Editorial

Relapsed acute myeloblastic leukemia: first pediatric randomized study

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The current cure rate achieves 80% of long-term survival in childhood acute lymphoblastic leukemia (ALL) and only 50-60% in acute myeloblastic leukemia (AML) (1). However, in patients who relapse following treatment of AML, the odds are not as far in their favor, and the probability of overall survival is 16-34% (2,3).

In a recent manuscript published in the *Journal of Clinical Oncology*, Kaspers *et al.* (4), report results of a randomized phase III study by the International Berlin-Frankfurt-Münster Study Group in pediatric relapsed AML, with the use of liposomal daunorubicin. Previous studies have suggested that liposomal daunorubicin (DNX, DaunoXome) is effective and less cardiotoxic than daunorubicin, which is important in this setting.

So far, optimal reinduction therapy is unknown for relapsed AML in children. Kaspers *et al.* included patients with relapsed or primary refractory non-French-American-British type M3 AML who were younger than 21 years of age. Patients were randomly assigned to fludarabine, cytarabine, and granulocyte colony-stimulating factor (FLAG) or to FLAG plus DNX in the first reinduction course. The primary end point was status of the bone marrow (BM) sampled shortly before the second course of chemotherapy (the day 28 BM). Data were presented according to intention-to-treat for all 394 randomly assigned patients with median follow-up of 4.0 years.

Results were encouraging. In this multinational setting, Kaspers *et al.* achieved the best outcome for these children reported so far, with the complete remission (CR) rate of 64%, and a 4-year probability of survival (pOS) of 38%. The day 28 BM determined as ≤20% leukemic blasts was good in 80% of patients randomly assigned to FLAG/DNX and 70% for patients randomly assigned to FLAG. Concerning secondary end points, the CR rate was 69% with FLAG/DNX and 59% with FLAG, but overall survival was similar. However, in the subgroup of patients, with core-binding factor (CBF) AML treated with FLAG/DNX resulted in pOS of 82% versus 58% with FLAG, what is a unique result of the study. Another important issue is similar grade 3/4 toxicity in both groups. Kaspers *et al.* concluded, that DNX added to FLAG improves early treatment response in pediatric relapsed AML. Overall long-term survival was similar, but CBF-AML showed an improved survival with FLAG/DNX.

So far, there have been no randomized clinical trials in children with relapsed AML. Kaspers *et al.* showed that international collaboration was feasible and resulted in the best outcome for pediatric relapsed AML reported so far. DNX added to FLAG in the first reinduction course significantly improved the early response rate as primary end point from 70% to 80%. The CR rate also improved from 59% to 69%. Although, OS was similar with FLAG and FLAG/DNX, patients with CBF-AML had a 24% higher 4-year pOS when treated with FLAG/DNX. The question arises, why a better early treatment response did not translate into a significantly better OS. This may partially be explained by the fact that several patients were treated with FLAG plus an anthracycline or gemtuzumab ozogamicin, introducing an unintended cross-over effect. In addition, the quality of remissions achieved with FLAG/DNX may have been relatively poor in many patients, and subsequent therapy could not prevent second relapse.

Important finding of the study is that increased antileukemic activity with FLAG/DNX was not associated

with increased toxicity during chemotherapy, except for a modest increase in skin toxicity. Concerns for late cardiotoxicity associated with higher cumulative doses of anthracyclines and related drugs are valid (5). DNX is a liposomal anthracycline that might be less cardiotoxic because of its pharmacology. One may argue that the clinical benefit of DNX is unknown at best, because OS did not improve significantly. However, it should be taken into account that therapy after induction was heterogeneous and may have been intensified in patients with a poor early treatment response.

The study has several limitations, such as unsatisfactory results after the first course of reinduction therapy in patients with nonfavorable cytogenetics. Another limitation of this study is the heterogenous first-line treatment used in the study patients, even if usually treated with cytarabine-based treatment combined with an anthracycline. In spite of these limitations, this study is the first important step towards improvement of outcome in pediatric relapsed AML.

The next step in therapy of relapsed AML in children should be randomized study that will check the benefit of adding gemtuzumab ozogamicin to a backbone of fludarabine, cytarabine, and liposomal daunorubicin, and the use of sorafenib in patients with FLT3-mutated AML cells. Hopefully, Kaspers *et al.* will study these effects in their next international randomized pediatric Relapsed AML 2010/01 study.

The study of Kaspers *et al.* has shown that pediatric relapsed AML might be curable in a significant proportion of patients. Despite an encouraging improved outcome in pediatric relapsed AML in this study, prognosis is still unsatisfactory. Further international collaboration is necessary in the treatment of pediatric relapsed AML.

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Footnote

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