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Chronic Lymphocytic Leukemia: A Case-based Discussion of Recent Advances in Patient Management

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Chronic Lymphocytic Leukemia: Recent Advances in Patient Management

Abstract

Chronic lymphocytic leukemia (CLL) is a hematologic malignancy affecting CD5-positive B cells. In the United States, an estimated 15,490 new cases occurred in 2009, and 4,390 deaths were estimated to be due to CLL. Patients with early-stage CLL are usually not treated, but instead are managed with a watch-and-wait observational approach. Once CLL progresses and the patient begins to experience symptoms, therapeutic options include radiation, cytotoxic chemotherapy, monoclonal antibody treatments, and stem cell transplant. A chemoimmunotherapeutic regimen, in which a chemotherapeutic agent is combined with an antibody, is an increasingly important strategy. Chemoimmunotherapy is an especially attractive alternative for elderly patients, for patients with significant comorbidities, and for those patients who otherwise are not candidates for intensive treatment.

Chronic lymphocytic leukemia (CLL) is a malignant disorder arising from lymphocytes that are morphologically mature but immunologically less developed.¹ These B cells exhibit a unique immunophenotype, characterized by CD5 and CD23 expression. Because mantle cell lymphoma is also a CD5-positive B-cell malignancy, it is also necessary to determine the cyclin D1 expression status, which is negative in CLL.² Currently, 2 different staging systems are used to classify CLL. Both classifications provide prognostic information. The low Rai stage (stage 0) is associated with low-risk disease, Rai stages I–II with intermediate-risk disease, and Rai stages III–IV with high-risk disease. Alternatively, the Binet staging system (consisting of stages A, B, and C) considers the number of involved areas together with the level of hemoglobin and platelets.

Several genetic markers have been found to be of prognostic value in CLL. Mutations within the immuno-

globulin variable region (IgV_H) are associated with a more favorable outcome, whereas CD38 expression and zeta-associated protein 70 (ZAP-70) expression are correlated with a poorer patient outcome. Interestingly, both CD38 and ZAP-70 expression inversely correlate with IgV_H mutation status.³⁻⁵ Chromosomal aberrations, detected by fluorescence in situ hybridization (FISH), are also of prognostic significance. Typical chromosomal aberrations in CLL include deletions such as del(13q), del(11q23), and del(17p), and Trisomy 12.²

Several treatments are now available for both front-line and subsequent CLL therapy. CLL treatment was revolutionized with the approval of rituximab, an anti-CD20 monoclonal antibody. The addition of rituximab to conventional chemotherapy has been shown to significantly improve progression-free survival as well as tumor response. According to the National Comprehensive Cancer Network (NCCN) guidelines, frontline treatment options include (with or without rituximab): chlorambucil with or without prednisone; fludarabine either alone or in combination with cyclophosphamide (FC); cyclophosphamide with or without vincristine and/or prednisone; or cyclophosphamide plus doxorubicin, vincristine, and prednisone (CHOP). The alkylating agent bendamustine has recently been approved for CLL, and the NCCN guidelines recommend its use as a single agent for frontline therapy or, for second-line therapy, as either a single agent or combined with rituximab.²

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Case Presentations

Kanti R. Rai, MD

Case 1

B.C. is a vigorous, athletic elderly man. For the past 25 years, B.C. has traveled to Wyoming each winter to participate in competitive skiing events; he is also a dedicated runner. Despite being diagnosed with early-stage CLL at the age of 72, B.C. has maintained his active lifestyle. At the time of diagnosis, his CLL was found to be between stage 0 and 1 with minimal palpable adenopathy, and he was therefore managed with observation only. Five years after his diagnosis, B.C. developed bulky adenopathy, with progressively larger lymph nodes in the cervical and axillary area, although they remained minimal in the inguinal area. He had no clinically palpable spleen. His total white cell count was not extremely high, but elevated (40,000–45,000). FISH analysis revealed an 11q chromosomal deletion. Based on these symptoms, a decision to initiate treatment was made. B.C. received 4 cycles of FC plus rituximab (FCR) chemoimmunotherapy; treatment was stopped when all of the clinically visible disease had disappeared. He tolerated the treatment. Blood lymphocytes were reduced to between 800–1,000 by 4 months after the last FCR cycle, and his hemoglobin and platelet levels were normal.

