



Optimal Practices in Unrelated Donor Cord Blood Transplantation for Hematologic Malignancies



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Unrelated donor cord blood transplantation (CBT) results in disease-free survival comparable to that of unrelated adult donor transplantation in patients with hematologic malignancies. Extension of allograft access to racial and ethnic minorities, rapid graft availability, flexibility of transplantation date, and low risks of disabling chronic graft-versus-host disease (GVHD) and relapse are significant advantages of CBT, and multiple series have reported a low risk of late transplantation-related mortality (TRM) post-transplantation. Nonetheless, early post-transplantation morbidity and TRM and the requirement for intensive early post-transplantation management have slowed the adoption of CBT. Targeted care strategies in CBT recipients can mitigate early transplantation complications and reduce transplantation costs. Herein we provide a practical “how to” guide to CBT for hematologic malignancies on behalf of the National Marrow Donor Program and the American Society of Blood and Marrow Transplantation’s Cord Blood Special Interest Group. It shares the best practices of 6 experienced US transplantation centers with a special interest in the use of cord blood as a hematopoietic stem cell source. We address donor search and unit selection, unit thaw and infusion, conditioning regimens, immune suppression, management of GVHD, opportunistic infections, and other factors in supportive care appropriate for CBT. Meticulous attention to such details has improved CBT outcomes and will facilitate the success of CBT as a platform for future graft manipulations.

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INTRODUCTION

Unrelated donor (URD) cord blood (CB) is well established as an allogeneic hematopoietic stem cell (HSC) source that extends allograft access. Volunteer donor searches are much less likely to identify a matched URD in patients of non-European and mixed descent, owing to diverse HLA haplotypes, lower representation in URD registries, and an increased risk of poor donor availability. A recent National Marrow Donor Program (NMDP) study has demonstrated that

whereas approximately 75% of white European patients are likely to identify an 8/8 HLA-matched URD, the rate is much lower in minority patients with availability for donation, further compromising access [1]. In the absence of a suitable URD, CB and haploidentical related donor transplants are alternative options.

Owing to the less-stringent HLA matching requirement, CB transplantation (CBT) has been shown to extend access to the majority of adults in all ancestry groups [1,2]. A further advantage of CB is its rapid availability, permitting flexibility of scheduling for transplantation. This greatly facilitates the care of patients with high-risk malignancies and avoids the adverse effects of delayed transplantation [3].

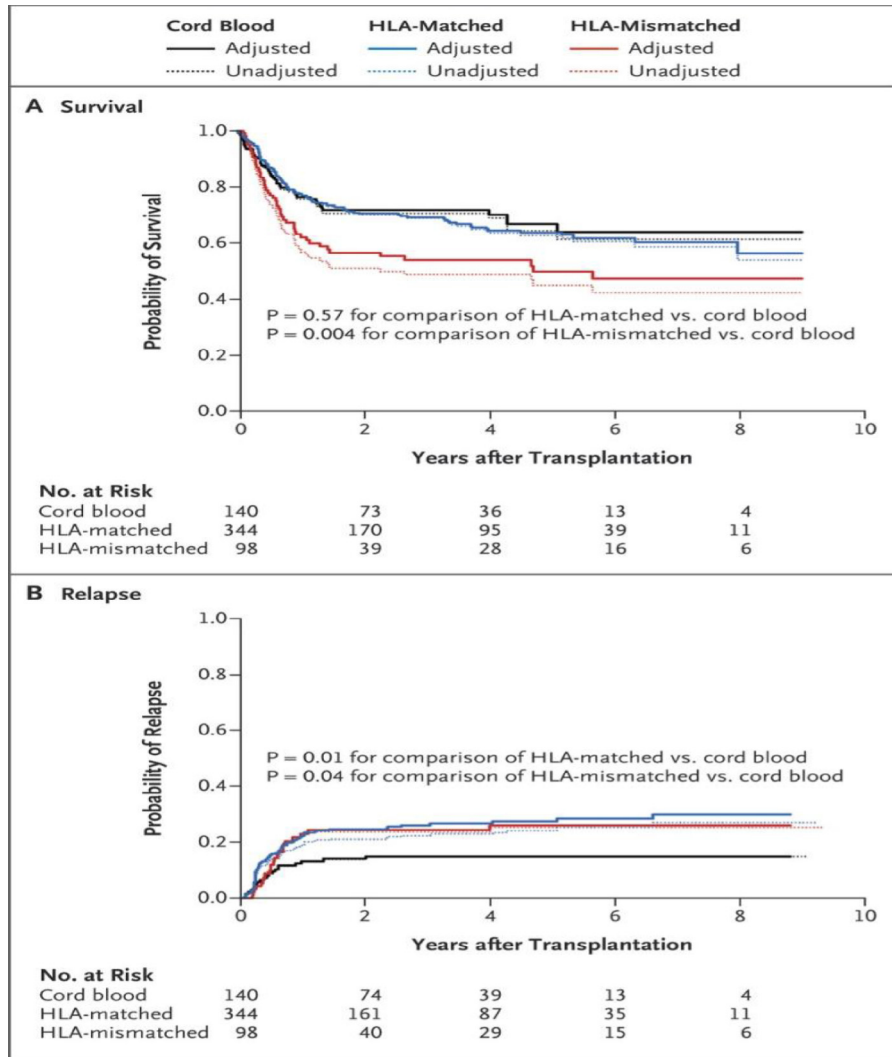
Multiple retrospective studies have demonstrated that CBT performed in experienced centers can achieve disease-free survival (DFS) rates comparable to those of the gold standard of HLA-matched URD transplantation in patients with hematologic

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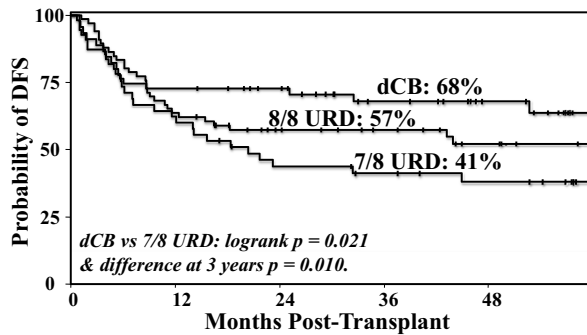
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A



B

Figure 1. Comparison of survival in CBT recipients and URD transplant recipients. (A) Acute leukemia/myelodysplasia syndrome survival at FHCRC after unmodified adult donor allografts and CBT [8]. The hazard ratio (HR) for death in HLA-matched versus CBT recipients was 1.12 (95% CI, .77 to 1.63; $P = .57$), and the HR in HLA-mismatched versus CBT recipients was 1.91 (95% CI, 1.23 to 2.98; $P = .004$). The HR for relapse in HLA-matched versus CBT recipients was 1.95 (95% CI, 1.16 to 3.27; $P = .01$), and the HR in the HLA-mismatched versus CBT recipients was 1.97 (95% CI, 1.04–3.73; $P = .04$). (B) MSKCC analysis demonstrating DFS in adults with acute leukemia (dCBT compared with T cell-depleted URD allografts) [6]. In this analysis, CBT recipients had significantly higher DFS than HLA-mismatched URD recipients.

