blood advances

Prophylactic VSTs: a promising start but still work to do

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In this issue of *Blood Advances*, Dadwal et al[1] share the results of a phase 2 trial evaluating the safety of and response to posoleucel, an off-the-shelf, multivirus-specific T-cell product. In this single-arm study, posoleucel was given prophylactically (ie, before the development of clinically significant infection [CSI]) as serial infusions after allogeneic hematopoietic cell transplantation (HCT). The patients were followed up for 6 months after HCT. Overall, the rate of CSI in this cohort was quite low (12%), and posoleucel appeared well tolerated.

Viral infection causes substantial morbidity in patients who undergo HCT.[2] The concept of treating viral infections with adoptive virus-specific T cells (VSTs) was introduced in 1990,[3] and the field has grown exponentially over the intervening decades. VSTs are manufactured by ex vivo expansion or direct isolation. In the former, peripheral blood mononuclear cells are stimulated with peptide libraries that represent viral antigens. Virus-reactive T cells are then selectively expanded in culture to form a product of polyclonal T cells directed against 1 or more viruses. Dadwel et al have leveraged this technology to develop posoleucel, a product with T-cell activity against many common and potentially morbid post-HCT viruses, including herpes viruses (cytomegalovirus [CMV], Epstein-Barr virus [EBV], and human herpesvirus-6), polyomaviruses (BK virus [BKV]and JC virus), and adenovirus (AdV).[4]

Although multiple single-arm studies have suggested the efficacy and safety of VSTs for the treatment of viral infections,[5] less is known about the use of these agents prophylactically. Prophylactic VST administration is an intuitively appealing approach in the early period after HCT, when few functioning endogenous T cells are present. Furthermore, VSTs may be favorable than pharmacologic-based strategies in the early post-HCT period, given the side effect profile of currently available antivirals. The multivalent nature of posoleucel makes it ideal for prophylactic use because predicting for any individual patient which viral infection(s) may occur is challenging.

Dadwal et al enrolled 26 patients who had undergone alternative donor HCT and were therefore at higher risk of CSI. The patients received posoleucel once every 14 days for 14 weeks, starting at a median of 42 days after HCT. A serial infusion approach like this one is favored in prophylactic VST studies to encourage persistence in the absence of a viral stimulus. In this study, most patients (88% and 73%) remained free of CSIs for 3 and 6 months, respectively. The infections that were seen were CMV viremia (n = 5), EBV posttransplant lymphoproliferative disease (PTLD; n = 1), and adenoviremia (n = 1). In contrast, low-level viremia was common, occurring in 85%. These results are comparable to those of prior studies on trivalent (CMV, EBV, and AdV)[6] and septivalent (CMV, EBV, AdV, BKV, varicella-zoster virus, influenza, and *Aspergillus fumigatus*)[7] VSTs in adults. The results were comparable to those of a trial of donor-derived quadrivalent (CMV, EBV, AdV, and BKV) VSTs in pediatric patients; however, the posoleucel study had the relative advantage of identifying a cell line in 35 of 36 screened patients, whereas the inability to produce a VST product occurred in 32.9% of patients in the pediatric study, perhaps related to a shorter timeline to start prophylactic infusions (by day +21).[8]

Assays of VST expansion demonstrated substantial increases in the number of interferon gamma–producing cells in response to viremia. Although the assay used cannot distinguish between posoleucel and endogenously derived immune cells, the early post-HCT time point suggests a contribution of the investigational product. T-cell receptor sequencing demonstrated detectable posoleucel in most patients, albeit at low levels, up to 3 months after infusion. The durable persistence of VSTs, even without viral stimuli, has been shown in other settings[6] and underscores the benefit of polyvalent

products that can respond to any of several low-level viremias to be present at the time of viremia from a virus with higher pathogenic potential.

The safety signal of the posoleucel was overall reassuring. Four (15%) of patients discontinued posoleucel due to adverse events, including graft-versus-host disease (GVHD) in 2 patients and pancreatitis and dyspnea in 1 patient each. Of course, the attribution of these events to posoleucel is difficult to distill, as rates of adverse events after HCT are high, providing a rationale in support of randomized, placebo-controlled studies.

Importantly, patients could not have grade 3+ GVHD or required high-dose steroids at the time of study enrollment (although they could receive steroids and other immunosuppressants during the treatment period). Although a common exclusion VST trial is due to the risk of exacerbating GVHD and concerns about the impact of immunosuppression on VST persistence, it is precisely these patients who are at the highest risk of morbidity from viral infections. Therefore, understanding how to effectively deliver VSTs to patients on immunosuppression is of utmost importance. Recently, CRISPR-CRISPR–associated protein 9 technology was used to develop a VST product without glucocorticoid receptors, which has the potential to facilitate the coadministration of steroids and VSTs.[9]

Although these results are promising, comparative trials of VSTs are imperative to define the efficacy of these agents. This is particularly important after HCT, in contrast to after solid organ transplantation or among patients with inborn errors of immunity, as the immune system after HCT will improve with time. Since the submission of this manuscript detailing phase 2 results, the phase 3 study of posoleucel prophylaxis was suspended after the preplanned futility analysis concluded that it was unlikely to meet its primary end point.[10] Two additional phase 3 studies of posoleucel investigating this product as a treatment for hemorrhagic cystitis and AdV were closed concurrently for similar reason. Importantly, no safety concerns were identified. Although disappointing with regard to the efficacy signal of posoleucel, this experience underscores the need for randomized trials and should set a standard in the field. Detailed results from these phase 3 experiences are eagerly awaited to inform the next generation of VST trials.

In the meantime, research on other off-the-shelf VST products continues to expand. The ALLELE trial, a global, open-label, single-arm phase 3 trial, studied the use of tabelecleucel, an off-the-shelf EBV-specific VSTs, in patients with relapsed or refractory PTLD, demonstrating a promising overall response rate of 50% in the HCT cohort,[11] with similar results in the parallel expanded access study.[12] Research is ongoing to understand the use of this agent in other EBV^+ diseases (NCT04554914), although not yet as a prophylaxis. Other products are being evaluated in a trial comparing prophylactic treatment of VSTs in pediatric patients (NCT04230356).

Prophylactic VSTs are potentially transformative to the landscape of viral disease prevention after HCT. However, the success of this approach is based on the existence of an available and suitably matched product that will readily proliferate in response to stimuli, will generate a memory pool for long-lasting immunity, and can be safely administered, even early post-HCT, without increasing the risk of GVHD. This study by Dadwel et al demonstrates the early steps toward this goal.

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