Now 80 years old, B.C. is approaching 3 years after the end of treatment, and a total of 8 years from the time of his original diagnosis. He is beginning to exhibit similar signs of bulky adenopathy, although not to the same extent as before. Analysis of the newer prognostic markers has revealed that he has no IgV_H gene mutations, and that he is ZAP-70–positive. Should treatment be resumed, and if so, should FCR or another regimen be used?

Discussion

Wolfgang U. Knauf, MD, PhD Excellent remissions can be expected with FCR treatment in many patients, even elderly patients whose overall condition is good and who do not exhibit any significant comorbidities. B.C. represents a very good example of a case in which an elderly patient may be treated with an intensive chemoimmunotherapy regimen such as FCR. Because the patient responded so well to FCR as first-line therapy, it is quite possible that he will have a similar response now. However, it is important to be cautious when repeating FCR therapy, as it could have cumulative effects on bone marrow function and the

immune system. Ultimately, the decision to use FCR or a similar regimen in an older (≥ 70 years) patient should be based on the presence or absence of comorbidities, as well as the patient's general condition.¹

Kanti R. Rai, MD B.C.'s cytogenetic analysis suggests that he has a relatively unfavorable prognosis. Additionally, we hesitated to administer FCR again, due to the increased risk of the development of myelodysplastic syndromes.^{2,3} The combination of bendamustine/rituximab is an alternative regimen, which has provided encouraging results in CLL thus far. In a phase II study presented by Fischer and colleagues at the 2008 American Society of Hematology (ASH) Annual Meeting and Exposition, the bendamustine/rituximab combination was found to be effective in patients with relapsed and/or refractory CLL (n=81), with an overall response rate of 77.4% (complete response: 14.5%; partial response: 62.9%).⁴ Interestingly, this study also showed that 74.4% of high-risk patients with unmutated IgV_H responded to this combination. When presented with bendamustine/rituximab as an alternative, B.C. was agreeable to it, although it has not yet been initiated.

WK Yes, thus far the data involving bendamustine/rituximab in pretreated CLL patients are promising, and they suggest that this combination is a favorable alternative to an FC or FCR regimen.

Case 2

N.Q. was diagnosed with CLL in his early 50s, a relatively young age to be diagnosed with this disease. For the past 4 years, N.Q. has been managed with observation. He has recently experienced progressively increasing bouts of fatigue. N.Q. remains very busy with a full-time job, although he is not as active as he would like to be. His white blood cell count remained in a slow-growth phase over the first 2.5 years of observation, but recently it has been showing evidence of increasing. During the past year, his white blood cell count has progressively risen, reaching 150,000, while at the same time his hemoglobin levels have been declining from 14 g (3 years ago) to between 9 and 10 g now. The spleen, which was barely palpable at the time of initial diagnosis, has progressively become larger over the past 6–8 months, reaching approximately 8 cm below the

left costal margin. Cytogenetic analysis revealed mutated IgV_H but positive ZAP-70 expression.

Because of his relatively young age and desire for an active lifestyle, we believed it was important to focus on achieving the best possible complete remission with N.Q.'s therapy. In addition, if he did experience a complete response, he could be a candidate for a mini-allogeneic stem cell transplant (SCT). With this in mind, we proceeded with a combination of bendamustine/rituximab chemoimmunotherapy, to which he had an excellent response. Unfortunately, following treatment, N.Q. experienced a profound case of herpes zoster, which covered 2 dermatomes in the L3 and L4 area and spread widely on the right side, with painful blisters and eruptions. The blisters took approximately 1.5 months to clear, and N.Q. now suffers from significant postherpetic neuralgia, which is treated with narcotic analgesics.

Discussion

WK N.Q. was diagnosed with CLL at an unusually young age, and it appears he is affected with a very aggressive subtype of the disease. Attaining a durable progression-free survival or a complete remission was the correct goal at the initiation of therapy.

KR N.Q. is now asking whether he should go ahead with mini-allogeneic SCT. Thus far, we have hesitated to perform the procedure, mainly because we have not wanted to induce further immunosuppression-related exacerbation of the herpes zoster infection. However, N.Q. will turn 56 years old later this year, and he is therefore very anxious to try a potentially curative treatment. Should mini-allogeneic SCT be delayed, and if so, for how long?

