Abstract: Chronic lymphocytic leukemia (CLL) is the most frequently diagnosed hematologic malignancy in the United States. Although several features can be useful in the diagnosis of CLL, the most important is the immunophenotype. Two staging systems—the Binet system and the Rai classification—are used to assess risk. After diagnosis, the first major therapeutic decision is when to initiate therapy, as a watchful waiting approach is often appropriate for patients with asymptomatic disease. Once a patient has met the criteria for treatment, the choice of therapy is the next major decision. Younger patients (<65 years) often receive more aggressive treatment that typically consists of cytotoxic chemotherapy. There is a great unmet need concerning treatment of older patients with CLL, who often present with more comorbid conditions that can decrease their ability to tolerate particular regimens. The current standard of care for older patients with CLL is rituximab plus chlorambucil. The concept of targeted agents is currently an area of intense interest in CLL. The Bruton’s tyrosine kinase inhibitor ibrutinib is the targeted agent that is furthest along in clinical development. It is associated with an overall survival rate of 83%. Idelalisib targets the phosphatidylinositol 3-kinase and is under evaluation in pivotal trials. Targeted agents offer much promise in terms of efficacy, toxicity, and oral availability. They will change the management of patients with CLL.
Chronic lymphocytic leukemia (CLL) is the most common leukemia subtype among adults in North America. Approximately 15,680 cases were diagnosed in 2013. As of 2010, the estimated prevalence in the United States was approximately 120,000 cases. Interestingly, CLL appears to occur more frequently in North America and Western Europe compared with other areas of the world. For example, CLL is rare in Japan. The median age of diagnosis is 72 years.

Diagnostic Characteristics of CLL

On a peripheral blood smear, CLL classically appears as mature resting B cells with a large number of smudge cells (Figure 1). A diagnosis of CLL is made when greater than 55% of the lymphocytes present on peripheral blood smear are prolymphocytes. Based on the International Workshop on CLL (IWCLL) 2008 criteria, an absolute B-lymphocyte count of more than 5000 cells/mm³ in the peripheral blood is required for a diagnosis of CLL. This threshold is an important distinction, as patients with fewer than 5000 cells/mm³ in the absence of lymphadenopathy, bone marrow infiltration, or cytopenias are diagnosed with monoclonal B-lymphocytosis, which is a separate disease entity with a different prognosis. Small lymphocytic leukemia (SLL) is a different manifestation of the same malignancy, in which the abnormal lymphocytes are predominantly found in the lymph nodes. The diagnosis of SLL requires a limit of 5000 cells/mm³ in the peripheral blood and the presence of lymphadenopathy, splenomegaly, or cytopenias.

Another characteristic of CLL is lymphocyte involvement of at least 30% of the bone marrow. Although a bone marrow aspirate or biopsy is typically not required for a diagnosis of CLL, each can help in the evaluation of underlying cytopenias.

Immunophenotyping is necessary for the diagnosis of CLL. According to the National Comprehensive Cancer Network (NCCN) guidelines, the recommended panel for immunophenotyping includes CD light chains, CD19, CD20, CD5, CD23, CD10, and immunocytochemistry for cyclin D1. The typical immunophenotype of CLL cases is CD5-positive, CD10-negative, CD19-positive, CD20-dim, surface immunoglobulin–dim, CD23-positive, and cyclin D1–negative. Most patients with CLL will show dim surface expression of CD20, but some subgroups—such as those with trisomy 12—will show brighter staining.

CLL is often thought to be derived from 2 stages of B-cell maturation. The first subtype, which consists of...
CLL cases with nonmutated cells, was thought to derive from a naive resting B cell. The second subtype, which consists of CLL cases with mutated cells, was thought to derive from a marginal zone or memory B cell. Emerging evidence, however, has suggested that both nonmutated and mutated forms of CLL are derived from post–antigen-experienced B cells. The difference between the nonmutated and mutated forms arises in how the B cell became experienced, with nonmutated CLL cells arising from T cell–independent antigen B-cell maturation and mutated CLL cells arising from T cell–dependent antigen B-cell maturation.

Classification of CLL

CLL patients have disease that is disseminated from the outset, so it is important to have a staging system that provides prognostic information. Two staging systems are widely used in CLL in both clinical practice and clinical trials.

The original clinical staging system for CLL, published in 1975, is the Rai classification. In this system, stage 0 refers to patients with only a lymphocytosis in the blood or bone marrow. These patients are considered to be at low risk, with a survival rate essentially similar to age-matched controls. Patients with lymphocytosis with enlarged nodes are classified as stage 1. Patients with lymphocytosis plus hepatosplenomegaly, with or without lymphadenopathy, are categorized as stage 2. Stage 1 and stage 2 patients are considered to be at intermediate risk. Patients with anemia or thrombocytopenia in addition to lymphocytosis are categorized as stages 3 or 4, respectively. Survival by stage, at the time of publication in 1975, was more than 150 months for low-risk (Rai stage 0), 71 to 101 months for intermediate-risk (Rai stage 1 and 2), and 19 months for high-risk (Rai stage 3 and 4) patients. In a 2007 update by Wierda and colleagues, the estimated median survival times were not reached for low-risk patients, 10.3 years for intermediate-risk patients, and 5.4 years for high-risk patients.

