilization.[119] Lenalidomide does impair stem cell mobilization.[120]

Stem cell transplantation Stem cell transplantation for multiple myeloma should be considered the default standard of care for patients who are 70 years of age or younger and for selected patients as old as 75 years with a good performance status. Because stem cell transplantation has been proven to improve overall survival, substitution of conventional therapy with or without novel agents should be considered only in the context of an investigational trial. High-dose therapy followed by stem cell reinfusion can result in response rates over 90%, complete response rates of 50 to 60%, and mortality of 1 to 2%. A second stem cell transplantation has been demonstrated to be appropriate for selected patients who do not achieve a complete response or very good partial response with their first transplantation.[121] The standard conditioning regimen is melphalan 200 mg/m^2 for a first transplantation reduced by 30% for patients who have renal insufficiency or are elderly. Recently, posttransplantation maintenance therapy with thalidomide has been shown to improve survival in multiple myeloma patients.[122] Lenalidomide has also been shown to improve relapse-free survival when used as posttransplantation consolidation and maintenance. There have been questions regarding the value of autotransplantation in older patients when compared with thalidomide-based conventional regimens.[123]

One study compared tandem autologous stem cell transplantation with a single autologous transplantation followed by an allogeneic transplantation for those with an HLA-identical sibling donor. The event-free survival of 80 patients with matched siblings assigned to auto transplantation followed by a reduced-intensity allogeneic stem cell transplantation was longer than that of the 82 patients without a sibling donor assigned to tandem autologous stem cell transplantation (35 versus 29 months; $p = .02$). Overall survival was also superior for patients assigned to allogenic transplantation (80 versus 54 months; $p = .01$) at a median follow-up of 45 months.[124] The role of allogeneic transplantation continues to be evaluated in ongoing clinical trials.

Waldenström Macroglobulinemia

WM has an overall incidence of approximately three cases per 1 million persons per year, accounting for 1 to 2% of hematologic cancers. The median reported age varies between 63 and 68 years. Its etiology is unknown. WM is a malignant lymphoplasmacytic proliferative disorder characterized by the production of a monoclonal IgM protein. The bone marrow demonstrates small lymphocytes, lymphoplasmacytoid cells, and plasma cells. The only characteristic chromosome finding in this disorder is deletion 6q21-22.1. The gene associated with this deletion is *blimp1*, a tumor suppressor gene, the master gene regulator for B lymphocyte cell proliferation and differentiation.[125] The majority of cells express CD20, CD19, and CD22 and are negative for CD38 and CD10. In practice, a $CD5^-$, $CD10^-$, $CD19^+$, $CD20^+$, $CD23^-$ immunophenotype with lymphoplasmacytic lymphoma in the bone marrow would be consistent with WM.[126] Patients with a diagnosis of WM have symptoms attributable to either direct tumor infiltration of lymph nodes and bone marrow or complications of the monoclonal serum protein. Bone marrow infiltration leads to cytopenias, and progressive anemia is the most common indication for the initiation of therapy. Serum hyperviscosity is the most distinguishing feature of WM but is observed in less than 15% of patients. The symptoms of hyperviscosity appear when the viscosity level of blood reaches 4 to 5 centipoises and will include oral or nasal bleeding and ocular, neurologic, and cardiovascular manifestations. Peripheral neuropathy has been reported in 15 to 30% of patients with IgM monoclonal gammopathies, most commonly encountered as a

symmetrical polyneuropathy. The differential diagnosis of WM includes low-grade lymphoma, chronic lymphatic leukemia, and splenic marginal zone lymphoma. WM is unique, having discrete morphologic and cytogenetic differences from these other entities. The prognosis in WM is predicted by the level of serum β_2-microglobulin.[127] An international prognostic staging system has been developed incorporating age, hemoglobin, M protein size, β_2-microglobulin level, and platelet count.[128]

Asymptomatic patients are not treated. The primary choices for patients who need therapy are alkylating agents, PNA, and the monoclonal antibody rituximab. Plasma exchange is rarely required. Recent experience with thalidomide, lenalidomide, everolimus, and bortezomib also suggests that these are active agents in the disease. The role of stem cell transplantation remains undefined in this disorder but appears promising.[129] Common antilymphoma regimens are effective in the management of WM and include rituximab alone, RCVP (rituximab, cyclophosphamide, vincristine, prednisone), and RCHOP (rituximb, cyclophosphamide, hydroxydaunomycin [doxorubicin], Oncovin [vincristine], prednisone). The use of fludarabine or cladribine with an alkylating agent such as cyclophosphamide with or without dexamethasone and rituximab has also been reported to produce excellent response rates.

