

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Clara D. Bloomfield, MD

## Advances in CLL

Susan O'Brien, MD  
Professor and Internist  
Department of Hematology  
University of Texas M. D. Anderson Cancer Center

### **H&O** How is chronic lymphocytic leukemia diagnosed?

**SO** The diagnosis of chronic lymphocytic leukemia (CLL) generally occurs when a person presents with lymphocytosis, often discovered accidentally during a routine physical or if the patient has noticed enlarged lymph nodes in the neck. Most patients are over age 60, but the disease also occurs in younger people. The simplest way to make the diagnosis is to use flow cytometry to document the presence of the particular phenotype found in CLL, which is CD5-positive B cells, which are CD20-positive. The only other disease in which CD5 is routinely expressed is mantle-cell lymphoma, which can sometimes present in the leukemic phase, but which has a fairly different morphologic picture. If the morphology is questionable, CD23 positivity distinguishes CLL from mantle-cell lymphoma, which would be CD23-negative. Additionally, due to the specificity of the flow cytometry and the ease of making the diagnosis from the peripheral blood, it is not necessary to examine the bone marrow in regular practice. In the setting of a clinical trial, assessment of the marrow may be useful for other reasons. In regular practice, however, if a patient has significant anemia, it may be helpful to assess whether red-cell precursors are present in the marrow.

### **H&O** Can you discuss prognostic markers in CLL?

**SO** Some exciting new developments have occurred in assessing prognosis. At the time of diagnosis, it is useful to check on the flow cytometry panel whether CD38 is present on the cells, as expression of CD38 indicates poor prognosis. Most commercial laboratories that offer CLL flow panels for diagnosis now include assessment of CD38. Commercial laboratories also use fluorescence in

situ hybridization to test for four genetic abnormalities in CLL: 13q deletion, trisomy 12, 11q deletion, and 17p deletion. If a patient has 13q deletion as the sole abnormality, it appears to be somewhat favorable as opposed to normal cytogenetics. The 11q and 17p deletions are both poor-prognostic abnormalities, with 17p deletions being particularly bad. Another prognostic marker which is not readily available in the community but has strong associations with poor prognosis is immunoglobulin heavy chain gene mutation. The reason this test is not readily available is that in order to know whether the cell has undergone somatic mutation or not, it is necessary to sequence the heavy-chain gene and compare that sequence to the known germline sequence. If the sequences are more than 2% different (some laboratories use 3% as the cut-off point), somatic mutation has occurred, which indicates a better prognosis. The unavailability of this test, based on the complexity of sequencing the gene, has stimulated the search for other prognostic markers that might correlate with mutation status but be easier to obtain. CD38 was initially thought to be an acceptable surrogate, but further data have shown that although it correlates, meaning CD38-positive patients are more likely to be unmutated, a 25% discrepancy exists. A one-to-one correlation status was hoped for, but as this was not the case, another marker was sought, which led to the discovery of ZAP-70 from array data.

When gene expression profiles are examined, there is no clear difference overall between mutated and unmutated patients. The profiles are more alike than different in CLL, which is not the case for large-cell lymphoma. Knowing which samples are mutated or unmutated prior to being loaded onto the chip allows assessment of which genes are differentially expressed. It was found that ZAP-70 is highly expressed in patients with unmutated V genes and vice versa. Again, the original impression was that a one-to-one correlation existed for ZAP-70 and mutation status, but a very large series published in the *New England Journal of Medicine* showed a 20–25% discrepancy. The CLL Consortium examined the time from diagnosis to requirement for therapy, and found that the shortest time to requiring treatment occurred in patients who were ZAP-70–positive irrespective of whether they were mutated or unmutated. Therefore, ZAP-70 status trumps mutation status as a prognostic marker. However

if patient's cells were ZAP-70–negative in this research then mutation status did provide additional information. Patients who were mutated and ZAP-70–negative had the longest time from diagnosis to treatment. Whereas CD38 has been easy to assess, ZAP-70 is quite difficult because it is a cytoplasmic antigen rather than a surface antigen, requiring a more elaborate assay in terms of permeabilizing the cells. Generally speaking, the test for ZAP-70 is considered unreliable. Until there is standardization across commercial laboratories, I would recommend the use of other prognostic markers that are more reliable.

