ADVANCES IN LLM

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

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Gemtuzumab: Time to Bring Back on the Market?

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H&O What is gemtuzumab ozogamicin?

JF Gemtuzumab ozogamicin, also known by the trade name Mylotarg (Pfizer), was the first monoclonal antibody approved by the US Food and Drug Administration (FDA) in acute leukemia. It was granted accelerated approval for patients aged 60 years and older in first relapse of CD33-positive acute myeloid leukemia (AML) who were not considered candidates for cytotoxic chemotherapy. Gemtuzumab targets CD33, which is present on the myeloid blasts of approximately 85% of patients with AML. This recombinant, humanized anti-CD33 monoclonal antibody attaches to the cytotoxic antitumor antibiotic calicheamicin. In this conjugate, the antibody binds to and is internalized by tumor cells expressing the CD33 antigen, and the attached calicheamicin is directly delivered to CD33-expressing tumor cells. Calicheamicin causes double-strand DNA breaks and inhibits DNA synthesis. It is a clever way of targeting a toxin to particular cells.

H&O Why was gemtuzumab removed from the US market in 2010?

JF Gemtuzumab was voluntarily removed from the market by Pfizer in 2010 after the postapproval trial that intended to provide confirmatory evidence of clinical benefit did not meet its endpoints. The not yet formally published S0106 trial, conducted by the Southwest Oncology Group (SWOG), was designed to determine whether adding gemtuzumab to standard chemotherapy demonstrated improved survival in previously untreated de novo AML patients ages 18–60 years. The trial was stopped early when no improvement in clinical benefit was observed and toxicity concerns were reported. Excess liver toxicity was of particular concern in patients who went on to receive a bone marrow or stem cell transplant and in those who were receiving concurrent chemotherapy.

There was also an Eastern Cooperative Oncology Group (ECOG) trial called E1900 that investigated administration of gemtuzumab right before autologous stem cell transplant in younger AML patients who were in first remission. No clinical benefit was shown in the E1900 trial, and a British trial did not show an overall survival advantage.

H&O Can you please discuss the Acute Leukemia French Association (ALFA 0701) study, which was presented at the 2011 American Society of Hematology (ASH) meeting?

JF In the ALFA trial, 280 patients with newly diagnosed AML who were 50–70 years of age underwent induction, as well as first and second consolidation with daunorubicin plus cytarabine. Half of the patients were randomly assigned to also receive gemtuzumab, which was added to the chemotherapy at each stage of treatment. Gemtuzumab was administered at a lowered dose schedule, in hopes that the toxicities of the drug could be reduced. The fractionated dosing schedule of gemtuzumab consisted of 3 mg/m^2 on days 1, 4, and 7.

The addition of gemtuzumab significantly improved both event-free and overall survival. The number of patients experiencing events during 3 years of follow-up was lower by approximately 25% in the gemtuzumab arm (76 vs 104), and the median overall survival was 34 months versus 19.2 months, respectively (P=.046). Toxicity was acceptable. There were 3 cases of veno-occlusive disease in the gemtuzumab

arm, including 2 that resulted in death. However, overall rates of fatal events that were possibly or probably related to treatment were only marginally higher with gemtuzumab (8.7% compared with 6.7% in the chemotherapy-alone group). Overall survival was particularly evident in the subgroup of patients with favorable or intermediate cytogenetics.

H&O Are there other studies showing promising results with gemtuzumab?

JF Also presented at the 2011 ASH meeting was a study by the National Cancer Research Institute (NCRI) AML Working Group in the United Kingdom, led by Dr. Alan Burnett. This study involved patients with AML who were fit to receive chemotherapy; most were older than 60 years. Patients were randomly assigned to receive standard induction and postremission chemotherapy, with the experimental group receiving a low dose of gemtuzumab on day 1 of therapy. The addition of a single dose of gemtuzumab on day 1 resulted in improved event-free survival, less benefit in relapse-free survival, and a notable improvement in overall survival (from 20% at 3 years in the control group to 25% in the gemtuzumab group).

H&O Is gemtuzumab under investigation in any other areas?

JF Responses to gemtuzumab in patients with acute promyelocytic leukemia (APL), a subtype of AML, have been encouraging. This activity is attributable to at least 2 factors. First, APL blasts typically have high and homogeneous expression of the CD33 antigen. Second, they lack or have very low levels of p-glycoprotein 1 (Pgp), a multidrug transporter that reduces the bioavailability of many medications via drug efflux. Additionally, expression of Pgp is inversely related to CD33 expression. Should gemtuzumab become commercially available in the future, I believe APL patients would benefit from this additional treatment option.

H&O What does the future hold for gemtuzumab in AML?

JF It is clear that there are subsets of AML patients that benefit from the addition of gemtuzumab to initial and salvage therapy. Other AML subtypes, such as patients with unfavorable risk cytogenetics, do not achieve the same benefit from this drug. However, it is important to consider data that demonstrate therapeutic benefits of gemtuzumab in well-defined molecular subgroups. In the past, the approach to treating leukemias was "one size fits all." We are now moving toward personalized medicine, as it is clear that cancers classified based on traditional morphologic assessments are heterogeneous. Researchers should not expect the same outcome in all patients with AML, especially when molecularly targeted agents are used. It will be of use to further analyze available data, such as the study by Burnett and colleagues, in order to better understand the diversity of AML, and to design individualized regimens for AML subsets. The more we can direct gemtuzumab treatment to the right patients, the better the outcomes will be.

Suggested Readings

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