

COMMENTARY

Transplantation of allogeneic cryopreserved hematopoietic cell grafts during the Covid-19 pandemic: A National Marrow Donor Program perspective

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Logistical challenges imposed by the SARS-CoV-2 pandemic (Covid-19) have forced a massive shift toward the use of cryopreservation of hematopoietic stem cell (HSC) grafts from both related and unrelated donors, in order to ensure patients have a graft available on the day of transplantation.¹ Although cryopreservation has been used as a standard for autologous and umbilical cord blood transplantation and is supported by a large body of clinical and technical literature, prior to the pandemic there was surprisingly little data beyond single center or small multi-center reports, with which to assure clinicians that cryopreservation of allogeneic grafts would not adversely impact critical post-transplant outcomes. These includes hematopoietic engraftment, graft vs host disease (GVHD), relapse, immune reconstitution, and overall survival.²⁻⁴ The Center for International Blood and Marrow Transplant Research (CIBMTR) has recently contributed important retrospective analyses suggesting cryopreservation should be avoided in patients with severe aplastic anemia due to high rates of graft failure but otherwise was not associated with adverse consequences in other settings, such as those that incorporate post-transplant cyclophosphamide (PTCy) to prevent GVHD.^{5,6} Another report from the CIBMTR in a large cohort of patients receiving more conventional GVHD prophylaxis is currently under review and should be available shortly. In this issue of *American Journal of Hematology*, a report by Alotaibi and colleagues from Princess Margaret Cancer Centre on the impact of planned cryopreservation on post-transplantation outcomes in a relatively large patient cohort at a single center adds important information to this literature and provides some reassurance to clinicians trying to decide in uncertain times whether to order a fresh vs a cryopreserved product. They evaluated the effect of cryopreservation of grafts on allogeneic transplant outcomes using related, unrelated and haploidentical donors collected following G-CSF mobilization to obtain peripheral blood stem cell (PBSC) for patients with a variety of hematological malignancies. Fresh grafts were received by 648 (68%) patients, 310 (32%) received cryopreserved. There was no difference between fresh vs cryopreserved grafts in neutrophil engraftment, platelet engraftment, graft failure, grade

II-IV acute GVHD, or overall survival. The incidence of moderate/severe chronic GVHD was higher in the recipients of cryopreserved grafts. The authors interpreted these findings to suggest that cryopreservation was a safe option for allogeneic HCT, a conclusion based on these results with which I generally agree, but with some caveats. For instance, this study was limited to recipients of PBSC grafts and the vast majority of donors were HLA-matched relatives. The report does not provide a lot of data on cryopreservation of unrelated donor (URD) products or product transit time. The results were obtained at a single center and cryopreservation was planned well in advance and was a common practice at this particular center. Whether these results are extrapolatable to other centers using different standards of care is not entirely clear.

How can these new data from Princess Margaret as well as recent CIBMTR retrospective analyses of cryopreservation impact be put into context? Viewing these data through the lens of my role as Chief Medical Officer at the National Marrow Donor Program (NMDP), none of the data can be considered definitive. However, this is the best we have to date and I do think they provide some important guidance for clinical decision making. When the NMDP made the decision in March of 2020 first to strongly recommend and then to require cryopreservation with limited exceptions, we knew we were making that decision with less than perfect information. What we did know was that as an organization charged with the awesome responsibility of delivering potentially life-saving products for patients in need, we could not allow even a single patient to receive myeloablative conditioning without a graft to infuse on the day of planned transplantation. That would clearly be unacceptable given the potentially devastating consequences. Assuring patient safety had to be our number one priority. Given the myriad uncertainties surrounding air travel logistics and risks of donors becoming infected with SARS-CoV-2 and unavailable after a patient initiated conditioning, we had no choice but to require the donor products we delivered be scheduled to arrive at the transplant centers prior to initiation of conditioning.

Historically, cryopreservation has always been an option for unrelated donor products collected and delivered by the NMDP. Prior to the pandemic, about 5%-8% of NMDP products have been cryopreserved annually prior to transplantation for a variety of reasons (donor preference for a particular date of collection, logistical difficulties, acute patient related reasons such as infections or disease progression,). But at the peak of the first wave of the pandemic from April through July 2020, approximately 95% of NMDP products were scheduled for cryopreservation, almost always at the transplant center but for some products scheduled for long flights (eg, Australia), the products have been cryopreserved at the collection or apheresis centers. Our organization's incredible operations team has worked tirelessly to solve many of the logistical hurdles related to delivering unrelated and related donor products during the pandemic. Unfortunately this is a moving target and new problems seem to arise almost daily. Nevertheless, as we have become more adept at facing all the challenges, we have been able to relax the cryopreservation requirement as of 10 August 2020 and since have observed that about 70% of NMDP products are planned for cryopreservation. To date, all products requested and collected have been infused into patients following conditioning.

