Biol Blood Marrow Transplant 25 (2019) e275–e276

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Recipe for a Graft: T Cell Dose Remains Elusive

Richard T. Maziarz*, Rachel J. Cook

Adult BMT and Cellular Therapy Section, Center for Hematologic Malignancies, Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon

Article history:
Received 15 July 2019
Accepted 16 July 2019

In this issue of BBMT, Saad et al. [1] set out to determine whether one can extract from the Center for International Blood & Marrow Transplant Research database evidence that T cell graft composition can impact graft-versus-host disease (GVHD) outcomes of patients with acute leukemia or myelodysplastic syndrome undergoing peripheral blood stem cell (PBSC) allogeneic transplantation using HLA-matched sibling donors or 8/8-matched unrelated donors. A large number of patients (n = 2376) were analyzed, allowing for predictive statistical analysis. Notably, on initial univariate analysis, no T cell dose cutoff could be identified that impacted relapse rate, nonrelapse mortality, disease-free survival, overall survival, or grade III-IV acute GVHD (aGVHD), although there did appear to be a discernable cutpoint for grade II-IV aGVHD in both cohorts. However, on more detailed multivariate analyses, the association was not substantiated. Thus, the authors concluded that currently used $CD3^+$ T cell doses of PBSC products did not significantly influence the risk of aGVHD, chronic GVHD (cGVHD), or other transplantation outcomes when using matched sibling donors or 8/8 matched unrelated donors in patients undergoing transplantation for acute leukemia or myelodysplastic syndrome.

The authors make some key observations and affirmations. Myeloablative regimens were more likely to be associated with more severe GVHD, as were advanced donor age and sex-mismatched grafts. The authors also referred to a study from the European Society for Blood and Marrow Transplantation that could discern the potential impact of $CD3^+$ T cell dose but, notably, had a different design [2]. Rather than targeting a cutoff value of $CD3^+$T cell dose, that study analyzed by interquartile range, thus allowing comparison of grafts with the lowest $CD3^+$ T cell dose and grafts with the highest $CD3^+$ T cell dose. In addition, the study was limited to patients with acute myelogenous leukemia undergoing reduced-intensity conditioning unrelated donor transplantation, with a much smaller number of patients analyzed (n = 203).

What are the take-home messages? First, before concluding that there is no ability to detect a T cell dose that reflects optimal graft composition, it is reasonable to reflect on the nature of the allogeneic response. T cells express the T cell receptor, which is designed to bind peptide antigen in context of major histocompatibility complex (MHC) antigens, with the strength of the interaction influenced by adhesion molecules between the effector cells and target cells. The inflammatory response will trigger enhancement of the adhesive interactions, promoting T cell recognition of the target [3]. The observations that were "positive" are consistent with this basic tenet of immunology. Myeloablative conditioning is more likely to cause host tissue damage with the release of inflammatory signals that will recruit effector cells to the site, the so-called "cytokine storm" [4], but also, through cellular lysis, lead to the individual cellular expression of more endogenous self peptides in context of self MHC, which will recruit a broader repertoire of T cells to generate an aGVHD response. Similarly, the observation that sex-mismatched grafts contributed to higher rates of grade II-IV aGVHD and cGVHD likely reflects enhanced donor minor histocompatibility peptide antigens presented in the context of self MHC to the donor T cell pool [5]. This issue of polymorphisms in the peptide pool (as well as greater limitation of MHC allele utilization) has been addressed by Oh et al. [6], who demonstrated that in the more homogeneous populations found in Japan and Scandinavia compared with related transplantations in Irish and white and black Americans, higher rates of GVHD were seen in the more outbred populations compared with populations that have been relatively isolated. Finally, the authors touch on the issue of differences in graft composition that could be influenced by donor age, as well as variabilities in the host. Thus, when one considers the breadth of qualitative differences that can exist in the transplant interaction between donor and host, it becomes imperative to have a very large cohort that theoretically could lead to balancing these variables, which we might have predicted could have been obtained with a cohort of 2736 adult patients.

