Editorial

Dexamethasone *vs*. prednisone in pediatric acute lymphoblastic leukemia

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With contemporary multi-agent chemotherapy regimens, nearly 90% of children with acute lymphoblastic leukemia (ALL) can be cured (1,2). Glucocorticoids have remained an essential part of the induction chemotherapy regimen in childhood ALL for decades (3). Both prednisone (PDN) and dexamethasone (DXM) are glucocorticoids used in induction therapy, with different anti-leukemic efficacy, central nervous system (CNS) penetration, and toxicity profiles. In general, DXM contains more potent cytotoxic glucocorticoids with better CNS penetration, which is particularly appealing to T-cell ALL with higher rates of CNS disease (4-7). However, the benefits of DXM have been offset by the higher incidence of fatal infection in induction, and more treatment-related toxicity such as avascular necrosis (AVN) (8,9). Despite previous attempts to directly compare the effects of two glucocorticoids during induction by several randomized clinical trials, no consensus has been reached regarding the optimal glucocorticoid in induction, at which dose, and the duration of therapy (8,10-12).

The collaborative clinical trial Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP)-Berlin-Frankfurt-Munster (BFM) ALL 2000 conducted between 2000 and 2006 by AIEOP and BFM ALL study group revisited this question by randomizing patients to receive DXM or PDN during induction (13). The primary objective of the study was to determine whether DXM in induction can provide a better event free survival (EFS) in children with newly diagnosed ALL. Events were defined as non-response, relapse, secondary neoplasm, or death from any cause. The randomization was stopped for patients ≥10 years of age on October 2004 due to excessive death and toxicity in older patients receiving DXM.

All patients received a 7-day PDN prephase. After the prephase, a total of 3,720 patients aged 1–17 years were randomized to receive either PDN (60 mg/m^2/day) or DXM (10 mg/m^2/day) for an additional 21 days with a subsequent taper. Patients were further classified into standard risk, medium risk, and high risk post induction, based on the response to PDN prephase, complete remission (CR) on day 33, cytogenetics, and minimal residual disease (MRD). Subjects continue to receive multi-agent chemotherapy for a total of 2 years, or receive allogeneic hematopoietic stem cell transplantation in first CR in selected patients with very high risk features. Some patients also received cranial radiation based on predefined criteria in the protocol.

The results were striking. Using DXM instead of PDN for only 3 weeks in the 2 years course of multi-agent chemotherapy reduced the relapse risk by 31% (*Table 1*). The benefit is seen in all types of relapses, including isolated bone marrow (BM), isolated extramedullary (CNS and testes), and combined BM/CNS relapse, with a greater reduction in extramedullary relapse (*Table 1*). However, there was a 2.4-fold increased death rate in patients treated in the DXM arm compared to PDN arm (*Table 1*). Most of the deaths are related to infection. Despite the significant increase in death rate in the DXM arm, induction death remains a rare event. On balance, there was a significant improvement in EFS, the primary end point of the study, in the DXM arm (*Table 1*).

Table 1 Comparison of DXM *vs.* PDN during induction in all patients

	DXM (%)	PDN (%)	Reduction of relapse in DXM arm (%)	P value
5-year CIR	10.8±0.7	15.6±0.8	31	<0.0001
Isolated BM	7.6±0.6	9.7±0.7	22	0.013
Isolated CNS	0.9±0.2	1.9±0.3	53	0.019
Isolated testes	0.4±0.1	1.1±0.2	64	0.016
Combined CNS/BM	0.7±0.2	1.5±0.3	53	0.027
Induction death	2.4	1	—	0.0011
5-year EFS	83.9±0.9	80.8±0.9	—	0.024
5-year OS	90.3±0.7	90.5±0.7	—	0.61

BM, bone marrow; CIR, cumulative incidence of relapse; CNS, central nervous system; EFS, event free survival; OS, overall survival; PDN, prednisone; DXM, dexamethasone.

Table 2 Comparison of DXM *vs.* PDN during induction in T-ALL patients with PDN good response

	DXM	PDN	P value
5-year CIR	7.2±2.2	17.2±3.2	0.007
Induction death	2.1	0.7%	0.62
5-year EFS	87.8±2.8	79.2±3.4	0.037
5-year OS	91.4±2.4	82.6±3.2	0.036

CIR, cumulative incidence of relapse; EFS, event free survival; OS, overall survival; ALL, acute lymphoblastic leukemia; PDN, prednisone; DXM, dexamethasone.

When looked at carefully among subgroups, the reduced relapse in patients ≥10 years of age in the DXM arm did not result in improved EFS due to the higher incidence of induction death in this group. In patients with PDN poor-response, no difference in the relapse rate and EFS was observed in both B- and T-ALL, suggesting switching to DXM during induction cannot overcome the intrinsic glucocorticoids resistance in the leukemia blasts. This is in contrast to the patients with PDN good response, where a significantly lower incidence of relapse and better EFS was observed in the DXM arm compared to the PDN arm in patients with both B- and T-ALL.

Unfortunately, the improved EFS in the DXM arm did not translate into improve overall survival (OS). With a median follow up of 8.8 years, the OS curve looked identical (*Table 1*). Why is there no advantage in OS is observed, despite the significantly improved EFS in the DXM arm? This could be explained by the observation that DXM has greatest impact in preventing relapses that are easier to be salvaged by second line therapy, such as isolated extramedullary relapse or late relapse of B-ALL. Therefore, the survival rate after relapse in the PDN arm exceeded the survival rate after relapse in the DXM arm and no OS benefit can be identified.

However, this is not the whole story. When we carefully examine different patient subsets, one subgroup of patients clearly had lasting benefit in both EFS and OS when treated with DXM. T-ALL comprises 15% of all childhood ALL. Approximately 1/3 of the patients have PDN poor response after 7 days of PDN prephase. There is no difference in the relapse rate, EFS, and OS in these patients between the two arms. In contrast, among T-ALL patients with PDN poor response (2/3 of the T-ALL patients), there is a 58% reduction in the relapse rate (*Table 2*). This resulted in the improved 5 year EFS and OS (*Table 2*). In this subset of patients, the EFS curves diverged early, before the end of the first 12 months of therapy, suggesting DXM prevented relapses that could not be salvaged easily with second line therapy, such as early relapse in these patients. Therefore, DXM is clearly superior to PDN in T-ALL patients with PDN good response.

Interestingly, a parallel randomized clinical trial to compare DXM *vs.* PDN during induction in children with high risk ALL was conducted by the Children's Oncology Group in North America, Australia, and New Zealand (9). This study showed that in children ≥10 years of age, there is no difference in EFS when received 14 days course of

DXM at 10 mg/m^2/day or 28 days of PDN at 60 mg/m^2/day, although the patients received PDN had a much lower risk of developing AVN.

Two key findings in this study will have impact in contemporary therapy of childhood ALL: (I) the lack of OS benefit in B-ALL, despite an improved EFS in the DXM arm highlights the importance of identifying effective therapy to prevent early BM relapses, which will likely improve the survival; (II) the survival benefit of DXM in T-ALL patients with PDN good response prompts the current AIEOP-BFM ALL 2009 clinical trials using DXM during induction in this subgroup of patients. Moving forward, the results from this trial continue to suggest that there is no universal straightforward answer to whether one glucocorticoid is superior to another during ALL therapy; rather, there is benefit to selective patient subgroups, and new therapies need to be identified to prevent relapses that are difficult to salvage. Furthermore, strong supportive guidelines need to be implemented in the protocol to prevent severe infectious complications.

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Footnote

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