



Prednisone and dexamethasone in acute lymphoblastic leukemia in children: which is the better option?

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Modern therapy for childhood acute lymphoblastic leukemia (ALL) composes of multi-agent chemotherapy regimens. During remission induction therapy, systemic chemotherapy consists of three to four agents together with intrathecal chemotherapy. Among them, corticosteroid is one of the important anti-leukemic agents. Either prednisone (or prednisolone) or dexamethasone is being used in the remission-induction therapy in various single center or multi-center collaborative studies. At the earlier days of ALL treatment, prednisone was the first corticosteroid used in induction therapy. Interest in substituting dexamethasone for prednisone arise from subsequent studies which suggested dexamethasone having more potent anti-leukemia activity, and better central nervous system penetration. However it may be associated with more treatment related toxicities. The choice of corticosteroid, its optimal dose and duration of use within the regimen of childhood ALL therapy remained controversial (1,2).

There are a number of published studies from large cohorts comparing prednisone and dexamethasone in treatment of childhood ALL. Children's Cancer Group (CCG)-1922 for National Cancer Institute (NCI) standard risk ALL and Medical Research Council (MRC)-ALL 97, demonstrated that the substitution of prednisone by dexamethasone could decrease the risk of CNS relapse (3.7% *vs.* 7.1%; and 2.5% *vs.* 5.0%) with higher event free survival (85% *vs.* 77%; and 84.2% *vs.* 75.6%) (3,4). However, corticosteroid randomization in those two trials was not limited to induction therapy but also encompassed other treatment phases including consolidation and

maintenance therapy. Some protocols included prednisone during induction and dexamethasone during the consolidation or delayed intensification. The combined use of two corticosteroids during different phases of treatment further complicates the evaluation of steroid choice in the whole regimen. These variables and confounders cannot be fully addressed without a randomized trial with a large cohort.

Results of Associazione Italiana di Ematologia e Oncologia Pediatrica-Berlin-Frankfurt-Munster (AIEOP-BFM) ALL 2000 trial was recently published (5). Over 3,700 children with ALL were randomized to either dexamethasone or prednisone in induction therapy after initial 1 week of prednisone pre-phase. The trial directly compared a high dose steroid regimen with dexamethasone (dose at 10 mg/m²/day) with prednisone (dose at 60 mg/m²/day) both given for 3 weeks. The result, in term of relapse reduction, was impressive with relapse rate reduced by one-third when dexamethasone was substituted for prednisone (relapse rate 10.8% *vs.* 15.6%). This is the most remarkable success in reducing in relapse achieved in the last 3 decades in the BFM group by substitution of only one agent with another (6).

The efficacy of dexamethasone over prednisone was supported by results from other recently published trials. The results from Children's Oncology Group (COG) AALL0232 study (for NCI high risk ALL) was also published recently (7). The patients were randomized to prednisone and dexamethasone during induction at the same dosage as AIEOP-BFM ALL 2000, but a shorter

duration of dexamethasone for 14 days comparing with 28 days of prednisone. The trial design also included second randomization to Capizzi regimen with lower, escalating doses of intravenous methotrexate (C-MTX) *vs.* high-dose methotrexate (HD-MTX) in interim maintenance I. For efficacy, this study also showed patients age 1 to 9 years who received dexamethasone and high dose methotrexate had superior event free survival 91.2%, compared with 83.2% (dexamethasone, C-MTX), 80.8% (prednisone, HD-MTX) and 82.1% (prednisone, C-MTX). The Dana-Faber Cancer Institute (DFCI) ALL Consortium Protocol 00-01 compared dexamethasone and prednisone, administered as 5-day pulses every 3 weeks, and also compared a novel dosing method for L-asparaginase. The dexamethasone group had superior 5-year event free survival (90% *vs.* 81%) (8).

