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The Effect of Donor Graft Cryopreservation on Allogeneic Hematopoietic Cell Transplant Outcomes: A CIBMTR Analysis. Implications During The COVID-19 Pandemic

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Abstract

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The COVID-19 pandemic has resulted in the increased use of cryopreserved grafts for allogeneic hematopoietic cell transplantation (HCT). However, information about the effect of cryopreservation on outcomes for patients receiving allogeneic donor grafts is limited.

We evaluated outcomes of HCT recipients who received either fresh or cryopreserved allogeneic bone marrow or peripheral blood stem cell (PBSC) grafts reported to the CIBMTR. A total of 7,397 patients were included in the analysis. Recipients of cryopreserved graft were divided into three cohorts based on graft source: HLA matched related PBSC (n=1,051), matched unrelated PBSC (n=678), and matched related or unrelated bone marrow donors (n=154). These patients were propensity score matched with 5,514 patients who received fresh allografts. The primary endpoint was engraftment.

Multivariate analyses showed no significant increased risk of delayed engraftment, relapse, NRM, or survival with cryopreservation of marrow grafts. In contrast, cryopreservation of related donor PBSC grafts was associated with decreased platelet recovery (HR=0.73, CI=0.68–0.78, p<0.001) and an increased risk of grade II-IV (HR-1.27, CI=1.09–1.48, p=0.002) and grade III-IV (HR=1.48, CI=1.19–1.84, p<0.001) acute GVHD. Cryopreservation of unrelated PBSC grafts was associated with delayed engraftment of neutrophils (HR=0.77, CI=0.71–0.84, p<0.001) and platelets (HR=0.61, CI=0.56–0.66, p<0.001) as well as an increased risk of NRM (HR=1.4, CI=1.18–1.66, p<0.001) and relapse (HR=1.32, CI=1.11–1.58, p=0.002) and decreased PFS (HR=1.36, CI=1.20–1.55, p<0.001) and OS (HR=1.38, CI=1.22–1.58, p<0.001). Reasons for cryopreservation were not routinely collected, however in a subset of unrelated donor HCT the reason was typically a change in patient condition. Products cryopreserved for patient reasons were significantly associated with inferior OS in MVA (HR=0.65, CI=0.44–0.96, P=0.029).

We conclude that cryopreservation is associated with slower engraftment of PBSC grafts which may be associated with inferior transplant outcomes in some patient populations. However the small numbers in the cryopreserved BM cohort and the lack of information on the reason for cryopreservation in all patients suggests that these data should be interpreted with caution, particularly in the context of the risks associated with unexpected loss of a graft during the pandemic. Future analyses addressing outcomes when cryopreservation is universally applied are urgently required.

Keywords

cryopreservation; Peripheral blood stem cell graft; bone marrow graft

INTRODUCTION

Donor grafts in allogeneic hematopoietic cell transplants (HCT) are generally administered fresh.[1] Cryopreservation of the donor graft is typically performed only if there are difficulties in coordinating the procurement of the graft or a situation develops in the recipient where the graft cannot be given immediately after collection, often due to unexpected clinical findings. There is an abundance of data on the safety and efficacy of cryopreserved marrow[2] and PBSC[3] grafts in the autologous setting. The limited data that exist on the effect of cryopreservation of the graft on both engraftment and survival[4–9] from allogeneic donors suggest that cryopreservation does not appear to have a significant impact

on survival or incidence of graft-vs-host disease (GVHD) regardless of donor source with the exception of a recent publication that showed higher one-year mortality in patients receiving cryopreserved marrow grafts for aplastic anemia[10].

The COVID-19 pandemic adversely affected the ability to infuse fresh donor cells, largely due to travel restrictions, both domestically and internationally, but also due to potential delays related to donor availability for a variety of reasons including quarantines and infection of the donor with SARS-CoV-2. To ensure HCT grafts were available at the scheduled time of infusion, the American Society for Transplantation and Cellular Therapy (ASTCT) and National Marrow Donor Program (NMDP) strongly recommended that all unrelated donor (URD) products be cryopreserved (at the transplant center) prior to starting the recipient's conditioning regimen.[11, 12] This became mandatory in the US on March 30, 2020, when the NMDP specified that cryopreservation was required of all URD grafts. Although no such guidelines exist for related donors, many transplant centers started cryopreserving these products, for the same concerns. Historically, some transplant centers are known to routinely cryopreserve related donor products.

With the increased utilization of cryopreserved grafts, the CIBMTR rapidly published two studies addressing the impact of cryopreservation on outcomes. The first analysis in HCT patients receiving post-transplant cyclophosphamide for hematologic malignancies as GVHD prophylaxis, and who mostly received PBSC grafts, found no impact on survival or engraftment,[9] but another in patients transplanted for severe aplastic anemia using mostly bone marrow grafts found, as noted above, an adverse impact of cryopreservation on graft failure and survival[10]

Here we evaluate the impact of cryopreservation on engraftment and other key outcomes, in related and unrelated donor HCT recipients performed for hematologic malignancies using conventional calcineurin inhibitor based GVHD prophylaxis.

METHODS

The CIBMTR® is a research affiliation between the NMDP and the Medical College of Wisconsin (MCW) collecting detailed data on transplant recipients from more than 320 transplantation centers worldwide. Participating centers are requested to report all transplantations consecutively and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The NMDP, Institutional Review Board (IRB), which is the IRB of record for the CIBMTR's database protocols, approved this study.

Data Sources

Detailed patient-, disease-, and treatment data were retrieved from the CIBMTR database. Additional data concerning graft origin, transit times and reasons for cryopreservation (in URD) were obtained from the NMDP.

