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Diagnosing and Treating Chronic Lymphocytic Leukemia in 2009

Matthew Kaufman, MD_Assistant Professor_Department of Medicine_Division of Hematology-Oncology_Albert Einstein College of Medicine_Long Island Jewish Medical Center

Jason Rubin, MD_Fellow_Department of Medicine_Division of Hematology-Oncology_Long Island Jewish Medical Center

Kanti Rai, MB, BS_Professor_Department of Medicine_Division of Hematology-Oncology_Albert Einstein College of Medicine_Long Island Jewish Medical Center_New Hyde Park, New York

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ABSTRACT

Over the past decade, major breakthroughs have been made in both the molecular understanding and the treatment of chronic lymphocytic leukemia (CLL). In this article, old and new concepts of CLL biology are explored and insights into the relevance of the newer prognostic factors are discussed. The therapeutic landscape has changed dramatically with the advent of purine analogs, monoclonal antibodies, and combination therapy. As opposed to older agents, these new therapies commonly yield complete remissions. This improvement has spurred a debate as to new goals in treating CLL patients.

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in the Western hemisphere. Both the Rai and Binet staging systems have been important clinical tools for predicting outcomes of this heterogeneous disease. In the past 10 years, an explosion of research using newer techniques has helped us to learn more about the molecular biology of CLL and the impact it has on prognosis. In tandem with this increased knowledge on the molecular level, the menu of treatment options has improved significantly.

Diagnosis

CLL is commonly found when an absolute lymphocytosis is discovered in an entirely asymptomatic person. Other patients notice some degree of painless lymphadenopathy and consult a physician. A minority of patients present with typical B symptoms of lymphoma (weakness, night sweats, weight loss, or fever). Finally, some patients present with an infection or autoimmune phenomenon (such as hemolytic anemia) related to immune dysfunction.

The threshold for diagnosing CLL was originally 5,000 lymphocytes/ μ L.[1] A recent update of the 1996 National Cancer Institute–Working Group requires the presence of 5,000 B

lymphocytes/ μ L (past guidelines did not specify B lymphocytes).[2] Examination of the peripheral blood smear should reveal many small morphologically mature lymphocytes with a narrow border of cytoplasm and a dense nucleus.[2] Flow cytometry must demonstrate clonality, as determined by kappa or lambda light chain restriction, with CD19, CD20, CD23, and CD5 coexpression. Surface membrane immunoglobulin and CD20 are typically dim. Most other types of B-cell lymphoproliferative disorders are associated with high expression of surface membrane immunoglobulin and cells that do not express CD5. The exception is mantle cell lymphoma, which expresses CD5 but usually can be distinguished from CLL by lack of CD23 positivity and an overexpression of cyclin D1.

A bone marrow biopsy is not required for the diagnosis of CLL. However, if performed, it will show either hyper- or normocellularity, with a nodular or diffuse pattern of lymphocytic infiltration representing more than 30% of all nucleated cells. Prognostic tests such as molecular genetics, fluorescence in situ hybridization (FISH), mutational status of immunoglobulin heavy chain genes, and expression of ZAP-70 or CD38 are not required for the diagnosis of CLL.[2]

Biology and Prognostic Markers

Rai and Binet Staging Until recently, the prognosis of patients with CLL was based solely on clinical stage. Two staging systems, Rai and Binet, are used to describe extent of disease and portend prognosis.[3,4] In the series published by Rai and colleagues, median survival from time of diagnosis ranged from 150 months for stage 0 patients to only 19 months for those with stage III and IV disease.[3] Binet and colleagues categorized patients as low risk (stage A), intermediate risk (stage B) and high risk (stage C), which correspond, respectively, to Rai stage 0, I or II, and III or IV.[4]

The staging systems are most useful in predicting outcomes in patients with advanced disease (Rai stage III/IV or Binet stage C). Patients in the low- and intermediate-risk groups have a varied clinical course that may ultimately prove to be indolent or aggressive. New prognostic factors have allowed some degree of predictability of disease course in these patients with early-stage disease, and have also shed light on the biology of CLL growth.