malignancies [4–8]. For example, the University of Minnesota (UMN)/Fred Hutchinson Cancer Research Center (FHCRC) reported comparable 5-year DFS after myeloablative matched related, matched URD, mismatched URD, and double-unit CB (dCB) transplantation [4]. Recent single-center comparisons have

demonstrated comparable DFS in recipients of 8/8 HLA-matched URD and CB transplants (Figure 1 A,B) [6,8]. These analyses are notable for the low rates of relapse after CBT. Moreover, the recent FHCRC analysis has shown a markedly reduced relapse rate after CBT compared with URD transplantation in patients who undergo

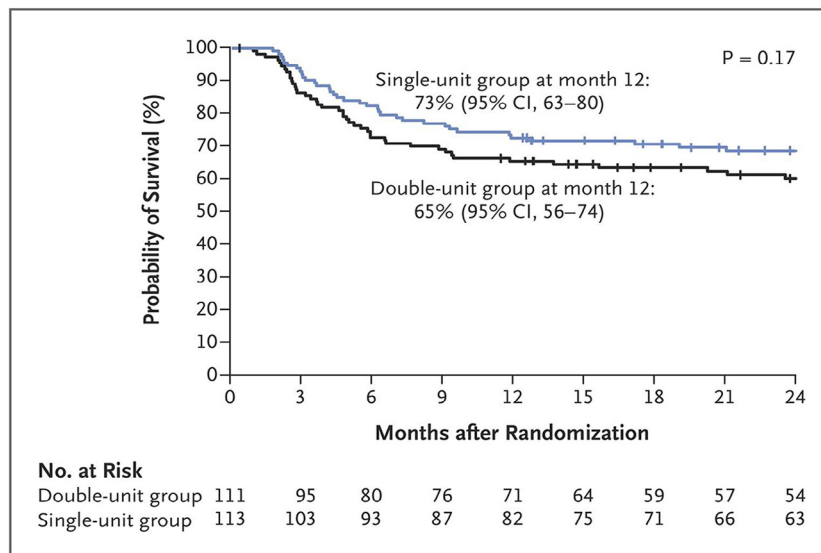


Figure 2. One-year survival after pediatric myeloablative single-unit versus double-unit CBT [23]. Survival in this BMT CTN randomized trial did not differ between single-unit and double-unit CBT recipients.

transplantation with minimal residual disease [8]. Mechanisms of relapse protection are currently under investigation [9,10].

Single-center and registry retrospective series are also emerging reporting disease-specific outcomes in patients with acute myelogenous leukemia [11,12], acute lymphoblastic leukemia [13,14], myelodysplasia [15], myelofibrosis [16,17], non-Hodgkin or Hodgkin lymphoma [18–20], and multiple myeloma [21,22]. In addition, a number of prospective studies have now been reported. For example, in the Bone Marrow Transplant Clinical Trials Network (BMT CTN) randomized study of myeloablative CBT in children and adolescents with hematologic malignancies, there was no difference in the 1-year overall survival of 73% (95% CI, 63% to 80%) after infusion of single-unit grafts and 65% (95% CI,

56% to 74%) after infusion of double-unit grafts (Figure 2), with high survival in both groups [23]. In a phase II multicenter adult myeloablative double-unit CBT trial, the 50% (95% CI, 37% to 63%) 3-year DFS was comparable to that achieved after URD bone marrow or peripheral blood HSC transplantation [24]. In the nonmyeloablative (NMA) setting, multicenter parallel BMT CTN phase II trials have reported comparable DFS after dCB and haploidentical transplants [25], and a randomized comparison is ongoing.

The foregoing results establish CBT as a standard therapy for patients with high-risk hematologic malignancies. Moreover, a recent NMDP analysis of transplantation outcomes in the United States has demonstrated improved engraftment after CBT (Figure 3) [26], and CBT survival has improved with time [27].

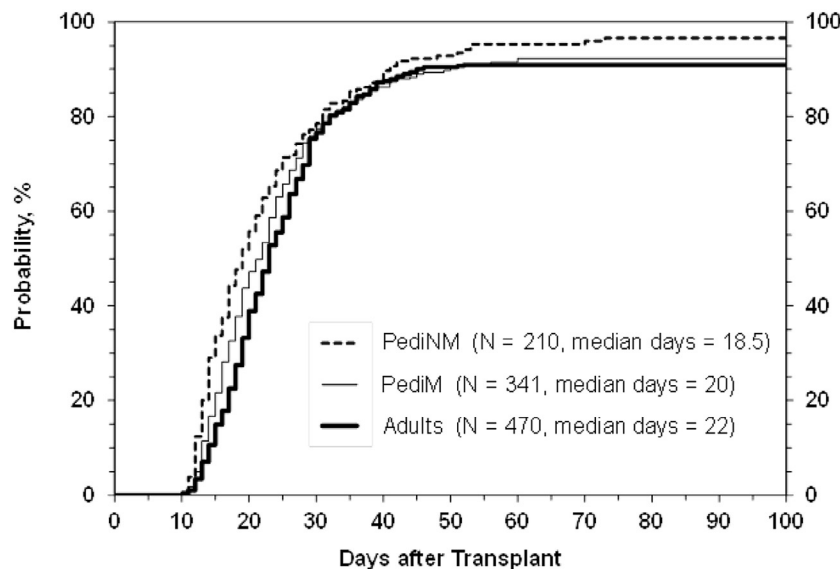


Figure 3. Neutrophil engraftment after myeloablative CBT in patients treated on the National Marrow Donor Program's Cord Blood Access Protocol (10-CBA; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01351545) NCT01351545) with unlicensed units. Shown is neutrophil engraftment in 1021 patients who underwent transplantation between October 2011 and December 2014 with either single- or double-unit 4–6/6 HLA-matched CB grafts [26]. The cumulative incidence of engraftment at 42 days was 89% (95% CI, 86% to 91%) in adults with malignancy, 88% (95% CI, 84% to 91%) in children with malignancy, and 92% (95% CI, 88% to 95%) in children with nonmalignant disorders.

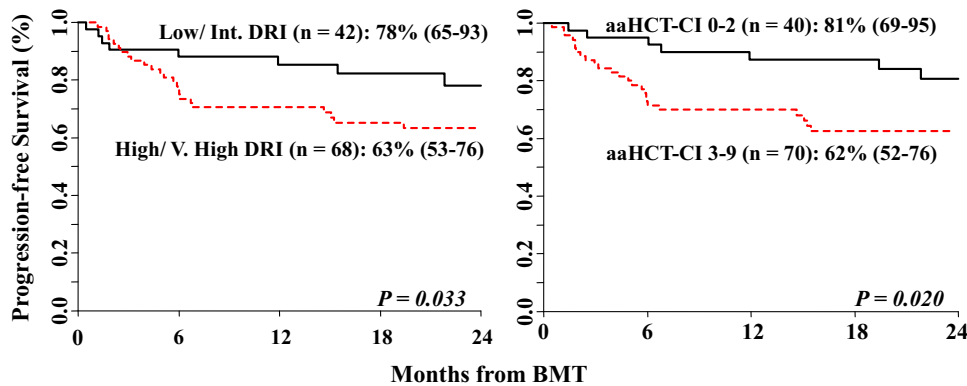


Figure 4. Two-year PFS by rDRI and aaHCT-CI in adult CBT recipients ($n = 110$; median age, 51 years) who underwent transplantation with cyclophosphamide 50 mg/kg, fludarabine 150 mg/m², thiopeta 5 to 10 mg/kg, 400 cGy total body irradiation, and CSA/MMF for the treatment of acute leukemia/myelodysplasia or myeloproliferative disease ($\leq 10\%$ blasts pre-CBT), B cell non-Hodgkin lymphoma, or Hodgkin lymphoma (Unpublished data, J. Barker, Memorial Sloan Kettering Cancer Center, 2016).