On the flip side of the coin is the reality that planned cryopreservation sets up a scenario whereby some of the products NMDP collects ahead of time from our courageous volunteer donors may not be used.¹ Since the product arrives before the initiation of conditioning, the transplant centers can review product cell counts and/or viability following cryopreservation to determine whether the product is of sufficient quality to be used safely in their patient. Also, it is possible that a patient's underlying disease could progress or the intended recipient may otherwise clinically deteriorate in the interim. We are aware of at least 32 products collected by NMDP since March 2020 that will not be transplanted, usually on account of low cell count (TNC for bone marrow, CD34+ cell count for PBSC) or poor product viability and CD34+ cell recovery (usually <50% CD34+ cell viability). This represents less than 1% of the products NMDP delivered since the start of the pandemic. Although this figure seems acceptable, some have raised concerns around the ethics of exposing volunteer donors to a potentially harmful procedure (bone marrow harvest or apheresis and G-CSF exposure) without benefitting a patient.⁷ While we certainly share this concern we believe most of the time these situations are unavoidable. The ultimate decision to infuse a product or not based on quality should rest with the transplant team, as they are most knowledgeable about the patient and their clinical condition. From the donor perspective, efforts are made ahead of collection to inform them as to the potential risk that the product collected from them may never be used. It seems that as long as the donors are well informed about this possibility, and have the autonomy to make their own decisions, most will understand and will still willingly donate, particularly during these very challenging times.

Ultimately, each transplant center will need to weigh the advantages and disadvantages of cryopreservation and discuss these with their patients before making a decision as to which choice is best for a particular individual. The advantages include receipt of a product with

a known cell dose prior to starting conditioning, assuring greater patient safety, and often resulting in an easing of logistical scheduling hurdles. Disadvantages are both real and theoretical. There are added costs, potential of additional toxicity related to DMSO, loss of cell viability, particularly with products enduring increased transit times, and clear resource strains on transplant center staff. There are additional challenges to cryopreservation of bone marrow relative to PBSC, and many centers have chosen to avoid cryopreserving bone marrow if at all possible. Theoretical concerns that cryopreservation of an allogeneic product could result in functional immunological changes (eg, CD62 loss, T cell suppression,) that may impact immune reconstitution, relapse, and risk of GVHD can be found in the scientific literature yet are not clearly supported by clinical observational research.^{1,8,9}

Unrelated donors are chosen primarily based on HLA-matching but other characteristics such as age, sex, or cytomegalovirus (CMV) status are strongly considered.¹⁰ There are many patients who are fortunate to have multiple well matched URD choices, and for them logistics may also need to be factored into the equation during the pandemic. For US transplant centers in particular, it might be prudent to consider a roughly equivalent donor collected at a domestic site, in order to reduce the transit times that could impact product quality.¹¹ For adult patients with hematological malignancies, it may also be prudent to choose PBSC over BM as there are greater difficulties scheduling operating room time for bone marrow harvests, risks that asymptomatic donors will test positive for SARS-CoV-2 and be rendered unavailable, and greater chance of receiving a high quality PBSC product relative to BM. Pediatric patients and adults with severe aplastic anemia under most circumstances should preferentially be transplanted using bone marrow, and it seems wisest to order a fresh product if it can be done safely, after consultation with an NMDP case manager. Here again, it may also be better to order a product that can be collected domestically.

At the time of this writing, the US is experiencing a 76% increase in Covid-19 cases over a 14-day span, and lockdowns are reemerging globally.¹² Thus it is hard to imagine that there will be a substantial decline in the demand for cryopreserved products in the foreseeable future. We are generally supportive of current American Society of Transplantation and Cellular Therapy (ASTCT)/ EBMT/ World Marrow Donor Association (WMDA) guidelines for the choice of cryopreservation, where providers are asked to consider a variety of the factors mentioned above before deciding which to choose.¹³ In the meantime, we are also reviewing patient and donor related adverse events and product quality issues on a daily basis. While we are aware of some cases of primary graft failure, it is still too early to determine whether any of this has to do with receipt of a cryopreserved product. We are reviewing our CIBMTR database as the engraftment data provided on the day 100 follow up forms come in, but these data are inherently lagging. One of the confounding issues related to the prior CIBMTR observational studies of cryopreservation impact is that we do not routinely record the reason for cryopreservation. This confounds interpretation of the data. The pandemic has created a situation where virtually every TC has the same reason for ordering a cryopreserved product, so we will have a more homogeneous group to compare to historical controls.

We are rapidly working on gathering the data from the CIBMTR database on neutrophil and platelet engraftment kinetics, graft failure, and overall mortality at day 100, and plan to compare to appropriately matched controls receiving fresh grafts prior to the pandemic. We intend to share these data with the BMT community as soon as possible.

Finally, we need to be reminded what a courageous sacrifice it is to donate HSC during a pandemic. We are the stewards of donor safety and must not ask too much of them. As such, we generally do not advocate that transplant centers request excessive cell doses to compensate for anticipated cell loss during cryopreservation. We also do not advocate for nor can we generally support requests for a second day of donor collection simply to collect additional cells, given the potential adverse impact on donor safety.¹⁴ To date, 95% of our unrelated donor PBSC collections are completed in 1 day as the median CD34+ cell dose obtained from our database of more than 15 000 G-CSF mobilized volunteer donors is $6.85 \times 10^6/\text{kg}$, which is quite sufficient, even if scheduled for long transit and cryopreservation. So, we thank Alotaibi and colleagues for their valuable contribution to the literature, giving us a little more assurance that the transplantation of cryopreserved allogeneic PBSC products is generally safe, particularly in light of all the uncertainties associated with the ongoing Covid-19 pandemic.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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