The Rai classification system identifies a patient’s risk of progression and provides guidance as to when a treatment intervention is required. Overall, the majority of patients present with asymptomatic disease. The diagnosis is often made in the course of routine blood work. However, some patients experience painless lymphadenopathy or occasional B symptoms, including fever, chills, night sweats, and weight loss. Approximately one-quarter of patients also experience immune dysregulation, most commonly manifested as autoimmune hemolytic anemia or immune thrombocytopenic purpura. Interestingly, the autoimmunity observed in CLL seems to be restricted to blood-borne targets, as shown by the fact that thyroiditis and type 1 diabetes are not more common in these patients.

Progression to symptomatic CLL typically occurs through the accumulation of lymphocytes in various organs, leading to lymphadenopathy or hepatosplenomegaly when they accumulate in the lymph nodes, liver, or spleen, and anemia or thrombocytopenia when they accumulate in the bone marrow. Up to 75% of patients with CLL will demonstrate hypogammaglobulinemia, which can lead to recurrent infections, most commonly a sinusitis or bronchitis. It is interesting to note that CLL patients also demonstrate defects in T-cell function, as demonstrated by an increase in shingles and pneumocystis pneumonia infections. It is certainly possible that the B-cell deficit leading to hypogammaglobulinemia is secondary to T-cell dysfunction.

The Binet staging system is somewhat similar to the Rai system, in that it is based on levels of hemoglobin and platelets, as well as the number of involved areas. During the 1990s, approximately 72% of patients were diagnosed with Binet stage A disease, the earliest stage. Interestingly, this percentage represents a major shift from earlier cohorts of patients; for example, only 26% of patients were diagnosed with Binet stage A disease between 1970 and 1979. This shift toward an earlier stage at diagnosis has allowed patients to live much longer with CLL. However, it is important to realize that the advances that have been made in the treatment of CLL have focused primarily on the more advanced Binet stage C disease.

CLL Prognosis

Patients with CLL demonstrate a tremendously variable course of disease progression. Approximately 70% of patients with CLL will die of their disease or a complication of it; therefore, physicians must confront this topic with their patients. It is critical to identify which patients will require early therapy. Many of the current therapies are associated with adverse events, and it is important to treat only those patients who genuinely require intervention in order to spare others from treatment-related toxicities. Numerous prognostic markers have been reported in CLL (Table 1). Among the traditional group of biomarkers are Rai stage, lymphocyte doubling time, pattern of bone marrow infiltration, age, sex, karyotype, \( \beta_2 \)-microglobulin levels, and the number of circulating prolymphocytes. Novel prognostic markers in clinical use include the immunoglobulin heavy-chain variable region \( (IgV_H) \) gene mutational status, CD38 expression, ZAP-70 expression, and interphase fluorescence in situ hybridization (FISH) abnormalities.

Using these prognostic markers, one can generate survival curves and assign individual patients to a particular curve. It is important to remember that these curves are only prognostic in nature, and they do not provide information on optimal clinical management. Additionally, it
is important to consider that these prognosis curves can predict only how a population of patients with similar characteristics will perform; they cannot be used to determine exactly how an individual patient with CLL will fare.

Unlike the prognosis curves, clinical stage can be used to help determine when to initiate therapy in a patient. Two areas where prognostic markers can impact upon the clinical management of patients including the clinical stage and the interphase FISH abnormality. Clinical stage helps to determine when treatment is indicated, by demonstrating the patient’s disease has become active. Interphase FISH abnormalities can help identify the likelihood of a patient responding to a therapy. Data from the German CLL Study Group CLL4 trial comparing fludarabine to fludarabine plus cyclophosphamide (FC) demonstrated that patients with a deletion of 11q responded favorably to the combination of FC, whereas they responded poorly to fludarabine alone.11-13 Additionally, patients with deletion 17p tended to respond poorly to all chemotherapy.

Zap-70 and immunoglobulin mutational status are very effective in determining prognosis, but at this time, there are no clinical data supporting making treatment decisions based upon these results. Many additional prognostic markers exist, each demonstrating the ability to predict outcome. Information gained by identifying these prognostic markers will be helpful in improving our understanding of CLL.14,15 ZAP-70–positive CLL cases with a mutated \( IgV_{\mu} \) have a far more aggressive course compared with ZAP-70–negative cases with a nonmutated \( IgV_{\mu} \) gene. Patients with nonmutated \( IgV_{\mu} \) rearrangements involving the VH3-21 gene tend to have a poor prognosis equal to that of patients with nonmutated \( IgV_{\mu} \).

Acknowledgment

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References

Deciding When to Begin Treatment

The major question when managing a patient with CLL is when to initiate therapy. The answer is dictated primarily by the course of the disease and the pattern and timing of progression to a symptomatic presentation. Most clinical practices rely on recommendations from the IWCLL to guide therapeutic decisions.1 Typically, newly diagnosed patients with asymptomatic early-stage disease can be observed with a watchful waiting approach until evidence of disease progression. Progression to intermediate-risk or high-risk Rai stages is not in itself sufficient to warrant treatment initiation, as a subset of these patients can still be effectively monitored without therapy with no detriment to their overall survival.