Nonetheless, CBT in patients with hematologic malignancies will be further improved if the early post-transplantation morbidity and transplantation-related mortality (TRM) can be reduced. In addition to novel technologies (eg, ex vivo expansion) currently under development, TRM can be mitigated by expert transplantation care, and an extensive literature now supports many aspects of CBT practice. Recognition of the clinical challenges in CBT and review of the management strategies instituted by experienced transplantation centers that have evolved over time can aid the optimization of patient care and reduce costs. A review of areas of controversy also will highlight topics for further investigation and stimulate discussion and information exchange between centers. Thus, in a joint NMDP and ASBMT initiative, we outline our “how we treat” at 6 expert US transplantation centers that have a special interest in CBT for the treatment of hematologic malignancies.

PATIENT SELECTION

In our centers, disease eligibility definitions are largely similar to those for transplantation with other allogeneic stem cell sources, with the exception of less common allograft indications, such as advanced myelofibrosis or multiple myeloma, for example. Moreover, disease risk is a major determinant of DFS in all allograft recipients, including CBT recipients. Importantly, although CBT has been associated with robust graft-versus-leukemia/graft-versus-malignancy effects, as with transplantation with all other HSC sources, CBT in patients with acute leukemia in full morphologic relapse or aggressive chemorefractory non-Hodgkin lymphoma, for example, is associated with a low likelihood of success. Delay in transplantation can increase patient risk owing to worsening disease burden and/or therapy complications. Thus, an important consideration in the management of high-risk patients is that a delay in proceeding to CBT owing to a failed URD search can adversely affect survival.

Patients of advanced age (ie, >65 years) or those with extensive previous therapy, treatment complications, or other serious comorbidities might not tolerate the longer cytopenias combined with calcineurin inhibitor (CNI)-based graft-versus-host disease (GVHD) prophylaxis associated with CBT. Few centers would consider CBT in patients age >70 years, whereas CB is an excellent graft source in children and adults with a low hematopoietic cell transplantation comorbidity index (HCT-CI) score. For example, a recent analysis found an 81%

2-year PFS in adult dCBT recipients with hematologic malignancies (Figure 4). Thus, the patient’s score is critically important in determining CBT outcome [28–30]. HCT-CI calculation is recommended before selecting the conditioning regimen intensity for CBT (see the Conditioning section). Furthermore, adequate creatinine clearance is critical to the success of CNI-based CBT. Center criteria for the upper age limit and the lower limit of organ function are presented in Table 1. In children, previous mechanical ventilation, deep tissue fungal or antibiotic-resistant bacterial infections, and very prolonged pretransplantation neutropenia are associated with increased risk of TRM.

GRAFT SELECTION

URD and CB Searches

Efficient management of URD searches is mandatory in centers that prioritize an HLA-matched URD in the absence of a matched sibling donor. Our centers frequently prioritize a CB graft over a 7/8 HLA-matched URD, a practice strongly supported by single-center analyses [4,6,8]. Knowledge of the patient’s ancestry, use of computerized programs based on population haplotype frequencies (eg, the NMDP’s Haplogic and search prognosis tool [31,32]), and consultation with HLA experts can rapidly determine the likelihood of identifying an 8/8 HLA-matched URD as soon as the recipient’s HLA typing and preliminary search results are obtained. Because prolonged URD searches and donor drives are very unlikely to result in the acquisition of a suitably matched URD if one is not identified within the first days to weeks of the search, futile URD searches must be avoided, with timely consideration of other stem cell sources. If CBT is an alternative, then URD and CB searches should be initiated simultaneously to guarantee a suitable graft. This is especially important for patients without multiple likely 8/8-matched URDs and those that require urgent transplantation. If a center is proficient in CB searches, units can be identified, confirmatory-typed, and shipped within 1 to 3 weeks. Efficiency is enhanced if the center has clear criteria for unit selection. The CB unit characteristics considered by our 6 centers for patients with hematologic malignancies are summarized in Table 2.

Cell Dose in Unit Selection

Although total nucleated cell (TNC) dose is a well-established determinant of engraftment and survival after CBT, the definition of an “adequately dosed” single unit has not

Table 1
Center Practice for Patient Selection, Conditioning Regimens, GVHD Prophylaxis, and G-CSF Use in Patients with Hematologic Malignancies

Criteria	Boston	Duke	FHCRC	MDACC	MSKCC	UMN
Standard remission requirement: AML/MDS/MPD	AML in morphologic CR; MPD avoided	Children: <5% blasts Adults: AML <5% blasts; MDS/MPD <10% blasts	<5% blasts by morphology/flow cytometry	AML in morphologic CR	≤10% blasts and not rapidly progressive disease	Morphologic CR; MPD avoided
Standard remission requirement: ALL/aggressive NHL	ALL in morphologic CR; NHL in CR or chemosensitive PR	Children: ALL in morphologic CR Adults: ALL < 5% blasts; NHL in CR or chemosensitive PR	ALL <5% blasts by morphology and flow; NHL in CR or chemosensitive PR	ALL in morphologic CR; NHL in CR or chemosensitive PR	ALL in morphologic CR; NHL in CR	ALL in morphologic CR; NHL CR or chemosensitive PR
Remission requirement other NHL/HL	Chemosensitivity by CT or PET					
Upper age limit	Not defined	Not defined	<70 yr	≤ 65 yr	<70 yr	≤75 yr
Lower limit of acceptable organ function*	EF ≥50%; spirometry/DLCOhb ≥50%; bilirubin <1.5 times ULN; transaminases <3 times ULN; creatinine clearance ≥50 mL/min	EF ≥50%; spirometry/DLCOhb ≥50%; bilirubin <1.5 times ULN; transaminases <3 times ULN; creatinine clearance ≥60 mL/min	EF ≥45% if ablative (35% if NMA); spirometry/DLCOhb ≥50%–70% (depending on intensity); bilirubin ≤2 times ULN; transaminases <3 times ULN; creatinine clearance ≥40–60 mL/min	EF ≥45%; spirometry/DLCOhb ≥50%; bilirubin <1.5 times ULN; transaminases <3 times ULN; creatinine clearance ≥60 mL/min		EF ≥35%; spirometry/DLCOhb ≥40%; bilirubin < 2.0 times ULN; transaminases <3 times ULN; creatinine clearance ≥40 mL/min
High-dose regimens	Cy 120/Flu 75/TBI 1200–1375	Children:† Cy 120/Flu 75/TBI 1320 Adults: TBI 1350/Thio 10/Flu 160	Cy 120/Flu 75/TBI 1320	Flu 100/Clo 30/Bu (4 d)/ TBI 200	Cy 120/Flu 75/TBI 1375	Children:‡ Cy 120/Flu 75/TBI 1320 Adults: Cy 120/Flu 75/TBI 1320
Intermediate dose regimens	Flu 180/Mel 100/TBI 200	None	Treo 42/Flu 150–200/TBI 200	Flu 160/Mel 140	Cy 50/Flu 150/ Thio 10/TBI 400 or Flu 150/Thio 10/Mel 100–140 or Mel 140/Flu 150	None
NMA regimens	Cy 50/Flu 150/TBI 200		Cy 50/Flu 150/TBI 200–300	Cy 50/Flu 150/TBI 200		
ATG inclusion	Yes	No		ATG including and excluding protocols	No	ATG including and excluding protocols
GVHD prophylaxis‡	Tacrolimus i.v./ sirolimus	Tacrolimus i.v./MMF i.v.	CSA i.v./MMF i.v.	Tacrolimus i.v./MMF i.v.	CSA i.v./MMF i.v.	CSA i.v./MMF i.v. or MMF i.v./sirolimus
Day of G-CSF start	Day +5	Children: day +1 Adults: day +2	Day +1	Day 0	Day +7	Day +5

