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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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Disclosures

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We are writing in reference to the recently published report from the Children's Oncology Group, Hogan et al, *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, Haematologica Vol. 110 No. 12 (2025): December, 2025* which details their use of an intensive chemotherapy reinduction regimen based on the mitoxantrone based UKALL R3 backbone followed by risk adapted therapy incorporating blocks of Blinatumomab.[1] The authors note that AALL1331 Block 1 therapy was associated with high adverse event rates (72.6% ≥ grade 3, 27.7% ≥ grade 4), and relatively poor responses, with 54.5% of patients with BM±EM relapse being minimal residual disease (MRD)-positive at the end of reinduction. Furthermore, for patients who were a reinduction failure or unable to proceed with post induction therapy, the survival outcomes were dismal. 3-year event free survival/overall survival were 49.0±2.0% and 69.6±1.8%, respectively for the entire cohort mirroring similar overall survival published for the UKALL R3 trial. Based on their analysis, the authors do not feel that the UKALL R3 mitoxantrone based backbone is justified for use in this patient population. While we commend the authors for trialing a mitoxantrone based reinduction regimen in a very well-designed large clinical trial, we believe that there remains an important role for mitoxantrone reinduction in pediatric ALL relapse and that improved safety and efficacy is possible.

In our recently published study *Mitoxantrone in combination with clofarabine (MITCL) in children, adolescents and young adults with relapsed/refractory acute leukaemia: final results of a phase I/II trial,*[2] we looked at pediatric patients with relapsed or refractory leukemia who underwent chemotherapy reinduction with standard dose mitoxantrone and escalating doses of clofarabine. We were able to establish safety and efficacy of this combination among 18 patients

in a Phase I cohort and established a Phase II dose combination of mitoxantrone 12mg/m^2/dose and clofarabine 35mg/m^2/dose. An additional 22 patients were treated at the recommended phase two dose for a total of 40 patients enrolled and treated overall. Thirty-three of 39 (85%) leukemia patients achieved a complete response and of these patients, 88% achieved MRD negativity. The majority of patients who achieved a complete response (CR) eventually went onto planned allogeneic stem cell transplant (HSCT). The event free survival/overall survival at 1 year was 74% for the entire cohort and 85% (95% CI 0.67–0.93) for responding patients who proceeded to stem cell transplant with 3-year survival for post HSCT patients 73% (95% CI 0.54–0.85).

Infection prophylaxis consisted of pneumocystis pneumonia, fungal and bacterial prophylaxis per institutional preference. Filgrastim was administered until absolute neutrophil count recovery. The median time to neutrophil recovery (≥1000/mm3) was 24 days (range, 19–39 days). As expected, all patients developed Grade IV hematologic toxicity as well as transient Grade II-III transaminitis. The next most common grade III or greater adverse events were Grade III infection (44%) and transient Grade III hyperbilirubinemia (11%). Overall, toxicities were expected and manageable. There were no Grade IV or Grade V infections in our cohort and importantly, thirty-two of 33 patients who achieved a CR were able to proceed with planned allogeneic hematopoietic stem cell transplantation. We did not find any increased toxicities of transplant related to prior mitoxantrone/clofarabine exposure.

Our study included patients who were induction or consolidation failures as well as 1^{st}, 2^{nd} or 3^{rd} relapse. We were able to show an excellent response in ALL patients regardless of disease status at enrollment. Of the 22 ALL patients enrolled on study, 91% achieved complete remission with 90% MRD negativity. To compare to the study population reported by Hogan et al, a sub analysis of just our pediatric ALL patients in 1^{st} or greater relapse reveals 10/12 (83%) patients

attained a complete remission with 70% of these patients being MRD negative following reinduction. Ultimately, the majority of relapsed patients were able to attain an MRD negative CR and safely proceed with stem cell transplant. Of the 10 ALL patients in this cohort, 2 patients died of known transplant related toxicities and 1 patient died of relapsed disease post-transplant.

Our MITCL mitoxantrone/clofarabine reinduction strategy has led to high CR rates, low or absent MRD, manageable toxicity, and successful bridging to allogeneic HSCT. We have maintained excellent long-term event free survival post stem cell transplant, even for our high-risk patients. During recent years we, as have others, have had increased access to immune and cellular therapy strategies for patients who are refractory to initial therapy or reinduction strategies at relapse. We have continued to note less toxicities pre-, during and post stem cell transplant in patients who have proceeded directly from MITCL therapy compared to those patients who have seen 1 or more cycles of antibody or cellular therapy. Our rates of neurologic complications or veno-occlusive disease of the liver during stem cell transplant are minimal in the patients who are able to achieve MRD negative remission following mitoxantrone and clofarabine and proceed directly to HSCT. While we acknowledge the enormous benefits of immune and cellular therapies in the appropriate patient, we feel strongly that mitoxantrone in combination with clofarabine is a proven safe and extremely effective strategy at first relapse or refractory disease and advocate for its use in this high-risk population of pediatric leukemia patients.

References:

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2. Hochberg J, Oesterheld J, Gardenswartz A, et al. Mitoxantrone in combination with clofarabine (MITCL) in children, adolescents and young adults with relapsed/refractory acute leukaemia: final results of a phase I/II trial. EClinicalMedicine. 2025;83:103211.