The IWCLL lists several criteria based on disease-related symptoms that can be used to assess patients for initiation of therapy; at least 1 of these criteria must be met before treatment is started.1 The criteria include (1) evidence of progressive bone marrow failure, manifested by development or worsening of anemia and/or thrombocytopenia; (2) massive, progressive, or symptomatic splenomegaly; (3) massive nodes or progressive or symptomatic lymphadenopathy; (4) progressive lymphocytosis with an increase of greater than 50% over a period of 2 months or a lymphocyte doubling time of fewer than 6 months; (5) autoimmune anemia and/or thrombocytopenia poorly responsive to standard therapy; and (6) constitutional symptoms, including unintentional weight loss, significant fatigue, fevers, and night sweats. Lymphocyte count may also be used as an indication for treatment, particularly when it exceeds 300,000 cells/mm³. Most patients develop at least 1 of the criteria for treatment before their lymphocyte level approaches this figure. Although lymphocyte doubling time is included as one of the IWCLL criteria, its use as a trigger for treatment initiation is becoming less widespread because this value can be misleading when it is low in a patient with no other symptoms.

A question to consider is why treatment is initiated in CLL patients only when they become symptomatic. This recommendation is based on several older randomized studies that failed to demonstrate a survival advantage, or any other benefit in outcome, with the use of alkylating agent–based therapy in patients with early-stage CLL.2-4 A meta-analysis of 6 trials that investigated immediate vs deferred introduction of chemotherapy in early-stage CLL reported that 10-year overall survival was slightly worse in patients treated with immediate chemotherapy compared with those who underwent watchful waiting (44% vs 47%), although this difference did not reach statistical significance.5 It is important to note that these trials were all conducted during the 1990s; since then, a number of prognostic factors have been identified that may provide some measure to assess early-stage patients for treatment. Furthermore, there may be a better justification for treatment with some of the newer agents for CLL in this setting. These issues will be investigated in ongoing and future clinical trials.

Once a patient has met the criteria for treatment, the choice of therapy is the next major decision. This choice is dependent upon a variety of features. The tolerability of a particular treatment regimen must be considered in view of the patient’s physical fitness and overall health.6 For example, in the United States, patient age is one of the most important factors, whereas in Europe, functional status is the primary characteristic. Younger patients (<65 years) represent only one-third of patients with CLL, but they are disproportionately overrepresented in clinical trials. Patients in this age group often receive more aggressive treatment that typically

**Traditional Treatment Approaches in Chronic Lymphocytic Leukemia**

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consists of cytotoxic chemotherapy. There is a greater unmet need concerning treatment of older patients with CLL, who often present with more comorbid conditions that can decrease their ability to tolerate particular regimens.

**Choice of Frontline Therapy: Younger Patients**

The introduction of the CD20-targeted monoclonal antibody rituximab changed the approach to treatment of CLL. It was the first agent that, when added to chemotherapy, increased survival compared with the use of chemotherapy alone.\(^7\) Chemoimmunotherapy has now become the standard treatment approach for younger patients with CLL. The selection of a particular chemoimmunotherapy regimen is in part based on the interphase cytogenetics as assessed by FISH at the time of treatment.

In general, the presence of certain cytogenetic abnormalities, including deletion of chromosome 13q, trisomy 12, or deletion of chromosome 11q, leads to treatment with a chemoimmunotherapeutic regimen of fludarabine and cyclophosphamide plus rituximab (FCR). This treatment choice was established by the results of the large, international, randomized, phase 3 CLL8 study, which demonstrated improvements in several patient outcomes with this regimen when compared with FC alone.\(^7\) The patients’ median age in this study was 61 years. Compared with FC, FCR was associated with a higher overall response rate (88% vs 95%), complete response rate (22% vs 44%), median progression-free survival (33 months vs 52 months; \(P<.001\)), and overall survival at 3 years (83% vs 87%; hazard ratio [HR], 0.67; 95% CI, 0.48-0.92; \(P<.0001\)).

Treatment of patients with the del(17p) cytogenetic abnormality presents a greater challenge. Del(17p) abnormalities are associated with the worst outcomes, as these patients have short treatment-free intervals, poor response to chemotherapy, and short median overall survival time (32 months).\(^8\) In the CLL8 trial, this abnormality was identified as an independent predictor of poor survival outcomes, regardless of which treatment was used. For example, the 3-year progression-free survival rate with FCR was only 18% for patients with the del(17p) abnormality. Therefore, treatment of patients with this characteristic represents an unmet need in CLL. The approach to the treatment of younger patients with del(17p) has been to employ a cytoreduction therapy with either FCR or a nonchemotherapy-based treatment, such as rituximab plus high-dose methylprednisolone. Once the patient is successfully cytoreduced, he or she then has the option to undergo allogeneic stem cell transplantation from a related or an unrelated donor. This treatment approach may change, however, as targeted therapies increasingly become an option for these patients.

Patients with \(IgV_{H}\)-mutated disease account for approximately 40% of those who enroll in upfront studies with FCR. A study presented at the 2013 IWCLL reported an interesting observation made among patients with an \(IgV_{H}\) mutation who were followed for up to 10 years in a trial performed by MD Anderson and the German CLL Study Group.\(^9\) These patients seemed to reach a plateau in terms of the numbers who experienced disease relapse. Therefore, as we move forward into the era of targeted therapy; treatment of this patient group will become a matter of greater debate. It remains unclear whether these low-risk patients would benefit more from 6 months of the current standard therapy, or whether they should be treated with a novel alternative approach. The results of this study suggest that we are approaching a curative treatment for this particular subset of patients with CLL, although longer follow-up beyond 10 years is necessary for confirmation.

