HEMATOLOGY

Mitoxantrone improves the survival of children with first relapse of ALL

Children with relapsed acute lymphoblastic leukemia (ALL) have substantially better progression-free survival and overall survival when treated with induction therapy containing mitoxantrone compared with that containing idarubicin, data from the ALL R3 trial shows. In fact, because the interim data showed such a profound survival benefit (over 20%) in the mitoxantrone group, randomization of patients into the trial was stopped early. This work provides an important advance for the treatment of relapsed ALL.

Survival of children with ALL has improved substantially in recent years, with current 5-year survival rates around 80%. However, Vaskar Saha, senior researcher of the ALL R3 trial, notes that "no improvement has occurred in children with relapsed ALL for over two decades." For example, the overall survival in this subgroup was between 46% and 56% in the UK from 1991 to 2003. Moreover, the pattern of relapse has changed during this period, with central nervous system recurrence becoming more common. Thus, new methods of managing relapsed ALL are needed to address these issues.

The ALL R3 trial investigated the effects of induction treatment with a four-drug regimen that included either idarubicin or mitoxantrone. Idarubicin is an established agent for the treatment of relapsed ALL. Mitoxantrone is a relatively cheap, widely available drug that has been shown to improve outcomes in children with ALL.

Patients (age 1–18 years) with first relapse of ALL were enrolled from 31 centers in the UK, Ireland, Australia and New Zealand. These patients were randomly assigned to induction therapy containing either idarubicin ($n = 109$) or mitoxantrone ($n = 103$). However, randomization was closed during an interim analysis, under the recommendation of an independent data-monitoring committee. This decision was made owing to the observation of an obvious survival advantage in the mitoxantrone group. The investigators carried out their final analysis 2 years later, allowing the data to mature.

"The survival outcome of patients treated with mitoxantrone is twice that of the patients who received idarubicin," Saha comments; "one of the biggest differences ever reported for a single agent effect in leukemia trials," he adds. The estimated 3-year progression-free survival rate was 64.6% in the mitoxantrone group compared with 35.9% in the idarubicin group. This difference was attributed to a notable decrease in disease-related events and disease-related death rather than an increase in adverse effects from idarubicin treatment. Overall toxic effects were lower in the mitoxantrone group, although hematological toxic effects were worse in this group in the later phases of treatment. The 3-year overall survival rates for patients treated with mitoxantrone or idarubicin were 69.0% and 42.5%, respectively.

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Aside from the impressive survival benefits, the study produced another important finding. Minimal residual disease—considered a major prognostic factor in leukemia—was measured in intermediate-risk patients at the end of the randomized treatment period. Measuring minimal residual disease has been incorporated as a measure of outcome in studies in order to quickly assess new drugs. However, no difference in minimal residual disease was detected between the two groups in ALL R3, despite the obvious difference in outcomes. The researchers note that this combination of drugs would not have been considered for further assessment had minimal residual disease been considered as a surrogate end point.

Image courtesy of V. Saha

The researchers postulate that mitoxantrone might alter the hematopoietic stem-cell niche, making the environment less favorable to leukemic cells, but may encourage successful allografts. Therefore, Saha's group plan to study this activity in more detail: "the effect on the normal hematopoietic niche is being investigated in the laboratory."

The ALL R3 trial shows that conventional cytotoxic agents are still useful in lieu of the awaited development of targeted therapies, the researchers conclude. In light of the positive results, Saha and colleagues plan to take this work forward; "mitoxantrone will now be tested in a larger cohort of patients in an international trial."

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