IgVH Mutation Approximately half of all CLL cases display evidence of having undergone somatic hypermutation in the immunoglobulin heavy chain variable-region gene (IgVH). These CLL cases are considered “mutated” or “IgVH mutation positive.” Two landmark studies demonstrated that patients with this mutation have a favorable prognosis, whereas the absence of the mutation (“unmutated”) is associated with a more aggressive clinical course and a worse overall prognosis.[5,6] Though not entirely understood, this phenomenon is thought to be related to the disease-promoting roles of antigens in CLL. Patients with unmutated IgVH genes have B-cell receptors that may have a greater capacity to bind self-antigens and activate proliferative pathways downstream.[5,6]

ZAP-70 ZAP-70 or zeta-associated protein-70 is a 70-kD intracellular protein tyrosine kinase involved in cell activation. It is normally found in T cells and NK cells, but rarely in B cells. In some cases of CLL, ZAP-70 is aberrantly expressed, and has been found to be an independent predictor of aggressive disease.[7] Its expression does not always correlate with unmutated IgVH, and there is some debate as to which marker has more prognostic power.[7-9]

CD38 CD38 is another potentially useful prognostic marker. It is a transmembrane glycoprotein found on B cells and functions as a modulator of intracellular signaling. Among other mechanisms, it is believed to be associated with the upregulation of Bcl-2 and the prolonged survival of CLL cells. Its high expression in CLL cells is associated with a worse prognosis.[5,10,11]

Cytogenetics Several cytogenetic aberrations have shown prognostic significance in CLL. These abnormalities are typically detected by fluorescence in situ hybridization (FISH) techniques. Dohner and colleagues showed that 13q14 deletion was associated with a relatively favorable disease course, while deletions at 11q23 and 17p13 confer a poor prognosis with the shortest overall survival (Figure 1). They involve loss of the ATM and p53 genes, respectively.[12] Large randomized trials have demonstrated shorter durations of remission for these genetic lesions as well.[13] Not surprisingly, these mutations occur more often in patients with unmutated disease.[11] Trisomy 12 and normal cytogenetics are considered to be intermediate risk.[12,14]

Unlike the other prognostic markers, cytogenetic abnormalities may impact treatment decisions in current clinical practice. Though not universally true, 17p is often associated with disease resistance to alkylating agents and purine analogs. As such, a more aggressive approach to these patients is reasonable, preferably in a clinical trial. Alemtuzumab (Campath) has been shown to have significant activity in both 17p- and 11q-deleted CLL, and therefore should be considered in these patients. In contrast to the other prognostic factors discussed above, new cytogenetic abnormalities may be acquired over time, and in fact 17p deletions are far more common in later-stage, pretreated patients.[15,16]

Interpretation and Use of Prognostic Markers Multiple problems are associated with the prognostic markers in CLL. Traditionally, IgVH mutational status was difficult to obtain, but commercial labs have made this test widely available. ZAP-70 testing remains notoriously inconsistent, and no true standard among commercial labs exists. CD38 can be obtained by flow cytometry, but it may change over time, and some researchers question its utility.[17] Other less expensive markers of disease such as beta-2-microglobulin have been correlated with prognosis in clinical trials and may ultimately prove useful.[17,18]

Interpreting prognostic markers can be difficult. Whereas some markers may suggest a particular finding, frequently there is discordance among them and no clear conclusion can be drawn. One study suggested that ZAP-70 was the strongest predictor for disease progression but the issue remains highly controversial.[19] An important clinical question is whether early treatment of high-risk patients leads to improved outcomes. This risk-adapted approach is the subject of ongoing clinical trials.[20] Currently, no evidence supports the early initiation of treatment in patients in any risk category. As such, the utility of obtaining these tests outside of a clinical trial is debatable. Testing for cytogenetic abnormalities prior to treatment is an exception due to the potential impact that the discovery of a 17p deletion can have in selecting an agent or combination.[17] Irrespective of prognostic marker findings, the clinical picture of the patient in all phases of the disease (pre-, mid- or posttreatment) must remain the critical factor in management.

Indications for Treatment

Patients with asymptomatic, early-stage CLL should be monitored without initiating therapy. This so-called “watch and wait” approach is based on studies that failed to show a survival benefit for the treatment of early-stage disease.[21-24] Indeed, as a significant number of patients ultimately never require treatment for CLL, treating patients early will expose many unnecessarily to the toxicity of chemotherapy. With recent breakthroughs in both new treatments and prognostic markers, this issue is being revisited with ongoing studies that apply a risk-adapted approach to early-stage patients.

The International Workshop on CLL (IWCLL) Working Group has made specific recommendations as to when treatment should be initiated in current clinical practice.[2] These include patients with symptoms such as unintentional weight loss of 10% or more within the prior 6 months, significant fatigue, night sweats, and fever that is not due to an infection. Symptomatic anemia or thrombocytopenia secondary to progressive marrow failure (Rai stage III or IV) is also

considered a reason to treat. It is important to distinguish these cytopenias from immune-mediated cytopenias, which commonly occur in CLL. In the case of immune-mediated cytopenias, a trial of steroids should be given rather than immediately initiating chemotherapy.