**Choice of Frontline Therapy: Older Patients**

A somewhat different approach is taken for the treatment of older patients (>65 years) with CLL. Although FC and FCR have demonstrated a benefit in younger patients, their role is less clear in older patients. For example, the phase 3 CLL5 study randomized older patients (median age, 70 years) to frontline treatment with either fludarabine or chlorambucil.\(^10\) Fludarabine was associated with a significantly higher rate of overall response (72% vs 51%) and complete response (7% vs 0%) compared with chlorambucil, but there was no significant difference in median progression-free survival (19 months with fludarabine vs 18 months with chlorambucil) or median overall survival (46 months with fludarabine vs 64 months with chlorambucil). The Kaplan-Meier survival curves from this study suggested a slight benefit with chlorambucil compared...
Obinutuzumab is a type 2 anti-CD20 antibody. This trial randomized CLL patients of any age (mean age, 72 to 74 years across arms) to treat- ment with obinutuzumab plus chlorambucil and 15.2 months with rituximab plus chlorambucil.13 In updated results of the phase 3 CLL11 trial, overall survival was significantly higher with obinutuzumab plus chlorambucil compared with chlorambucil alone. The updated analysis showed similar results. Progression-free survival was superior with both combination regimens as compared with chlorambucil alone. The updated median PFS was 26.7 months with obinutuzumab plus chlorambucil, 15.2 months with rituximab plus chlorambucil, and 11.1 months with chlorambucil alone (Figure 3). Overall survival was improved with rituximab plus chlorambucil as compared with chlorambucil alone, but the difference was not significant. The rates of toxicity with obinutuzumab compared with rituximab were similar, with obinutuzumab associated with a higher risk of infection. Although there was also an increased rate of neutropenia in the antibody arms, it did not lead to a higher risk of infection.

Further exploration of the combination of chlorambucil and rituximab was prompted by data in younger patients showing that rituximab improved survival when added to fludarabine compared with single-agent fludarabine alone.7 This combination has been evaluated in phase 2 trials. In a multicenter study of older Italian patients (median age, 70 years), induction therapy consisted of chlorambucil combined with rituximab; responding patients were randomized to receive up to 2 years of maintenance treatment with rituximab or observation only.8 The overall response rate following the induction phase of this study was 81%, with 16.5% of patients experiencing a complete response. A trial in the United Kingdom that enrolled older patients (median age, 70 years), demonstrated a similar overall response rate (80%) and complete response rate (12%) following combination therapy with chlorambucil plus rituximab.9

Two recent studies have investigated chlorambucil in combination with novel anti-CD20 antibodies. The 2-arm, phase 3 CLL11 trial was presented at the 2013 American Society of Clinical Oncology Annual Meeting and updated at the 2013 American Society of Hematology meeting.10,11 This trial randomized CLL patients of any age (mean age, 72 to 74 years across arms) to treatment with either obinutuzumab (GA101) plus chlorambucil, rituximab plus chlorambucil, or single-agent chlorambucil.12 Obinutuzumab is a type 2 anti-CD20 antibody that may lead to more potent CLL cell death. In the earlier analysis, the combination of obinutuzumab plus chlorambucil resulted in more than a doubling of median progression-free survival compared with chlorambucil alone (23 months vs 10.9 months; P<.0001). The updated analysis showed similar results. Progression-free survival was superior with both combination regimens as compared with chlorambucil alone. The updated median PFS was 26.7 months with obinutuzumab plus chlorambucil, 15.2 months with rituximab plus chlorambucil, and 11.1 months with chlorambucil alone (Figure 3). Overall survival was significantly higher with obinutuzumab plus chlorambucil as compared with chlorambucil alone. Overall survival was improved with rituximab plus chlorambucil as compared with chlorambucil alone, but the difference was not significant. The rates of toxicity were relatively similar across the treatment arms, with the exception of a higher number of infusion reactions in the antibody arms; these reactions tended to be more severe with obinutuzumab compared with rituximab. Although there was also an increased rate of neutropenia in the antibody arms, it did not lead to a higher risk of infection.

A recent phase 3 trial reported significant improvement in progression-free survival with ofatumumab plus chlorambucil vs chlorambucil alone.14 The trial enrolled patients with previously untreated CLL who were not candidates for fludarabine-based therapy. The combination of ofatumumab plus chlorambucil resulted in a significantly prolonged progression-free survival compared with single-agent chlorambucil (22.4 vs 13.1 months; HR, 0.57; P<.001).

