

A step forward in acute lymphoblastic leukemia

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Acute lymphoblastic leukemia (ALL) is the most frequent pediatric malignant disease. It originates in a single B- (85%) or T-lymphocyte (15%) progenitor. With a current cure rate of childhood ALL of more than 80% in developed countries, the evolution of therapies for this disease is one of the unprecedented success stories in the history of modern medicine. Yet, there are subgroups of children with ALL who have lower chances to be cured, such as patients with slow initial response to therapy. The most important criteria determining slow response to initial chemotherapy include: poor response after one week prednisolone therapy (occurring in 8-9% of patients), and persistence of minimal residual disease (MRD) after one-month induction therapy (usually in 20-30% of patients). Noteworthy, poor response to initial therapy is more often seen in patients with T-lineage ALL. In other words, patients with T-ALL have higher risk for slow response to therapy. This is important, as both prednisolone poor responders, and MRD-positive patients have lower than 50% chances to be cured (1,2). Some study groups have even used T-ALL patients with poor early chemotherapy response to allocate to hematopoietic stem cell transplantation (HSCT) already in first complete remission.

The last decade has brought to the clinic a number of new compounds that were tested as possible antileukemic agents. So far, none of them has shown significant impact in improving outcome in pediatric patients presenting unfavorable prognostic factors. The experience with nelarabine in phase I and phase II studies has identified it as a promising agent for patients with T-ALL, but the effect was however limited by neurotoxicity.

Recent study by Dunsmore *et al.* in *Journal of Clinical Oncology* (3), has added 2 very breakthrough information to our knowledge in the use of nelarabine in children with T-ALL, in the area of safety and efficacy.

With respect to safety, it has been shown by the Authors that five or six 5-day courses of nelarabine could be added safely to BFM86-based chemotherapy in patients with newly diagnosed T-ALL. This discrepancy with previous results indicating neurotoxicity can be explained by the fact that patients treated in the phases I and II nelarabine trials had relapsed leukemia, and many were heavily pretreated with therapy. The differences in neurotoxicity between that study and earlier trials suggest that therapies with significant toxicity in the relapse setting may be better tolerated in newly diagnosed chemotherapy naive patients. Interestingly, addition of nelarabine did not lead to increased hematologic or infectious toxicities.

With respect to efficacy, the results of the study are very optimistic, even if this study was not powered to determine the efficacy of adding nelarabine to intensive chemotherapy. Poor-prednisolone responders patients treated with nelarabine, who were expected to have treatment outcomes in the range of 30-50%, had a 5-year disease-free survival rate of 69%, identical to that of good-prednisolone-responding patients who did not receive nelarabine. The cure rate for slow responder patients treated with nelarabine in the Dunsmore *et al.* study compares favorably with that obtained for patients receiving HSCT in equivalent to 50-73% survival in German protocols BFM 90 and 95, and is also greatly improved over 14% survival seen in patients with similar MRD-positive ALL (1-3).

In conclusion, patients with T-ALL with a poor early treatment response that predicted for poor outcomes in previous trials when treated with intensive chemotherapy plus nelarabine can reach a cure rate comparable to cure rate of patients with positive risk factors. This achievement opens new possibilities in therapy of pediatric T-cell acute lymphoblastic leukemia.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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