Symptomatic or massive splenomegaly, lymphadenopathy, progressive lymphocytosis (with an increase of more than 50% over a 2-month period in lymphocyte count or a lymphocyte doubling time of less than 6 months) are other indications for treatment. In considering lymphocyte counts, it is important to look at a trend rather than a single result. A transient increase in lymphocyte counts often occurs due to a variety of factors including infections, steroid use, and inflammation. There is no evidence to support treatment based on absolute lymphocyte count alone, although many oncologists initiate treatment at $250,000/\mu\text{L}$ due to purely theoretical concerns of hyperviscosity.

Treatment

Alkylating Agents Until recently, the alkylating agent chlorambucil (Leukeran) was essentially the sole choice of treatment for CLL, offering a typically modest goal of palliation with a partial response. Its use is waning with the advent of newer therapies. Estimates of overall response rate for chlorambucil either alone or in combination with prednisone range from 38% to 75% with very few complete remissions.[25-27] Clinical trials have failed to show an advantage of combinations such as COP (cyclophosphamide, vincristine [Oncovin], prednisone) or CHOP (cyclophosphamide, doxorubicin HCl, vincristine, prednisone) over chlorambucil.[25-27] Cyclophosphamide, another alkylating agent, is currently used in modern combination regimens.

Purine Analogs Chlorambucil has been largely supplanted by newer agents, with purine analogs being the backbone of most modern regimens. Fludarabine has been the most widely tested purine analog in CLL. Its superiority has been demonstrated over chlorambucil and alkylator-containing combination regimens. In a North American trial, Rai and colleagues compared chlorambucil to fludarabine in previously untreated CLL patients in a prospective, randomized phase III trial. The results showed a significantly higher overall response rate (63% vs 37%) and complete remission rate (20% vs 4%) for the fludarabine-containing arm.[28] Median progression-free survival and duration of response were prolonged in the fludarabine-containing arm, but overall survival was not significantly different. This may have been due to the crossover design of the study. Patients who initially failed on chlorambucil had a 46% response rate when they crossed over to fludarabine, whereas only 7% of those patients with disease progression after receiving fludarabine showed a response to chlorambucil.[28]

A study comparing fludarabine to chlorambucil in patients over 65 years of age was carried out by the German CLL Study Group with similar results, including significantly higher complete and overall response rates as well as improved quality of life.[29] Other studies from Europe compared single-agent fludarabine to alkylator-based combinations and found fludarabine to be superior in terms of both complete response rates and durability of remissions.[30,31] Generally, fludarabine has shown greater myelosuppression than chlorambucil, with a higher incidence of neutropenia, but without increased infections.

Notably, these trials comparing fludarabine to alkylators and alkylator-based combinations, failed to show a survival advantage for fludarabine. Again, this is likely due to the crossover design of most of these trials. The superior activity of fludarabine in CLL, however, is clear. Other purine analogs—ie, pentostatin and cladribine (2-CdA)—have also been shown to have significant activity in CLL, both in the upfront and relapsed settings.[32-36]

Bendamustine Although bendamustine (Treanda) has been used in Eastern Europe since the 1970s, it is new to the United States and Western Europe, and it recently received US Food and Drug Administration (FDA) approval for its use in front-line CLL therapy. The structure of bendamustine is that of a nitrogen mustard derivative with alkylating properties and a benzimidazole ring believed to impart it with antimetabolite activity similar to that of a purine analog. Its approval was based on a randomized, controlled, multicenter comparison to chlorambucil in 319 patients with previously untreated CLL.[37] The overall response rate was

68% for bendamustine vs 31% for chlorambucil ($P < .0001$). Bendamustine therapy also produced a superior median progression-free survival (21.6 vs 8.3 months).[37] Adverse reactions in the bendamustine arm included anemia and neutropenic fever, resulting in a greater need for red blood cell transfusions and a higher number of hospital admissions in this group of patients. The number of deaths were similar in both treatment arms, and the toxicities were generally manageable.[37] Bendamustine's use continues to grow, but the role of this agent is still evolving.

