Improved chemo regimen for childhood leukemia may offer high survival, no added heart toxicity

May 23 2013

Treating pediatric leukemia patients with a liposomal formulation of anthracycline-based chemotherapy at a more intense-than-standard dose during initial treatment may result in high survival rates without causing any added heart toxicity, according to the results of a study published online today in *Blood*, the Journal of the American Society of Hematology (ASH).

Acute myeloid leukemia (AML), the second most common form of leukemia in children, is a blood cancer in which the bone marrow makes a large number of abnormal white blood cells that crowd out other healthy blood cells over time, leading to infection, anemia, or excessive bleeding. Most adults and children with AML receive a first line of treatment (known as induction therapy) soon after diagnosis with a class of chemotherapy drugs called anthracyclines. Standard induction regimens in children typically consist of three days of an anthracycline such as daunorubicin or idarubicin and seven to 10 days of another chemotherapy such as cytarabine. Approximately 60 to 70 percent of children with AML achieve long-term survival with this combination of drugs.

Recent evidence has suggested that increasing the intensity of induction treatment might improve remission rates and perhaps overall survival in AML patients. However, clinicians have used this approach sparingly in pediatric patients because of documented dose-related anthracycline

toxicity in children, particularly the significant risk of damage to the developing heart muscle. In an effort to increase the effectiveness of this treatment for children with AML but reduce the cardiac risk profile, researchers are now investigating a liposomal (or lipid-based) formulation of the anthracycline daunorubicin (L-DNR) that allows for more targeted delivery of the drug in the cancerous cells and diffuses at a slower pace in the body which leads to a lower accumulation in the heart. Results from early pre-clinical studies of the lipid-based formulation suggest that L-DNR may be effective at higher-than-standard doses without causing added cardiotoxicity.

"We know that the standard induction treatment regimen is effective in pediatric leukemia patients, but recognize that the toxicities associated with this therapy can be damaging to young patients who are still growing and developing," said lead study author Ursula Creutzig, MD, of the Hannover Medical School in Germany. "This unique formulation of daunorubicin might offer us a way to effectively manage AML in these young patients while reducing their risk of experiencing the acute and long-term toxicities associated with traditional regimens."

To evaluate this hypothesis, Dr. Creutzig and a team of researchers initiated a trial to determine if L-DNR at intensified dosages in child and adolescent patients would improve their outcomes without added treatment-related acute and long-term cardiotoxicity. Between 2004 and 2010, 521 patients under 18 years of age were randomly assigned to treatment with either L-DNR or idarubicin induction therapy. Patients treated with L-DNR received a higher dose (80 mg/m^2/day/x3) than the equivalent dose of idarubicin (12 mg/m^2/day/x3) during induction. Both groups also received additional treatment with cytarabine and etoposide. High-risk patients (defined roughly as those who were not in the favorable cytogenetic group) also received supplemental treatment with a chemotherapeutic agent (2-CDA) after the induction period. Additional cycles of maintenance treatment were administered to all

participants, excluding those who received a stem cell transplant.

After a five-year observational period, researchers noted similar results in both treatment arms (76% overall survival in the L-DNR group vs. 75% in the idarubicin group). The probability of event-free survival (or pEFS) was also similar in the L-DNR (59%) and idarubicin groups (53%), as were pEFS results for standard risk (72% for L-DNR vs. 68% for idarubin) and high-risk patients (51% vs. 46%, respectively).

Overall, treatment with this intensified induction regimen had a similar safety and tolerability profile to the traditional idarubicin dose. Treatment-related mortality was lower in the L-DNR group than in the idarubicin group (2/257 vs. 10/264 patients), and there were no unusual or persistent toxicities seen when compared with previous related trials. The team observed generally low rates of cardiotoxicities across the treatment groups in the study, though fewer events were reported among the L-DNR treated patients than the idarubicin-treated patients. In the L-DNR group, there were four reports of severe acute cardiotoxicities, such as functional impairment, versus five events in the idarubicin group. There was a single patient reported to have late cardiotoxicity during follow-up in the L-DNR group, as compared with three patients in the idarubicin treatment group.

"These findings signal an important step forward in our goal to identify treatments that can give pediatric patients the best chance for long-term survival with minimal toxic side effects, and we believe the approach could have a number of extended applications. For example, this treatment formulation may be appropriate to use in adults or elderly patients to reduce the toxicity profile, or it may be of value for other malignant diseases in both children and adults," said Dr. Creutzig. "We look forward to further investigating L-DNR as the standard anthracycline induction treatment in future studies."