Asparaginase dosing for acute lymphoblastic leukemia: more questions than answers

Etan Orgel

Cancer and Blood Disease Institute, Children's Hospital Los Angeles and Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

Correspondence: E. Orgel
eorgel@chla.usc.edu

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In the current issue of *Haematologica*, Panetta *et al.*[1] report the results of a secondary analysis addressing the question of whether obesity influenced toxicity and outcomes in the St. Jude Children's Research Hospital (SJCRH) Total XVI trial in children with acute lymphoblastic leukemia (ALL).

Asparaginase was first discovered as a therapeutic agent to treat pediatric ALL in the 1960s. In the more than six decades since, it has become both an integral part of combination chemotherapy regimens responsible for improved cure rates for children, adolescents and young adults and a Pandora's box of off-target toxicities requiring extensive supportive care.[2]

Obesity is associated with increased toxicity in those receiving asparaginase products.[3-7] This observation led to the common practice of "dose-capping" asparaginase for patients with obesity on contemporary ALL protocols.[2] In Total XVI (NCT00549848), patients received one or two doses of 3,000 IU/m^2 of pegaspargase (Servier Pharmaceuticals) during the initial treatment phase, and were then randomized to continue with either the standard pediatric dose of 2,500 IU/m^2 or a higher dose of 3,500 IU/m^2, without dose-capping for obesity. The primary endpoint of the trial revealed that there was no dose-related effect from asparaginase late in therapy on toxicity risk. Panetta *et al.* used this dataset to investigate the association of obesity (defined using population thresholds for body mass index), with asparaginase-associated toxicities (AAT), disease response (by minimal residual disease), and survival. Importantly, this secondary analysis of Total XVI included a population pharmacokinetic model to determine whether drug exposure from asparaginase differed between those with or without obesity.

Though the study was limited through reliance on routine reporting via an older version of the Common Terminology Criteria for Adverse Events, a thorough and convincing examination of AAT by different grades of severity, and at different timepoints, did not reveal any significant association of obesity with clinically relevant AAT (apart from transient transaminase elevations). Similarly, obesity was not found to have any adverse impact on risk of poorer disease response or survival. The pharmacokinetic model also did not identify any differences in overall drug exposure at either timepoint, despite reduced clearance in those with obesity late in therapy. Even with the significant limitations that body mass index has for capturing changes in body composition during ALL therapy,[8] the lack of association between obesity and AAT or outcome in the Total XVI trial is striking. As the majority of AAT occur early in therapy, the lack of association between obesity at diagnosis and induction AAT is particularly notable to support a true absence of a relationship in this trial.

This new finding continues a trend noted in past SJCRH trials. Significant obesity-associated differences in toxicity and/or outcome have been reported independently in children and adolescents and young adults from multiple international consortia,[3-7,9] but this same association has not been found consistently across the series of SJCRH Total ALL trials (XII, XIIIA, XIIIB, XIV, XV).[10,11] This discrepancy from over 30 years of prospective trials may in and of itself be an important clue. The authors highlight several small studies to question if a "true" association between obesity and outcomes exists. The more compelling question may not be "if" but instead "why"? (Figure 1). Why is this association observed among other consortia ALL regimens but not in the Total trials? Are there nuanced differences in timing and/or composition of the multi-agent regimens, or in delivery of the drug itself? Inherited variation in risk for individual AAT has been identified, including among Hispanic or Latino populations.[12] Could population level differences in cohorts be contributing to the disparity in AAT rate? Contrasting the Total trials with other contemporary ALL regimens through the lens of AAT may offer insights and new avenues to target the profound, treatment-interrupting, and often debilitating side effects of asparaginase. Though the toxicity data on obesity from Total XVI may not