AML indicates acute myelogenous leukemia; MDS, myelodysplasia; MPD, myeloproliferative disease; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; G-CSF, granulocyte colony-stimulating factor; Cy, cyclophosphamide; Flu, fludarabine; Thio, thiotepa; TBI, total body irradiation; Mel, melphalan; EF, ejection fraction; DLCOhb, diffusing capacity corrected for hemoglobin; ULN, upper limit of normal; CSA, cyclosporine-A; MMF, mycophenolate mofetil.

* ULN guideline for bilirubin does not apply to patients with Gilbert syndrome.

† Alternatives for pediatric patients who are not candidates for radiation include Bu/Cy/ATG, Flu/Bu/Cy ± ATG, Flu/Bu/Mel, and low-dose Flu/Cy/TBI. MSKCC has also investigated clofarabine-based regimens.

‡ Most centers start CNI in the morning of day -3 or -2, but the aim is therapeutic levels by day 0. See recent references for current MMF dosing guidelines [78,79]. For example, at MSKCC in patients age >12 years, MMF dose is 15 mg/kg i.v. every 8 hours (minimum 1 g every 8 hours, maximum 1.5 g every 8 hours).

been truly established, because the CD34⁺ dose must be considered in unit selection along with the TNC dose, and an adequate CD34⁺ dose has not been truly defined. Moreover, post-thaw CD34⁺ viability (ie, unit quality) must be taken into account. From the standpoint of TNC dose, the pediatric randomized trial of single-unit versus double-unit CBT (BMT CTN 0501) defined a sufficient cryopreserved TNC dose in a single unit as $\geq 2.5 \times 10^7$ /kg [23]; however, a registry study of 1568 myeloablative single-unit CBT recipients found increased TRM in recipients of units with a TNC $< 3.0 \times 10^7$ /kg [33]. Furthermore, a New York Blood Center analysis of 1061 myeloablative single-unit CBT recipients suggested that a higher TNC dose is required to compensate for an increasing degree of HLA mismatch [34].

In 2002, Wagner et al [35] reported that in 102 4–6/6 HLA-matched single-unit CBT recipients, there was a higher

probability of survival when units containing $> 1.7 \times 10^5$ CD34⁺ cells/kg were infused. More recently, the dominant unit infused viable CD34⁺ cell dose was identified as the sole critical determinant of the speed and success of neutrophil engraftment after dCBT [36]. Neutrophil engraftment was markedly impaired in patients with a dominant unit infused viable CD34⁺ cell dose $< 5 \times 10^5$ /kg. An important finding of this study was that selecting units based on the cryopreserved CD34⁺ dose was feasible, cryopreserved CD34⁺ dose was a better predictor than TNC of post-thaw CD34⁺ dose, and some units selected on adequate TNC dose will contain dangerously low CD34⁺ cell doses. It also should be noted that a higher cryopreserved TNC dose in units that are not red blood cell (RBC)-depleted does not necessarily reflect a higher progenitor cell content. Overall, most centers consider CD34⁺ cell dose a critical factor in optimal unit selection (Table 2).

Table 2
Center Criteria for CB Unit Selection in Patients with Hematologic Malignancies

Criteria	Boston	Duke	FHCRC	MDACC	MSKCC	UMN
Resolution of HLA typing	8-allele HLA-A, -B, -C, -DRB1					
Donor–recipient HLA match	≥4/6 alleles	≥4/6 HLA-A, -B antigens, -DRB1 alleles and ≥3/8 alleles	≥4/6 HLA-A, -B antigens, -DRB1 alleles		≥4/6 HLA-A, -B antigens, -DRB1 alleles and ≥3/8 alleles	≥4/6 HLA-A, -B antigens, -DRB1 alleles; 8 allele match grade also considered
Dose/kg, single unit*	Single unit grafts not done	TNC ≥2.5; CD34 ⁺ cells ≥1.5	TNC ≥2.5; CD34 ⁺ cells ≥2	TNC ≥2.5; CD34 ⁺ cells ≥1.5	TNC ≥2.5; CD34 ⁺ cells ≥1.5	TNC ≥2.5 if ≥5-6/6 and ≥5.0 if 4/6 HLA match; CD34 ⁺ dose also considered
Dose/kg/unit, double unit*	TNC ≥1.5/unit	TNC ≥1.5/unit; CD34 ⁺ cells ≥1.0/unit	TNC ≥1.5/unit; CD34 ⁺ cells ≥2.0/unit	TNC ≥1.5/unit; CD34 ⁺ cells ≥1.0/unit	TNC ≥1.5/unit; CD34 ⁺ cells ≥1.0/unit	TNC ≥1.5/unit
Avoidance of units against which recipient has DSA	Yes	Not if malignancy	Yes		Usually not if malignancy	Yes
Bank of origin major criteria in selection	Yes					
NetCord FACT accreditation considered	No	Yes				
Use of RBC-replete units	Sometimes	Avoid				
Mandatory testing of attached segment for identity	Yes					Yes [†]
Viability testing on thawed product (day 0)	Yes: % viable CD34 ⁺ cells by flow (7AAD)					
Backup unit policy	Haploidentical donor identified if possible	1-2 domestic units [‡]	No	1-2 domestic units [‡]		1 domestic CB unit or haploidentical donor [‡]

* TNC dose is $\times 10^7$ /kg; CD34⁺ cell dose is $\times 10^5$ /kg.
[†] Rarely, if identity confirmation was not available, emergency rapid serologic HLA typing can be done at thaw.
[‡] Units are reserved but not shipped, and released at time of patient engraftment. Some centers will use backup CB units if there were problems with shipment or unit quality problems, whereas a haploidentical donor would be the first choice in the event of graft failure.