WK Currently, only a small proportion of CLL patients are receiving SCT. In general, SCT is not a preferred treatment option for CLL patients, due both to the largely indolent course of the disease and to the fact that most of these patients are elderly.⁵ SCT is typically reserved for younger CLL patients with high-risk disease, usually in the setting of a clinical trial. Although little benefit has been associated with autologous SCT, allogeneic SCT has shown potential as a curative treatment.^{6,7} Traditional allogeneic SCT is associated with a high mortality rate, and reduced-intensity allogeneic SCT—or mini-allo SCT—has provided a less risky yet still effective alternative. Recently, early results from a study being led by the Fred Hutchinson Cancer Research Center in Seattle, Washington, suggested that mini-allo SCT was effective in CLL patients with fludarabine-refractory CLL, resulting in durable remissions.⁸ This 5-year follow-up reported a 55% rate of complete remission, and a 5-year overall survival rate of 50%. Despite these promising results, the risk of complications is still significant, and therefore

this immunosuppressive procedure should be delayed in the case of N.Q.

Case 3

S.T. is a 38-year-old man who was diagnosed 1 year ago with CLL. S.T. experienced a very rapid elevation in peripheral blood leukocyte numbers, which increased from 20,000 at baseline to 200,000 within his first year. His spleen is very large and palpable, occupying the entire left side of the abdomen and spanning the midline into the right side and the pelvis. He has no notable lymphadenopathy. This patient's prognostic markers indicate an unfavorable prognosis with unmutated IgV_H and positive ZAP-70 expression, as well as Trisomy 12; he does not have del(17p).

Discussion

WK In CLL patients, a large spleen may be acting as a filter, thus harboring vast amounts of leukocytes. Additionally, patients with large spleens should be examined for the possibility of complications arising from an obstruction.

KR Yes, but fortunately S.T. has no evidence of an obstruction. However, it is obvious that he needs treatment, and because of the aggressive nature of his disease, the decision of which therapy to administer needs to be made quickly. We are currently considering 3 choices: enrollment in an ongoing CLL Research Consortium study examining first-line treatment with lenalidomide plus rituximab⁹; chemoimmunotherapy with either bendamustine plus rituximab (BR) or FCR; or an immediate splenectomy, followed by BR or FCR. Because this patient has hyperleukocytosis, the white blood cell count may need to be reduced prior to splenectomy, as some patients with baseline hyperleukocytosis can experience a further increase post-splenectomy, causing potential issues with hyperviscosity.

WK S.T. is another example of an unusually young man with poor-prognosis CLL. In these patients especially, mini-allogeneic SCT should be considered at least for second-line treatment. Currently, there are not enough data to support mini-allogeneic SCT for frontline therapy of CLL. In terms of frontline therapy, the most experience with poor prognosis patients is with FCR.^{10,11} BR, if well tolerated, may also be as efficacious and therefore should be considered as well. A phase II German CLL Study Group (GCLLSG) trial, presented at the 2009 ASH Annual Meeting and Exposition, reported an overall response rate of 90.9%, with high response rates even in patients with poor prognostic markers (Trisomy 12: 89.5%; unmutated IgV_H: 88.9%).¹² Similar response rates observed with BR and FCR have prompted the GCLLSG to initiate a prospective, randomized trial

comparing the 2 regimens for frontline therapy in CLL.¹³ The results of this study will help to make this choice more clear in high-risk patients such as S.T. The opportunity to recruit this patient for a prospective trial such as the CLL Research Consortium study described here also provides a reasonable option.

KR Because this patient's spleen is so large, we have opted to avoid chemotherapy as much as possible. Therefore, our current plan is to administer single-agent rituximab with the goal of reducing his absolute white blood cell count and lymphocyte count. Once this goal is reached, we will then reconsider a splenectomy. The consulting surgeon has already decided that the size of the spleen will require an open resection as opposed to a laparoscopic procedure. Once S.T. has undergone the splenectomy, chemotherapy may then become necessary.

WK Yes, this sounds like a preferable treatment course for S.T.

