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CLINICAL TRIALS AND OBSERVATIONS

Comment on Maese et al, page 704

JZP458 closes the asparaginase allergy gap

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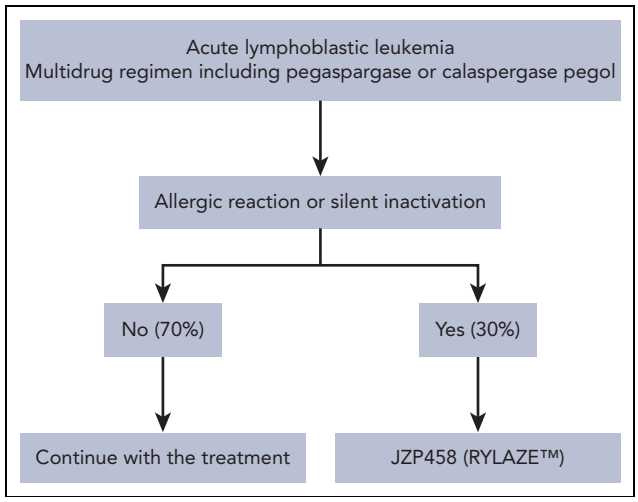
In this issue of *Blood*, Maese et al[1] showed that intramuscular (IM) JZP458 at 25/25/50 mg/m^2 given thrice weekly was an effective and safe alternative for patients with hypersensitivity to *Escherichia coli*–derived asparaginases (ASPs).

ASPs are one of the cornerstones of acute lymphoblastic leukemia (ALL) therapy and are included in multiagent chemotherapeutic regimens for children, adolescents, and adults with ALL and lymphoblastic lymphoma (LBL).[2,3] Pegylated *E coli*–derived ASP (pegaspargase) administered every 2 weeks is typically used in frontline and salvage protocols, and the longer-acting calaspargase pegol was approved by the US Food and Drug Administration (FDA) in December 2018 as part of multiagent therapy for ALL in pediatric and young adult patients from 1 month to 21 years old.[4] However, hypersensitivity reactions/silent inactivation (due to neutralizing anti-drug antibodies without allergy symptoms) limit the efficacy of both compounds. It has been hypothesized that the use of anti-CD20 monoclonal antibodies during the multidrug schedules could reduce the incidence of allergic reactions to *E coli*–derived ASP.[5] When these reactions occur, a change to native *Erwinia chrysanthemi*–derived ASP is mandatory,[6] but global shortages of this drug have resulted in poor availability. Recently, JZP458, a recombinant *Erwinia* ASP that utilizes a novel *Pseudomonas* fluorescent technology expression platform to produce an enzyme with no immunologic cross-reactivity to *E coli*–derived ASP was developed as a treatment for hypersensitivity reactions/silent inactivation due to *E coli* ASP. The results of a phase 1 study in healthy volunteers showed that a single IM dose of 25 mg/m^2 resulted in similar serum ASP activity (SAA) to 25 000 IU/m^2 of native *Erwinia* ASP.[7] On the basis of the interim results of the AALL1931 study performed in patients with ALL and LBL, JZP458 was approved in June 2021 by the FDA for use as a component of a multiagent chemotherapeutic regimen for the treatment of ALL or LBL in pediatric and adult patients 1 month and older who develop hypersensitivity to *E coli*–derived ASP.[8]



Management of asparaginase hypersensitivity and silent inactivation.

The phase 2/3 of the AALL1931 study is an open-label, multicenter, dose confirmation, and pharmacokinetic (PK) study of JZP458 in patients of any age with ALL/LBL who were hypersensitive to *E coli*–derived ASP (allergic reactions or silent inactivation).[1] This study was designed to assess tolerability and efficacy by measuring SAA. The first part (part A) of the study investigated the IM route of administration, including a Monday-Wednesday-Friday (MWF) dosing schedule. PK modeling and simulations of data from the first 2 cohorts (cohorts 1a and 1b) were used to assess the best dosing schedule to ensure optimal 48- and 72-hour SAA levels ≥0.1 IU/mL (cohort 1c), which were found to be 25/25/50 mg/m^2 administered by IM route with a 2-week MWF course. This schedule is slightly different from the FDA-approved dosage of 25 mg/m^2 administered IM every 48 hours. Treatment-related adverse events of special interest included allergic reactions (5.4%), pancreatitis (6.0%), thrombosis (1.2%), hepatotoxicity (19.8%), and hypertriglyceridemia (7.2%), with the safety profile of this schedule being similar to that observed in other ASPs. However, some patients did not complete the treatment at the time of the analysis, and a complete safety follow-up will be required