HLA Match in Unit Selection

Acceptable donor–recipient HLA match in CBT has traditionally been at 4-6/6 HLA-A and -B antigens and -DRB1 alleles, although, as shown in Figure 5, considering only the traditional 4-6/6 HLA-match grade permits the transplantation of units with a very high degree of HLA mismatch [37]. Recently, a 1568-patient registry study demonstrated a progressively increasing TRM with increasing 8-allele mismatch independent of TNC dose and patient age [33]. MDACC data also have shown increased TRM with increasing HLA

mismatch [38]. In contrast, a recent UMN analysis reported that a high degree of HLA allele mismatch did not adversely affect transplantation outcomes [39], and such findings also have been reported in MSKCC and Spanish analyses [30,40] and in the CTN prospective trial [23]. Notably, a subset analysis in the UMN study suggested that transplantation of dCB grafts with a 2-5/10 HLA allele match was associated with a reduced risk of relapse in patients with acute leukemia [39].

Further investigation is needed to resolve this controversy, with the most critical question being how to trade-off a

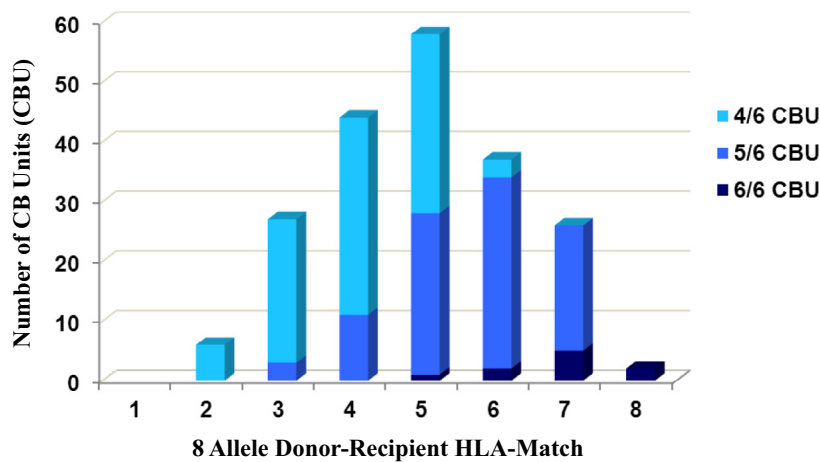


Figure 5. Demonstration of the extent of mismatch at 8 HLA alleles of CB units selected based on 4 to 6/6 HLA-A, -B antigen, and -DRB1 allele donor–recipient HLA match (n = 377) [37]. The 4 to 6/6 HLA-A, -B antigen, -DRB1 allele donor–recipient match to the patient is shown. At high resolution, the median donor–recipient HLA match at HLA-A, -B, -C, and -DRB1 alleles was 5/8 (range, 2 to 8/8). Although 6/6 matched units (n = 10) were at least 5/8 HLA-allele matched, 5/6 units (n = 94) were as low as 3/8 matched, and 4/6 units (n = 96) were as low as 2/8 allele matched to the recipient.

high-resolution HLA match against the TNC and CD34⁺ cell doses. The lower limit of acceptable HLA match at the allele level also is unknown, and it should be noted that the use of units that are 4/6 HLA matched by traditional match criteria and 3–4/8 HLA allele matched extends the access to transplantation for minority patients. At this time, many centers consider units that are at least 4/6 by traditional matching criteria and then select unit(s) for the graft based on the match at 8 HLA alleles, because considering the donor–recipient HLA-A, -B, -C, and -DRB1 allele match can help avoid the most extreme mismatch. The practices of different centers are detailed in Table 2.

Unit Quality

Early in the practice of CBT, CB unit quality was recognized as an important additional factor that can influence engraftment. For example, a number of studies have supported the importance of post-thaw colony-forming unit (CFU) dose in engraftment success [41,42]. In addition, units with a low percentage of viable CD34⁺ cells after thawing have been shown to have very poor engraftment potential [43]. Units from NetCord Foundation for the Accreditation of Cellular Therapy (FACT)-accredited banks reportedly have greater CD34⁺ cell recovery, and units from such banks with standard cryovolumes of approximately 25 mL are more likely to have high post-thaw CD34⁺ cell viability [36]. Based on center experience and such data, all of our 6 centers consider the bank of origin in unit selection. If unit segment potency testing can be standardized [44] and shown to reflect unit content, such assays may assist in pre- and post-thaw quality assessment. In the interim, post-thaw assays of HSC potency [43] are critical, because they are available within hours of thawing at the transplantation center making the shipment of a backup unit possible in the unlikely event of a poor-quality unit [45]. This is especially important in single-unit CBT, because poor graft potency at the time of transplantation would dictate the need to immediately ship and infuse a backup graft.

Selection of Single-Unit versus Double-Unit Grafts

Single-unit CBT is well established in pediatric patients. In the BMT CTN pediatric myeloablative CBT study that randomized single-unit grafts with a TNC dose $\geq 2.5 \times 10^7$ /kg against the addition of a second unit showed similar neutrophil engraftment and 1-year overall survival in the 2 groups (Figure 2) [23]. A recent European study reported similar findings, although in that study a higher TNC dose threshold was required for eligibility [46]. Many adults and some larger-sized children do not have access to adequately dosed single units, however. dCBT has been highly successful in such patients, despite the fact that only 1 unit dominates in almost all recipients. In a Center for International Blood and Marrow Transplant Registry study in adult CBT recipients with acute leukemia, even though double-unit recipients received grafts composed predominantly of 2 inadequately dosed units, their engraftment and survival was comparable that seen in single-unit recipients who received a TNC dose $\geq 2.5 \times 10^7$ /kg. That study and another study [47] suggested that double-unit grafts successfully extend the application of CBT in adults with inadequate single units.

A recent analysis of 129 dCBT recipients has shown that in patients with a low-dosed dominant unit (ie, infused viable CD34⁺ cell dose $< 1.2 \times 10^5$ /kg), a higher infused TNC dose in the nondominant unit was associated with improved neutrophil recovery. This observation suggests that although the nonengrafting unit does not contribute to hematopoiesis, it

may have a facilitatory effect on engraftment [48]. Moreover, although it has not been definitively established, some retrospective and randomized studies have suggested that dCBT may be associated with a reduced risk of relapse [19,46,49–51], with 1 analysis also identifying dCBT as cost-effective compared with single-unit CBT [51]. These findings support the continued use of dCBT in many adult patients. Unit selection principles for single-unit and dCB grafts are described in Table 2 and Figure 7. Importantly, if a double-unit graft is selected, the same unit selection principles with adequate CD34⁺ dose should apply to each unit, because either unit could engraft, and the engrafting unit cannot be predicted at the time of selection. Moreover, to date there are no data supporting incorporating unit–unit HLA match into double-unit graft selection [52].

Other Considerations

Whether other factors beyond cell dose, HLA match, and unit quality are important has not been established. The issues with RBC content are discussed in the Thaw and Infusion section. The relative importance of avoidance of units against which the patient may have donor-specific anti-HLA antibodies (DSA) is controversial, with conflicting studies reporting that they may [53,54] or may not [55,56] be important. Further investigation is needed to resolve this question, taking into account factors such as previous therapy (which could influence the risk for T cell–mediated rejection), intensity of the conditioning regimen and use of antithymocyte globulin (ATG), type of graft, and the number of antibodies, their titer, and complement fixation. It is appropriate to avoid units targeted by high titer DSA in patients without previous immunosuppressive therapy at increased risk for graft rejection. How to trade-off avoidance of units against which the patient has DSA versus the donor–recipient HLA match and cell dose of the selected unit(s) has not yet been determined.