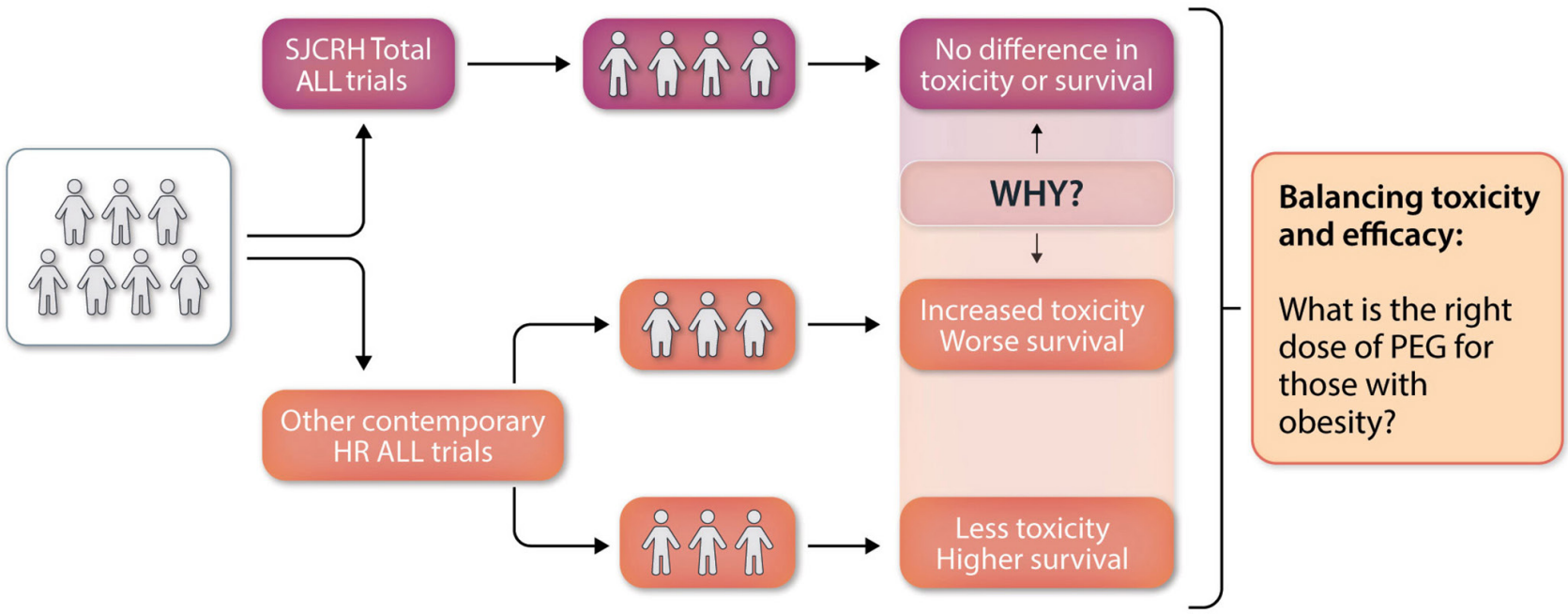

Figure 1. Deriving clues from contrasting cohorts to optimize asparaginase use. SJCRH: St. Jude Children's Research Hospital; ALL: acute lymphoblastic leukemia; HR: high risk; PEG: pegaspargase.

be generalizable to other regimens, Total XVI provides some important information. The findings of the trial randomization strongly suggest a saturation effect for toxicity risk above an exposure threshold. No difference in drug exposure was seen for patients with obesity enrolled into Total XVI and dosed above this toxicity "saturation threshold." However, extrapolating data from this trial to patients with obesity receiving lower doses is less certain, and where pharmacokinetics data otherwise remain scant.

One might now ask the provocative question: for those with obesity, should the goal no longer be to maximize exposure to asparaginase, but to instead determine the "minimal effective dose" balancing its toxicity and antileukemic effects? This question is particularly timely with the new integration of immunotherapies into frontline ALL regimens to potentially salvage early suboptimal chemotherapy responses. Indeed, ALL regimens for adults who are at greater baseline risk of AAT have trialed decreased asparaginase dosing (500 IU/m^2 – 2,000 IU/m^2) with some success in mitigating toxicity while preserving survival rates, even without immunotherapy.[12]

We must also recognize that AAT is not a single entity: a dose effect is consistently reported for certain toxicities (e.g., hepatotoxicity), not for some (e.g., pancreatitis), and data are mixed for yet others (e.g., venous thromboembolism). Pre-emptive dose adjustments, such as those crudely yet pragmatically accomplished by 'dose-capping,' may therefore prevent some but not other serious AAT and should not be considered a panacea for AAT. Conversely, if increased exposure is found to be required for efficacy, integrative approaches under investigation may also provide alternative opportunities for safe delivery of the drug.[2] Lastly, data for obesity, dosing, and AAT to date are predominantly limited to patients treated with pegaspargase. The recent replacement in the United States with longer-acting calaspargase-pegol (Servier Pharmaceuticals) raises yet another question for at-risk patients. Children and adolescents and young adults with obesity receiving this newer formulation will require additional scrutiny across regimens to ensure an equivalent safety signal.

Even with the advent of immunotherapies, asparaginase retains a critical role in pediatric ALL therapy. In this new era of routine chemo-immunotherapy to treat ALL, developing refined dosing and integrative strategies to balance toxicity and efficacy from multi-modality regimens will be an important step forward. While the study by Panetta *et al.*[1] raises more questions than answers, what is clear is that our understanding of how best to deliver this drug in contemporary regimens remains uncertain.

Disclosures

EO is a consultant for Jazz Pharmacueticals.

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