Patients

All patients undergoing an allogeneic HCT from 2013 through 2018 for hematologic malignancies were included in this analysis. Diagnoses was limited to acute leukemias in first or second complete remission (CR1/CR2), chronic leukemias or myelodysplastic syndrome (with <5% blasts at HCT) and lymphomas. Donors included HLA-identical siblings and matched or mismatched URD. Mismatched related donors were excluded. Grafts were either bone marrow or PBSC. Grafts that were T-cell depleted or GCSF stimulated were excluded. Umbilical cord blood grafts, due to universal cryopreservation, and patients who received post-transplant cyclophosphamide (± calcineurin inhibitor and/or mycophenolate mofetil) as GVHD prophylaxis were also excluded from the analysis.

Definitions and Study Endpoints

The primary endpoint was time to engraftment. Neutrophil recovery was defined as the first of 3 successive days with absolute neutrophil count (ANC) ≥500/μL. Platelet recovery is defined as a platelet count 20,000/μL or higher in the absence of platelet transfusion for 7 consecutive days. Primary graft failure was defined as lack of neutrophil recovery before 28 days. Secondary graft failure was not assessed. All total nucleated cells (TNC) and $CD34^+$ cell content of the graft were calculated at time of graft infusion. Secondary endpoints included acute and chronic GVHD, non-relapse mortality (NRM), progression/relapse and progression-free survival (PFS) and overall survival (OS). NRM was defined as death without evidence of disease relapse/progression; relapse/progression was considered a competing risk. Relapse/progression was defined as morphologic, cytogenetic, or molecular disease recurrence for leukemias and myeloid malignancies, or as progressive lymphoma after HCT or lymphoma recurrence after a CR; NRM was considered a competing risk. For PFS, a patient was considered a treatment failure at the time of relapse/progression or death from any cause. Patients alive without evidence of disease relapse or progression were censored at last follow-up. For OS, death from any cause was considered an event and surviving patients were censored at last contact. The intensity of allogeneic HCT conditioning regimens was categorized as myeloablative (MAC) or reduced-intensity/non-myeloablative conditioning (RIC/NMA) using consensus criteria.[13] Disease risk index (DRI) was assigned as previously reported.[14] Acute GVHD[15] was graded using standard criteria. For neutrophil and platelet recovery and calculation of incidence of acute GVHD, death without the event was considered a competing risk.

Statistical analysis

Analyses were done separately for three cohorts of BM grafts, PB grafts with matched related donor [MRD], and PB grafts with unrelated donor [URD]. A total of 1,883 patients were identified who met the eligibility criteria described above who received cryopreserved grafts were matched with 5,514 patients who received fresh grafts using a mixed method of direct matching and propensity score matching. The propensity score is the probability of a given patient to receive the cryopreserved graft, based on the observed covariates of the patient and was predicted for each patient using logistic regression accounting for following risk factors: recipient age, race, ethnicity, Karnofsky Performance Score (KPS) (≥90 vs. <90%), HCT-comorbidity index (0 vs. 1–2 vs. ≥3), disease histology (acute myeloid

leukemia vs. acute lymphocytic leukemia vs. chronic myeloid leukemia vs. chronic lymphocytic leukemia vs. myelodysplastic syndrome vs. non-Hodgkin lymphoma vs. Hodgkin lymphoma), DRI (low risk vs. intermediate risk vs. high risk), interval from diagnosis to transplant, conditioning intensity (MAC vs. RIC/NMA), use of total body irradiation (TBI), GVHD prophylaxis, donor -recipient cytomegalovirus (CMV) matching, donor-recipient sex matching, year of transplant, and use of in vivo T-cell depletion (anti-thymocyte globulin (ATG) or Campath). Two patients with equal propensity scores meant they had similar probabilities of receiving a cryopreserved graft. The distributions of estimated propensity scores between cryopreserved and fresh grafts were examined. Within each of the three donor type/graft type cohorts, we matched each recipient of a cryopreserved graft with up to 3 controls receiving fresh grafts, using exact matching on DRI and recipient age (within 5 years), and then performing greedy (or nearest neighbor) matching among potential exact matches using the propensity score (restricted within 1 standard deviation (SD))[16].

Almost all cases were matched to 3 controls. One-hundred fifteen cases had 2 controls and 7 cases had one control. Fifty-two cases were removed due to missing covariate data (50 cases) or inability to match (2 cases).

Patient-, disease- and transplant-related factors were compared between matched cases and controls using the Chi-square test for categorical and Mann-Whitney test for continuous variables. The Kaplan-Meier estimator was used to evaluate the probability of OS and PFS.[17] Cumulative incidence rates were calculated for hematopoietic recovery, GVHD, NRM and relapse, while accounting for competing events.[18] The marginal Cox model was applied to evaluate the main treatment effect, while adjusting for the potential correlation within each matched pair. Stepwise variable selection was used to identify additional covariates to adjust for among the same list of variables as used in the propensity score model. The assumption of proportional hazards for the main risk factor (cryopreserved graft vs. fresh graft) for each outcome was tested by adding a time-dependent covariate. Hazard ratios (HR) (95%CI) and p-values were reported for each clinical outcomes of interest comparing the cryopreserved graft treatment group with the fresh graft group. E-values were also presented to assess potential impact of unmeasured confounders on the estimated effect of cryopreservation; these are defined as the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome, conditional on the measured covariates, to fully explain away a specific exposure–outcome association.[19]. Due to the large number of comparisons required, p-values < 0.01 were considered statistically significant, except for the subgroup analysis of the reason for cryopreservation were $p<0.05$ (minimal comparisons). All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

A total of 7,397 patients were included in the analysis. Outcomes for patients receiving cryopreserved PBSC grafts were analyzed separately by donor source, HLA-identical sibling (n=1051) or URD (n=678). As analysis of cryopreserved related and unrelated bone marrow

grafts did not show a difference between donor sources, the cohorts were combined (n=154) (data not shown). The baseline patient, donor, and transplant related characteristics are shown in Tables 1–3. Overall, the patient and donor characteristics of the cryopreserved and fresh cohorts were similar.

