

ADVANCES IN LLM

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

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The Evolving Use of Gemtuzumab Ozogamicin in Acute Myeloid Leukemia



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H&O What type of drug is gemtuzumab ozogamicin?

RW Gemtuzumab ozogamicin (Mylotarg, Pfizer) is an antibody-drug conjugate that consists of a humanized anti-CD33 antibody attached to a cytotoxic agent, which is a calicheamicin derivative. The drug attaches to CD33 and is internalized into the cell. The toxin is then released and causes DNA double-strand and single-strand breaks. If the cell is unable to repair these breaks, the targeted cell undergoes apoptosis and eventually dies.

In the United States, gemtuzumab ozogamicin is approved in combination with intensive chemotherapy that contains daunorubicin and cytarabine for the up-front treatment of CD33-positive acute myeloid leukemia (AML). Initially, the approval was limited to adults with this indication. More recently, the approval was expanded to include pediatric patients ages 1 month and older. Gemtuzumab ozogamicin is also approved as a single agent for the treatment of adults with newly diagnosed CD33-positive AML, as well as for the treatment of relapsed or refractory, CD33-positive AML in adults and pediatric patients ages 2 years and older.

H&O Could you please discuss the pivotal study data of gemtuzumab ozogamicin in acute myeloid leukemia?

RW In 2001, gemtuzumab ozogamicin was approved

by the US Food and Drug Administration (FDA) for the treatment of relapsed/refractory AML that is CD33-positive in adults who are not considered candidates for intensive chemotherapy. At that time, the pivotal data were drawn from three phase 2 trials in the relapsed setting, which showed that the drug could induce remissions in a subset of patients. However, because of the lack of overall survival improvement and a slight increase in early deaths with gemtuzumab ozogamicin in SWOG S0106—a randomized phase 3 trial conducted in the up-front setting to fulfill the postapproval commitment of the drug manufacturer to the FDA—the drug was temporarily withdrawn from the market in 2010. Gemtuzumab ozogamicin reemerged after combined analyses of 5 randomized studies in the up-front setting reported that the addition of this drug reduced the risk of relapse and improved survival in at least a subset of patients. These 5 studies, which notably include the S0106 trial, led the FDA to reconsider approval. Among these 5 studies, the study that the FDA placed the most emphasis on was performed in France. Data supporting the use of gemtuzumab ozogamicin in patients with relapsed or refractory AML overall are weaker, with no data from randomized trials available. For its approval, the FDA primarily considered a single-arm, relatively small study also conducted in France that showed relatively high remission rates with monotherapy.

The 5 randomized up-front studies provided slightly different data concerning overall outcomes and the

subgroups that benefited. A meta-analysis published in 2014 by Dr Robert Hills and colleagues summed up the data. The analysis included over 3300 patients treated in the randomized studies. It showed that gemtuzumab ozogamicin did not have a major impact on early events, but it did reduce relapse rates and prolong survival. The benefit in overall survival was primarily seen in patients with favorable-risk leukemia, and to a smaller degree in patients with intermediate-risk leukemia. A benefit was not seen in patients with high-risk disease. These findings influence the use of gemtuzumab ozogamicin in the clinic.

H&O Are there more recent studies in AML?

RW There is still clinical trial interest in gemtuzumab ozogamicin. Studies in adults were followed by studies in children, which led to the expanded indications. A randomized study performed in Germany evaluated gemtuzumab ozogamicin in a subset of patients with *NPM1*-mutated leukemia. This study highlights some of the challenges with gemtuzumab ozogamicin, particularly the associated toxicity. Increased early deaths offset some of the benefits. However, the study also confirmed that gemtuzumab ozogamicin reduces the risk of relapse and can lead to deeper remissions after induction chemotherapy, with higher proportions of patients achieving minimal residual disease–negative remissions. There are smaller studies reporting data in different subsets of patients on a regular basis.

H&O Has the use of gemtuzumab ozogamicin in clinical practice evolved?

RW It has. As mentioned before, the drug originally received accelerated approval for the treatment of relapsed/refractory AML, and it was first used in this setting.

After randomized trials demonstrated benefit with gemtuzumab ozogamicin in patients with previously untreated AML, interest is now focused on combining this agent with intensive chemotherapy in the up-front setting, at least in patients with favorable-risk disease. This combination treatment may also be an option for some patients with intermediate-risk disease, in whom the meta-analysis by Hills showed a small benefit regarding longer survival. Gemtuzumab ozogamicin is still used in the relapsed setting, although as mentioned, the data are less robust. The switch toward use in the up-front setting is a newer development based on the randomized studies.

H&O What are the adverse events?

