ADVANCES IN LLM

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

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The Use of Obinutuzumab in Chronic Lymphocytic Leukemia

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H&O What is obinutuzumab?

WW Obinutuzumab (Gazyva, Genentech) is a CD20 monoclonal antibody that was approved by the US Food and Drug Administration in October 2013 for the treatment of patients with chronic lymphocytic leukemia (CLL) who have comorbidities. In this setting, obinutuzumab was approved as initial treatment in combination with the chemotherapy drug chlorambucil.

H&O Is obinutuzumab different from other CD20 monoclonal antibodies?

WW The advent of CD20 antibodies has led to significant improvements in outcomes for patients with CLL. The use of the CD20 antibody rituximab (Rituxan, Genentech/Biogen Idec) with chemotherapy leads to longer overall survival time compared with the same chemotherapy without a CD20 antibody. For example, the combination of fludarabine, cyclophosphamide, and rituximab is significantly better at treating CLL compared with fludarabine plus cyclophosphamide alone.

Obinutuzumab is distinct from other CD20 monoclonal antibodies available for the treatment of hematologic malignancies, particularly rituximab and ofatumumab (Arzerra, GlaxoSmithKline). The latter 2 drugs are referred to as type 1 CD20 monoclonal antibodies. They are highly effective at mediating antibody-dependent cellular cytotoxicity (ADCC) and/or complement-dependent cytotoxicity (CDC). They are less effective at directly inducing apoptosis, and thus have less of an ability to directly kill leukemia or lymphoma cells.

Obinutuzumab is a type 2 antibody, and was engineered to have improved clinical therapeutic activity compared with type 1 antibodies. First, it has enhanced activity in direct induction of apoptosis. In addition, owing to glycoengineering, it is a better mediator of ADCC.

H&O Is it possible to pinpoint the molecular structures responsible for this enhanced activity?

WW Although the differences in activities and cell-killing action can be observed in a side-by-side comparison of the type 1 and type 2 antibodies, exactly why obinutuzumab is better at directly inducing apoptosis is likely multifactorial.

Most likely, the enhanced activity is a result of where or how it binds on the CD20 molecule. Obinutuzumab is an engineered monoclonal antibody originally generated in a mouse and then made into a chimeric molecule with some glycol modifications. We know that it is possible to modify glycosylation on an antibody and that such modification can enhance ADCC activity. Glycoengineering of obinutuzumab was done specifically to enhance ADCC in comparison with type 1 monoclonal antibodies.

H&O You mentioned that obinutuzumab is approved for the treatment of patients with CLL who also have comorbidities. Was this drug created to address a treatment need for this specific patient population?

WW For patients who have CLL and comorbidities, historically the standard treatment was chlorambucil, a chemotherapy drug that has been available for decades.

No agent has proven more effective for this population than chlorambucil alone; historically, the objective for treatment in such a population has been symptom control and palliation. Obinutuzumab was evaluated in combination with chlorambucil in this group of patients in order to determine whether the combination was more effective than chemotherapy alone.

H&O Could you describe the clinical trial that led to the approval of obinutuzumab?

WW This phase 3 study by the German CLL Study Group, with Goede as its first author, is referred to as the CLL11 trial. In this large trial, patients were randomized to one of 3 arms: chlorambucil monotherapy, chlorambucil plus rituximab, or chlorambucil plus obinutuzumab (also known as GA101).

The eligibility criteria required that patients have a comorbidity score of greater than 6. Because comorbidities occur more frequently among older patients, selecting patients for a trial based on comorbidity index naturally skews the population toward older patients, which is what happened with the CLL11 trial.

The aim of the study was to compare chlorambucil vs each arm containing a CD20 monoclonal antibody plus chlorambucil. The initial analysis, which was published in *Leukemia* in 2013, showed improved outcomes among patients receiving the CD20 antibody plus chlorambucil vs chlorambucil alone. The primary endpoint for that analysis was progression-free survival, and both antibody-containing arms were superior in this regard.