Recognizing that there are potentially vast qualitative differences that influence the GVHD question, then one could choose to evaluate whether there are quantitative differences in donor T cell grafts that could influence transplantation outcomes. The authors chose to use a relatively homogeneous

* Correspondence and reprint requests: Richard T. Maziarz, MD, Knight Cancer Institute, Oregon Health and Science University, Mail code 3181, SW Sam Jackson Park Road, Portland, OR 97239.
E-mail address: maziarzr@ohsu.edu (R.T. Maziarz).

https://doi.org/10.1016/j.bbmt.2019.07.023

population by restricting their cohort to HLA-matched sibling or unrelated donor and PBSC allografts. We have already learned from BMT CTN 0201 that there is no difference in aGVHD rates between bone marrow and PBSC allografts, despite the 1 log difference in anticipated T cells dose in PBSC versus bone marrow grafts [7]. Gugliemi et al. [8] demonstrated that GVHD rates after donor leukocyte infusions for patients with relapsed CML could be impacted by T cell dose, but with significant dose differences. Similarly, using haploidentical transplantation procedures with pretransplantation graft manipulation, logarithmic quantitative differences will influence outcomes [9]. Even in the current era of chimeric antigen T cell therapy, how T cell dose impacts the biological response remains unclear. With tisagenlecleucel, a range of doses has been used without discernable clinical differences, whereas with axicabtagene ciloleucil, a single fixed dose can be associated with variable efficacy and toxicity [10].

This study is important for demonstrating that our current retrospective analyses cannot easily demonstrate a quantitative breakpoint for determining an optimal $CD3^+$ T cell dose that will provide our best transplantation outcomes. In effect, it validates our historical in vitro limited dilution analysis studies demonstrating that some allo-antigens can provoke a more robust immune response than others but that over time, even a less potent antigenic allogeneic signal still remains immunogenic and will lead to T-cell proliferation. The immune system is complex, not simple, providing protection against environmental challenge, and remains an evolutionary roadblock to transplantation between organisms.

A successful stem cell graft is not an easy recipe to deconstruct. Saad et al. undertook a large retrospective study to determine whether T cell dose makes a difference, a hypothesis rooted in biology, intuition, and experience. Instead, they fortified findings that will continue to improve our ability to choose the optimal donors and conditioning regimens for our patients. The T cell content predictive of the most successful grafts will remain a "secret sauce."

REFERENCES

1. Saad A, Lamb L, Wang T, et al. Impact of T cell dose on outcome of T cell-replete HLA-matched allogeneic peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant*. 2019;25:1875–1883.
2. Czerw T, Labopin M, Schmid C, et al. High $CD3^+$ and $CD34^+$ peripheral blood stem cell grafts content is associated with increased risk of graft-versus-host disease without beneficial effect on disease control after reduced-intensity conditioning allogeneic transplantation from matched unrelated donors for acute myeloid leukemia: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Oncotarget*. 2016;7:27255–27266.
3. Springer TA, Dustin ML. Integrin inside-out signaling and the immunological synapse. *Curr Opin Cell Biol*. 2012;24:107–115.
4. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet*. 2009;373:1550–1561.
5. Salman A, Koparde V, Hall CE, et al. Determining the quantitative principles of T cell response to antigenic disparity in stem cell transplantation. *Front Immunol*. 2018;9:2284.
6. Oh H, Loberiza Jr FR, Zhang MJ, et al. Comparison of graft-versus-host-disease and survival after HLA-identical sibling bone marrow transplantation in ethnic populations. *Blood*. 2005;105:1408–1416.
7. Anasetti C, Logan BR, Lee SJ, et al. Peripheral blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367:1487–1496.
8. Guglielmi C, Arcese W, Dazzi F, et al. Donor lymphocyte infusion for relapsed chronic myelogenous leukemia: prognostic relevance of the initial cell dose. *Blood*. 2002;100:397–405.
9. Ho VT, Soiffer RJ. The history and future of T-cell depletion as graft-versus-host disease prophylaxis for allogeneic hematopoietic stem cell transplantation. *Blood*. 2001;98:3192–3204.
10. Abramson JS, Lunning M, Palomba ML. Chimeric antigen receptor T-cell therapies for aggressive B-cell lymphomas: current and future state of the art. *Am Soc Clin Oncol Educ Book*. 2019;39:446–453.