Significant differences in graft and transplant characteristics were seen in the three cohorts. In the BM cohort, cryopreserved BM donor grafts had a lower median total nucleated cell dose (TNC) compared to fresh BM grafts (2.67×10^8 cells/kg vs. 3.02×10^8 cells/kg, p=0.007) However, no statistically significant difference in $CD34^+$ cell dose was seen between the two groups (3.1×10^6 cells/kg vs. 3.3×10^6 cells/kg, p=0.73).

In the MRD PBSC cohort, cryopreserved graft recipients were more likely to receive MA conditioning (59% vs. 54%, p=0.004) and were less likely to receive TBI (16% vs 21%, p<0.001) as part of their conditioning regimen. Donors of cryopreserved MRD PBSC products were more likely to be Caucasian (75% vs. 71%, p=0.002) then donors of fresh products. There was also a longer interval between diagnosis and transplant with cryopreserved MRD PBSC grafts (6.8 months vs. 6.3 months, p=0.002) and cryopreserved graft recipients received a lower $CD34^+$ cell dose overall (5.3×10^6 cells/kg vs. 5.6×10^6 cells/kg, p<0.001).

With the URD PBSC cohort, recipients of cryopreserved grafts were less likely to be Caucasian (86% vs. 89%, p=0.007) and had a longer interval of time between diagnosis and transplant. (8.4 months vs. 7.4 months, p=0.005). The median $CD34^+$ cell dose of cryopreserved grafts was also lower compared to fresh grafts (5.9×10^6 cells/kg vs. 6.2×10^6 cells/kg, p<0.001).

Engraftment

The effect of cryopreservation on engraftment varied according to donor source (Table 4). For bone marrow and MRD PBSC grafts, there were no differences in rates of graft failure between cryopreserved and fresh grafts. There was also no significant difference in neutrophil recovery at 28 days in either cohort. However, there was a significantly lower likelihood of platelet recovery at day 100 in the MRD PBSC setting with cryopreservation in univariate analysis (92% vs. 96%, p<0.001; Table 4) that remained significant in multivariate analysis (Table 5).

In the URD PBSC cohort, there was an increase in primary graft failure with cryopreservation (5% vs. 2%, p < 0.001) on univariate analysis. There was also a significantly lower likelihood of day 28 neutrophil (93% vs. 97% p<0.001) and day 100 platelet (87% vs. 94% p<0.001) recovery in univariate (Table 4) and multivariate analyses (Table 5).

GVHD and Relapse

There was no difference in the incidence of acute GVHD (aGVHD) of grades II-IV and III-IV at 100 days between fresh and cryopreserved grafts in the BM and URD PBSC cohorts. With matched related donors, cryopreservation was associated with a modest increase in incidence of Grades II-IV (35% vs. 30%, p=0.01) and III-IV (14% vs. 10%, p< 0.001)

aGVHD in univariate analyses, and remained significant in multivariate analysis (Table 5). There were no statistically significant differences in relapse between fresh and cryopreserved grafts in any of the cohorts in univariate analyses. However, in multivariate analysis, there was a statistically significant increase in relapse with cryopreserved URD PBSC grafts (HR=1.32, CI=1.11–1.58, p=0.002).

PFS, OS and NRM

Overall, there were no significant differences between cryopreserved and fresh grafts in NRM, OS, or PFS in the bone marrow cohort or in PFS and OS in the MRD PBSC cohort (Figure 1). There was a significant increase in rates of NRM in favor of fresh grafts in the MRD PBSC cohort in univariate analysis; however, these differences were not statistically significant on multivariate analysis.

In the URD PBSC cohort, however, a significant increase in mortality was associated with cryopreserved compared to fresh grafts (2 year OS: 46% vs. 57%, p< 0.001). The most common cause of death with both cryopreserved and fresh grafts was relapse of the primary disease. Univariate analyses found significant differences in NRM (p=0.002), PFS (p<0.001), and OS (p<0.001) at all timepoints (Table 4). These differences remained significant in multivariate analyses (Table 5).

Because cryopreservation of URD PBSC grafts produced outcomes that were significantly different in comparison to the other groups, we performed an in-depth analysis of this cohort. Information regarding the time between collection of the graft and receipt at the transplant center (transit time) was obtained for 1235 fresh and 398 cryopreserved domestic URD PBSC grafts. Transit time was not available for international URD PBSC donor grafts. Median time of transit was similar between the two cohorts (8.68 hours vs. 8.82 hours respectively) and was not statistically significant. Analysis of survival endpoints between domestic and international URD PBSC grafts revealed no statistically significant differences (data not shown).

A subset analysis of the reason for cryopreserving URD PBSC grafts in 299 donors where this information was available revealed patient condition, including change in disease status, reaction to conditioning regimen and infection, was the most common reason for cryopreservation (56%, Table 6). Multivariable analysis showed significantly inferior OS in patients whose products were cryopreserved due to patient condition compared to other reasons (HR=0.65, CI=0.44–0.96, P=0.029).

DISCUSSION

This is the largest study about the effect of cryopreservation on HCT outcomes using allogeneic donor grafts. In bone marrow and related PBSC grafts, the impact of cryopreservation appears to be minimal, with delayed platelet engraftment and an increased risk of grade II-IV and grade III-IV aGVHD at 100 days seen in cryopreserved related PBSC grafts. No statistically significant effect on NRM, relapse, PFS, and OS was observed with either cohort. This is similar to previously published reports.[4–7] Early studies comparing matched related donor cryopreserved bone marrow grafts with fresh marrow grafts revealed

no differences in engraftment, however, it was unclear whether there was an effect on the incidence of acute GVHD.[4,5] With related PBSC grafts, there appears to be no effect of cryopreservation on engraftment from earlier studies, however, the effect of cryopreservation on GVHD was not consistent, with one trial reporting no difference in GVHD[6], while another showed a statistically significant increase in acute GVHD in the cryopreserved cohort.[7]

Information on the effect of cryopreservation in unrelated donor grafts was not readily available from earlier reports as most studies combined unrelated and related donors. One report of 76 cryopreserved PBSC allograft recipients, of whom 19 were from unrelated donors, revealed delayed platelet engraftment and an increased incidence of chronic GVHD.[8] There was no effect of cryopreservation observed on relapse and survival. Another report of 274 patients who received cryopreserved allogeneic grafts (mostly PBSC grafts) followed by post-transplant cyclophosphamide prophylaxis found no significant effect of cryopreservation on engraftment or survival.[9] In contrast, an analysis of 52 recipients of cryopreserved BM and PBSC allografts for patients with aplastic anemia found inferior 1-year survival in the cryopreserved cohort.[10] In our analysis, cryopreservation was associated with a statistically significant negative impact in URD PBSC grafts, resulting in more primary graft failures, slower engraftment of neutrophils and platelets, as well as increased NRM, relapse and decreased PFS and OS.