Single-agent bendamustine was compared with single-agent chlorambucil in a pivotal phase 3 trial of patients with previously untreated CLL.15 Compared with chlorambucil, treatment with bendamustine led to a significantly higher overall response rate (31% vs 68%; P<.0001), as well as a significantly higher complete response rate (2%...
vs 31%; P < 0.0001). Median progression-free survival was significantly increased with bendamustine (9 months vs 21 months; P < 0.0001; Figure 4). Importantly, the benefit associated with bendamustine was maintained in a separate subgroup analysis of older CLL patients.18

Based on these data, the current standard of care for older patients with CLL is rituximab plus chlorambucil. In the near future, however, it is likely that another option will include chlorambucil in combination with obinutuzumab and/or ofatumumab. If the patient has cytogenetic abnormalities that do not include del(17p), the combinations of chlorambucil plus an anti-CD20 antibody or bendamustine plus an anti-CD20 antibody would be appropriate. For patients with the del(17p) abnormality, rituximab plus high-dose methylprednisolone is an adequate cytoreductive regimen. Along with younger patients, this population will likely be among the first to move to targeted therapy.

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References

Targeted Agents in Chronic Lymphocytic Leukemia

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The concept of targeted agents is currently an area of intense interest in CLL. Targeted therapy for CLL is based on the understanding that it is a disease of B cells. Inhibition of the B-cell receptor on these cells could interfere with the strong proliferative advantage and survival advantage that it normally confers, thus providing a favorable impact against the disease. Thus far, the molecules that have been targeted by agents in clinical trials for CLL are all kinases situated within the B-cell receptor pathway. Another similarity is that they are all orally available, which offers an attractive option from a patient perspective.

The first targeted agent developed in CLL was fostamatinib, a somewhat nonspecific inhibitor of the spleen tyrosine kinase (Syk). Fostamatinib was evaluated in a phase 1/2 clinical trial among patients with recurrent B-cell non-Hodgkin lymphoma, including 11 patients with SLL/CLL. The overall objective response rate of 22% increased to 55% in the SLL/CLL cohort. Since this initial report, however, clinical development of fostamatinib has occurred primarily in rheumatoid arthritis, where phase 3 clinical trials were reported earlier this year.

The overall objective response rate of 22% increased to 55% in the SLL/CLL cohort. Since this initial report, however, clinical development of fostamatinib has occurred primarily in rheumatoid arthritis, where phase 3 clinical trials were reported earlier this year.

More recently, targeted therapies in CLL have focused on inhibition of Bruton’s tyrosine kinase (BTK), a cytoplasmic kinase that is a downstream component of the B-cell receptor pathway. The BTK inhibitor ibrutinib is the targeted agent that is furthest along in clinical development. Data were recently reported from a phase 1b/2 multicenter study among 85 patients with relapsed CLL. Two doses were evaluated: 420 mg and 840 mg. Most of the adverse events reported were grade 1 or 2, and there were minimal hematologic toxicities. The overall response rate was 71% in both dosage groups: 20% and 15% of patients experienced a partial response in the 420-mg and 840-mg groups, respectively. At 26 months, estimated progression-free survival was 75%, and overall survival was 83% (Figure 5). Ibrutinib is currently under further investigation in pivotal trials and was recently submitted as a new drug application to the US Food and Drug Administration. In November 2013, ibrutinib was approved as a single agent for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

Another major target for CLL is phosphatidylinositol 3-kinase (PI3K), a key downstream regulator of the B-cell receptor pathway that is involved in cellular trafficking, survival, and proliferation. Among the PI3K-targeted agents, the furthest in clinical development is idelalisib. Final results of a phase 1 study of idelalisib in 54 patients with CLL showed a 56% overall response rate and a median progression-free survival of 17 months. Several patients also experienced resolution of splenomegaly and normalization of cytopenias. Grade 3 or higher adverse events included pneumonia (19%), diarrhea (6%), pyrexia (4%), fatigue (2%), and increased liver enzymes (2%). Idelalisib is now under evaluation in pivotal trials. Results from a phase 3, randomized, double-blind, placebo-controlled trial of idelalisib plus rituximab in high-risk patients with heavily pretreated, relapsed CLL who were not suitable for cytotoxic chemotherapy were presented by Dr Richard Furman in a late-breaking abstract at the 2013 American Society of Hematology meeting. As compared with rituximab alone, the combination of idelalisib plus rituximab improved progression-free survival (HR, 0.15; P<.0001), overall response rate (odds ratio, 29.92; P<.0001), lymph node response

Figure 5. In a phase 1b/2 multicenter study examining ibrutinib in patients with relapsed chronic lymphocytic leukemia, the overall survival was 83% at 26 months. Adapted from Byrd JC et al. N Engl J Med. 2013;369(1):32-42.®
(odds ratio, 264.46; \(P<0.0001\)), and overall survival (HR, 0.28; \(P=0.018\)). The safety profile was acceptable.

Interestingly, ibrutinib and idelalisib are associated with similar patterns of response. The initial response is very rapid and marked by a dramatically quick reduction in adenopathy associated with a rising lymphocyte count. This response is distinct from what is observed with chemotherapy and anti-CD20 monoclonal antibodies. Early in the phase 1 trials described above, some patients were taken off the study because physicians interpreted a rise in lymphocyte count as disease progression. It became clear, however, that disease progression was not the explanation, as patients were also showing concurrent shrinkage of adenopathies that were sometimes very large. Preclinical studies have now demonstrated that some of the chemokines that cause the cells to chemotax and adhere to the stroma are being interrupted with these agents. When these cells are inhibited, they begin to leave the stroma and progress into the circulation. There also seems to be some degree of direct cell death, because if all of the cells were released into the peripheral blood, then the lymphocyte count would be even higher than it is.