RW There are several main adverse events. Infusion-related toxicity is a well-known event that was seen early in

the clinical testing of the drug. As a protein therapeutic, gemtuzumab ozogamicin is associated with infusion toxicities such as fevers, chills, and changes in blood pressure. The FDA label recommends the use of prophylactic medications, such as corticosteroids, H2 blockers, and acetaminophen, to mitigate these risks. Gemtuzumab ozogamicin can cause tumor lysis syndrome, which is also seen with other leukemia drugs.

There are 2 adverse events that are specific to gemtuzumab ozogamicin. Related to the expression of CD33 on some of the normal blood cells, gemtuzumab ozogamicin can cause myelosuppression, including, most notably, neutropenia, monocytopenia, and thrombocytopenia. Gemtuzumab ozogamicin can prolong the duration of cytopenia if it is added to other chemotherapy drugs. This possibility is a concern because of the increased risk of infection related to the prolongation of myelosuppression. A more unique toxicity reported is sinusoidal obstruction syndrome, formerly known as veno-occlusive disease. It is thought that the risk of sinusoidal obstruction syndrome decreases when gemtuzumab ozogamicin is used at lower doses. The trials in the up-front setting administered gemtuzumab ozogamicin at lower doses, which appears to have reduced some of the dose-dependent toxicities, including sinusoidal obstruction syndrome. However, sinusoidal obstruction syndrome is an important toxicity because it appears to occur more frequently in patients who undergo transplant in a relatively short period of time after they receive gemtuzumab ozogamicin, or when the drug is given to a patient who recently underwent transplant. Sinusoidal obstruction syndrome is potentially life-threatening and can be fatal, and the treatment options are limited.

H&O Has the COVID-19 pandemic impacted the administration of gemtuzumab ozogamicin?

RW At my institution, we use a somewhat atypical backbone for induction chemotherapy, and we administer gemtuzumab ozogamicin primarily as part of a clinical trial. For a while, almost all clinical trial activities were halted at my institution. At the beginning of the pandemic, there were also discussions that the prolongation of low blood counts and possibly the increased risk of infection with gemtuzumab ozogamicin might be a concern. Obviously, keeping blood counts low would make vulnerable people more vulnerable, which can be problematic during an infectious disease pandemic that seems to disproportionately affect people with weakened immune systems. That said, we continued to enroll patients into our clinical trial of gemtuzumab ozogamicin in combination with intensive chemotherapy and, in fact, we completed accrual last fall.

H&O Do you have any other observations regarding the use of gemtuzumab ozogamicin?

RW Gemtuzumab ozogamicin is probably most efficacious in acute promyelocytic leukemia, a disease that has a very high chance of cure with all-trans retinoic acid and arsenic-based therapy. Even with the high cure rate, there are still patients with high-risk acute promyelocytic leukemia who might require additional drugs. Gemtuzumab ozogamicin may have a role in this setting, although this use has not been well-studied because the patient population is so small. Gemtuzumab ozogamicin is not currently FDA-approved for these patients, which is unfortunate.

As mentioned above, gemtuzumab ozogamicin is approved for relapsed/refractory AML in the United States. Interestingly, it is not approved for this indication in Europe, which may reflect how the different regulatory authorities interpret the strength of data. To address the lack of data from randomized trials in these patients treated with gemtuzumab ozogamicin, we need studies providing robust data to guide use in the relapsed setting.

There is currently great interest in newer approved drugs that allow lower-intensity up-front treatments. The most notable drug is venetoclax (Venclexta, AbbVie/Genentech). My colleagues and I have very recently published laboratory studies showing that gemtuzumab ozogamicin is affected by Bcl-2 proteins, which venetoclax inhibits. In the laboratory, it is possible to sensitize leukemia cells to gemtuzumab ozogamicin by using a drug such as venetoclax. This observation begs the question of whether there is a role for combination therapies consisting of gemtuzumab ozogamicin plus a venetoclax-containing backbone. Ongoing trials are evaluating this strategy.

Gemtuzumab ozogamicin has been widely used, and there is much published data to support it. It is clear that the drug does not work for all patients, but rather is effective in only a subset. There is still a need to determine which patients should receive the drug. Cytogenetic risk can help guide treatment decisions, based on data from the meta-analysis. However, even a favorable genetic risk profile does not guarantee that a patient will benefit. Initially, there was interest in drug transporter proteins, which the cytotoxic agent is very sensitive to. More recently, there had been interest in CD33 expression and CD33 gene polymorphisms as response biomarkers. However, there is still room for biomarkers to help reliably distinguish likely responders from nonresponders and thereby guide treatment decisions.

Disclosure

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Suggested Readings

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