

# ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

## New Antibodies for Acute Lymphocytic Leukemia



**Anjali S. Advani, MD**  
Associate Professor  
Departments of Hematology and Oncology  
& Translational Hematology and Oncology Research  
Cleveland Clinic  
Cleveland, Ohio

**H&O** Antibodies became available for acute lymphocytic leukemia (ALL) several years ago. What did they add to the treatment of this cancer?

**ASA** Rituximab (Rituxan, Genentech/Biogen Idec) was one of the first monoclonal antibodies used in the treatment of ALL. This naked, anti-CD20 antibody was studied in 2 trials in combination with chemotherapy for newly diagnosed ALL. The results of these trials were similar: for patients less than 60 years of age with newly diagnosed CD20-positive ALL, adding rituximab to chemotherapy improved the rates of both relapse and overall survival compared with historical cohorts. It is important to note, though, that for both of these studies—one published in the *Journal of Clinical Oncology* in 2010 and the other presented by Hoelzer at the American Society of Hematology annual meeting in 2010—the control arm was a historical comparison. In the Hoelzer study, the investigators also evaluated minimal residual disease (MRD) and found that the addition of rituximab to chemotherapy was associated with an improvement in MRD negativity. There is an ongoing randomized study of rituximab in combination with chemotherapy for newly diagnosed CD20-positive ALL patients. However, CD20 is expressed in only approximately 50% of pre-B ALL cases; therefore, other targets and treatments are needed.

**H&O** Is CD20 positivity still considered an indicator of high-risk disease?

**ASA** Being CD20-positive used to be considered an indicator of a poor prognosis. However, the advent of

rituximab has led to outcomes that are just as good. In addition, research has shown that chemotherapy can upregulate CD20 expression on leukemia cells. That upregulation can enhance the activity of rituximab.

**H&O** How is alemtuzumab used in the treatment of ALL?

**ASA** This drug is a humanized, anti-CD52 monoclonal antibody. Interestingly, alemtuzumab does not have the same limitation that rituximab has because almost all ALL—both T-cell and B-cell—has CD52 expression

The clinical data are not quite as clear with alemtuzumab as with rituximab. The initial studies of this drug for ALL were in the refractory setting and showed limited clinical activity. Following a successful phase 1 study incorporating alemtuzumab into treatment for newly diagnosed ALL, investigators with the Cancer and Leukemia Group B study recently completed a phase 2 study of chemotherapy plus alemtuzumab followed by maintenance chemotherapy. There seemed to be a high incidence of infectious complications. However, the early results with respect to MRD negativity, relapse-free survival, and overall survival, as presented at the 2009 American Society of Hematology meeting by Dr Wendy Stock, were encouraging.

**H&O** What new antibodies are currently in development?

**ASA** The 2 new antibodies that have been garnering the most attention recently are blinatumomab and inotuzumab. In addition, there is a third antibody called SGN-

CD19A that is being developed, and some immunotoxin and immunoconjugate compounds for which there are fewer data.

### H&O What is blinatumomab?

**ASA** Blinatumomab belongs to a class of agents known as bispecific T-cell engaging (BiTE) antibodies. It is made up of 2 arms, one that engages the T-cell and the other that attaches to the tumor cell antigen. One of the arms in blinatumomab targets CD19, which is expressed in almost all pre-B-cell ALL, and the other arm targets CD3. These features enable blinatumomab to engage the leukemia and the T-cell, and leads to proliferation of cytotoxic T cells, and apoptosis of the leukemia cells.

### H&O What have studies shown so far about its efficacy in ALL?

**ASA** A group of German investigators led by Dr Max Topp evaluated patients with ALL who had persistent or relapsed MRD after having received treatment with chemotherapy. In other words, these patients did not have fully relapsed disease, but showed early signs that relapse was likely to occur, as MRD is a prognostic marker of relapse. In this phase 2 study, which was published in the *Journal of Clinical Oncology* in 2011, 80% of patients treated with blinatumomab converted from MRD-positive to MRD-negative disease.

A subsequent trial by Topp and colleagues that was presented at the 2014 American Society of Clinical Oncology annual meeting evaluated blinatumomab in patients with relapsed and refractory ALL. Forty-three percent of patients (82 of 189) experienced a complete remission or a complete remission with partial hematological recovery.

Currently there is an ongoing, US intergroup study evaluating this antibody plus chemotherapy vs chemotherapy alone in adult patients with ALL. If this study supports an improved outcome in terms of relapse rate or overall survival, then blinatumomab could be approved in the upfront setting. Ongoing studies are also being performed in the relapsed ALL population with the hopes that the drug will be approved by the US Food and Drug Administration for relapsed disease.