Because of this unique pattern of cellular response, the definition of clinical response to these agents is currently not well established. For example, a patient who achieves an 80% reduction in lymphadenopathy very early in treatment will probably not have a lymphocyte count that is 50% below baseline, and therefore he or she would not meet the definition of even partial response according to traditional IWCLL criteria. This phenomenon has led to use of the terms nodal partial response and partial response with lymphocytosis, in an attempt to account for the unique response induced by these agents (Figure 6). As the lymphocytosis resolves over time, the patient will then meet the traditional definition of partial response. The primary responses to these targeted agents will be nodal responses, particularly early in the course of therapy, but the interpretation of these responses changes depending on when they are evaluated.

There have been several exciting findings associated with the use of targeted agents. They have achieved durable responses even in highly refractory patients. For example, the median rate of progression-free survival was 18 months for idelalisib and has not been reached at 24 months for ibrutinib.\(^9,10\) Another advantage is that these agents cause much less myelosuppression than chemotherapy, an important point because myelosuppression (and associated infection) is one of the most frequent complications when treating CLL. Myelosuppression adds to the immunosuppression already present at baseline in CLL patients, making it by far the most difficult complication encountered. Myelosuppression is especially important among older patients with CLL, in whom infection often has significant consequences.

![Figure 6](Image)

**Figure 6.** The unique pattern of cellular response associated with novel agents such as ibrutinib led to use of the term partial response with lymphocytosis in a phase 1b/2 multicenter study examining ibrutinib in patients with relapsed chronic lymphocytic leukemia. Adapted from Byrd JC et al. *N Engl J Med.* 2013;369(1):32-42.\(^3\)

Notably, even patients with the del(17p) cytogenetic abnormality, who typically do poorly with standard frontline chemoimmunotherapy regimens, seem to respond well to these targeted agents. In refractory del(17p) patients, ibrutinib achieved higher rates of response and longer median progression-free survival than seen in previously untreated del(17p) patients receiving initial chemoimmunotherapy.\(^11\)

**Questions Regarding the Use of Targeted Agents**

There is no doubt that these drugs offer much promise in terms of their efficacy, toxicity profile, and oral availability. They will change the way patients with CLL are managed. Several questions, however, have arisen regarding their use. It is not yet known whether these drugs will be used as single agents or as part of combination regimens. If they are used in combination, what will they be combined with? The rationale for using them in combination regimens is partly based on the dramatic lymphocytosis that occurs with upfront use, as well as the fact that most remissions are only partial. There is the potential that deeper responses will be achieved with a combination regimen. Achievement of a complete response may allow patients to stop treatment, although this possibility must be tested.

Another important question is whether targeted agents should be used in patients who are likely to show no evidence of disease progression, even at 10 years of follow-up, after treatment with FCR. There are rare but serious late complications of FCR, such as treatment-related myelodysplastic syndrome, that could possibly be averted by a switch to targeted therapy, but no targeted therapy has yet produced such durable remissions.
Unmet Needs in the Treatment of Chronic Lymphocytic Leukemia: General Discussion

Susan M. O’Brien, MD  How will the new targeted agents be incorporated into CLL treatment?

John C. Byrd, MD  The issue you raised concerning when these agents will be used is very important. It is likely that their initial approval in CLL will be for salvage therapy, and approval for frontline use will come later. Physicians may be tempted to give these agents before they are needed, especially for the frontline treatment of elderly patients. Some patients will be able to go a long time without needing treatment. It will be important not to ignore the criteria that we use to decide when to initially begin therapy, until we have data—perhaps in high-risk patient populations—showing that these agents afford a benefit with early use. Although targeted treatments are associated with fewer adverse events, they still should not be used until benefit clearly outweighs any risk. It is possible that late side effects will occur with prolonged use of these agents.

Susan M. O’Brien, MD  I agree that early use of these agents will be tempting. For example, I have been asked how to treat early-stage patients with del(11q), non-mutated IgV_{\mu}, and ZAP-70–positive status. In these patients, the question is when, not whether, treatment will be needed. But it cannot be assumed, without any clinical trial data, that frontline targeted agents will create better responses. It is a fair question for a clinical trial.

Richard R. Furman, MD  The advent of these nontoxic, highly effective therapies is a tremendous step forward for patients with CLL. Their availability raises important questions, such as whether early treatment of high-risk patients might help avoid complications such as genomic instability and Richter syndrome. This notion is alluring, but it must be evaluated in a clinical trial. It is still necessary to delay treatment until patients meet the established criteria in published guidelines.

Susan M. O’Brien, MD  When ibrutinib and idelalisib receive FDA approval for CLL, will you use them as single agents or in combination with another drug in patients with relapsed disease?

John C. Byrd, MD  The most compelling data support ibrutinib as monotherapy.1 Ongoing randomized studies are investigating ibrutinib in combination with bendamustine or rituximab. As of yet, no data show that the addition of chemotherapy or an antibody improves progression-free survival compared with ibrutinib alone. These combinations would increase the toxicity profile.

