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Critical Role of Mismatched HLA in Hemorrhagic Cystitis after Haploidentical Hematopoietic Stem Cell Transplantation

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Hemorrhagic cystitis (HC) remains a potentially serious complication in patients after allogeneic hematopoietic stem cell transplantation (HSCT). HC is defined as a diffuse inflammatory condition of the lower urinary track and clinically manifests as a range of signs from painless, microscopic hematuria (grade 1) to severe bladder hemorrhage (grades 2 to 4), with the potential to cause significant morbidity and in some cases mortality [1].

HC is likely a multifactorial disease, and several factors are associated with damage to the bladder epithelium and subsequent development of HC, including toxins, pathogens, radiation, drugs, or disease. In the context of allogeneic HSCT, the complex interaction of variables such as previous treatment, conditioning, graft type, or intensity of the immunosuppressive regimen [1] complicates the identification of factors influencing HC and, consequently, the best way to treat or even to prevent its development. Accordingly, any information that can shed new light on the pathogenesis of HC or that can help to identify at-risk patients would be an important step in reducing the incidence of this distressing condition.

In this issue of *Biology of Blood and Marrow Transplantation*, Copelan et al. [2] made the interesting observation that under identical conditions of cell source and immunosuppression, patients transplanted with HSCs from a haploidentical donor had a higher incidence of HC than patients transplanted with HSCs from a matched related donor, pointing to differences in HLA as a key factor of later HC development. They retrospectively analyzed 122 patients who underwent allogeneic HSCT at their institution between March 2014 and June 2018. Thirty-nine patients received cells from a matched-related donor, and 83 patients were transplanted with cells from a haploidentical donor. Both groups were similar in terms of age, diagnosis, disease status, and conditioning, and although there was a difference in the age of the donors (younger when donors were matched related), there were no differences in the prescribed immunosuppressive regimen, with all patients receiving identical post-transplantation cyclophosphamide-based therapy, including tacrolimus and mycophenolate for the prevention of graft-versus-host disease (GVHD). Because of the study characteristics allogenic donor type was the only variable between groups, and consequently the outcome of HC could be a priori linked to this factor. The authors observed that the cumulative incidence of HC and grades 3 to 4 HC was higher in patients who received cells from haploidentical donors than from matched-related donors (54.9% versus 25.6% and 17% versus 5.1%, respectively). In both groups the cumulative incidences of GVHD (acute and chronic), relapse and nonrelapse mortality, and progression-free and overall survival were similar.

The use of haploidentical HSCT has grown over recent years because it increases the chance of finding a potential donor for most patients [3]. However, because of partial mismatch of the HLA type between donor and patient, the immunosuppressive regimen is generally more intense than that used for matched-related HSCT to minimize GVHD. The obvious drawback of this stronger immunosuppression is an impairment of the immune system, facilitating the later reactivation of viruses such as BK virus, which itself is a potential initiator of HC. Interestingly, although both groups of patients analyzed by Copelan et al. received the same immunosuppressive regimen, the incidence of HC with BK viruria at the time of HC diagnosis was higher in the group transplanted with haploidentical HSCs (30.2% versus 15.4%). Excluding the immunosuppressive regimen, the only remaining explanation for their observations is again the mismatch between HLA types, which would have a negative impact on the ability of antigen-presenting cells to trigger a proper immune response by T cells and might lead to immune cell exhaustion by the continued exposure to the virus, thereby allowing virus expansion.

In the final part of their study, Copelan et al. cited a recent innovative approach to boost the immune response against BK virus by adoptive transfer of donor-derived viral-specific

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T cells [4,5]. In situations where pharmaceutical therapy is not available or if it leads to additional toxicity, this approach could be used as a treatment or even as prophylaxis to prevent BK viremia or other viral infections that could cause complications after haploidentical HSCT [6]. Interestingly, the current methodology to specifically select viral-specific T cells, avoiding alloreactive T cells, would permit their isolation both from the original donor and from haploidentical third-party donors, in the case that the original donor was seronegative for the viral-specific T cell of interest [7].

REFERENCES

1. Lunde LE, Dasaraju S, Cao Q, et al. Hemorrhagic cystitis after allogeneic hematopoietic cell transplantation: risk factors, graft source and survival. *Bone Marrow Transplant*. 2015;50:1432–1437.
2. Copelan O, Sanikommu SR, Trivedi JS, et al. Higher incidence of hemorrhagic cystitis following haploidentical related compared to matched related donor transplantation. *Biol Blood Marrow Transplant*. 2019;25:785–790.
3. Passweg JR, Baldomero H, Bader P, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. *Bone Marrow Transplant*. 2017;52:811–817.
4. Bollard CM, Heslop HE. T cells for viral infections after allogeneic hematopoietic stem cell transplant. *Blood*. 2016;127:3331–3340.
5. Barrett AJ, Prockop S, Bollard CM. Virus-specific T cells: broadening applicability. *Biol Blood Marrow Transplant*. 2018;24:13–18.
6. Qian C, Campidelli A, Wang Y, et al. Curative or pre-emptive adenovirus-specific T cell transfer from matched unrelated or third party haploidentical donors after HSCT, including UCB transplantations: a successful phase I/II multicenter clinical trial. *J Hematol Oncol*. 2017;10:102.
7. Withers B, Clancy L, Burgess J, et al. Establishment and operation of a third-party virus-specific T cell bank within an allogeneic stem cell transplant program. *Biol Blood Marrow Transplant*. 2018;24:2433–2442.