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Case Presentations

Wolfgang U. Knauf, MD, PhD

Case 1

V.P. is a 68-year-old woman who was diagnosed with CLL 4 years ago, when she initially presented with Binet stage A disease without any symptoms. She was observed for the first 3 years, after which she exhibited a rapid increase of leukocytes and a lymphocyte doubling time of less than 12 months. She additionally exhibited a continuous decrease of hemoglobin, declining from approximately 14 g down to 11–12 g. Cytogenetics did not find any chromosomal aberrations; there were no data on ZAP-70 expression, but she was found to be CD38-negative. V.P. is in very good condition with no relevant comorbidities, and she is well-informed and interested in participating in a randomized trial.

Because of her good condition despite rapidly progressive CLL, we offered her participation in the GCLLSG study comparing BR and FCR.¹ V.P. was then randomized to receive 6 cycles of BR. She tolerated the therapy well, and the entire treatment was administered without any dose reductions or delays, with no need to substitute blood products, and with no infectious episodes. Following treatment, her lymph nodes, liver, and spleen were not palpable. She was in good condition, and her hemoglobin levels had risen to 12.5 g, with normalized platelets. Importantly, there was no morphologic or immunologic evidence of CLL in her bone marrow. This complete remission was initially uncertain, because she also had slightly low leukocyte counts of approximately 2,500. However, subsequent tests of her peripheral blood continue to suggest that the CLL was eradicated. V.P. is currently in a watch-and-wait observation period.

Discussion

Kanti R. Rai, MD Obviously, this patient is an example of a very good success story. It seems likely that V.P. will achieve clinical complete remission in response to 6 cycles of BR, because the cytopenia was not very dramatic and she exhibited good hemoglobin levels and platelet counts. Additionally, her bone marrow showed no evidence of residual disease.

Wolfgang U. Knauf, MD, PhD Yes, that is correct—she most likely is in complete remission, and we expect that her leukocyte count will increase steadily over the next several weeks.

KR Because this patient's cytogenetics were unclear, it is hard to determine what the long-term therapeutic endpoint should be. If cytogenetic studies are performed and the patient is found to be IgV_H mutated, then this status—along with her CD38-negative status—would suggest that she should remain under observation for the next several years. Conversely, if a cytogenetic analysis reveals that she is IgV_H unmutated, V.P. should be considered for maintenance therapy if the study protocol allows it.

Case 2

A.T. is an 80-year-old woman in relatively poor condition. She was diagnosed with Binet Stage A CLL approximately 13 years ago, in 1997. In the summer of 2009, A.T. experienced disease progression to Binet Stage B, with a high leukocyte count, splenomegaly, and multiple palpable peripheral lymph nodes. She also now has significant comorbidities, including chronic obstructive lung disease, which has led to her being considered as Eastern Cooperative Oncology Group (ECOG) 2 status. She was diagnosed with breast cancer in 1998, and she was treated with surgery, radiotherapy, and 5 years of endocrine treatment. In 2002, A.T. underwent chest surgery due to a suspected malignant tumor, which was ultimately diagnosed as a tuberculoma.

It was determined that, overall, A.T. was not fit enough to undergo intensive therapy, although she had several indications to begin treatment (including night sweats, growing lymph nodes, increasing spleen size, and a highly elevated leukocyte count of approximately 200,000). At the time, rituximab was not yet approved to treat CLL patients in Europe, where this patient lived. The decision was made to administer chlorambucil, based on published data from this patient's age group indicating that this agent could result in delayed disease progression and improved survival time. After half a year of therapy,

A.T. has attained a partial remission and has a good quality of life. Her leukocyte count declined to 25, and her hemoglobin has remained stable at approximately 13. Although her platelet counts are in the lower range of normal, they have remained stable.

Discussion

KR At this point, it is sensible to add rituximab—which has now been approved in Europe for combined treatment of CLL—to her chlorambucil therapy. Because of this elderly woman's significant comorbidities and hyperleukocytosis, the therapeutic objective should be to keep the disease under control without worsening the quality of life.

WK This approach is in fact what we have discussed with her, with the goal of inducing an improved partial response and attempting to prolong her progression-free survival.

