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Comment on: Severe toxicity and poor efficacy of reinduction chemotherapy are associated with overall poor outcomes in relapsed B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group AALL1331 trial

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Comment on: Severe toxicity and poor efficacy of reinduction chemotherapy are associated with overall poor outcomes in relapsed B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group AALL1331 trial

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Note: we used ChatGPT in order to improve readability and language.

To the Editor:

We read with interest the report by Hogan et al. on the outcomes of the Children's Oncology Group AALL1331 trial.[1] This landmark study offers an essential, comprehensive view of contemporary therapy for first relapse of B-cell acute lymphoblastic leukemia (B-ALL). While the trial successfully demonstrated the benefits of incorporating blinatumomab for randomized patients, the data concerning the common reinduction Block 1, which was modeled on the UKALLR3 mitoxantrone backbone, reveal profound and troubling shortcomings in our current standard approach. The findings present a compelling case that this widely used reinduction strategy carries an unacceptable toxicity burden for a disappointingly low degree of efficacy, ultimately undermining outcomes for a significant proportion of patients.

The toxicity profile of Block 1 chemotherapy is profoundly concerning. The observation that 72.6% of patients experienced a grade 3 or higher adverse event transforms reinduction from a therapeutic bridge into a period of extreme vulnerability.[1] With 30.3% of patients developing febrile neutropenia, 36.6% infections, and 10.1% sepsis, the protocol effectively induces a state of severe immunosuppression. This is catastrophically reflected in the 24 treatment-related deaths during Block 1, 95.5% of which resulted from infection.[1] When nearly 4% of patients die from treatment complications before induction, we must immediately reassess whether the treatment itself has become as lethal as the disease. This mortality rate aligns with prior trial data (4.8%)[2], indicating a potential systemic risk inherent to the regimen. Furthermore, the significantly higher rates of severe infections, sepsis, and mucositis in older adolescents and young adults highlight that this regimen is particularly poorly tolerated beyond early childhood.[1] The pronounced toxicity directly contributed to protocol attrition, as 19.4% of enrolled patients never proceeded to risk assignment or randomization, often due to adverse events or physician discretion following a toxic reinduction.[1] Their subsequent dismal survival (4-year overall survival 19.8%) mirrors that of patients with overt treatment failure, underscoring that severe toxicity is not merely a transient setback but a definitive negative prognostic event.[3]

Such profound toxicity might be defensible if it reliably secured deep, durable remissions. The data, however, reveal a stark efficacy deficit. Despite intensive chemotherapy, 54.5% of patients with bone marrow involvement remained minimal residual disease (MRD) positive ($\geqslant$0.01%) at the end of Block 1. This failure to achieve MRD negativity in most patients is therapeutically problematic, given the unequivocal role of MRD as the paramount prognostic factor in relapsed ALL.[4,5] Extensive literature establishes that MRD positivity after reinduction predicts a significantly inferior outcome.[4,5] The reported 4-year event-free survival of 9.6% for patients with early marrow relapse, a cohort with a 67.9% MRD positivity rate,

exemplifies this dire correlation. The authors note that the MRD negativity rate in AALL1331 appears inferior to the 64.6% 3-year progression-free survival reported for the UKALLR3 mitoxantrone arm.[3] While cross-trial comparisons are limited, this discrepancy, alongside the higher treatment-related mortality in AALL1331, raises serious concerns about the generalizability and current suitability of this decades-old backbone.

The juxtaposition of high toxicity and low efficacy creates a troubling therapeutic imbalance. We are subjecting patients to a regimen with a 3.6% risk of fatal infection to achieve an MRD-negative response in fewer than half. This calculus is unsustainable. The findings from AALL1331 resonate with other studies of intensive reinduction.[6,7] For instance, the COG AALL07P1 trial, employing a different intensive block, achieved complete remission in only 68% of high-risk B-ALL patients in first relapse, with a mere 29% attaining MRD negativity.[7] Similarly, the ALL-REZ BFM trials have long stratified patients based on early response, implicitly acknowledging that many will not respond adequately to initial chemotherapy.[8] The consistent theme is that intensive chemotherapy alone is insufficient for a substantial subset of relapsed B-ALL.[8]

Therefore, the central imperative illuminated by Hogan et al. is the need to move beyond reliance on maximally intensive chemotherapy for reinduction. The future must pivot towards smarter, more selective strategies that prioritize efficacy while mitigating harm. The logical path forward is earlier integration of novel immunotherapies. Blinatumomab has already proven its superiority over chemotherapy in the consolidation phase of AALL1331.[9] The critical question now is whether moving it upfront, potentially following brief, reduced-intensity cytoreductive chemotherapy, can improve the therapeutic index. Could a strategy using less toxic chemotherapy for initial cytoreduction, followed rapidly by blinatumomab for deep MRD clearance,[9] reduce the incidence of fatal infections while improving response rates? Ongoing trials exploring such approaches are eagerly awaited. Furthermore, the role of other modalities like inotuzumab ozogamicin or chimeric antigen receptor T-cell therapy in the first-relapse setting requires exploration, especially for high-risk subgroups.

In conclusion, the AALL1331 report serves as a powerful critique of the status quo in reinduction therapy for relapsed pediatric B-ALL. It documents with unequivocal data that the standard intensive chemotherapy backbone is both unacceptably toxic and insufficiently effective. To continue employing it without modification is to disregard evidence at the potential expense of patient lives. The study’s own results point the way forward: it is time to replace toxic, nonspecific chemotherapy with more precise, immune-based strategies from the very beginning of reinduction. Our patients deserve a reinduction paradigm where the bridge to consolidation is not fraught with preventable harm.

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