It is unclear why cryopreservation was associated with inferior outcomes in unrelated in contrast to related PBSC grafts. One possibility is there may be a delay between collection and cryopreservation due to the additional transit time between the donor center and transplant center and delays in cryopreservation might have reduced the product's hematopoietic potency. At most centers, allogeneic donor grafts are typically delivered unmanipulated to the transplant center, which then cryopreserves the graft. In contrast, with related donors, the donor center and the transplant center are either at the same site or are very close to each other, allowing for cryopreservation within hours of procurement of the graft. In the unrelated donor setting, however, donor grafts can be in transit for a significant amount of time. Additionally, there may be delays in cryopreservation if arrival occurs at night. Our analysis did not show any significant differences in transit time between fresh and cryopreserved unrelated PBSC grafts, however, time between receipt of the graft and cryopreservation was not available. In cord blood grafts, it is known that delays in cryopreservation results in decreased mononuclear cells, particularly in the granulocyte and mature B- and T-cell subsets.[20] Significant declines in CFU recovery is also observed post-thaw, which is more pronounced the longer the interval between collection and cryopreservation.[21,22] Additionally, there is a negative impact of increased transit time on platelet recovery and mortality with unrelated bone marrow graft recipients.[23] In allogeneic PBSC grafts, cryopreservation has been shown to decrease CFU post-thaw,[6] however, the effect of the duration of cryopreservation on grafts is unknown. Information concerning allogeneic graft composition in this study was restricted to parameters tested at infusion. Unfortunately, information about graft-composition and graft viability post-thaw was not available for this analysis.

The observation of an increase in relapse and decreased PFS and OS in cryopreserved unrelated PBSC grafts was unexpected. It is likely that patients who require cryopreserved grafts had multiple reasons for delays in transplantation, such as infection or disease relapse. A review from Aziz, *et al.* found the most common reason for cryopreservation was due to patient related (infection, relapse, deconditioning, etc.) or donor related (availability, workup, etc.) issues.[24] Although there is limited data from the NMDP about the reason for cryopreservation, our analysis supports this observation. It is possible delays for patient factors, such as infection, result in recipients becoming more "fragile" compared to their matched controls. If extra courses of chemotherapy were required for relapse or inadequate control of the underlying disease, this may indicate a more biologically aggressive disease compared to their corresponding controls, resulting in the increased relapse and decreased survival in this cohort. Multivariate analysis of the reason for cryopreservation in our analysis did show significantly decreased OS in grafts which were cryopreserved for patient factors supporting the hypothesis that these patients differ in characteristics to those receiving fresh grafts. Cryopreservation may also affect expression of surface molecules in mononuclear cells, in particular CD62L, which is found in $CD34^+$ cells and lymphocytes, and is decreased after cryopreservation.[25–27] CD62L also contributes to the activity of regulatory T-cells, which exerts a protective effect against GVHD and may be associated with the graft-vs.-tumor effect and decreased relapse rates.[28] Another factor to consider is the process of cryopreservation introduces a cryoprotective agent into the recipient which can result in adverse reactions and can potentially impact survivals.[29]

There are several strengths as well as significant limitations with this study. This is the largest number of cases yet studied and case matching provides control for a number of potential confounding variables, providing much more precise estimates of outcomes than previously available. It must be acknowledged, however, that despite the large size, there are still a relatively small number of cases in some cohorts, especially the BM cohort, which limits the power of those analyses. Other limitations include lack of information concerning the reasons for cryopreservation and the time between graft procurement and cryopreservation. Thus, the differences seen, despite adjusting for multiple known covariates, may be a surrogate for other factors accounting for inferior outcomes, rather than graft injury from the cryopreservation. Note that many of the E-values are in the plausible range of a potential unmeasured confounder, which could account for the apparent effects of cryopreservation. Additional studies assessing quantitative and qualitative changes in the graft before and after cryopreservation and their impact on clinical outcomes are needed.

In summary, although some differences in outcomes were seen, cryopreservation of allogeneic donor grafts is a suitable option for transplant recipients, especially in cases where there is difficulty with coordinating the administration of donor grafts without modification or if there are recipient factors which preclude the immediate use of the donor graft. That we do not know the reason for cryopreservation (in a population of patients where this is not the norm) is a significant limitation of this study and suggests that the results should be interpreted with caution. Balancing the risk of not having an available graft in a myeloablated patients against the risk of possible effects on clinical outcomes is critical. The use of routine cryopreservation during the COVID-19 pandemic may help in further

defining the effects of cryopreservation on allogeneic transplant outcomes, and analyses to study this are urgently needed.

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Highlights

- Cryopreservation of Bone Marrow grafts is not associated with stasticially significant delays in engraftment or inferior survivals.
- Cryopreservation of related PBSC grafts is associated with delayed platelet engraftment and increased risk of acute Grade II-IV and III-IV GVHD.
- Cryopreservation of unrelated PBSC grafts is associated with delayed engraftment, increased NRM and relapse, and decreased survival.
- Difference in survival between cryopreserved vs. fresh unrelated donor grafts may be due to difference in recipient factors, highlighting the need for further studies addressing outcomes during the COVID era.