Case 3

L.Z. is a 69-year-old man first diagnosed with CLL in 2003. He received no treatment until 2008, at which time he began to experience hyperleukocytosis, night sweats, and a steadily decreasing hemoglobin level, along with an enlarged spleen. His cytogenetic profile revealed a mixed prognosis, with a 13q14 deletion and positive CD38 expression. Based on this profile, as well as his progression to advanced disease (from Binet Stage A to Stage C), it was determined that he required treatment. At that time, rituximab had not yet been approved for the treatment of CLL, and thus we offered single-agent bendamustine therapy. Following the first bendamustine cycle, L.Z. exhibited a very rapid decrease in leukocyte count, from over 200,000 down to 5,400, within the first 10 days of therapy. Fortunately, this decrease occurred without any symptoms of tumor lysis syndrome, likely due to prophylactic allopurinol and adequate intravenous hydration. L.Z. continued to receive 6 cycles of bendamustine, and he attained a hematologic

complete remission with normalized blood counts and no evidence of organomegaly or palpable lymph nodes. L.Z. then proceeded to be followed with observation, and he has maintained his clinical remission for more than 20 months. His lymphocyte levels have now slowly begun to rise in his peripheral blood.

Discussion

KR The question now is whether this patient should be advised to undergo additional therapy, and, if so, what that therapy should be.

WK Based on encouraging data from the GCLLSG, it appears that BR is effective in the second-line treatment of CLL.² Alternatively, impressive results of second-line therapy with FCR have been shown by Robak and colleagues, who demonstrated its significantly improved efficacy compared with FC alone in patients with previously treated CLL.³

KR Both options would be appropriate choices for the patient.

WK L.Z. is a well-informed patient who follows the medical literature. As it becomes necessary for him to receive therapy, we will consider both options in the context of his condition and any comorbidities arising in the future.

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Question and Answer Forum

Is the choice between FCR versus BR clear for the frontline treatment of CLL?

Kanti R. Rai, MD No, unfortunately there is quite a bit of subjectivity involved in the decision between FCR and BR. Often, it is dependent on the personal experiences of the treating physician. In some cases, FCR is chosen simply because it has been around longer, and thus the physician is more familiar with it. BR is a relatively new regimen that physicians are only now beginning to use with increasing regularity.

Wolfgang U. Knauf, MD, PhD One of the main reasons why one of these regimens has not become firmly established as superior over the other is because they have thus far not been compared in a head-to-head comparison. Therefore, a randomized phase III trial has now been initiated by the GCLLSG, and it is currently recruiting patients with previously untreated CLL.¹ The study has an estimated enrollment of 550 patients, who will be randomized to receive 6 cycles of either BR or FCR. Patients will be observed to compare not only the efficacy of each of these regimens (primary endpoint: 24-month progression-free survival), but their associated toxicities (such as myelosuppression, infections, and secondary neoplasms).

KR Until this trial is completed, however, many physicians will continue to use their own judgment in the absence of clear clinical guidance. Impressive results with BR have prompted some physicians to switch to BR, especially with indications that it may be associated with less myelotoxicity than FCR. However, there is no proof of this benefit, and there will not be until completion of the GCLLSG study.

How do newer therapeutic regimens impact the treatment of older patients who are unable to tolerate intense treatments?

KR Recently, several new agents have received approval from the US Food and Drug Administration (FDA) for the treatment of CLL patients. One of these, bendamustine,

has already been discussed here in the context of a combination regimen with rituximab. However, it has also been shown to be effective as a single-agent therapy both for previously untreated CLL and relapsed/refractory CLL. In fact, bendamustine was shown by Knauf and colleagues to be significantly superior to chlorambucil, which led to its approval.²

Alemtuzumab is a monoclonal antibody directed against the lymphocyte surface protein CD52.³ Alemtuzumab was approved for frontline therapy based on an open-label, randomized study in which it was compared to chlorambucil.⁴ This study demonstrated a significant advantage in progression-free survival for alemtuzumab, as well as improved overall response rates and complete response rates.

The monoclonal antibody ofatumumab has also recently received FDA approval for CLL. Like rituximab, ofatumumab is directed against the surface protein CD20, although it targets a unique epitope within the protein. Ofatumumab is approved for patients with previously treated or refractory/resistant CLL in whom fludarabine-based regimens and alemtuzumab have failed. In an interim analysis of an international study evaluating its safety and efficacy, it was found to be active and well-tolerated even among patients with poor-prognosis CLL.⁵ However, there is very little experience with ofatumumab in the frontline setting.

