blood advances

Blood stem cell grafts: frozen is fine, but fresh is best

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Comment on Devine et al, page 5982

In this issue of *Blood Advances*, Devine et al[1] compared the outcomes of allogeneic stem cell transplantation using a peripheral blood stem cell graft that was either fresh or previously cryopreserved. Although the authors found no negative impact of cryopreservation on 1-year overall survival, there were statistically significant negative effects on graft failure, relapse, and disease-free survival.

As the practice of medicine gradually goes back to its way before the COVID-19 pandemic, we find many examples of new approaches that we are inclined to retain. Hybrid scientific conferences, for example, allow those unable to attend to experience and absorb content in real-time. Those who desire collegiality and intellectual stimulation of in-person gatherings can do so once again. This approach is likely to continue. However, some COVID-19 era adjustments must be abandoned in favor of the old way of doing things. The paper by Devine et al suggests that this is the case with mobilized peripheral blood stem cell grafts that are used for allogeneic stem cell transplantation.

Since 1987, the National Marrow Donor Program (NMDP)/BeTheMatch has provided unrelated donor stem cell grafts to stem cell transplantation candidates without a suitable related donor. The stem cell transplantation procedure is intricately choreographed, such that the day of stem cell collection corresponds to the completion of an intensive pretransplantation bone marrow conditioning regimen. Until the pandemic hit, the NMDP was miraculously able to overcome nearly all logistical hurdles to provide timely arrival of freshly collected donor stem cell products, often collecting thousands of miles from the transplantation center. The logistical disruptions that accompanied the COVID-19 pandemic along with the constant threat that the unrelated donor may contract COVID-19 and be unable to donate forced a change in practice. Thus, with NMDP's guidance, transplantation centers moved away from using fresh stem cell grafts and began cryopreserving mobilized peripheral blood stem cell grafts before starting the patient's pretransplantation conditioning regimen.[2] With the product safely stored on site, the transplantation centers were reassured that stem cells would be infused on time.

Cryopreservation of stem cell grafts is not new. Since the 1070s, hematopoietic recovery after bone marrow ablative chemotherapy has been reliably observed using cryopreserved autologous hematopoietic stem cell transplantation. However, allogeneic stem cell transplantation is more nuanced. In addition to stem cells providing hematopoietic recovery, the graft provides adoptively transferred donor T cells and NK cells that participate in an antitumor response that may culminate in a cure. The clinical impact of cryopreserving this fraction of the donor graft has, until now, been less well understood.

A careful review of the data would suggest a deleterious impact of cryopreservation on the lymphoid cell fraction of the peripheral blood stem cell graft as an explanation for the authors' findings. Even the uptick in primary graft failure could be a consequence of compromised T-cell function through delayed or incomplete clearance of residual chemotherapy or radiation-resistant host lymphoid cells capable of slowing or even rejecting the donor graft. It is not surprising that donor lymphocytes were lost, and viability diminished during the freeze/thaw cycle. However, a renewed interest toward the impact of lymphocyte cryopreservation has become a part of the manufacturing and storage of newer and more efficacious immune effector cells. These studies have shown that the representation of CD3 and CD4 T-cell subsets and the CD4:CD8 ratio are preserved after a freeze/thaw cycle. Conversely, the

proliferative capacity of T cells along with their ability to secrete proinflammatory cytokines, such as interferon-gamma and interleukin-13, is markedly diminished when the cells are frozen. It appears that the $CD56^{+}$ NK cell fraction, thought to be critically important in the so called graft-versus-tumor response, is even more sensitive to the stress of cryopreservation than their T-cell counterparts. In addition to cell death, NK cells that survive thawing exhibit compromised cytotoxic activity.[3,4] Storage of cells in a buffer containing 10% dimethyl sulfoxide as part of the cryopreservation process has been implicated in these deleterious effects.[5]

NMDP deserves the highest praise for brilliantly navigating the COVID-19 pandemic and continuing to provide life-saving donor stem cell products to allogeneic transplantation recipients. The recommendation to cryopreserve stem cell grafts was an important part of this adjustment. Despite the easing of both the logistical hurdles of graft transport and the concern about donor COVID-19 infection, many might be inclined to continue using cryopreserved grafts. Having stem cells safely stored on site before starting the transplantation procedure simplifies coordination and adds flexibility for both the patient and busy cellular therapy services. The data presented by Devine et al suggests that we must resist this urge and return to the practice of using fresh donor stem cell grafts. However, as the authors point out, cryopreserved grafts are a safe and effective option when fresh grafts are not feasible.

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