Other than anti-leukemia efficacy, the potential treatment related morbidity and mortality must be considered for the choice of therapy. Compared to prednisone, dexamethasone was reported to be associated with more bone toxicities, proximal myopathy, mood and behavior changes, neuro-cognitive impairment and life threatening infections (9). As the survival rate of childhood ALL reach above 90% with current therapy, minimizing treatment related toxicity and mortality is as important as maintaining treatment efficacy. As discussed in the report of the AIEOP-BFM ALL 2000 trial, no difference was detected between the two groups in terms of overall survival. More children died during induction in dexamethasone group (2.5%) in comparison with prednisone group (0.9%) due to life-threatening infections (both bacterial and fungal infections), neurological and gastrointestinal complications. Moreover, patients who had relapsed on the dexamethasone arm had more adverse prognostic factors compared to the patients in the prednisone arm. This suggests that the efficacy of dexamethasone in terms of relapse reduction may not translate into overall survival advantage for all patients with ALL. The AIEOP-BFM 2000 study did identify a subgroup, patients who had T-cell ALL and prednisone good response, where clear survival benefit was seen with dexamethasone (in both event free survival and overall survival). This was incorporated into the criteria for treatment stratification in the successor AIEOP-BFM 2009 study.

In the AIEOP-BFM 2000 cohort, increased risk of serious complications in the adolescent patients in dexamethasone arm led to stopping corticosteroid randomization for patients above 10 years of age after

interim analysis. The COG AALL0232 study, along the same line, found that the patients aged above 10 years in dexamethasone arm had excess toxicity but no benefit, leading to the amendment of study to exclude them from steroid randomization. In adolescent patients, the potential benefit from dexamethasone did not out-weight the associated toxicities. Nevertheless, the COG trial did not observe increase in treatment related deaths in the dexamethasone arm. This suggested the use of shorter duration of dexamethasone for 2 weeks in younger children instead of 3 weeks as in the AIEOP-BFM trial in induction could be a feasible option.

Dose conversion of prednisone to dexamethasone is also a controversial issue. In most published studies, the dose ratio of dexamethasone to prednisone was at 6:1 (prednisone 60 mg/m² to dexamethasone 10 mg/m²) or 7:1 (prednisone 40 mg/m² to dexamethasone 6 mg/m²). This was based on the generally assumed biologically equivalent anti-inflammatory potency. Many of these studies demonstrated superior efficacy of dexamethasone to prednisone or prednisolone. Some studies have compared prednisone and dexamethasone at a different dose conversion ratio. The Tokyo Children's Cancer Study Group L95-14 trial used a prednisone to dexamethasone ratio of 7.5:1 (10). The European Organization for Research and Treatment of Cancer (EORTC) 58951 study used a dose ratio of 10:1 (11). Both studies showed no difference in survival outcomes between the two types of steroids. When the relative dose of dexamethasone is smaller, the superiority over prednisone for relapse reduction was no longer apparent.

As we have more long term survivors of childhood malignancy, there is increased concern on the long term sequelae of therapy, and some of these consequences could be irreversible with debilitating impact on the quality of life in survivors. Osteonecrosis is one of the known complications after high dose corticosteroid. In COG AALL 0232 report, higher incidence of osteonecrosis was seen in the older patients. The continuous exposure to dexamethasone, despite shortened to 14 days, was associated with higher incidence of osteonecrosis than prednisone. In contrast, no statistically significant difference was shown between dexamethasone and prednisone across both the younger and older age groups in the AIEOP-BFM 2000 trial. The AIEOP-BFM trial did not include the steroid pulse in the maintenance phase; therefore the cumulative dose of steroid may be lower than the other trials.

Neuro-cognitive impairment is another significant aspect on long term survivors. CNS toxicity related

to dexamethasone is a concern as it has better CNS penetration. Corticosteroids had already been shown to affect neuro-cognitive development in non-cancer patients. Preterm neonates with post-natal dexamethasone therapy for lung disease were associated with lower IQ and worse visual-motor coordination (12). In the St. Jude Lifetime Cohort, previously treatment with dexamethasone in survivors of childhood ALL patients (who had not received cranial RT) was associated with impaired attention and executive function (13). Cognitive function assessment on 92 subjects in the CCG-1922 cohort showed mild decrease in word reading ability in dexamethasone treated group (14). Neuropsychological assessment on 170 survivors from DFCI ALL Consortium Protocol 00-01 reported lower score on fluid reasoning with greater utilization of special education services in dexamethasone group (15). Long term follow up for the neuro-cognitive outcome in the large AIEOP-BFM 2000 and the COG AALL 0232 cohorts would provide additional insight to this question.

The comparison of prednisone versus dexamethasone in childhood ALL had been addressed in a number of randomized trials, as well as systemic reviews and meta-analysis (16). Until now there is still no simple answer. Well-designed clinical trials to compare the two agents at different dosage and schedules for a protocol with best efficacy and minimal toxicity will continue to be the aim for pediatric oncologists.

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Footnote

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