COMMENTARY

blood advances

TO THE EDITOR:

Possible roads to improve hemophagocytic lymphohistiocytosis outcome

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We read with interest the article by Bergsten et al on the outcomes of patients with hemophagocytic lymphohistiocytosis (HLH) enrolled in the HLH-2004 protocol and treated with allogeneic hematopoietic stem cell transplantation (HSCT).[1] The investigators analyzed 187 children treated with the HLH-2004 protocol who received HSCT between 2004 and 2012. The 5-year projected overall survival and event-free survival after HSCT for the entire cohort were 66% (95% confidence interval [CI], 59-72) and 60% (95% CI, 52-67), respectively. Median time from diagnosis to transplant was 148 days, and approximately two thirds of patients were transplanted within 6 months from the start of therapy. Notably, a time to transplant $>$ 6 months was not associated with a worse outcome, as reported in the study published by the Italian Association for Pediatric Hematology and Oncology group.[2] Remarkably, most of the events occurred in the first year after HSCT. Achievement of complete remission at the time of transplant was associated with an improved outcome, although this advantage was not statistically evident when a ferritin threshold of 2000 ng/mL, instead of 500 ng/mL, was used to define response.[3] There was no difference in outcome when patients were stratified according to the type of conditioning regimen used, although there was a trend toward an improved outcome for patients receiving treosulfan-based conditioning, as also suggested by previous studies.[2,4] The investigators concluded that "post-HSCT survival in FHL remains suboptimal" and that "we are optimistic that post-HSCT survival in FHL can be improved based on […] rapid availability of functional and genetic diagnostic tests leading to earlier transplants, on promising studies of treosulfan-based conditioning […], on targeted sub-myeloablative busulfan administration and on more experience with fludarabine-based reduced-intensity conditioning (RIC)."

Although we agree with the investigators that we need to improve HSCT outcomes in this particular disease, we do not believe that this can be achieved only through the strategies proposed in the article by Bergsten et al. The most challenging obstacles for a successful posttransplant outcome in patients with HLH are fatal liver or lung toxicities[1] and a high-risk for primary or secondary graft failure.[5] These findings provided the rationale for considering the use of conditioning regimens that are potentially able to promote sustained donor engraftment while avoiding life-threatening toxicities. Such approaches have resulted in promising outcomes, although primarily in small cohorts of patients[2,6,7] and with the caveat that a significant proportion of patients given a RIC regimen need posttransplant interventions (ie, donor lymphocyte infusions or a second transplant) for a definitive resolution of the disease.[8] In addition, it has to be emphasized that HSCT outcomes in HLH depend on other variables related to the patient, including disease and performance status, as well as infections occurring before the allograft. Transplant characteristics, such as type of donor with the related HLA-compatibility, graft manipulation, and graft-versus-host disease prophylaxis, also affect patient outcome. The observation by Bergsten et al that overall survival and event-free survival did not improve over time confirms data reported by the Italian Association for Pediatric Hematology and Oncology group[2] and indicates that the sole amelioration of transplant techniques, including supportive therapies, does not seem to be able to significantly improve HSCT outcomes in HLH.

In light of all of these considerations, innovative treatments, such as emapalumab,[9] alemtuzumab,[10,11] and, potentially, ruxolitinib,[12,13] that are able to improve disease control before the allograft and to prevent the occurrence of toxicities related to the use of cytotoxic agents and high-dose steroids are needed. In particular, neutralizing interferon-γ (IFN-γ)[14] by emapalumab is particularly attractive, offering

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the advantages typical of molecularly targeted precision medicine. The results of the open-label single-group phase 2/3 trial on the use of emapalumab for the treatment of patients with primary HLH (which led to US Food and Drug Administration approval of the drug for the treatment of primary HLH patients with refractory, recurrent, or progressive disease or who are intolerant to conventional therapy) have been recently published.[9] In that study, in which 79% of the population consisted of children who already failed or were intolerant to front-line therapy, the 1-year probability of overall survival for the 22 patients who proceeded to transplant was 90.2% (95% CI, 66.2-97.5). The estimated probability of survival at 12 months after transplantation was 89.5% (95% CI, 64.1-97.3) among children who already failed or were intolerant to front-line therapy; moreover, 18 patients did not have any event up to 12 months after transplantation. The presence of ≥20% to 30% donor cells in HLH is believed to be protective with respect to disease relapse/flare.[15] Chimerism data reported in the phase 2/3 trial of emapalumab are promising,[9] because complete donor chimerism was observed in all but 1 surviving patient at 1 year of follow-up, as opposed to several reports documenting high rates of mixed and often unstable chimerism in transplanted HLH, especially when a RIC regimen is used.[8,16] There could be several reasons for the improved transplant outcomes in HLH patients treated with a monoclonal antibody neutralizing IFN-γ, and they likely involve the possibility of tapering steroids before HSCT (in 47% of patients treated with emapalumab, dexamethasone was tapered by more than 50% of the initial dose).[9] Although a specific analysis of the correlation between steroid exposure and outcome in HLH has not been formally performed, steroids have been associated with an increased incidence of viral[17] and fungal[18] infections in the posttransplant period. Other possible explanations for the improved transplant outcomes of HLH patients treated with emapalumab and given an allograft include the lower incidence of graft failure (primary or secondary) or mixed chimerism (IFN-γ has a detrimental effect on hematopoietic stem cells)[19] and the favorable safety profile related to the targeted mechanism of action, not causing myelosuppression and, thus, not associated with a generalized risk for infections. Moreover, it should be considered that IFN-γ is involved in the pathophysiology of graft-versus-host disease, and its neutralization could prevent the occurrence of this potentially fatal complication.[20,21] Because emapalumab half-life ranged from 2.5 to 18.9 days in pediatric patients with primary HLH,[22] a twice-a-week administration schedule could be hypothesized to obtain IFN-γ neutralization. This post-HSCT approach has been pioneered in 4 recently reported cases.[19,23] Potentially, other already clinically available or experimental drugs could play a role in improving HSCT outcomes in HLH.[24,25] Indeed, although the efficacy of interleukin-1 (IL-1) or IL-6 blockade in primary HLH has not been clearly proven, anakinra and tocilizumab have been used anecdotally in some forms of the disease.[25,26] Finally, inhibition of IL-18 through IL-18BP (tadekinig alfa) is being explored in pediatric patients with HLH (NCT03113760).

Future investigations are needed to address these hypotheses in larger cohorts of patients with HLH. In the meantime, these innovative pretransplant approaches should always be considered and discussed as new strategies to be explored for improving the cure rate of children with primary HLH.

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