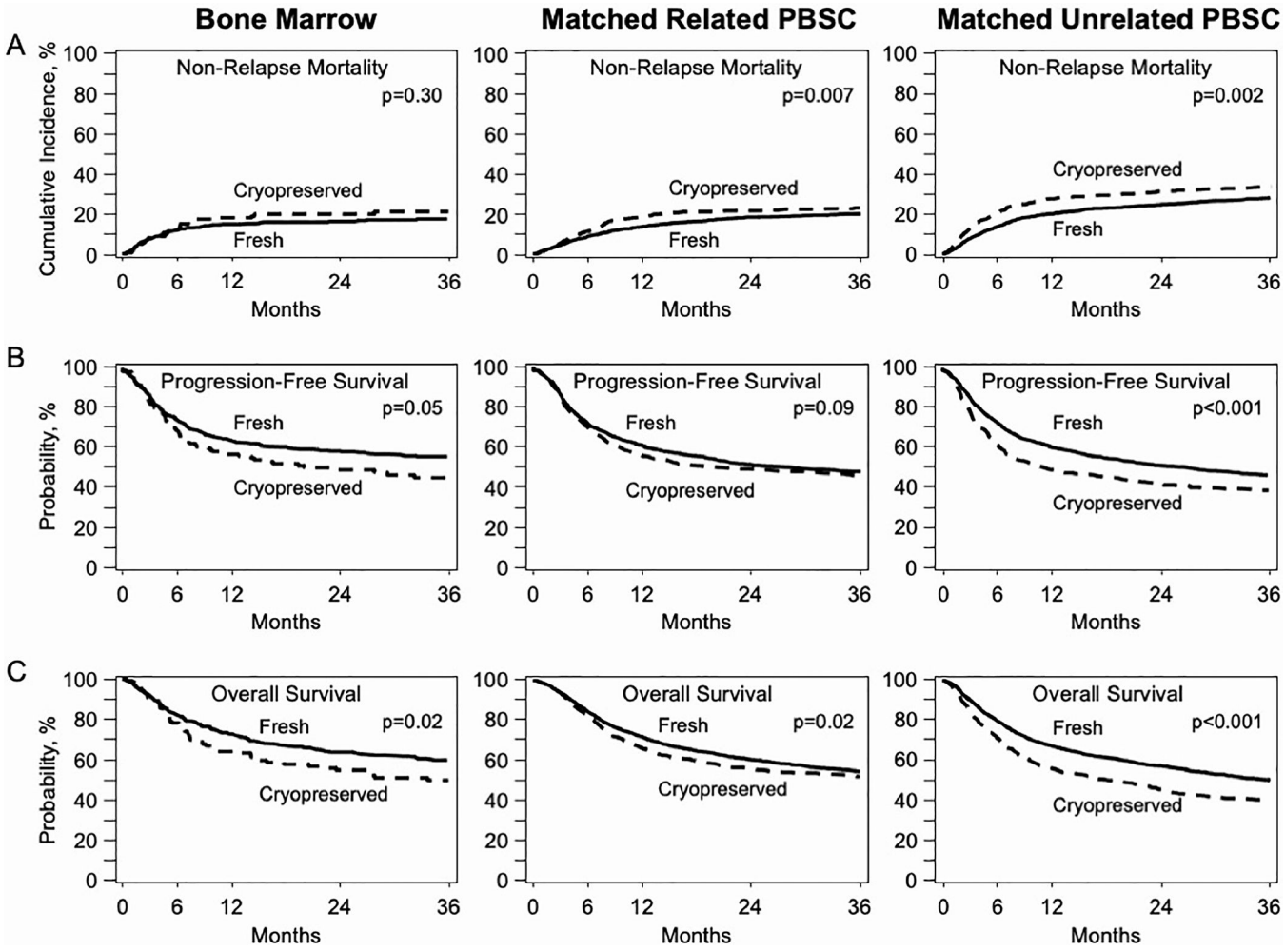

Figure 1.

Kaplan-Meier curves in BM, MRD, and URD grafts. (A) Treatment-related mortality. (B) PFS. (C) OS.

Table 1

Baseline Characteristics

	BM			Related PBSC			Unrelated PBSC		
Characteristic	**Fresh**	**Cryo**	***P***	**Fresh**	**Cryo**	***P***	**Fresh**	**Cryo**	***P***
No. of patients	456	154		3030	1051		2028	678	
Median age at transplant (y)	32.5 (0.6–79.8)	34.7 (0.4–75.1)	.74	56.8 (3.7–76)	56.9 (7.6–77.7)	.52	54.7 (0.9–83.4)	54.9 (0.9–77.9)	.93
Male Sex (%)	235 (52)	80 (52)	.73	1767 (58)	645 (61)	.03	1220 (60)	394 (58)	.21
Race (%)			.29			.03			.007
Caucasian	374 (82)	120 (78)		2440 (81)	871 (83)		1795 (89)	581 (86)	
African-American	21 (5)	10 (6)		161 (5)	60 (6)		72 (4)	32 (5)	
Other	22 (4)	10 (7)		228 (7)	60 (6)		70 (3)	31 (5)	
Missing	39 (9)	14 (9)		201 (7)	60 (6)		91 (4)	34 (5)	
KPS >=90, n(%)	289 (63)	102 (66)	.57	1688 (56)	612 (58)	.16	1114 (55)	353 (52)	.24
HCT-CI			.39			.04			.97
0	163 (36)	54 (35)		675 (22)	193 (18)		384 (19)	133 (20)	
1–2	139 (30)	42 (27)		872 (29)	305 (29)		574 (28)	193 (28)	
3+	154 (34)	58 (38)		1483 (49)	553 (53)		1070 (53)	352 (52)	
Primary disease			.95			.66			.87
AML	201 (44)	64 (42)		1230 (41)	454 (43)		906 (45)	291 (43)	
ALL	115 (25)	43 (28)		461 (15)	151 (14)		316 (16)	111 (16)	
CML	23 (5)	8 (5)		82 (3)	24 (2)		72 (4)	24 (4)	
MDS/MPD	82 (18)	29 (19)		855 (28)	274 (26)		447 (22)	160 (24)	
Other acute leukemia	14 (3)	5 (3)		31 (1)	14 (1)		32 (2)	10 (1)	
NHL	13 (3)	3 (2)		304 (10)	113 (11)		208 (10)	69 (10)	
Hodgkin lymphoma	8 (2)	2 (1)		67 (2)	21 (2)		47 (2)	13 (2)	
DRI, n(%)									
Adult			.92			.74			.58
Low	25 (5)	8 (5)		196 (6)	72 (7)		163 (8)	56 (8)	
Intermediate	149 (33)	49 (32)		1734 (57)	582 (55)		997 (49)	335 (49)	
High	69 (15)	21 (14)		762 (25)	277 (26)		507 (25)	172 (25)	
Very high	13 (3)	5 (3)		104 (3)	36 (3)		123 (6)	42 (6)	
Pediatric (adult definition)			.93			.76			.08
Low	5 (1)	2 (1)		1 (0)	1 (0)		11 (1)	2 (0)	
Intermediate	70 (15)	24 (16)		13 (0)	2 (0)		23 (1)	5 (1)	
High	67 (15)	25 (16)		15 (0)	5 (0)		12 (1)	1 (0)	
Very high	0	0		1 (0)	0		2 (0)	1 (0)	