Another agent that has received FDA approval is the oral formulation of fludarabine. Prior to this approval, fludarabine had only been available via intravenous infusion in the United States, although the oral formulation has been available in Europe and Canada for several years.

WK As physicians have begun to incorporate these newer therapies into their practice, they have learned to consider not only the chronologic age but the biologic age of the patient, as well as existing comorbidities. This information is then used to help determine what should be the most appropriate objective of treatment for an individual patient. For some patients, the goal should be a reduction of tumor burden and an alleviation of symptoms, whereas for others,

the goal is to achieve a complete remission or even negative minimal residual disease. When incorporating these newer therapies, the physician should treat each patient as a unique individual and determine how each would best be served by a particular therapy.

Regardless of chronologic age, there is a certain proportion of CLL patients who are not considered fit enough to undergo intensive therapy. For these patients, most physicians have relied on chlorambucil; however, increasing use of rituximab has provided these patients with an important alternative.

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Commentary

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The cases described in this monograph represent a number of relatively common yet challenging issues in the management of patients with CLL. In the first from Dr. Rai, the patient was elderly, although fit. The treatment was with FCR, which is not routinely tolerated well by patients over the age of 65 years, although this patient did relatively well with it. In most patients in this age group, FR or BR would be the regimens of choice, preferably the latter given the subclinical renal dysfunction often encountered. In contrast was Case 2, a relatively young patient with a quiescent course for several years that began to accelerate with an increasing white blood cell count and splenomegaly, as well as progressive anemia, all indications to prompt consideration of therapy. Chemotherapy with BR was complicated by severe herpes zoster. This case raises several issues: in general, prophylactic antimicrobials are not recommended with the use of BR because of the low incidence of opportunistic infections. However, this patient was one of the unfortunate ones. The role of bone marrow transplantation remains controversial in CLL. Autologous transplantation has no role at the present time. The results with submyeloablative allogeneic transplants have been encouraging. However, in the absence of unfavorable biologic factors, I would not recommend this approach to a patient with a CR from induction treatment, and I generally reserve bone marrow transplant for younger patients with an unsatisfactory or short-lived response to initial treatment. The third case is a patient with an extremely poor prognosis. I wonder if the cytogenetic studies reported were at diagnosis or at the time of rapid disease progression. If the former, I would repeat the FISH, as clonal evolution should be considered when the disease undergoes a marked change in pace. A transplant should be considered if disease control is achieved.

In Dr. Knauf's first case, the question of maintenance therapy is raised if the patient achieved a complete response (CR) despite adverse prognostic factors. However, there are no data to support such an approach, and it should be considered only in the context of a clinical trial. Moreover, the agent to use is not clear: those to be considered for study would be rituximab, ofatumumab, or lenalidomide. The second case is of an elderly, medically unfit woman eventually treated with chlorambucil. It has been many years since

I have considered that agent. I would be more likely to use bendamustine at a lower dose (eg, 70 mg/m² on days 1 and 2), and, if she improves, I would consider adding rituximab. The final case raises the issue of what to do when CLL recurs post-bendamustine therapy. Currently, there are no data for salvage regimens in this setting, and the best approach would be a clinical trial when the patient meets indications for treatment, which is not clear at the present time.

The therapy for patients with CLL is clearly in a state of evolution. For more than 20 years, fludarabine has been the standard initial therapy, yet it required 8 years of follow-up of an important Cancer and Leukemia Group B (CALGB) study to demonstrate a survival benefit over the previous standard, chlorambucil.¹ Treatment strategies underwent a seismic shift with the availability of the safe and effective monoclonal antibody, rituximab. As a single agent in relapsed and refractory patients, activity was disappointing. As initial treatment, response rates of over 50% were reported, but they were of a relatively brief duration. It was not until rituximab was combined with fludarabine by Byrd and colleagues² or fludarabine and cyclophosphamide by Keating and coworkers³ that clear benefit was apparent, with an increase in overall response rates to 90% or better, and complete remissions in the 50–75% range, with historic comparisons suggesting a survival benefit. Whether FCR was superior to FR has been a topic of controversy that is being addressed in a national intergroup study conducted by CALGB, ECOG, and the Southwest Oncology Group. The benefit of the addition of rituximab was solidified in 2 recent studies: the CLL-8 trial in previously untreated patients, where the addition of the antibody prolonged survival,⁴ and the REACH (A Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF alpha Chimeric Monoclonal Antibody in Pediatric Subjects with Moderate to Severe Crohn's Disease) trial in relapsed and refractory patients, where progression-free survival was significantly prolonged.⁵ The result of these studies was that a new standard of care was established, at least for patients who would have been eligible for the studies—those who were considered suitably fit to tolerate this level of treatment.