Amyloidosis

Amyloidosis is characterized by the extracellular deposition of fibrillar amyloid protein. Amyloid is defined by its staining with Congo red. The symptoms of the disorder include fatigue, edema, and weight loss. Amyloidosis should be considered in the differential diagnosis of any patient presenting with nephrotic range proteinuria, unexplained cardiomyopathy, unexplained hepatomegaly, or peripheral and autonomic neuropathy and in the differential diagnosis of all patients presenting with a monoclonal gammopathy.[130]

Suspicion of amyloidosis should lead to immunofixation of the serum and urine and an immunoglobulin-free light chain assay. One of these three will be abnormal in 99% of patients with amyloidosis. The diagnosis will be established in 85% by doing Congo red stains on a bone marrow biopsy and subcutaneous fat aspirate. In the remaining patients, biopsy of the symptomatic organ, that is, the liver, kidney, or heart, will result in a confirmation of the diagnosis.

The prognosis of amyloid is determined by the functional impairment that results from cardiac amyloid infiltration. Assessment of cardiac function with two-dimensional echocardiography and measurement of the levels of the cardiac biomarkers troponin and brain natriuretic peptide are important in assessing the ultimate prognosis for this disease.[131] The treatment of amyloidosis remains inadequate. The diagnosis is often made late in the course of the disease, when advanced organ dysfunction is present. Effective suppression of light chain production will not result in reversal of advanced impairment of organ function, and the natural history of the disease will not be altered. The standard of therapy has been the use of oral melphalan and prednisone, with a median survival of 15 to 18 months. New therapy for the management of amyloidosis includes melphalan and dexamethasone and the combination cyclophosphamide, thalidomide, and dexamethasone. These regimens produce high response rates. The impact on survival is not, as yet, known. High-dose therapy with stem cell transplantation has been introduced in selected patients with amyloidosis in an attempt to improve response and survival. Because of the widespread organ dysfunction in these patients, the day-100 mortality ranges from 12 to 25%. In a registry study of 107 patients from 48 transplant centers, a 30-day treatment-related mortality of 18% was reported. Only 11% of patients had progression of disease posttransplantation. The median projected survival is 47 months.

Stem cell transplantation has not been proven to be superior therapy for amyloidosis. Patients eligible for autologous transplantation are younger, with a lower proportion with advanced cardiac involvement. A case-matched control series has suggested an improved outcome for those patients eligible for transplantation who receive a transplant compared with their matched controls treated conventionally.[132] Amyloidosis should be considered in all patients who have a monoclonal protein associated with albuminuria, cardiomyopathy, peripheral neuropathy, hepatomegaly, or atypical multiple myeloma. New chemotherapy regimens reported to have high activity in amyloidosis include melphalan-prednisone-lenalidomide, melphalan-dexamethasone-bortezomib, and bortezomib-dexamethasone.[133,134]

Resources

Information about chronic lymphoid leukemias and plasma cell disorders for clinicians and patients is available on the Internet [*see Sidebar* Internet Resources for Chronic Lymphoid Leukemias and Plasma Cell Disorders].

Internet Resources for Chronic Lymphoid Leukemias and Plasma Cell Disorders

Chronic lymphocytic leukemia, prolymphocytic leukemia, hairy cell leukemia

National Cancer Institute
www.cancer.gov/cancertopics/pdq/treatment/CLL/Patient

Leukemia Lymphoma Society
www.leukemia-lymphoma.org

Multiple myeloma, Waldenström macroglobulinemia, amyloidosis

mSMART
http://www.msmart.org

Multiple Myeloma Foundation
http://www.multiplemyeloma.org

Amyloidosis Support Network
http://www.amyloidosis.org

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