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To Augment or Not to Augment Consolidation Therapy for High-Risk Childhood Acute Lymphoblastic Leukemia

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Nachman et al in the year 1998 published the results of the Children's Cancer Group (CCG)-1882 study in which they explored the role of augmented intensive postinduction therapy among children with high-risk acute lymphoblastic leukemia (ALL).[1] Following this study, the augmented Berlin-Frankfurt-Munster (BFM) consolidation which consists of additional vincristine and asparaginase during periods of myelosuppression of the standard IB phase became the preferred postinduction therapy for high-risk ALL across several cooperative groups. Nearly 25 years later, the intercontinental BFM group have published results of the BFM-2009 study, which aimed to address a similar question.[2] In the BFM-2009 study, patients belonging to the intermediate-/high-risk group were randomized following induction therapy to either the standard IB phase or the augmented IB phase. The results of this study showed no difference in relapse incidence (19.1% vs. 20.5%; $p = 0.55$) or overall survival (OS) (81.9% vs. 80.3%; $p = 0.46$) between the standard IB and augmented IB phases, respectively. Further, a subgroup analysis failed to demonstrate an impact of the augmented regimen on either risk group (intermediate-risk or high-risk) or immunophenotype (B-ALL or T-ALL). In addition, the incidence of allergic reactions to asparaginase, infections, and pancreatitis were higher in the augmented IB arm. In contrast to the results of the BFM-2009 study, the CCG-1882 randomized study showed a significant improvement in survival following postinduction augmentation of therapy.[1] So, what accounted for the disparity between the two studies? First, the CCG-1882 study included National Cancer Institute (NCI) high-risk (age $\geq$ 10 years or total leukocyte count [TLC] $\geq 50 \times 10^9$ /L) patients with poor early response defined as $>$ 25% marrow blasts on day 7, whereas the BFM-2009 study employed a different age (6 years) and TLC cutoff ($\geq 20 \times 10^9$/L) in addition to day 15 measurable residual disease (MRD) and adverse cytogenetics to define risk groups eligible for randomization. Moreover, the CCG-1882 study extended intensification not only to the IB phase but also to the interim maintenance and delayed intensification phases, while the BFM-2009 study limited augmentation to the IB phase. A significant difference was also observed in the central nervous system (CNS) prophylaxis between the two studies. The BFM-2009 study restricted cranial radiotherapy (CRT) exclusively for CNS-3 disease and offered high-dose methotrexate (HDMTX) to all patients, whereas the CCG-1882 offered Capizzi I escalating intravenous MTX without leucovorin rescue plus asparaginase and prophylactic CRT for all patients. The promising results of the CCG-1882 study led to a similar randomized study (CCG-1961) but among NCI high-risk patients with rapid early response ($<$ 25% marrow blasts on day 7), which again concluded in favor of the augmented regimen.[3] More recently, the Medical Research Council group in their UKALL-2003 trial also studied the role of postinduction augmentation in a randomized manner among high-risk ALL patients.[4] In this study, standard intermediate-risk patients, defined based on NCI risk and day 8 response, were randomized to receive augmented postinduction therapy or risk-specific standard therapy if they had a MRD of more than 0.01% on day 29 of induction. Augmented therapy in this context consisted of an additional eight doses of pegylated asparaginase and extra 18 doses of vincristine during consolidation and delayed intensification phase along with Capizzi I escalating MTX. The study's findings indicated superior event-free survival (89.6% vs. 82.8%, $p = 0.04$) and OS (92.9% vs. 88%, $p = 0.16$) among patients receiving the augmented therapy. While this study highlights the importance of augmenting therapy among

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patients with persistent disease at the end of induction, it does not definitely establish the benefit of augmented BFM consolidation.[4] Several previous studies have shown the importance of achieving clearance of MRD by day 78 (end of consolidation), in both B- and T-cell ALL.[5–8] In the COG AALL0232 study, all high-risk B-ALL patients received four-drug induction followed by augmented IB consolidation.[6] Among the 2,473 patients evaluated for MRD in this study, 685 patients had a positive ($\geq$ 0.01%) MRD at the end of induction while only a small proportion of patients ($n = 45$) remained MRD positive at the end of consolidation.[6] This suggests that employing augmented IB consolidation might be justified for a subset of high-risk ALL patients defined based on day 29 MRD, as it has the potential for a more effective clearance of MRD. A limitation of the BFM-2009 study was the lack of day 29 MRD details, which could have shed light on the benefit of the augmented IB consolidation for patients with MRD positive disease receiving a BFM backbone chemotherapy. It is also important to note that patients in the COG AALL0232 study were randomized to receive either Capizzi I MTX or HDMTX during interim maintenance and the effect of HDTMX (compared to Capizzi I MTX) was more pronounced among patients who were MRD positive. Based on the data from the COG ALL0232 study and more recent findings from the UKALL-2011 study, HDMTX may have an important role in mitigating bone marrow disease and its benefit may not be limited to only sanctuary sites.[9]

Needless to say, such cross-comparisons across trials for childhood ALL are fraught with limitations, including differences in risk stratification among cooperative groups, variations in MRD detection methods and time points, and even disparities in the number of chemotherapy cycles administered. Nevertheless, following the two successive randomized CCG studies, augmented BFM consolidation IB regimen became the standard of care for pediatric and young adult with high-risk ALL across several cooperative groups. However, the results of the BFM-2009 study challenge the necessity of augmenting the standard BFM consolidation, particularly with the inclusion of HDMTX, a notable absence in both the CCG studies and the UKALL-2003 trial. Given the higher incidence of toxicities and the lack of survival benefits in the BFM-2009 study, routine use of the augmented IB regimen during consolidation phase for intermediate- or high-risk ALL patients, especially when treated with BFM chemotherapy, would be inappropriate. Nonetheless, the augmented IB regimen could still hold value for certain high-risk ALL defined based on end of induction MRD, and contribute to the eradication of residual disease.

Conflict of Interest
None declared.

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