Combination Chemotherapy_Three phase III trials have compared the combination of fludarabine plus cyclophosphamide (FC) to fludarabine alone, all demonstrating the superiority of combination chemotherapy over single-agent fludarabine.[38-40]

The US Intergroup E2997 trial randomized 278 patients to FC or fludarabine alone.[38] Patients treated on the FC containing arm achieved a superior overall response rate (74% vs 59%), complete response rate (23% vs 4%), and duration of progression-free survival (32 vs 19 months). The German CLL study group also compared FC to fludarabine in previously untreated patients age 65 or younger and demonstrated superiority in the FC arm in overall response rate (94% vs 83%), complete response rate (24% vs 7%), and median progression-free survival (48 vs 20 months).[39] Investigators in the United Kingdom conducted a three-arm trial of 777 patients randomized to chlorambucil, fludarabine, or FC.[40] Once again, a superiority in overall response rate, complete response rate, and 5-year progression-free survival was observed in the combination-chemotherapy arm.

Rituximab_The introduction of rituximab (Rituxan), a chimeric, murine anti-CD20 monoclonal antibody, has had a significant impact on CLL treatment. As a single agent, however, its activity is limited. Multiple studies with single-agent rituximab have been performed in both untreated and previously treated CLL patients showing only modest response rates and relatively short durations of response.[41-44] That CLL typically has only dim expression of CD20, along with the presence of soluble CD20 found in CLL patients (which could theoretically bind and clear rituximab) may explain its modest activity as a single agent.[45] Higher doses have improved response rates, but again, with short durations.[46] It is in combination with chemotherapy that rituximab has its primary use in CLL (see Chemoimmunotherapy section, below).

Alemtuzumab_CD52 is expressed on the surface of lymphocytes, as well as on a minority of myeloid cells. Alemtuzumab, a humanized monoclonal antibody that targets this protein, is approved for CLL treatment in both upfront and relapsed settings. It has demonstrated potent activity in treating the peripheral blood, bone marrow, and spleen but with a weaker effect on bulky lymph nodes.

Initial FDA approval for alemtuzumab in relapsed CLL was based on a trial involving 93 fludarabine-refractory patients.[47] An overall response rate of 33% was achieved, with 2% of patients achieving a complete response. Patients with small lymph nodes had notably superior responses to those with bulky lymph nodes. Subsequent studies provided additional evidence of alemtuzumab's profile of efficacy, both in terms of its greater benefit in patients with small lymph nodes and its potent effect on the bone marrow and spleen. In a UK study of 91 patients with relapsed CLL, among 33 patients with no lymphadenopathy, the response rate was 87% and for those with lymph nodes > 5 cm, the response rate was only 9%.[48] Approximately 20% of patients had no detectable CLL in the bone marrow.

A study by the German CLL Study Group explored the use of subcutaneous alemtuzumab for patients with relapsed CLL and found efficacy results similar to those seen in prior trials using intravenous administration.[49] Though no head-to-head data exist, this German study provides evidence that subcutaneous injection is a viable means of administration for alemtuzumab.

The CAM307 study explored alemtuzumab's use as an upfront agent in CLL and ultimately led to its approval as first-line therapy.[50] This prospective phase III trial randomized 297 previously

untreated patients to either oral chlorambucil or intravenous alemtuzumab. Alemtuzumab demonstrated a superior overall response rate (83% vs 55%), complete response rate (22% vs 2%), and time to alternative treatment (23 vs 15 months).[50] This, along with prior studies, also generated evidence of alemtuzumab's relative efficacy in high-risk cytogenetic abnormalities. In CAM307, alemtuzumab-treated patients with deletions of 11q and 17p—associated with refractoriness to treatment—showed impressive responses of 87% and 64%, respectively.[50]

Immunosuppression and infections are the main complications of alemtuzumab. Primary infectious concerns are *Pneumocystis jirovecii* pneumonia (PCP), varicella zoster virus (VZV), and cytomegalovirus (CMV). Patients should be placed on prophylactic therapy for PCP and VZV infection/reactivation while on alemtuzumab and for several months thereafter.[51,52] Monitoring for CMV antigenemia by polymerase chain reaction testing is also critical both during and for at least 2 months following treatment.[52] CMV reactivation should be treated with ganciclovir or valganciclovir (Valcyte). For infectious manifestations of CMV, alemtuzumab should be held until the infection resolves. Notably, in the CAM307 trial, patients who had alemtuzumab held for treatment of CMV infections achieved overall and complete response rates comparable to those in other patients.[50]