Most of the trials with idelalisib have studied combination regimens.2 I delalisib will likely be approved in combination with rituximab. The duration of response is not quite as robust for idelalisib as for ibrutinib. Therefore, I will likely use idelalisib in combination with an anti-CD20 antibody (but not chemotherapy).

References


Richard R. Furman, MD  An important consideration is that we are not seeing deep complete responses, or even a large number of complete responses, with these novel targeted agents. I am concerned that persistent disease will lead to resistance. One possible approach might be to use a monoclonal antibody after patients achieve resolution of lymphocytosis and a low level of disease. This strategy would take advantage of different mechanisms of action to eradicate the few remaining cells. It might be an important approach to consider, given the fact that we do not yet know what will happen 5 or more years following treatment with targeted agents. It is preferable to avoid chemotherapy now that patients with CLL are living beyond 10 years after treatment and are susceptible to any late toxicities that might occur with extended treatment.

Susan M. O’Brien, MD  Whether there is any benefit to the faster response observed with these agents is an interesting question. We know that as long as CLL cells are present, the crosstalk with the T cells is abnormal. Does this persistent lymphocytosis increase the risk of continued infections? Extrapolating from chronic myelogenous leukemia, the faster the clone is eradicated, the better. The implication is that more-sensitive patients clear the clone faster. Another possible benefit is that there is less time for resistant-type mutations to develop. There are no data yet regarding progression-free survival with combination therapy, but there are some efficacy data. The data for ofatumumab and ibrutinib are impressive; they showed a 100% response rate with no additional toxicity. Dr Byrd, does that not sway you to use ibrutinib with an antibody?

John C. Byrd, MD  As the data mature, the remissions will probably become deeper. A fascinating aspect concerning ibrutinib is its efficacy in the complex karyotype del(17p) patients. However, even patients with small yet persistent disease are not relapsing. The most compelling reason for these combinations is the possibility that therapy could be stopped at some point. With idelalisib, long-term use might be limited by side effects. With ibrutinib, however, the ability to continue will not necessarily be driven by toxicity. Most likely, it will be driven by the cost of treatment.

Susan M. O’Brien, MD  These targeted therapies have been compared with the tyrosine kinase inhibitors used in chronic myelogenous leukemia, but these agents are in fact dissimilar. The tyrosine kinase inhibitors are associated with molecular remissions, which is why stopping treatment is an area of discussion in chronic myelogenous leukemia. In CLL, however, we are not yet at that point. We could get there with effective combinations; one possibility might be a targeted agent, an antibody, and chemotherapy. There is an urge to avoid chemotherapy because of short-term and long-term toxicities. But would frontline ibrutinib be appropriate for a 64-year-old patient who is IgVH mutated, has trisomy-12, is ZAP-70-negative, and who has progressed enough to need treatment?

Richard R. Furman, MD  In the 1102-CA trial, only 1 patient in the treatment-naive group discontinued therapy, which suggests that resistance does not occur in patients whose disease has not yet developed the secondary genomic instability markers that typically occur with chemotherapy. This finding argues for the upfront use of targeted agents in all patients. That approach would be my preference, especially for the patient you described.

Susan M. O’Brien, MD  One possibility to lessen the late toxicity of chemoimmunotherapy would be to use fewer than 6 cycles of FCR, and this approach should be studied in a trial. Some data suggest that patients who have no minimal residual disease (MRD) after 3 cycles of FCR will not necessarily benefit from further therapy. In our database, only approximately one-third of patients are MRD-negative at that point. It is possible to identify those patients who are going to be in that 10-year plateau. The addition of ibrutinib might increase rates of MRD negativity at 3 months, which would allow the discontinuation of FCR at that point in more than half of patients. This strategy could markedly reduce the late complication of myelodysplastic syndrome or acute myelogenous leukemia, which are the most feared and negative late complications in patients with CLL. These events are infrequent but demoralizing for both patients and physicians because they are associated with poor outcomes. That said, patients who are close to requiring treatment are excited about the oral drugs that will likely soon

John C. Byrd, MD  I agree. But it made me pause when we saw the long-term disease-free survival curves of the German CLL8 study, as well as the work from the MD Anderson group that has shown plateaus in disease progression among low-risk patients treated with FCR. These finding suggest that a subset of patients can achieve prolonged remissions with a 6-month course of chemoimmunotherapy. Although we hesitate to say that these patients are cured, the longer sustained remissions continue, the more likely it becomes. That said, perhaps we can learn from the experience in chronic myelogenous leukemia, in which more aggressive therapies can be applied after the tyrosine kinase inhibitors stop working. We do not know whether that strategy will work in CLL. The emerging sense is that if patients break through, they will respond to other treatments unless they are truly end-stage. That has been our experience.
be available. Some patients have expressed interest in using an oral agent first and then progressing onto chemotherapy later. We do not know whether patients who develop resistance upfront will have the same response to chemotherapy that they would have had otherwise. They may not. The paradigm in CLL is that the first treatment always impacts outcome going forward. However, this concept was based on the use of traditional chemotherapy-based regimens.