### H&O Does blinatumomab cause severe side effects?

**ASA** Blinatumomab has been fairly well tolerated. There are some logistical concerns because blinatumomab must be given as a continuous infusion. Some patients have experienced neurologic side effects, such as seizures, but

the incidence has been low and the problems have been reversible. Some patients have had infusion reactions, but this side effect has also been easily managed.

### H&O What is inotuzumab?

**ASA** Inotuzumab is an anti-CD22 antibody attached to calicheamicin, a chemotherapy agent. The rationale behind this design is to deliver chemotherapy to leukemia cells in a more targeted way. CD22 is present on most cases of pre-B-cell ALL. As noted above, this limits the usefulness of the antibody because patients with T-cell ALL will not benefit from it; however, B-cell ALL constitutes about 80% of ALL.

The structure of inotuzumab is similar to that of gemtuzumab, which had been approved for the treatment of acute myeloid leukemia but was then taken off the market. Inotuzumab was initially evaluated in lymphoma, a B-cell malignancy, but the developers then turned their focus to ALL, with phase 1 and 2 studies now completed.

Inotuzumab can be given either once every 3 weeks or weekly with a break between the cycles.

### H&O Could you discuss the study findings?

**ASA** One study was led by Dr Hagop Kantarjian and published in *Cancer* in 2013, and the other study was led by Dr Daniel DeAngelo and myself and sponsored by Pfizer. In the former study, the total remission rate was 58%. The data from the latter study, which was completed recently, are not yet published, but are comparable.

These outcomes, as well as those seen with blinatumomab, have not been seen with chemotherapy alone. These remissions are not durable, so patients do still need to proceed to bone marrow transplant. However, there seems to be an improvement over what we have previously been able to achieve solely by increasing doses of chemotherapy.

The toxicities seen with inotuzumab include neutropenia and thrombocytopenia, which sometimes makes further treatment difficult. The major concern with inotuzumab is that some patients have experienced hepatic veno-occlusive disease. For patients proceeding to bone marrow transplant, this possibility needs to be kept in mind when planning treatment. For example, clinicians need to leave an appropriate amount of time between the last dose of the drug and the timing of the transplant. The occurrence of hepatic veno-occlusive disease may also be due to the fact that patients were heavily pretreated. In addition, in the study by Kantarjian and colleagues, altering the chemotherapy regimen used to prepare patients for bone marrow transplant may have reduced the occurrence of this side effect.

## H&O Are there other noteworthy new antibodies for ALL currently being studied?

**ASA** An agent named epratuzumab has been studied in both pediatric and adult ALL patients. In a clinical trial by Raetz and colleagues in which epratuzumab was combined with chemotherapy for the treatment of children with ALL, the remission rate did not appear to be altered by the addition of the experimental drug; however, there was an increased incidence of MRD negativity as compared with historical controls. In addition, long-term disease-free and overall survival are still being evaluated. A randomized trial known as IntReALL (International Study for Treatment of Childhood Relapsed ALL), in which pediatric patients with relapsed ALL will receive either chemotherapy or chemotherapy plus epratuzumab, is planned.

For adult patients, the Southwest Oncology Group conducted a trial in which epratuzumab was added to a backbone chemotherapy regimen for patients with relapsed/refractory disease. In this study, which was published in the *British Journal of Haematology* with myself as the first author, the remission rate was approximately 50%, which was encouraging to see in this heavily pre-treated group of patients.

A large, randomized study is needed in order to more clearly determine the potential benefit of epratuzumab for adult patients with ALL. Conducting such a trial is difficult, however, because of the many new drugs now being investigated.

## H&O Do you anticipate any of these agents being used as upfront therapy?

**ASA** Blinatumomab may be beneficial as upfront therapy, but we need to wait for the results of the current phase 3 intergroup trial. There are also plans to study inotuzumab in the upfront setting in combination with chemotherapy for young adults with ALL.

## H&O With so many antibodies in development for ALL, is it difficult to enroll enough patients in any given trial?

**ASA** No, mainly because we are seeing more patients willing to enroll in trials. In the past, the only treatment we had to offer many patients outside of these ongoing studies was high-dose chemotherapy. The results with these new agents are encouraging and exciting.

## H&O Does the emergence of new antibodies for ALL stem from recent new understandings about the biology of the disease?

**ASA** The current antibodies are not very specific to the inherent biology of the disease, but are tied to cell surface antigen expression. Currently there is a bit more enthusiasm in the oncology community about the immunoconjugates and BiTE-specific antibodies because they may eliminate the need for chemotherapy, particularly in the relapsed setting.

## Suggested Reading

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