A second analysis was a comparison of the 2 CD20 monoclonal antibody–containing arms. Here, the primary endpoint was again progression-free survival. In this analysis, published in the *New England Journal of Medicine* in 2014, obinutuzumab plus chlorambucil was associated with a longer progression-free survival than rituximab plus chlorambucil. Response rates, particularly the complete remission rate, were also higher for the obinutuzumab-containing arm vs the rituximab-containing arm.

This analysis also confirmed that treatment with obinutuzumab plus chlorambucil was associated with improved overall survival compared with chlorambucil monotherapy.

H&O Do obinutuzumab and chlorambucil work together in the body, or are their effects distinct?

WW We believe that there is synergy between the 2 agents, although there are limited data to back up this assertion. The general thinking among clinical researchers is that CD20 antibodies work better when they are combined with chemotherapy, especially in the treatment of CLL.

H&O Is there interest in creating a chlorambucil-free regimen for CLL?

WW There is certainly interest in finding an effective approach to treat CLL without chlorambucil, and other chemotherapy agents for that matter. Of the chemotherapy options, chlorambucil may be the least effective. Fludarabine, fludarabine plus cyclophosphamide, and bendamustine could potentially be combined with obinutuzumab. Such combinations may be more active and effective than combinations with other CD20 antibodies, but there are no published data yet demonstrating safety or activity with these combinations. In general, one would expect synergy between a CD20 monoclonal antibody and any chemotherapeutic agent.

H&O How was obinutuzumab tolerated in the clinical trial?

WW Obinutuzumab was well tolerated in the clinical trial, though there were some issues with infusion-related reactions. Splitting the first dose so that a patient received 100 mg on day 1 and then 900 mg on day 2 for first dose appeared to reduce the severity of the initial infusion-related reactions. Some patients receiving chlorambucil plus obinutuzumab experienced neutropenia and thrombocytopenia, with a higher rate than was observed among patients receiving chlorambucil as monotherapy or with rituximab.

Infusion-related reactions occur with rituximab, and splitting the first dose has helped minimize this side effect. Corticosteroids have also been used to minimize these reactions. The data indicated that the incidence of grade 3 and greater infusion-related toxicities was higher for obinutuzumab than rituximab, but the true incidence may be lower because split–first dose obinutuzumab and increased premedication were instituted mid-trial.

H&O Should obinutuzumab be used for the treatment of CLL?

WW The CLL11 trial establishes obinutuzumab with chlorambucil as a standard first-line treatment for CLL patients with comorbidities, particularly the elderly, in combination with chlorambucil. In this setting it clearly shows superiority of obinutuzumab over rituximab. Obinutuzumab is approved for this indication, and this population is the only one for which peer-reviewed phase 3 clinical trial data are currently published. How we use obinutuzumab needs to be based on data showing safety and efficacy. Right now, the only published data we have is for obinutuzumab combined with chlorambucil in CLL11.

H&O What other issues need further research with regard to the treatment of CLL with obinutuzumab?

WW More data are needed to clarify the circumstances for which this drug might be used. Data from the CLL11 trial are very important because they demonstrate the improvement of efficacy for obinutuzumab vs rituximab. However, it is important to keep in mind that all patients in this trial received chlorambucil, which leads to several questions. For example, would outcomes be further improved if a different chemotherapy agent were given in combination with obinutuzumab? Also, several new, nonchemotherapy agents are in development or recently approved, such as ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech). What would be the outcomes from a regimen combining one of the nonchemotherapy agents with obinutuzumab?

H&O Might obinutuzumab be effective in the treatment of patients whose disease has progressed following treatment with rituximab?

WW Obinutuzumab certainly may be useful in this setting. We need to research its benefit for patients with relapsed disease and for those who are refractory to rituximab.

Suggested Reading

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