Minimal Residual Disease Alemtuzumab's potency in clearing the bone marrow has led to the investigation of minimal residual disease (MRD) negativity. MRD negativity is defined by complete eradication of leukemic cells assessed by either four-color flow cytometry or allele-specific nucleotide polymerase chain reaction markers.[53] In the UK study discussed above, patients who achieved MRD negativity had a significantly longer treatment-free survival than those who achieved a complete response but had residual disease in the marrow (not reached vs 20 months).[48] The correlation of MRD negativity to improved outcome has been found in other studies as well.[53-55] A debate continues as to how best to balance the risks of treatment with pursuit of a more profound response. Both a German trial and a US Cancer and Leukemia Group B (CALGB) study evaluating alemtuzumab consolidation therapy after fludarabine-based induction chemotherapy found significant toxicity.[56,57] At this time, MRD negativity as a therapeutic endpoint remains investigational and should not be considered a goal of therapy in clinical practice.

Chemoimmunotherapy A purine analog combined with rituximab has become the mainstay of front-line CLL treatment. The CALGB 9712 trial compared concurrent fludarabine plus rituximab (FR) and sequential fludarabine followed by rituximab with further consolidation rituximab in both arms and demonstrated a significantly higher complete response rate with concurrent therapy (47% vs 28%).[58] A retrospective analysis compared those patients who received FR in CALGB 9712 and those who received single-agent fludarabine in the CALGB 9011 trial and found a significantly higher complete response rate (38% vs 20%), 2-year disease-free survival rate (67% vs 45%), and 2-year overall survival rate (93% vs 81%) for patients receiving combination therapy.[59]

Phase II data have shown impressive overall and complete response rates using the triple-drug regimen of fludarabine, cyclophosphamide, and rituximab (FCR). In one single-institution, single-arm study, 300 patients were treated with FCR and had a complete response rate of 72%, with an overall response rate of 95%. [60] The most frequent adverse reaction was grade 3/4 neutropenia, occurring in over half of the patients. At 6 years' follow-up, the overall survival rate was 77%. [61]

Two multicenter phase III trials presented at the 2008 annual meeting of the American Society of Hematology showed a benefit for the addition of rituximab to FC in a prospective, randomized manner.[62,63] In the CLL8 trial, carried out by the German CLL Study Group, 817 treatment-naïve patients were randomized to six cycles of either FCR or FC. The FCR arm demonstrated superiority in complete response (52% vs 27%) and progression-free survival rates (76.6% vs 62.3%) at 2 years.[62] These benefits were largest in patients with earlier-stage disease. As had been observed in phase II trials, neutropenia was common in the FCR arm, though there was no

increase in the infection rate.[62]

The REACH trial was a multicenter phase III trial that compared FC to FCR in 552 relapsed or refractory CLL patients.[63] Eligibility criteria excluded prior combination therapy with rituximab and fludarabine or with rituximab alone, and the majority of patients had been previously treated with single-agent alkylator therapy. After three cycles of FCR or FC, patients were restaged and those with disease progression were taken off study while those with complete or partial responses or stable disease continued treatment for another three cycles. The overall response rate was 70% for the FCR group, compared with 58% for the FC group. Median progression-free survival was significantly prolonged by 10 months in patients treated with FCR (30.6 vs 20.6 months). The median overall survival has not yet been reached for the FCR arm and was 53 months for the FC arm.[63] A CALGB trial is underway, comparing FR and FCR in a randomized, prospective manner.

The combination of pentostatin, cyclophosphamide, and rituximab (PCR) has also been evaluated in both upfront and relapsed settings.[36,64] In a single-arm study of previously untreated patients with CLL, PCR yielded an overall response rate of 91% and complete response rate of 41%.[36] More recently, early results from a phase III study comparing FCR to PCR showed a significantly higher complete response rate in the FCR arm without more infections.[65] Notably, the dose of pentostatin in this trial was higher than in most other front-line PCR data.[36] An additional trial using PCR in the relapse setting demonstrated good response and relative safety as well.[64]

Novel Agents—Despite the durable responses that newer agents have provided in CLL, patients typically relapse and eventually develop refractory disease. Many investigational agents have shown promise and are being evaluated in clinical trials. • **Lenalidomide**—Lenalidomide (Revlimid), currently used in multiple myeloma and 5q deletion myelodysplastic syndrome, has shown significant activity in CLL. It is classified as an immunomodulatory agent. Its antitumor effects are likely mediated through the inhibition of tumor necrosis factor (TNF)-alpha and other pro-survival cytokines, activation of T_H cells and NK cells, as well as antiangiogenic activity.