John C. Byrd, MD Most patients will want to use an oral agent first before chemotherapy. Unfortunately, use of these oral agents may be influenced by their expense. Where does lenalidomide fit into the treatment of CLL? There are some impressive data with lenalidomide as an immune restoring agent.8

Susan M. O’Brien, MD An attractive aspect of lenalidomide is its ability to induce long-term MRD-negative remissions in patients with relapsed CLL as a single agent. Only a minority of patients will achieve this outcome, but it is impressive when it does occur. The trade-off to the use of lenalidomide is adverse events; unlike the other drugs we have discussed, lenalidomide is myelosuppressive. Another advantage to lenalidomide is that it appears to be immunorestorative. Dr John Gribben’s group has shown that lenalidomide restores the normal B-cell/T-cell synapse needed for adequate crosstalk between the B cells and the T cells, which is markedly impaired in patients with CLL.9 Lenalidomide also increases immunoglobulins, whereas chemotherapy-based regimens do not.

There are no data to suggest that the newer therapies are immunorestorative. This issue is especially important in CLL because these patients do not have a normal immune system even during remission. This deficiency has various ramifications, including a poor response to vaccinations. After we are able to achieve high response rates and durable remissions in CLL, the next major issue will be restoration of the immune system.

Richard R. Furman, MD Recent data show that patients who received ibrutinib for at least 1 year had fewer infections later in the course of therapy compared with earlier. This finding suggests that CLL cells may interfere with the immune synapses, and a reduction in the cell burden may result in some restoration of normal immune function.

Richard R. Furman, MD Once these targeted agents are approved, what will be the best way to sequence them with chemotherapy? Would you suggest using the chemotherapy upfront and the targeted agent subsequently to eradicate remaining disease? Or should the targeted agent be used upfront and then chemotherapy agents initiated at month 6 or 9 to remove residual disease? With this approach, chemotherapy is reserved for when patients are in better shape to tolerate it.

Susan M. O’Brien, MD That is a provocative question that does not have any one answer. I would be inclined to achieve more rapid responses, which can be done with chemotherapy. As I alluded to earlier, I would be interested in adding the targeted agent to see if I could use less chemotherapy, and then potentially continue the targeted agent at a low dose to reach MRD negativity. There are no clear data on the best approach. Pilot trials have shown that when targeted agents are added to chemotherapy, the response rates are perhaps better than what is expected with chemotherapy alone.10 If there is a possibility that treatments will be synergistic, using them in sequence would not provide that benefit if it exists. I would therefore lean toward using combination therapy.

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**Diagnostic Characteristics of Chronic Lymphocytic Leukemia (CLL)**
- On a peripheral blood smear, CLL classically appears as mature-looking B cells with a large number of smudge cells.
- A diagnosis of CLL is made when the percentage of larger or atypical cells, cleaved cells, or prolymphocytes present in the blood lymphocytes is 55% or less.
- Based on the IWCLL 2008 criteria, an absolute B-lymphocyte count of more than 5000 cells/μL in the peripheral blood is required for a diagnosis of CLL.

**CLL Immunophenotyping**
- According to NCCN guidelines, the recommended panel for immunophenotyping includes CD light chains, CD19, CD20, CD5, CD23, CD10, and immunocytochemistry for cyclin D1.
- The typical immunophenotype of CLL cases is CD5-positive, CD10-negative, CD19-positive, CD20dim, surface immunoglobulin-dim, CD23-positive, and cyclin D1-negative.
- Most patients with CLL will show dim surface expression of CD20, but some subgroups—such as those with trisomy 12—will show brighter staining.

**CLL Prognostic Markers**
- Traditional biomarkers include Rai stage, lymphocyte doubling time, pattern of bone marrow infiltration, age, sex, karyotype, β2-microglobulin levels, and the number of circulating prolymphocytes.
- Novel prognostic markers in clinical use include the IgV<sub>κ</sub> gene mutational status, CD38 expression, ZAP-70 expression, and interphase FISH abnormalities.

**When to Initiate Therapy in CLL**
- The major question when managing a patient with CLL is when to initiate therapy.
- The answer is dictated primarily by the course of the disease and the pattern and timing of progression to a symptomatic presentation.
- Most clinical practices rely on recommendations from the IWCLL to guide therapeutic decisions.
- Typically, newly diagnosed patients with asymptomatic early-stage disease can be observed with a watchful waiting approach until evidence of disease progression.

**Choice of Frontline Therapy: Younger Patients**
- Currently, chemoimmunotherapy is the standard treatment approach for younger patients with CLL.
- The selection of a particular chemoimmunotherapy regimen is in part based on the interphase cytogenetics as assessed by FISH at the time of treatment.
- In general, the presence of certain cytogenetic abnormalities, including deletion of chromosome 13q, trisomy 17, or deletion of chromosome 11q, leads to treatment with a chemoimmunotherapeutic regimen of FCR.
- Treatment of patients with the del(17p) cytogenetic abnormality represents an unmet need.

**Choice of Frontline Therapy: Older Patients**
- The current standard of care for older patients with CLL is rituximab plus chlorambucil.
- In the near future, it is likely that another option will include chlorambucil in combination with obinutuzumab and/or ofatumumab.
- If the patient has cytogenetic abnormalities that do not include del(17p), the combination of chlorambucil plus an anti-CD20 antibody or bendamustine plus an anti-CD20 antibody would be appropriate.
- For patients with the del(17p) abnormality, rituximab plus high-dose methotrexate is an adequate cytoreductive regimen.
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