Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The Bottom Line

Securing the graft during pandemic: are we ready for cryopreservation for all?

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Allogeneic hematopoietic cell transplantation (allo-HCT) from an unrelated donor involves complex interplay of multiple organizations working together for a successful delivery of a stem cell graft to the recipient. Historically, cryopreservation of stem cell graft has been done only for a small fraction of allo-HCT due to concerns around negative impact of freezing and thawing on the viability of hematopoietic stem cells and function of donor lymphocytes [1]. Previous retrospective studies comparing allo-HCT outcomes of cryopreserved versus freshly infused peripheral blood stem cell (PBSC) graft from matched donors have shown comparable survival outcomes but marginally delayed neutrophil and platelet engraftment with cryopreservation [1,2]. Some of these studies have shown increased risk of graft-versus-host disease (GvHD) at least with matched sibling donor but results were not consistent with matched unrelated donor grafts [2–4]. In absence of a prospective randomized study, the question of, 'Can a cryopreserved graft replace the freshly-infused graft in allo-HCT without compromising the outcomes?' remain unanswered. In this issue, there are two studies based on the Center for International Blood and Marrow Transplant Research (CIBMTR) registry asking this question in different patient populations Hamdani *et al.* compared the outcomes of cryopreserved versus freshly infused stem cell graft in patients with hematological malignancy [5]. The study was limited to patients who received post-transplant cyclophosphamide (PTCy) and majority of the patients received a PBSC graft from a haploidentical related donor. A similar study by Eapen et al. focused on the patients with severe aplastic anemia (SAA) and included pediatric patients and all donor types except cord blood transplants [6].

The first study showed comparable survival outcomes between cryopreserved (n= 274) and propensity-matched freshly infused grafts (n= 1080). There was some suggestion of decreased risk for chronic GvHD and lower disease-free survival among the recipients of cryopreserved graft. The study did not detect any difference in overall survival however, sample size might be a limiting factor [5]. In the second study of patients with SAA, the use of cryopreserved graft was associated with increased risk for graft failure and reduced OS compared to a freshly infused graft [6]. The difference in the outcomes of these studies, can be explained by difference in underlying disease biology, conditioning regimen intensity and graft source between the studies (Table 1). A significant loss of total nucleated cells after cryopreservation of BM graft was noted which may have contributed to graft loss in patients with SAA. Studies have shown reduced viability, proliferation and cytokine release capacity of donor lymphocytes after cryopreserved. Impaired alloreactivity of graft T cell due to cryopreservation may be a reason for reduced chronic GvHD incidence but higher risk for disease relapse. Natural Killer (NK) cells (CD56+) appear to have low tolerance to freezing and thawing process compared to other mononuclear cells [7]. This becomes important given delayed NK-cell reconstitution/maturation seen with PTCy [8]. It could be another potential explanation for increased risk of disease relapse with cryopreserved graft, but this needs to be studied systemically. Type of cryopreservation media also appears to impact T cell viability which needs to further validated if cryopreservation becomes routine practice in the future [9]. The authors have correctly pointed out several limitations of the analysis, most importantly the lack of information about the reason for cryopreservation in individual patients. Additionally, immune reconstitution, surrogate markers of cell viability before and after cryopreservation and the influence of cryopreservation strategies require further study [9].

COVID-19 has emerged as an existential threat to humanity and it is going to have lasting impact on our healthcare system. Travel restrictions, donor availability, blood product shortage and strained health care system secondary to COVID-19 pandemic have forced us to re-evaluate the current model of allo-HCT. In face of these challenges, both the National Marrow Donor Program (NMDP) [10] and the European Society for

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Table 1
Baseline characteristics of cryopreserved cohorts and outcomes

	Hamadani et al.	Eapen et al.
Indiction for allo-HCT	hematologicla malignancies	severe aplasic anemia
Patent age, years	55	21
Fully HLA-matched donor	49%	71%
Graft source, bone marrow	7%	64%
Use of post-transplant cyclophosphamide	100%	12%
Neutrophil recovery by day 28, (95% CI)	93% (90-96)	83% (71-92)
Platelet recovery by day 100, (95% CI)	88% (87-91)	91% (79-98)
Grade II-IV acute GvHD, HR (95% CI)	1.10 (0.87-1.38)	0.93 (0.41-2.13)
Chronic GvHD, HR, (95% CI)	0.78 (0.50-1.22)	0.79 (0.41-1.50)

HLA- human leukocyte antigen; GvHD- graft versus host disease; HR-hazard ratio; CI- confidence interval

Blood and Marrow Transplantation [11] are strongly recommending cryopreservation of all unrelated donor grafts and some centers have moved to cryopreserve all related donor grafts. Thus, we welcome these data on cryopreserved grafts. There are several advantages of cryopreservation apart from logistical simplicity. Cryopreservation allows assurance that an adequate cell dose is available from an older or lower body mass related donor before conditioning regimen is started. It allows additional period of donor monitoring in case of exposure to a communicable disease such as COVID-19 before graft is infused. Cryopreservation may facilitate allocating a fraction of cells for storage for future donor lymphocyte infusion assuming pre-specified cell count thresholds are met [12].

One should also note a few pitfalls of routine cryopreservation of stem cell graft. The largest uncertainty pertains to whether the delayed cryopreservation after significant travel will be detrimental for unrelated donor grafts. Couriers chaperoning unrelated grafts may face unpredictable delays due to transportation challenges during COVID-19. The study by Hamadani *et al* included few unrelated grafts 56 (20%) which were not separately analyzed. Others have reportedeach day of delay of cryopreservation reduced viability by 5% for umbilical cords [13]. In one study showing significant engraftment failures, all failures occurred in patients receiving unrelated donor PBSC (9/25) as opposed to 0 of 8 receiving related PBSC grafts [14]. Apart from risks of infusion reaction from dimethyl sulfoxide, potential loss of cell dose from washing, routine cryopreservation is costly and may put further strain on stem cell processing facilities. Invariably, a few cryopreserved grafts will not be infused due to recipient related issues, which leaves the donor exposed to unnecessary health risks.

These registry-based analysis suggest relative safety of routine cryopreservation in the setting of PTCy and hematological malignancy but highlight the increased risk of graft failure with cryopreservation in patients with SAA. A prospective registry study with appropriate follow up is needed to establish safety and detect any shortcomings of graft cryopreservation. The new recommendation of NMDP to cryopreservation of all unrelated donors due to COVID-19 crises may serve as a good stage for a prospective observational study. We thank authors of both studies for doing these timely analysis as the results are rapidly applicable in the current era of COVID-19. It is important that our adaptations to post-COVID-19 world are rational and data-driven. The lessons learned from COVID-19 will only strengthen our ability to protect patients and donors from similar threats in the future.

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