Nevertheless, even more efficacious therapies are needed for patients with this incurable disease. The single

chemotherapy drug with the potential to advance the field is bendamustine, a bifunctional alkylating agent developed in the German Democratic Republic in the 1960s.⁶ Following a series of single-agent trials in Germany suggesting impressive response rates, Knauf and associates⁷ demonstrated bendamustine's clear superiority over chlorambucil as the initial treatment for patients with CLL. While this was occurring, the GCLLSG conducted a trial of bendamustine plus rituximab in relapsed and refractory CLL, which showed a response rate of 77.4%, including 15% CRs, even in poor-risk patients.⁸ The GCLLSG data in the upfront setting were even more encouraging, with a response rate of 90.9% including 33% CRs.⁹ These data compare favorably with previously published FR and FCR data. The ongoing GCLLSG CLL-10 trial directly comparing BR with FCR has the potential to, once again, change the treatment paradigm in CLL.

One issue that will eventually need to be addressed is whether different subsets of patients might preferentially benefit from one or another of these regimens, based on age and comorbidities, renal or hepatic dysfunction, or a history of recurrent infections—all of which favor BR—or the various unfavorable biologic and genetic subsets (eg, ZAP-70 positive, unmutated IgV_H gene, 17p deletion).

As the newer and more effective regimens are being used as the initial therapy of CLL, the management of patients with relapsed or refractory disease is becoming increasingly challenging. Allogeneic stem cell transplantation may be an option for a limited number of patients, especially those who are young, but who have experienced an incomplete or a brief response to initial therapy. The anti-CD52 monoclonal antibody alemtuzumab may be useful; however, it is associated with a considerable risk of cytomegalovirus reactivation as well as induction of other opportunistic infections. Thus, newer agents are needed. A particularly active area of research is focused on new monoclonal antibodies and related constructs. There are numerous anti-CD20s currently in clinical trials with activity in CLL. These include ofatumumab, GA-101, and veltuzumab.¹⁰ They remain to be directly compared with rituximab, and their activity in rituximab-resistant patients remains to be demonstrated. In non-Hodgkin lymphoma, there has been limited activity for ofatumumab in this setting. The small modular immunopharmaceutical (SMIP) TRU-016, derived from an anti-CD37 monoclonal antibody, targets an antigen present on lymphomas and CLL cells. It involves the CD37 binding domain linked to the IgG₁ hinge and CH₂ and CH₃ domains.¹¹ This drug is not only active in CLL, but it has demonstrated *in vitro* synergy with bendamustine and rituximab, and combination trials are being planned.

Like other B-cell malignancies, a number of intracellular pathways may serve as therapeutic targets in CLL. The

B-cell receptor is needed for the survival of the malignant cell. Once activated, the B-cell receptor signal is amplified by a number of pathways, including those modulated by spleen tyrosine kinase and Bruton's tyrosine kinase, which, when inhibited, results in apoptosis. Fostamatinib disodium and PCI-32765 inhibit these kinases, respectively, and have promising single-agent activity in CLL/small lymphocytic lymphoma.^{12,13} The PI3-kinase pathway is also important for oncogenesis and for proliferation and survival of malignant B cells. CAL-101 is a potent inhibitor of PI3-kinase 110 and has demonstrated impressive activity in a phase I study including patients with CLL.¹⁴ Further development is ongoing.