HCT-CI indicate Hematopoietic Cell Transplantation Comorbidity index; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MDS/MPD, myelodysplastic disease/myeloproliferative disease; NHL, non-Hodgkin's lymphoma

Table 2

Donor Characteristics

	BM			Related PBSC			Unrelated PBSC		
Characteristic	**Fresh**	**Cryo**	***P***	**Fresh**	**Cryo**	***P***	**Fresh**	**Cryo**	***P***
No. of patients	456	154		3030	1051		2028	678	
Donor type, n(%)			.59						.58
HLA-identical sibling	68 (15)	24 (16)							
Unrelated, 8/8	318 (70)	106 (69)					1696 (84)	566 (83)	
Unrelated, 7/8	70 (15)	24 (16)					332 (16)	112 (17)	
Donor age, yr, median (IQR)	29 (9–67)	28.8 (8.6–72.3)	.94	55 (0–78.4)	54.9 (1.8–79.6)	.12	28 (18–64.9)	28.3 (18.6–60.5)	.19
Donor race, n(%)			<.001			.002			<.001
Caucasian	279 (61)	87 (56)		2157 (71)	785 (75)		1137 (56)	353 (52)	
African-American	14 (3)	11 (7)		142 (5)	53 (5)		46 (2)	22 (3)	
Other	66 (15)	37 (25)		277 (9)	63 (6)		368 (18)	114 (17)	
Missing	97 (21)	19 (12)		454 (15)	150 (14)		477 (24)	189 (28)	
Donor/recipient CMV serostatus, n(%)			.98			.01			.04
+/+	173 (38)	60 (39)		1348 (44)	474 (45)		598 (29)	219 (32)	
+/−	61 (13)	20 (13)		349 (12)	105 (10)		232 (11)	85 (13)	
−/+	144 (32)	47 (31)		709 (23)	291 (28)		696 (34)	207 (31)	
−/−	78 (17)	27 (18)		624 (21)	181 (17)		502 (25)	167 (25)	
Donor/recipient sex match, n(%)			.91			.15			.43
Male-Male	154 (34)	51 (33)		956 (32)	337 (32)		888 (44)	300 (44)	
Male-Female	128 (28)	41 (27)		657 (22)	224 (21)		541 (27)	188 (28)	
Female-Male	81 (18)	29 (19)		811 (27)	308 (29)		332 (16)	94 (14)	
Female-Female	93 (20)	33 (21)		606 (20)	182 (17)		267 (13)	96 (14)	
Donor/recipient ABO match, n(%)			.34			.23			.26
Matched	104 (23)	28 (18)		1099 (36)	356 (34)		347 (17)	106 (16)	
Minor mismatch	24 (5)	14 (9)		267 (9)	71 (7)		158 (8)	58 (9)	
Major mismatch	36 (8)	12 (8)		237 (8)	94 (9)		125 (6)	54 (8)	
Bi-directional	4 (1)	5 (3)		57 (2)	20 (2)		47 (2)	20 (3)	
Not available	287 (63)	95 (62)		1369 (45)	510 (49)		1349 (67)	438 (65)	
Missing	1 (0)	0		1 (0)	0		2 (0)	2 (0)	

CMV indictates cytomegalovirus.