in the future. The second part (part B) of the AALL1931 study remains active to further confirm the dose and schedule for the intravenous route of administration.

The global shortage of native *Erwinia* ASP due to manufacturing issues is challenging and could negatively impact the efficacy of ALL therapy in patients who develop hypersensitivity reactions/silent inactivation to *E coli*–derived ASP. Omission of ASP in multidrug chemotherapy regimens can lead to a higher risk of relapse or poorer response to reinduction therapy in patients with relapsed ALL.[9] Fortunately, JZP458 provides a reliable treatment option that closes the gap of *Erwinia*-derived ASP availability for patients who develop these adverse events (see figure). This feature, together with the adequate ASP management, especially in adult patients, will contribute to improve the contribution of this essential drug to the treatment of ALL.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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Comment on Schuetz et al, page 713

The earlier, the better: RAG-deficient transplants

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In this issue of *Blood*, Schuetz et al[1] describe the largest international cohort of patients with combined immunodeficiency and autoimmunity caused by hypomorphic *RAG* variants who received a hematopoietic stem cell transplant (HSCT).[2-4] The only curative option for these patients with hypomorphic mutations in *RAG1 and RAG2* genes is HSCT, but the outcome data are sparse, mostly reported for complete loss of function.

The data reported in this comprehensive international multicenter effort examined risk factors for HSCT such as older age of diagnosis, persistent infection prior to and at time of transplant, organ damage at the time of transplant, and presence of autoimmunity at the time of transplant. Residual T-cell function in these patients can lead to a higher risk of graft rejection, increasing the risk of morbidity and mortality after transplant. Donor selection as well as type of conditioning used are extremely important elements to consider at the time of preparing these patients for an HSCT.[5] HSCT was performed at a median age of 3.5 years. Most patients received a matched unrelated donor transplant (48%), with the remainder receiving matched sibling/family donor (22%), mismatched family donor (18%), or mismatched unrelated donor (12%). T-cell depletion of the graft was performed in 25% of the patients, either by CD34 selection or αβ depletion. Serotherapy was administered in 49 patients. There was an equal distribution of the different intensity conditioning regimens: myeloablative, reduced toxicity, and reduced intensity/nonmyeloablative. Overall survival of the entire cohort was 77.5% at 1 year and 67.5% at 4 years after HSCT, with most patients dying of infections. Pre-HSCT organ damage (univariate and multivariate) and/or active infections (univariate) were associated with decreased overall survival, whereas autoimmunity had no impact. Therefore, prevention of infection and subsequent end organ damage are paramount to improved survival. T-cell depletion of the graft had a significant negative impact on survival, in addition to using a mismatched family donor, whereas intensity of the regimen posed no impact on survival. Interestingly, only 7 patients had graft failure, with most patients with donor chimerism (>90%), further delineating that good donor chimerism is achieved with a variety of conditioning regimens. Severe acute graft-versus-host disease was minimal, whereas chronic graft-versus-host disease (22%) remained problematic. Prompt and more robust CD4 immune recovery was seen in patients without infections, organ damage, or autoimmunity. Although autoimmunity had no impact on survival, it did seem to impact the CD4 recovery, suggesting that tight control of autoimmune manifestations leads to better CD4 recovery. Therefore, lower disease burden, early diagnosis, and HSCT improve thymic recovery and enhance survival.

Given that conditioning regimens did not impact survival but infections did, future studies are needed to evaluate the use of serotherapy and the kinetics of immune recovery in respect to infection-related mortality. In addition, mismatched family