Two trials have demonstrated clinical benefit in relapsed/refractory CLL. A group at Roswell Park Cancer Center administered 25 mg of lenalidomide for 21 days of a 28-day cycle to 45 patients and found an overall response rate of 47% and a complete response rate of 9%.[66] Another trial used lenalidomide at 10 mg daily and achieved an overall response rate of 32% and a complete response rate of 7%.[67] Lenalidomide has shown efficacy in the upfront setting as well.[68] Tumor flare, characterized by tender, swollen lymph nodes and fever was a significant side effect in all of these studies. The dosing and schedule of administration of this agent in CLL remain significant issues under investigation.

• **Ofatumumab, Lumiliximab, and Flavopiridol**—Ofatumumab is a fully humanized monoclonal antibody that targets CD20 at a distinct epitope from that targeted by rituximab. An interim analysis of a multicenter phase II study of ofatumumab in CLL patients who were either refractory to both fludarabine and alemtuzumab (double-refractory) or fludarabine-refractory with bulky lymph nodes showed impressive results. The 79 fludarabine-refractory patients with bulky lymph nodes and the 59 patients with double-refractory disease had overall response rates of 47% and 58%, respectively.[69] Additional clinical trials with ofatumumab are underway in both relapsed and first-line settings.

Lumiliximab is macaque-human primatized anti-CD23 monoclonal antibody. A phase II trial of 31 patients with relapsed/refractory CLL evaluating the combination of lumiliximab plus FCR yielded an overall response rate of 65% with 52% complete responses.[70] Patients with 11q deletion abnormalities had high response rates and durable remissions. A phase III trial comparing FCR plus lumiliximab to FCR alone is underway.

Flavopiridol is a cyclin-dependent kinase inhibitor that has shown impressive activity in CLL. A phase II trial of relapsed/refractory CLL demonstrated a response rate of 48%, with 6% of patients achieving a complete response.[71] Many of these patients had 17p and 11q deletions.

This agent may ultimately play an important role in bridging refractory patients to allogeneic transplants.

In addition to the agents discussed above, inhibitors of heat shock protein 90, bcl-2, telomerase, and protein kinase C are a few of the additional classes of agents showing promise in CLL.

Recommendations—Ample data exist regarding effective treatments in CLL, but many questions remain, even with currently accepted therapies. The heterogeneity of disease manifestations, and the varied fitness of CLL patients makes a straightforward algorithm for CLL treatment difficult. The first step is to determine the goals of treatment for a patient. In relatively young patients in otherwise good health, achieving the longest duration of remission possible is a reasonable goal. At this time, however, achievement of MRD negativity should remain an aim only in clinical trials. Either FCR or FR is an acceptable choice for these patients, and many clinicians reasonably use PCR as well.

As described above, in patients with high-risk cytogenetic lesions such as 17p deletion, legitimate concern exists regarding a resistance to traditional chemotherapies. A minority of patients will have adequate responses to these treatments, and a trial of these is appropriate as long as careful evaluation is made early in the treatment course. If there is evidence of resistance, then a quick change to another therapy should be made. Our first preference is a clinical trial in this setting, though a consideration of alemtuzumab-based treatment is reasonable if a trial is not possible.

In elderly patients, or patients with significant comorbid conditions, a conservative approach should be taken, with the endpoint being clinical improvement of symptoms or other disease-related manifestations. This may be achieved with a variety of agents or combinations, and there is no standard approach. An assessment of clinical response and toxicities should be performed with each cycle, and appropriate modifications should be made accordingly.

The approach to a relapsed patient also requires a plan tailored according to age, condition, and the nature of his or her response to the prior treatment. Both FCR and PCR have been used with success in the relapsed setting.[64,72] If an otherwise healthy person had a somewhat durable response to purine analog–based therapy, another trial would be reasonable, with or without modifications. For example, if FR was given initially, then FCR could be used for a relapse. Otherwise, a broadening array of monotherapies and combination therapies exist for these patients. Alemtuzumab often plays a critical role in relapsed patients, and more recently bendamustine has proved a valuable addition. Both of these agents have shown encouraging results when combined with rituximab, as well as other agents.[73-76]

Clinical trials are always the preferred option, and newer agents such as lenalidomide, flavopiridol, lumiliximab, and ofatumumab have shown promise in ongoing investigations. Allogeneic transplant is another important tool in relapsed patients. New data with reduced-intensity conditioning has demonstrated a reduction in morbidity and mortality with modest long-term success.[77-79] Although these data are still evolving, consideration of this option should be given to otherwise fit patients after relapse.

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