Currently, there is no established evidence suggesting that ABO match should be considered in CB graft selection. Moreover, the age of the unit has not been established as a unit selection criterion, although the quality of unit processing and standardization of progenitor measurements have improved in recent years. Policies concerning infectious disease markers and hemoglobinopathy screening are described elsewhere [57]. Nearly all centers consider confirmatory HLA typing of an attached segment as mandatory to confirm unit identity. In the United States, most centers do not take unit licensure or cost into account. The influence of KIR (killer-cell immunoglobulin-like receptor) alloreactivity on outcomes is highly controversial [58–64], and NK (natural killer) considerations have not been incorporated into unit selection practices at this time. Similarly, the influence of gene polymorphisms of the immune response [65] merits further investigation. The biological effects of NIMA (non-inherited maternal antigens) are of great interest as well, but their consideration often is not logistically feasible, being contingent on obtaining the maternal typing [66–68].

Efficient CB Search Management

To track the selection process, relevant unit characteristics (ie, bank of origin, TNC and CD34⁺ cell doses, HLA match, cryovolume, year of cryopreservation, licensure status, NetCord FACT or American Association of Blood Banks accreditation, and other information of interest) can be summarized in a 1-page search summary (Figure 6). Once all information and the confirmatory typing of units of interest are obtained, the graft and backup unit(s) can be easily selected. Some banks now also provide a measure of potency testing at the time

Patient CB Search Summary Report

Pt Name: Example, Patient		Weight: 70	Weight Date: 3/31/2016		Reviewed Date: 4/3/2016		Comments: Ancestry: Both Parents - India Last Re-run: 2/21/16				
MSKCC # 01234567		ABO Rh: O+		Referring MD: Dr. Smith							
DOB: 1/1/1950		Diagnosis: AML		BMT MD: Dr. Jones		Best Donor: 8/10 URD					

Rank	Donor ID #	Donor Bank	RBC-deplete	Final vol (ml)	ABO Rh	Sex	Birthdate	UCB Dose x10 ⁷ _TNC/kg	Attached Segments CD34/KG	HLA Match		HLA Comments	Licensed / Ineligible		IDM_Hbopathy Comments
										4-6	8		IDM Complete CT on AttSeg:		
1a	9999-8888-7	Domestic CBB 1	Yes	25.0	O+	Female	8/3/2011	142 2.03	Yes 145	5 6 6 8	C,DR,DQ	<input type="checkbox"/> / <input type="checkbox"/> Yes Yes		FACT 2005	
back-up	333333P&Q	Domestic CBB 2	Yes	50.0	A-	Female	2/24/2010	270 3.86	Yes 132	4 5 6 8	A, B, C - patient is homozygous at A	<input type="checkbox"/> / <input type="checkbox"/> Yes Yes		FACT 2003	
	DUCB123456	Int'l CBB 1	Yes	53.2	A+	Male	11/3/2009	225 3.21	Yes 105	4 4 6 8	B,b,C,dr,DQ	<input type="checkbox"/> / <input checked="" type="checkbox"/> No No		FACT 2003 Ineligible donor (residency in Europe); Repeat IDMs pending; Hemoglobin AF	
1b	334455P	Domestic CBB 2	Yes	25.0	B+	Female	7/28/2013	186.0 2.66	Yes 168	4 5 6 8	B,C,DR,DQ - unit is homozygous at B,C,DR,DQ	<input checked="" type="checkbox"/> / <input type="checkbox"/> Yes Yes		FACT 2003	
back-up	9876-5432-1	Domestic CBB 3	Yes	25.0	A+	Female	7/27/2007	178.0 2.54	Yes 100	4 5 6 8	A,C,DR,DQ,DO - patient is homozygous at A	<input type="checkbox"/> / <input type="checkbox"/> Yes Yes		FACT 2006	
	445566P	Domestic CBB 2	Yes	25.0	B+	Female	2/23/2007	172.0 2.46	Yes 81	4 4 6 8	A,b,C,DR,dq,dq - patient is homozygous at A	<input type="checkbox"/> / <input type="checkbox"/> No No		FACT 2003 NAT HIV & NAT HCV pending	

Figure 6. Example of a CB Search Summary Report. Patient demographics, the best available URD, the date of the most recent search, and the patient's current weight are indicated. The details of units of interest, including the bank of origin, unit volume (to reflect processing type and RBC depletion), collection date, TNC dose, CD34⁺ cell dose (listed here as $\times 10^3/\text{kg}$), traditional 4-6/6 HLA match, and 8-allele HLA match are listed. ABO/Rh group and donor sex are listed for future reference. The loci of mismatch are shown (lower case indicates HLA-allele mismatch only, and upper case indicates a full HLA-antigen mismatch). All listed mismatches are bidirectional unless indicated otherwise. The bank NetCord FACT accreditation, licensure, problems with unit availability (eg, reserved on another patient's search), or other issues making the unit ineligible (and thus requiring a Declaration of Urgent Medical Need in the United States) are listed under "comments." When all information is available, the unit rank is assigned in the first column (unit 1 if a single-unit graft, or 1a and 1b if a double-unit graft). Backup units are reserved at domestic banks.

of confirmatory typing, although this practice has not been standardized.

CONDITIONING

CBT for hematologic malignancies was initially performed after high-dose myeloablative conditioning regimens incorporating ATG with cyclosporine A and corticosteroids to mitigate the risks of graft failure and GVHD with the use of HLA-mismatched grafts. In the year 2000, in an effort to mitigate post-transplantation opportunistic infections, UMN investigators developed a regimen using cyclophosphamide 120 mg/kg, fludarabine 75 mg/m², and total body irradiation of 1320 cGy with cyclosporine and mycophenolate mofetil (MMF) for GVHD prophylaxis [69]. Thus, fludarabine replaced ATG, and MMF replaced corticosteroids. This regimen has been associated with high levels of engraftment and DFS in pediatric and young adult recipients [24,69]. Moreover, the similar outcomes of single-unit and double-unit CBT in children suggest that conditioning and immunosuppression are as important as the characteristics of the graft.

A significant limitation of high-dose regimens is that they can be extremely toxic in adults [24], especially in the setting of delayed engraftment. Consequently, to tailor conditioning intensity to recipient age and the HCT-CI, many adult centers have developed reduced-toxicity intermediate-intensity regimens to substitute for high-dose conditioning

(Table 1). Such regimens remain myeloblastic but are better tolerated than high-dose chemotherapy-radiation and also are more potent than NMA conditioning facilitating engraftment and improving disease control. These can be routinely offered to older adult patients with lower comorbidity scores (Figure 4). In an effort to avoid total body irradiation, some centers have developed chemotherapy-only-based regimens with success [70]. In the NMA setting, the most established regimen is cyclophosphamide 50 mg/kg, fludarabine 150 to 200 mg/m², and 200 cGy of total body irradiation [71,72]. NMA regimens have been associated with an increased risk of rejection in patients without previous immunosuppressive chemotherapy [71], as well as with higher rates of relapse [25]. Thus, they may be most appropriate for diseases in which the main efficacy of the allograft is based on a graft-versus-leukemia effect, such as indolent lymphomas, or for older adults and patients with multiple comorbidities or extensive previous therapy who are unable to tolerate more-intensive regimens.