Research is now under way to find out how to integrate prognostic markers. By way of example, how does a clinician know which prognostic marker is more important if a patient has an 11q deletion, which is poor, but is CD38-negative, which is good? Some data are beginning to emerge to answer these questions. Answers will entail having all parameters available for the patient population and doing multivariate analysis to assess which are the most useful, or, for example, in the presence of two markers, if a third is needed. This research is still, however, in its infancy. We do not yet have a robust algorithm for which test might be preferable or how to integrate or recommend markers beyond choosing those most easy to assess and most reliable.

### **H&O** What have been the historical methods of treating CLL?

**SO** Historically, the drug most commonly used to treat CLL was the alkylating agent chlorambucil, which is easily administered orally. In the early 1990s, fludarabine was approved for relapsed CLL, and it was associated with good response rates. The obvious question then was, if the drug is effective as salvage therapy, should it be used upfront? Some clinicians thus began to employ fludarabine in the frontline setting. The Intergroup trial published by Dr. Kanti Rai and colleagues in 2000 randomized patients to chlorambucil or fludarabine. Originally, the trial had a third arm, a combination of the two agents, which was closed early due to excessive toxicity, and accrual continued to the two single-agent arms. The data showed that both complete remission and overall response rates were significantly higher with fludarabine, and time-to-progression was substantially longer, approximately 1 year. However, there was no difference in survival. There are a couple of points to consider. First, the trial employed a crossover design, meaning that most patients received fludarabine during the course of their therapy. The second point, which is true for other chronic, relapsing diseases like low-grade lymphoma, is that a frontline study has the drawback of not taking into account the subsequent effects of salvage therapy, particularly if newer drugs are introduced later on. Third,

complete remission rates in that trial, indicating normal blood counts, normal exams, and no CLL in the bone marrow (not including assessment of residual disease) occurred in only 4% and 20% of patients with chlorambucil and fludarabine, respectively; the corollary to this finding is that our best therapy in the frontline setting results in 80% of patients unable to achieve a complete remission. Therefore, fludarabine can be characterized as significantly better than the previous standard of care, but great room for improvement existed.

### **H&O** What combination chemotherapeutic regimens were introduced as a result of these findings?

**SO** A number of different combinations of chemotherapeutic agents have been explored. Clearly, the most effective one to date has been the combination of cyclophosphamide and fludarabine, though it is associated with considerable toxicity. It was found in a number of phase II trials that this combination used upfront was associated with 80–90% response rates and, more importantly, complete remission in 30–35% of patients, better than fludarabine alone. This finding was then confirmed in randomized trials, one of which, from Germany, has been published and two of which were presented at meetings but have yet to be published. The German CLL trial, in which patients were randomized to fludarabine or fludarabine plus cyclophosphamide, showed that those who received the combination achieved higher complete remission and overall response rates, as well as significantly longer progression-free survival of almost 4 years. Another trial by the Eastern Cooperative Oncology Group used the combination in a slightly different schedule from the German trial but achieved similar results. Finally, a large British trial with three arms, chlorambucil alone, fludarabine alone, or fludarabine plus cyclophosphamide, showed that the combination arm achieved better results than either of the other arms.

### **H&O** How has the introduction of monoclonal antibodies affected treatment of CLL?

**SO** The effect of monoclonal antibodies has been significant. Two such therapies are used in CLL: rituximab (Rituxan, Genentech/Biogen Idec) and alemtuzumab (Campath, Genzyme/Berlex). Rituximab was approved by the US Food and Drug Administration for the treatment of low-grade lymphoma. In that setting, when used as a single agent in the standard schedule of 375 mg/m<sup>2</sup> weekly for 4 weeks, the response rate is approximately 50%. In CLL, the response rate with the same schedule is 10%. One hypothesis for the difference in response has been that the efficacy is related to the antigen density for CD20, rituximab's target, which is far lower on CLL

cells than follicular lymphoma cells. The dramatic effects seen with this agent occur when it is used in combination with chemotherapeutic agents such as fludarabine, which downregulates CD55 and CD59, two proteins that protect against complement-mediated lysis. In addition, rituximab downregulates Bcl-2, which sensitizes cells to chemotherapy. Two common off-label regimens in the United States for CLL are fludarabine and rituximab or fludarabine, cyclophosphamide, and rituximab (FCR). Both of these regimens are associated with high remission rates in patients with CLL although FCR may be associated with higher complete response rates.

