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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CLINICAL TRIALS AND OBSERVATIONS

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

donors and T-cell depletion should be avoided because of their negative impact on survival. Alternatively, cord blood products could be an attractive donor option to avoid delayed transplantation with its increased risk of end organ damage and life-threatening infections, as the regimens avoid serotherapy.[6,7] Recently, a single center cohort of 45 patients with immunodeficiency (35 severe combined immunodeficiency [SCID]), including 7 RAG cord blood transplants, showed very robust engraftment and early immune recovery with 91% survival after 2 years.[8]

In the era of newborn screening (NBS) for SCID, early detection and diagnosis has led to decreased infection-related mortality after transplant. As reported by Schuetz et al in 2014,[5] 8 patients were diagnosed by NBS, and survival was improved in patients aged <3.5 months, which is in line with historic data for transplant in SCID.[3,4] Hypomorphic *RAG* variants may still be missed, making early diagnosis more challenging. In addition, approximately one-third of these patients still present to transplant with active infections, even in the NBS era. For patients with complicated immune deficiency/dysregulation disorders such as hypomorphic RAG deficiency, efforts should be directed towards selecting donors and conditioning regimens associated with a prompt and more robust immune recovery, especially in the setting of pretransplant infections.

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IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Sharma et al, page 725

MLL1 is central to macrophage-mediated inflammation

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In this issue of *Blood*, Sharma et al[1] demonstrate that gene transcription in macrophages contributes to the development of virus-associated coagulopathy in mice infected with the murine coronavirus MHVA59, which was used as a surrogate for pulmonary SARS-CoV-2 infection in this study. Because coagulopathy is a major complication of SARS-CoV-2 infection, this mechanism of regulation may be relevant to the ongoing pandemic. In Sharma's study, transcriptional control is mediated through changes in chromatin structure wrought by the addition of a trimethyl group on the fourth lysine residue in the tail of histone 3 (H3K4Me3). Although many enzymes can set the H3K4Me3 mark, in this model the enzyme responsible is mixed lineage leukemia 1 (MLL1/KMT2a), which derives its name from gene rearrangements found in both lymphoblastic and myeloid leukemias. The team chose to assess the role of *MLL1* in viral infection because previous studies have demonstrated its importance in macrophage activation (see figure).

Sharma et al used a mouse model in which *MLL1* was deleted using a Cre/Flox system, where the Cre recombinase is expressed under the control of *Lyz2* gene promoter, resulting in *MLL1* deletion in myeloid cells. They demonstrate that mice with *MLL1*-deficient macrophages are less prone to coagulopathy, with increased bleeding times and decreased expression of urokinase, the urokinase receptor, and factor III. They then confirm their results in vitro through small interfering RNA (siRNA) knockdown of *MLL1* in macrophages. Given the essential role of MLL1 in hematopoietic cell expansion,[2] the results of the siRNA experiments are critical to demonstrate that the observed phenotype is not due to alterations in macrophage development. Instead, inhibition of *MLL1* just prior to macrophage stimulation reduces the transcription of genes related to coagulopathy. Finally, the team replicated their findings in humans. Their data demonstrate an increase in expression of *MLL1* and coagulopathy factors in peripheral blood monocytes from hospitalized patients with COVID-19 when compared with monocytes of hospitalized patients that were not positive for COVID-19.

In concurrence with previous research, the team identifies interferon α (IFN-α) and IFN-γ as potential cytokines that augment *MLL1* expression. From the prior study, we know that MLL1 increases STAT4 expression in macrophages.[3] STAT4 induces an antiviral program that