GVHD PROPHYLAXIS

Effective prophylaxis against GVHD is a critical component of CBT supportive care. Although multiple approaches, including a CNI, methotrexate, corticosteroids, and ATG were explored in the first decade of CBT use, the preferred regimen used by most centers today includes a CNI for 6 to 9 months

with MMF for 45 to 180 days. In pediatric patients receiving single units for transplantation, this regimen is associated with a 13% (95% CI, 7% to 20%) incidence of grade II-IV acute GVHD and a 9% (95% CI, 4% to 14%) incidence of extensive chronic GVHD, despite transplantation with HLA-mismatched grafts [23].

Although the reduced incidence of disabling chronic GVHD is a major advantage of CBT compared with URD transplantation [4,23,73,74], acute GVHD can still be a cause of significant morbidity and mortality. For example, grade II-IV acute GVHD rates of >50% have been reported in dCBT recipients treated with CNI/MMF immunosuppression without ATG [4,73]. Although many of these acute GVHD cases were grade II, these results suggest that augmented acute GVHD prophylaxis is appropriate (Table 1). Numerous strategies to reduce acute GVHD are under development. These include selecting units based on high-resolution donor–recipient matching to avoid an extreme mismatch [73,75]. Optimizing cyclosporine A levels early post-transplantation is critical [76,77]. Two recent analyses have independently identified the MMF dose as a critical determinant of acute GVHD and support intensified MMF dosing as the new standard in MMF-based CBT [78,79]. The monitoring of mycophenolic acid trough levels also may be of use [79]. Extending the duration of MMF prophylaxis (eg ≥ 100 days) has been investigated in recent years, and tailoring patient immunosuppression according to GVHD serum biomarkers also could be of use in the future [80].

In vivo T cell depletion of the CB allograft with ATG is an alternative strategy for GVHD prevention that has been associated with reduced rates of GVHD [81]. The inclusion of ATG in patients with hematologic malignancies is highly controversial, however. Whereas a Center for International Blood and Marrow Transplant Registry myeloablative CBT study analyzing children with acute lymphoblastic leukemia showed comparable 3-year DFS regardless of ATG inclusion [82], other series have demonstrated multiple disadvantages. The risk of viral infections, such as Epstein–Barr virus (EBV) post-transplantation lymphoproliferative disease (PTLD), is significantly increased [83]. Moreover, immune recovery is notably delayed [84], likely accounting for multiple reports of increased TRM and/or increased

relapse in children and adults [85–88]. However, the biological effects of ATG are altered by multiple factors, including patient age, diagnosis, conditioning intensity, pretransplantation lymphocyte count, and ATG dose, brand, and timing of administration relative to graft infusion, complicating the assessment of its role in CBT. The work of Admiraal et al [88,89] suggests that the safety of ATG-based regimens can be enhanced by performing ATG pharmacokinetics or dosing based on pharmacokinetic principles to greatly reduce or eliminate post-transplantation ATG exposure and thereby enhance immune reconstitution and disease-free survival.

THAWING AND INFUSION

Transplantation centers must have a standard of practice for the receipt of CB grafts to ensure appropriate handling on arrival and storage until the day of transplantation. The center should have previous knowledge of the container, cryovolume, RBC content, and type of access ports on the cryopreservation bag. Thawing techniques vary at experienced centers but should take the following factors into consideration: age of the patient, distance from the site of thawing to the patient, RBC content of the unit, ABO match of the unit if a RBC-containing unit is used, size of the patient, relative load of dimethyl sulfoxide (DMSO), and the planned final unit volume.

Practices used at our centers include dilution with Dextran 40 with 25% human serum albumin, followed by centrifugation (washing) [90] or dextran-albumin dilution only (Table 3). Washing has the advantage of longer product stability and DMSO/cellular debris removal but is associated with increased graft manipulation and technologist time, as well as increased potential for cell loss. Automated washing devices may have an advantage over manual washing from the standpoint of postwash viability. Dilution is faster, easier, and not associated with mechanical cell loss, but must be administered with increased attention to time from thawing to infusion, DMSO-associated infusion reactions, and volume overload [91].

With both techniques, adequate dilution (including before washing) in a controlled environment is critical. For this

Table 3
Overview of Guidelines for Thawing and Infusion of RBC-Depleted CB Grafts by Transplantation Center

Criteria	Boston	Duke	FHCRC	MDACC	MSKCC	UMN
Manual wash, automated wash or dilution only*	Manual wash	Automated wash	Dilution if recipient >20 kg; otherwise, manual wash	Automated wash	Dilution if recipient >20 kg*; otherwise, manual wash	Automated wash
Final volume	As clinically appropriate	Children: <5 mL/kg Adults: 50 mL	8-fold dilution	~ 50 ml	8-fold dilution	~ 100 mL
Premedication	Diphenhydramine Hydrocortisone	Acetaminophen; hydrocortisone	Acetaminophen; hydrocortisone	Hydrocortisone	Acetaminophen; lorazepam; hydrocortisone	Acetaminophen
Hydration	500 mL before infusion	Children: Twice maintenance for 4–6 h Adults: maintenance fluids	Twice maintenance 4–6 h before and 24 h after CBT	Twice maintenance 2 h before and 4 h after CBT	Twice maintenance 4–6 h before and 12 h after CBT if units not washed; furosemide to maintain fluid balance	2–6 h before and 12 h after CBT
Minimum infusion time	~45 min/unit	Children: ~15 min Adults: ~45 min	~30 min/unit		~ 30–45 min/unit	Infusion by gravity for small children; otherwise ~45 min/unit
Treatment of hypertension	Individualized to patient	i.v. hydralazine	i.v. hydralazine + furosemide	Antihypertensive \pm furosemide	i.v. hydralazine \pm furosemide	As clinically indicated

* Diluent used: 5:1 ratio of 10% dextran 40 (molecular weight 40,000) and 25% human serum albumin.

reason, our centers do not perform bedside thawing. Importantly, life-threatening infusion reactions have been reported with nonwashed RBC-replete units [92]. Dilution may be inadequate to mitigate severe infusional toxicity [93], and yet washing RBC-replete units requires considerable expertise, given the markedly increased risk for cell loss. Therefore, such units are avoided by most centers. Post-thaw rapid testing of hematopoietic potency is ideal to ensure the infusion of a product with high engraftment potential [43].

INFECTION PROPHYLAXIS, MONITORING, AND THERAPY

Supportive care to prevent or treat opportunistic infections until neutrophil and immune recovery has occurred is critical in CBT. Center practices are summarized in Table 4.