Alemtuzumab targets CD52, which is a panlymphocyte antigen present on B and T cells. In the pivotal trial of alemtuzumab in fludarabine-refractory patients the overall response rate was 33%. Most patients did not progress on therapy and a large cohort had stable disease, which is generally not a particularly useful result, but it was interesting to note that patients could have a complete remission in the blood and bone marrow but fail to qualify as even a partial remission due to bulky lymph-node sites that did not decrease by 50%. It is apparent that alemtuzumab's efficacy varies depending on the site of the disease. Alemtuzumab is effective at clearing blood and marrow, which has led to recent trials attempting to optimize the use of this antibody as a consolidation therapy. A patient is debulked with chemotherapy or chemoimmunotherapy and after that therapy, the location of residual disease tends to be the marrow. Therefore, a short course of alemtuzumab is used to convert patients with residual disease in the marrow to complete remitters. This strategy is perhaps a better use of alemtuzumab than waiting until patients are completely refractory, at which point they tend to be immunosuppressed and have bulky adenopathy.

### H&O Are these drugs palliative in nature?

**SO** Yes. Unfortunately, even though very durable remissions are possible after time, the curves do go down. Longer remissions are possible, and I believe we are affecting survival. Two pieces of data support this belief. Cancer and Leukemia Group B compared their data with the combination of fludarabine and rituximab that was obtained with single-agent fludarabine from the prior Intergroup study I mentioned (fludarabine versus chlorambucil) and found that the addition of rituximab in the frontline setting was associated with better response rates and survival. Of course, the caveat is that comparing data from two different trials may not account for differences in the populations. Nevertheless, our own data comparing the three-drug combination to historical controls found the same result, which is that survival is clearly improving with a 6-year time to progression. But the simple answer is that patients with CLL are not yet being cured.

### H&O What is the role of stem-cell transplantation in CLL?

**SO** In the past, when myeloablative transplantation was standard, not much data existed in CLL because patients with CLL were considered too old to be candidates for transplantation. Now, with reduced-intensity or nonmyeloablative transplantation, it is possible to offer transplantation to patients up to age 70 or even older with much lower treatment-related mortality. Some data exist showing that long-term survival is possible after transplantation, but I would be hesitant to call this a cure. Because not many patients received transplantation in the past, long-term data for myeloablative transplants is scanty. Nevertheless, there are some patients who have survived 10–15 years with no disease; therefore, we may be curing some of these patients through transplantation. I believe nonmyeloablative transplantations should be done in the setting of a clinical trial because many questions remain about which regimen is better and what are the long-term outcomes, and these answers can be generated only if we continue to treat patients in the setting of clinical trials. A relatively healthy patient with CLL in first relapse is a candidate for transplantation, but due to the long time to progression now obtainable with the three-drug combination, transplantation should not generally be considered during first remission. The risks with nonmyeloablative transplantation are considerably lower, but mortality is associated with the procedure because of graft-versus-host disease. Due to the risk:benefit ratio, transplantation should thus be considered only for patients in first remission who have a very suboptimal response to frontline therapy.

### Suggested Readings

- Rassenti LZ, Huynh L, Toy TL, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lymphocytic leukemia. *N Engl J Med*. 2004;351:893-901.
- Krober A, Bloehdorn J, Hafner S, et al. Additional genetic high-risk features such as 11q deletion, 17p deletion, and v3-21 usage characterize discordance of zap-70 and vh mutation status in chronic lymphocytic leukemia. *J Clin Oncol*. 2006;24:969-975.
- Keating MJ, O'Brien S, Albitar M, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2005;23:4079-4088.
- Moreton P, Kennedy B, Lucas G, et al. Eradication of minimal residual disease in b-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. *J Clin Oncol*. 2005;23:2971-2979.
- Montillo M, Tedeschi A, Miqueleiz S, et al. Alemtuzumab as consolidation after a response to fludarabine is effective in purging residual disease in patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2006;24:2337-2342.
- Ravandi F, O'Brien S. Alemtuzumab. *Expert Rev Anticancer Ther*. 2005;5:39-51.
- Eichhorst BF, Busch R, Hopfinger G, et al; German CLL Study Group. Fludarabine plus cyclophosphamide versus fludarabine alone in first-line therapy of younger patients with chronic lymphocytic leukemia. *Blood*. 2006;107:885-891.
- Rai KR, Peterson BL, Appelbaum FR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med*. 2000; 343: 1750-1757.