ADVANCES IN LLM

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

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The Use of Ibrutinib in Chronic Lymphocytic Leukemia

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H&O What are some general principles in the management of chronic lymphocytic leukemia (CLL)?

LD CLL is not curable with chemotherapy. The only known potential cure is allogeneic stem cell transplant. However, most patients with CLL are not eligible for transplant because they are older, could not tolerate the associated risks, or have a prognosis that is too good to justify the associated risks. Treatment is often initiated not at diagnosis but later when patients experience symptoms or complications of the disease. Such triggers include fevers; night sweats; weight loss; drop in healthy blood counts, such as neutrophils, hemoglobin, and platelets; painful enlargement of the spleen; and/or enlarged lymph nodes. The usual goal of treatment is to control the disease and correct complications, without any expectation of a cure.

Until the advent of rituximab (Rituxan, Genentech/Biogen Idec), there were no treatments in CLL that prolonged survival. It now appears that the addition of an immunotherapy agent, such as rituximab, to chemotherapy improves survival, but still without an expectation of cure.

In patients with CLL, deterioration of the immune system occurs primarily as a consequence of their disease and is further accelerated by their treatment. Treatment of CLL does not improve the patient's immunity, and infections inevitably develop in most patients with CLL over time.

H&O What are some recent advances in the management of CLL?

LD There are 2 major advances: the identification of biomarkers that can predict prognosis at diagnosis, and nonchemotherapy treatments. There are now several biomarkers with better accuracy than the clinical Rai staging system. For instance, the fluorescence in situ hybridization (FISH) karyotype is more prognostic than the standard bone marrow karyotype. Other prognostic indicators include the level of ZAP-70 expression and the mutation status of the immunoglobulin heavy chain gene variable region. Ongoing research is evaluating other ways to predict prognosis at diagnosis.

An important advance has been the identification of the 17p deletion, which is also a predictive marker. Presence of the 17p deletion is one of the worst findings in CLL. Patients with the 17p deletion require treatment more quickly after diagnosis, respond less well to standard chemotherapy, and have a shorter overall survival.

Management options now extend beyond chemotherapy to include immunotherapy and targeted agents. These treatments raise the possibility that use of chemotherapy might be delayed for the long-term in these patients. Therapies such as ibrutinib (Imbruvica, Pharmacyclics/Janssen), idelalisib (Zydelig, Gilead), rituximab, ofatumumab (Arzerra, Novartis), obinutuzumab (Gazyva, Genentech), and alemtuzumab (Lemtrada, Genzyme/Sanofi) are being incorporated into the management of CLL.

H&O How has the use of ibrutinib impacted the management of CLL?

LD Patients and physicians are interested in using ibrutinib rather than other types of chemotherapy. Patients are requesting use of ibrutinib as their first therapy for CLL, although the indication from the US Food and Drug Administration (FDA) lists frontline use only in

patients with the 17p deletion. There are, however, some data to support the use of ibrutinib as frontline treatment in patients with CLL who do not have the 17p deletion. Patients prefer to take a pill rather than receive repeated cycles of chemotherapy. Ibrutinib is associated with a few significant toxicities, such as exacerbation of atrial fibrillation and bleeding (especially when patients are receiving anticoagulation therapy).

H&O What research led to the use of ibrutinib in CLL?

LD Ibrutinib inhibits Bruton's tyrosine kinase (BTK). Basic science research led to the understanding that the survival pathways involving BTK and phosphoinositide 3-kinase (PI3K) are important in CLL, and that inhibiting them might have an impact on the natural history of the disease. Ibrutinib and idelalisib were developed in preclinical models to inhibit those survival pathways, thereby disrupting the proliferation and survival of the CLL cells, without directly causing cytotoxicity. Preclinical data strongly suggested that these targeted agents would have substantial activity in human CLL.

H&O Could you please describe the HELIOS trial?

LD I critiqued the randomized, phase 3 HELIOS (Ibrutinib Combined With Bendamustine and Rituximab Compared With Placebo, Bendamustine, and Rituximab for Previously Treated Chronic Lymphocytic Leukaemia or Small Lymphocytic Lymphoma) trial at the 2015 American Society of Clinical Oncology (ASCO) meeting, where it was presented as a late-breaking abstract. The study was published online in *Lancet Oncology* in December 2015. HELIOS enrolled patients with CLL who had previously received some type of chemotherapy. The study excluded patients with the 17p deletion, who have the worst prognosis. Enrolled patients received 6 cycles of standard immunochemotherapy, which was bendamustine (Treanda, Teva) and rituximab, plus the addition of either ibrutinib or placebo. Ibrutinib or placebo was continued until disease progression or unacceptable toxicity. The study incorporated a crossover component: placebo patients who progressed could switch to ibrutinib. The primary endpoint was progression-free survival, and the secondary endpoints were overall survival and response rate.

The trial demonstrated that progression-free survival was substantially better among patients who were randomly assigned to receive ibrutinib. At a median follow-up of 17 months, the median progression-free survival was not reached in the ibrutinib arm vs 13 months in the placebo arm. There was a trend toward improved overall survival in the ibrutinib arm, but the difference was not statistically significant. The overall response rate was much higher with ibrutinib, at 83%, vs 69% with placebo. The published study results provided information about the detection of minimal residual disease (MRD). An MRD-negative state was achieved by 9% of the ibrutinib arm vs 2% of the placebo arm, suggesting that a deeper remission was more likely with ibrutinib.