Almost 50 years ago, William Dameshek proposed that CLL was not a lymphoproliferative disease but a lymphoacumulative disorder: the malignant cells were not growing rapidly, they were just not dying. This concept subsequently became known as apoptosis. There are numerous small molecules that target the apoptotic pathways currently in clinical trials. Of particular note is ABT-263, which has single-agent activity and appears to enhance the efficacy of other drugs, such as rituximab.¹⁵ Trials combining this agent with bendamustine or rituximab are being designed.

Another important new agent is lenalidomide, whose mechanisms of action are incompletely understood, but which likely involve the microenvironment. This second-generation immunomodulatory drug has demonstrated single-agent activity in previously untreated and relapsed CLL, and it is currently being combined with other agents, including rituximab and bendamustine, to create more efficacious regimens.¹⁶ Unique adverse effects of this drug include tumor lysis syndrome and a tumor flare reaction.

Important goals in CLL include development of rational combinations directed at multiple therapeutic targets, limiting the likelihood of a resistant cell population. In addition, we need to achieve individualized therapies. We call the disease CLL, yet patients behave differently and respond differently to the same treatment. Only by incorporating scientific correlative studies within our clinical trials can we better understand this high level of patient heterogeneity.

The good news is that we have a wealth of new and potentially valuable agents for the treatment of patients with CLL and other lymphoid malignancies. This plethora of drugs will hopefully permit us to eventually move away from nonspecific cytotoxic drugs to the use of more targeted biologic therapies. The bad news is that so few patients currently enter into clinical trials that the effective agents take years before they are available outside of a clinical trials setting. It is the responsibility of patients and the physicians who care for them to participate in clinical research so that we will achieve the objective of a cure for CLL in the foreseeable future.

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Chronic Lymphocytic Leukemia (CLL)

- Arises from lymphocytes that are morphologically mature but immunologically less developed
- B cells exhibit a unique immunophenotype, characterized by CD5 and CD23 expression

CLL Staging: Rai System

- **Stage 0:** There are too many lymphocytes in the blood, but there are usually no other symptoms of leukemia. Lymph nodes and the spleen and liver are not swollen, and the number of red blood cells and platelets is normal
- **Stage I:** There are too many lymphocytes in the blood, and lymph nodes are swollen (lymphadenopathy). The spleen and liver are not swollen, and the number of red blood cells and platelets is normal
- **Stage II:** There are too many lymphocytes in the blood, lymph nodes are swollen, and either the liver is swollen (hepatomegaly) or the spleen is swollen (splenomegaly)
- **Stage III:** There are too many lymphocytes in the blood and too few red blood cells (anemia). Lymph nodes and the liver or spleen may be swollen
- **Stage IV:** There are too many lymphocytes in the blood and too few platelets (thrombocytopenia). The lymph nodes, liver, or spleen may be swollen, and there may be too few red blood cells (anemia)

CLL Staging: Binet System

- **Stage A:** Red blood cells and platelets are in the normal range, and there are <3 areas of lymphoid involvement
- **Stage B:** Red blood cells and platelets are in the normal range, and there are ≥3 areas of lymphoid involvement
- **Stage C:** Below normal numbers of red blood cells (anemia) and/or platelets (thrombocytopenia), regardless of the number of areas of lymphoid involvement

CLL Genetic Markers

- Mutations within the immunoglobulin variable region (IgV_H) are associated with a more favorable outcome
- CD38 expression and zeta-associated protein 70 (ZAP-70) expression are correlated with a poorer patient outcome

CLL Chromosomal Aberrations

- del(13q)
- del(11q23)
- del(17p)
- Trisomy 12

CLL Treatments

- Cytotoxic chemotherapy
- Monoclonal antibody treatments
- Stem cell transplant
- In exceptional cases:
 - Radiotherapy
 - Splenectomy

CLL Frontline Treatment Options

- Chlorambucil with or without prednisone
- Fludarabine either alone or in combination with cyclophosphamide (FC)
- Cyclophosphamide with or without vincristine and/or prednisone
- Cyclophosphamide plus doxorubicin, vincristine, and prednisone (CHOP)
- Bendamustine

All regimens can be combined with rituximab

Bendamustine in CLL

- Bendamustine has recently been approved for treatment of CLL patients
- NCCN guidelines recommend the use of bendamustine as a single agent for frontline therapy or, for second-line therapy, as either a single agent or combined with rituximab

NCCN=National Comprehensive Cancer Network

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