Table 3

Transplant Characteristics

	BM			Related PBSC			Unrelated PBSC		
Characteristic	**Fresh**	**Cryo**	***P***	**Fresh**	**Cryo**	***P***	**Fresh**	**Cryo**	***P***
No. of patients	456	154		3030	1051		2028	678	
MAC, n(%)	390 (86)	131 (85)	.66	1622 (54)	624 (59)	.004	1161 (57)	378 (56)	.54
TBI, n(%)	132 (29)	45 (29)	.89	647 (21)	165 (16)	<.001	427 (21)	168 (25)	.19
GVHD prophylaxis, n(%)			.74			<.001			.60
TAC + MMF ± other(s)	49 (11)	17 (11)		331 (11)	157 (15)		323 (16)	98 (14)	
TAC + MTX ± other(s)	315 (69)	108 (70)		1855 (61)	632 (60)		1280 (63)	456 (67)	
TAC + other(s)	7 (2)	2 (1)		362 (12)	62 (6)		139 (7)	41 (6)	
TAC alone	8 (2)	3 (2)		47 (2)	32 (3)		66 (3)	20 (3)	
CSA + MMF ± other(s)	13 (3)	4 (3)		128 (4)	26 (2)		58 (3)	19 (3)	
CSA + MTX ± other(s)	63 (14)	19 (12)		290 (10)	137 (13)		143 (7)	40 (6)	
CSA + other(s)	0	1 (1)		5 (0)	0		8 (0)	1 (0)	
CSA alone	1 (0)	0		12 (0)	5 (0)		323 (16)	98 (14)	
ATG/alemtuzumab	190 (42)	61 (40)	.64	245 (8)	73 (7)	.83	875 (43)	308 (45)	.37
Time from diagnosis to HCT, mo, median (IQR)	7 (1.4–182.9)	6.9 (1–111.1)	.25	6.3 (0.2–556.3)	6.8 (0.5–507.5)	.002	7.4 (0.7–490.5)	8.4 (1.7–302.2)	.005
Follow-up, mo, median (IQR)	35.9 (0.3–76)	36.3 (0.5–73.6)		36.1 (0.1–75.5)	36 (0.4–73.7)		35.7 (0.1–75.2)	35 (0–73.4)	
Cell dose, median (IQR)									
Nucleated cell dose, $\times 10^8$/kg	3.02 (0.03–19.9)	2.67 (0.01–11.36)	.007	–	–	–	–	–	–
CD34 cell dose, $\times 10^6$/kg	3.3 (0–37547.9)	3.1 (0–96.3)	.73	5.6 (0–57272.7)	5.3 (0–8863.8)	<.001	6.2 (0–262984.7)	5.9 (0–51.7)	<.001
RBC depletion, n(%)	152 (33)	56 (36)	.68	36 (1)	7 (1)	.04	39 (2)	10 (1)	.33
Time to recovery, d, median (IQR)									
Neutrophil	17.5 (1–77)	18.5 (1–37)	.02	14 (1–113)	14 (1–107)	<0.001	14 (1–89)	14 (1–96)	<0.001
Platelets	24 (1–246)	26 (1–471)	.07	16 (0–348	17 (1–253)	<0.001	17 (1–307)	19 (1–240)	<0.001

MAC indicates myeloablative conditioning; TBI, total body irradiation; TAC, tacrolimus; MMF, mycophenolate mofetil; MTX, methotrexate; CSA cyclosporine; ATG, antithymocyte globulin.

Table 4

Univariate Analysis of Major Endpoints in All Cohorts

	BM					Related PBSC					Unrelated PBSC				
	Fresh		Cryo			Fresh		Cryo			Fresh		Cryo		
Outcome	**N**	**% (95% CI)**	**N**	**% (95% CI)**	***P***	**N**	**% (95% CI)**	**N**	**% (95% CI)**	***P***	**N**	**% (95% CI)**	**N**	**% (95% CI)**	***P***
Primary graft failure (day 28)	456	35 (8)	154	14 (9)	.76	3030	42 (1)	1051	13 (1)	.57	2028	36 (2)	678	33 (5)	<.001
Neutrophil recovery (day 28)	456	91 (88–94)	154	90 (85–94)	.23	3018	98 (97–98)	1048	98 (97–99)	.08	2024	97 (97–98)	674	93 (91–95)	<.001
Platelet recovery (day 100)	452	87 (84–90)	153	84 (78–89)	.05	3017	96 (95–97)	1047	92 (90–94)	<.001	2016	94 (93–95)	671	87 (84–90)	<.001
Relapse/PFS	445		149		.05	2919		1012		.09	1930		645		<.001
6 mo		74 (70–78)		68 (61–75)			71 (69–73)		70 (67–73)			72 (70–74)		61 (57–65)	
1 yr		63 (59–68)		56 (48–64)			61 (59–62)		56 (52–59)			60 (58–62)		48 (44–52)	
2 yr		58 (54–63)		48 (40–57)			51 (49–53)		49 (46–52)			51 (48–53)		41 (37–46)	
3 yr		56 (51–61)		44 (36–54)			48 (46–50)		45 (42–49)			46 (43–48)		38 (34–42)	
Relapse/ Progression	445		149		.17	2919		1012		.57	1930		645		.09
6 mo		14 (11–17)		20 (14–27)			20 (19–22)		19 (17–22)			14 (13–16)		19 (16–22)	
1 yr		22 (18–26)		26 (19–33)			26 (25–28)		26 (23–29)			20 (18–22)		24 (21–28)	
2 yr		25 (21–30)		31 (24–40)			31 (29–33)		30 (27–32)			25 (23–27)		28 (24–31)	
3 yr		27 (22–31)		34 (26–43)			33 (31–35)		32 (29–35)			27 (24–29)		29 (25–32)	
Treatment related mortality	445		149		0.30	2919		1012		0.007	1930		645		0.002
6 mo		12 (9–15)		11 (7–17)			9 (8–10)		11 (9–13)			13 (12–15)		20 (17–23)	
1 yr		15 (12–18)		18 (12–25)			13 (12–15)		19 (16–21)			20 (18–22)		27 (24–31)	

Outcome	BM					Related PBSC					Unrelated PBSC				
	Fresh		Cryo			Fresh		Cryo			Fresh		Cryo		
	N	% (95% CI)	N	% (95% CI)	*P*	N	% (95% CI)	N	% (95% CI)	*P*	N	% (95% CI)	N	% (95% CI)	*P*
2 yr		16 (13–20)		20 (14–27)			18 (17–20)		21 (19–24)			25 (23–27)		31 (27–35)	
3 yr		18 (14–22)		21 (15–29)			20 (18–21)		23 (20–26)			28 (26–30)		33 (29–37)	
OS	456		154		.02	3030		1051		.02	2028		678		<.001
6 mo		82 (78–85)		78 (72–85)			84 (83–86)		82 (80–85)			80 (78–82)		71 (67–74)	
1 yr		73 (69–77)		64 (56–72)			72 (70–74)		66 (63–69)			67 (65–69)		56 (52–60)	
2 yr		64 (59–69)		55 (46–63)			60 (58–62)		56 (53–59)			57 (55–59)		46 (42–50)	
3 yr		60 (55–65)		50 (41–59)			54 (52–57)		53 (49–56)			50 (48–53)		40 (36–45)	
aGVHD at 100 d	456		154			3030		1051			2028		678		
Any grade		223 (49)		70 (45)	.04		1327 (44)		507 (48)	.08		1162 (57)		381 (56)	.86
Grade II-IV		151 (33)		47 (31)	.03		906 (30)		369 (35)	.01		803 (40)		265 (39)	.88
Grade III-IV		54 (12)		13 (8)	.04		295 (10)		143 (14)	<.001		282 (14)		102 (15)	.40