Ibrutinib was associated with more high-grade atrial fibrillation, a known concern. Rates of high-grade atrial fibrillation were 2.8% with ibrutinib vs 0.7% with placebo. Major bleeding occurred in 2.1% of the ibrutinib arm vs 1.7% of the placebo arm. These toxicities are of some concern in this older age group.

The authors concluded that the combination of bendamustine/rituximab/ibrutinib was superior to bendamustine/rituximab in terms of progression-free survival and overall response rate. They also noted a trend toward overall survival. I do not disagree with these conclusions, but I think these findings are not surprising. When treatment with an extremely active drug, such as ibrutinib, is continued indefinitely, it should be no surprise that progression-free survival improves. The point I made at last year's ASCO meeting was that a better scientific question would have been: What is the contribution of bendamustine and rituximab to ibrutinib? A study design in which all patients receive ibrutinib and then are randomly assigned to receive concurrent treatment with bendamustine/rituximab or not would show the value of adding immunochemotherapy to ibrutinib. To support that contention, I compared the results of the HELIOS trial with those from a previous trial of ibrutinib alone with a similar patient population. The results of these 2 trials were almost identical. Results from a previous pilot trial of ibrutinib/bendamustine/rituximab were also very similar to the HELIOS trial. Although it is necessary to be cautious when comparing data from a current trial to historical data, these prior results raise the possibility that the contribution of bendamustine/rituximab to ibrutinib might be small or even nonexistent.

H&O What are some drawbacks to the use of immunochemotherapy with ibrutinib?

LD The main concern is added toxicity, as well as added cost and inconvenience. With rituximab, there is the potential for long-term infections and other immune issues. There may be higher rates of infection with the addition of rituximab to ibrutinib, although data are still needed. It is not possible to predict the toxicity profile of new combination therapies. Without a substantial outcome benefit, it would be hard to justify added toxicity, cost, and inconvenience.

H&O Are trials evaluating whether chemotherapy can be omitted as first-line treatment for CLL?

LD There is much interest in avoiding chemotherapy as first-line treatment. Studies are evaluating immunotherapy and targeted agents to see if they can achieve good disease control and improve symptoms while avoiding chemotherapy complications. In 2015, Byrd and colleagues published 3-year follow-up data from a trial evaluating ibrutinib monotherapy in patients with CLL or small lymphocytic lymphoma (SLL). The trial included 31 treatment-naive patients. All patients were ages 65 years or older. The overall response rate among treatment-naive patients was 84%, which is extremely high. At 3 years, the progression-free survival was 96%, also very high. No new safety signals emerged.

Several ongoing trials are evaluating nonchemotherapy approaches as first-line therapy for CLL. In the ORIGIN (Study of the Effectiveness & Safety of Lenalidomide Versus Chlorambucil as First Line Therapy for Elderly Patients With B-Cell CLL) trial, the immunomodulatory agent lenalidomide (Revlimid, Celgene) was compared with oral chlorambucil (Leukeran, GlaxoSmithKline) in older patients. The lenalidomide arm was discontinued in 2013 owing to excess deaths in this group. A second approach is to combine immunomodulatory drugs (lenalidomide or thalidomide) with rituximab. Another trial is comparing bendamustine/rituximab, ibrutinib/rituximab, and ibrutinib alone in older, treatment-naive patients. This trial recently completed accrual. Burger and coworkers published results from a trial of ibrutinib and rituximab in 40 patients with high-risk CLL. Patients had relapsed disease with either a 17p or 11q deletion or were receiving frontline treatment for 17p deletion. The 18-month rate of progression-free survival was high, at 78%. This trial provides a baseline outcome that can be considered when interpreting future randomized data.

H&O Are there any other areas of research in CLL?

LD Idelalisib, which targets the PI3K inhibitor, is approved for relapsed/refractory CLL in combination with rituximab. At the 2015 American Society of Hematology (ASH) meeting, Zelenetz and colleagues presented results from a trial that followed a design similar to that of HELIOS, except with idelalisib. In contrast to HELIOS, this trial did include patients with the 17p deletion. All patients received bendamustine/rituximab, and half received idelalisib and the other half placebo. Unsurprisingly, long-term use of idelalisib improved progression-free survival. An interesting finding was that idelalisib also improved overall survival. Idelalisib has been associated with diarrhea and liver function test abnormalities, so these toxicities must be weighed against the benefits. Again, I would propose that a better question would be answered by a trial in which all patients receive idelalisib, and then half receive bendamustine/rituximab and half do not, to define the contribution of immunochemotherapy to idelalisib.

Venetoclax (ABT-199) is generating much interest. Venetoclax is a BCL-2 inhibitor that induces apoptosis of cells independent of the p53 pathway. This mechanism means that venetoclax should be effective in patients with the 17p deletion, where the p53 gene exists. Venetoclax is administered orally. At the 2015 ASH meeting, Stilgenbauer and coworkers presented data for a trial of 107 patients with relapsed/refractory CLL with the 17p deletion. The overall response rate was 79%, with a complete remission rate of 7.5%, in these patients known to have a poor prognosis. Venetoclax appears to have very high activity.

Suggested Readings

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