Table 5

Summary of Multivariate Analysis of Study Endpoints in All Cohorts

Endpoint	BM (Fresh = 456, Cryo = 154)				Related PBSC (Fresh = 3030, Cryo = 1051)				Unrelated PBSC (Fresh = 2028, Cryo = 678)			
	HR	**CI**	***P***	**E-value**	**HR**	**CI**	***P***	**E-value**	**HR**	**CI**	***P***	**E-value**
Neutrophil recovery (day 28)[*]	0.87	0.73–1.03	.109	1.44	1.06	0.99–1.14	.104	1.25	0.77	0.71–0.84	<.001	1.69
Platelet recovery (day 100)[†]	0.81	0.66–0.98	.028	1.58	0.73	0.68–0.78	<.001	1.79	0.61	0.56–0.66	<.001	2.16
Treatment-related mortality[‡]	1.28	0.84–1.94	.25	1.66	1.22	1.04–1.44	.015	1.56	1.4	1.18–1.66	<.001	1.84
Relapse/ Progression[§]	1.28	0.90–1.83	.164	1.66	0.96	0.84–1.10	.524	1.20	1.32	1.11–1.58	.002	1.72
Relapse/PFS[‖]	1.25	0.95–1.65	.107	1.61	1.07	0.97–1.19	.168	1.27	1.36	1.20–1.55	<.001	1.78
OS[/]	1.34	1.00–1.80	.052	1.75	1.12	1.00–1.25	.045	1.38	1.38	1.22–1.58	<.001	1.81
aGVHD (day 100)												
Grade II-IV[#]	1.09	0.73–1.65	.668	1.32	1.27	1.09–1.48	.002	1.64	0.96	0.81–1.15	.683	1.2
Grade III-IV[**]	1.44	0.80–2.57	.222	1.89	1.48	1.19–1.84	<.001	1.95	1.12	0.87–1.44	.381	1.38

[*]Additional covariates adjusted for in multivariate analysis for neutrophil engraftment: BM: recipient age, donor age, donor type/matching, and GVHD prophylaxis; related PBSC: ATC/Campath use. conditioning regimen intensity, disease, donor-recipient CMV status, GVHD prophylaxis, KPS, use of TBI.

[†]Additional covariates adjusted for in multivariate analysis for platelet engraftment: BM: donor type/matching, KPS; related PBSC: recipient age, disease, GVHD prophylaxis, HCT-CI, KPS, use of TBI; unrelated PBSC: recipient age, disease, donor-recipient CMV status, DRI, GVHD prophylaxis, HCT-CI, interval from diagnosis to HCT. KPS, year of HCT.

[‡]Additional covariates adjusted for in multivariate analysis for treatment-related mortality: BM: recipient age, donor type/matching, ethnicity; related PBSC: recipient age, disease, donor-recipient CMV status, DRI.ethnicity, GVHD prophylaxis, HCT-CI; unrelated PBSC: recipient age, conditioning regimen intensity, donor age, donor type/matching, donor-recipient CMV status, GVHD prophylaxis, HCT-CI, interval from diagnosis to HCT, KPS.

[§]Additional covariates adjusted for in multivariate analysis for relapse/progression: BM: DRI, TBI use; related PBSC: disease, donor-recipient CMV status, DRI, HCT-CI, interval from diagnosis to HCT, year of HCT; unrelated PBSC: disease, ORI.interval from diagnosis o HCT, year of HCT.

[‖]Additional covariates adjusted for in multivariate analysis for relapse/PFS: BM: recipient age, DRI, ethnicity; related PBSC: recipient age, disease, DRI, donor-recipient sex matching, ethnicity, HCT-CI, interval from diagnosis to HCT, KPS, year of HCT; unrelated PBSC: recipient age, conditioning regimen intensity, donor age, disease, donor type/matching, donor-recipient CMV status, DRI, GVHD prophylaxis, HCT-CI, interval from diagnosis to HCT, KPS.

[/]Additional covariates adjusted for in multivariate analysis for OS: BM: recipient age, DRI, ethnicity; related PBSC: recipient age, DRI, ethnicity, GVHD prophylaxis. HCT-CI, interval from diagnosis to HCT, KPS; unrelated PBSC: recipient age, conditioning regimen intensity, donor age, donor type/matching, donor-recipient CMV status, DRI, GVHD prophylaxis, HCT-CI, interval from diagnosis to HCT, KPS.

[#]Additional covariates adjusted for in multivariate analysis for aGVHD grade II-IV: BM: donor type/matching, disease. GVHD prophylaxis, ATG/Campath use; related PBSC: race, disease, GVHD prophylaxis, conditioning regimen intensity. ATG/Campath use; unrelated PBSC: disease, conditioning regimen intensity, donor age, ATG/Campath use.

[**]Additional covariates adjusted for in multivariate analysis for aGVHD grade III-IV: BM: donor type/matching; related PBSC: disease, GVHD prophylaxis; unrelated PBSC: sex, conditioning regimen intensity, donor type/matching, donor age, donor-recipient CMV status, ATG/Campath use.

Table 6

Reason for cryopreservation for NMDP products collected between 2016 and 2018

Reason	Number (%)
Total	299
Clinical Schedule*	81 (27)
Donor availability	25 (8)
PBSC or BM only donor	27 (9)
Patient condition†	166 (56)

*Clinical schedule: reasons such as insurance delay, dental work, issues related to the treatment schedule (eg, holidays, work disruptions, prep scheduling), or any issue related to patient's availability on a given date (eg, weddings, funerals, other life events).

†Patient condition: infection, adverse reaction to prep, or any change in status (eg, relapse, induction failure, waiting on additional tests, waiting on count recovery).