Bacterial Prophylaxis and Treatment of Febrile Neutropenia

Knowledge of the sensitivities of previous bacteremias and documentation of bacterial colonization (eg, methicillin-resistant *Staphylococcal aureus*, vancomycin-resistant

enterococci [VRE], and multiresistant Gram-negative bacteria) are important to guide antibiotic choices. A current standard in patients with neutropenia is to administer prophylaxis and treat fever according to transplantation center patterns (and sensitivities of previous infections, if applicable). VRE is a common cause of pre-engraftment bacteremia [94], and VRE-active antibiotics can be given preemptively at the onset of febrile neutropenia in colonized patients or at the time of notification of Gram-positive bacteremia.

Fungal Prophylaxis

Fungal prophylaxis, often with extended-spectrum azoles, is standard in most centers; however, owing to the risk of significant drug interactions, extended-spectrum azoles should be avoided during the preparative regimen, and careful CNI drug monitoring must be maintained when these drugs are used early post-transplantation [77]. No prophylaxis or an echinocandin can be used until the switch is made to an extended-spectrum azole (eg, voriconazole, posaconazole) post-transplantation, and our centers have a low threshold

Table 4
Overview of Guidelines for Infection Prophylaxis and Monitoring Early Post-CBT by Transplantation Center

Criteria	Boston	Duke	FHCRC	MDACC	MSKCC	UMN
Prophylaxis						
Bacterial	Levofloxacin or ciprofloxacin	Children: none Adults: ciprofloxacin from day -2	Levofloxacin starting with neutropenia	Levofloxacin or ciprofloxacin from day-1 to engraftment	Vancomycin/ ciprofloxacin from day -2 or at neutropenia	Levofloxacin
Fungal	Fluconazole or nothing	Voriconazole from day 0; micafungin if azoles not tolerated	Fluconazole starting with conditioning	Voriconazole or posaconazole from day -1 until off significant immune suppression.	Micafungin from admission, switching to voriconazole/ posaconazole as tolerated after day +7; micafungin if azoles not tolerated	Fluconazole or voriconazole in selected patients
Viral	Acyclovir or famciclovir	Acyclovir	Valacyclovir 2 g TID	Valacyclovir from day -1 to 12 mo	Acyclovir (gancyclovir during conditioning if recipient CMV+)	Acyclovir
Pneumocystis active drug: tri/sulpha, pentamidine, or atovaquone	During conditioning; resume after day +30	Preconditioning; resume after day +30	Tri/sulfa from start of conditioning to day -2; resume when engrafted (by day +30)	Tri/sulfa from day +30	During conditioning; resume on day +30	Tri/sulfa starting on day +28
Toxoplasmosis active drug: tri/sulpha, atovaquone, or pyramethamine	During conditioning; resume after day +30.	Children: after completion of conditioning Adults: preconditioning; resume on day +30		Pyramethamine or tri/sulfa	During conditioning; resume on day +14	
Monitoring by quantitative PCR						
CMV	Weekly	Weekly on days 0-100 then as clinically indicated	Weekly on days 0-100, then weekly to 1 yr	Twice weekly on days 14-100	Twice weekly from day +14 to day +60; if CMV+, weekly to day +100, then frequency based on patient risk	Weekly to day +100, then as clinically indicated (eg, if GVHD)
HHV-6	Weekly	Weekly from day 0 to day +100, then as clinically indicated	As clinically indicated	Weekly from day +14 to day +100	Once or twice weekly from day +14 to day +60	If clinically indicated
Adenovirus	Yes at Dana-Farber Cancer Institute; no at Mass General	As clinically indicated		Weekly from day +14 to day +100	Weekly from day +14 to day +60	No
EBV	Weekly	As clinically indicated		Weekly from day + to day +100, then as clinically indicated (eg, if GVHD)	Once or twice weekly from day +14 to day +60, weekly until day +100, then as clinically indicated (eg, if GVHD)	If ATG, weekly from day +30 to day +80
Toxoplasmosis	None	As clinically indicated	None	Weekly until discharge if seropositive recipient	Twice weekly from day +14 to day +60 if recipient seropositive	None

Tri/sulfa, trimethoprim/sulfamethozole.

for a noncontrast chest computed tomography scan to evaluate patients for occult fungal infections. Given that the success of transplantation is contingent on the maintenance of therapeutic CNI dosing, early post-transplantation avoidance of the nephrotoxicity of amphotericin is appropriate.

Viral Prophylaxis, Monitoring, and Therapy

Cytomegalovirus (CMV) reactivation in CMV-seropositive CBT recipients is as high as 100% in patients monitored by sensitive PCR [95]. CMV disease rates vary by series, and CMV infection can potentially increase the risk of TRM [95–97]. Our centers perform once- or twice-weekly PCR monitoring in seropositive patients early post-CBT, and owing to the risk of life-threatening CMV disease with delayed therapy, most centers will initiate preemptive therapy at the first or second low-level PCR detection [95,97]. CMV infection is treated with foscarnet before myeloid recovery and with ganciclovir or valganciclovir after myeloid engraftment for treatment of CMV viremia. New agents are needed, because delayed myeloid recovery can limit the early use of ganciclovir/valganciclovir, and the risk of nephrotoxicity complicates the combined use of CNI and foscarnet.

Although human herpesvirus 6 (HHV-6) viremia is common after CBT, the clinical impact of HHV-6 reactivation is controversial, with the reported incidence of encephalitis ranging from <2% to 9.9% [98,99]. Many centers perform PCR monitoring to facilitate early detection of high-level viremia and prompt recognition of end-organ disease, although preemptive foscarnet therapy in uncomplicated viremia might not be warranted [99]. Further investigation of the risks and benefits of HHV-6 viremia therapy and standardization of PCR testing is required. Although CBT can be a risk factor for adenovirus viremia, there is no agreement concerning the utility of prospective viremia surveillance. Brincidofovir has significant antiadenovirus activity, but the gastrointestinal (GI) toxicity of this drug must be weighed against the nephrotoxicity of i.v. cidofovir.

The risk of EBV reactivation and PTLD is markedly increased with ATG-based conditioning regimens, and such transplantations require close monitoring for EBV reactivation and preemptive therapy with rituximab [83]. A very low incidence of EBV-associated PTLD has been reported in recipients of CBT without ATG, although it may occur, and some centers monitor for EBV viremia. This is especially appropriate in patients on high-dose or prolonged systemic therapy for GVHD and in patients with documented poor T cell recovery.

Pneumocystis jiroveci (PCP)/Toxoplasmosis Prophylaxis

All of our centers initiate PCP prophylaxis by 1 month post-CBT. Most use either inhaled pentamidine or atovaquone until adequate hematopoiesis can permit the use of trimethoprim-sulfur. Patients should be screened pretransplantation for toxoplasmosis exposure. Those who are IgG-seropositive for toxoplasmosis are at significant risk for life-threatening infection, and prophylaxis is appropriate. Pretransplantation IgM seropositivity requires highly specialized management. Practices vary concerning the use of PCR surveillance for toxoplasmosis reactivation early post-CBT, but seropositive recipients are at risk.

Intravenous IgG Supplementation

Most centers administer repletion for hypogammaglobulinemia although the threshold for replacement varies by center (in adults, IgG <400 mg/dL or lower as guided by infection risk;

in children, <10% lower than the lower limit of normal for age for young children). Prophylaxis should be continued until there is evidence of functional B cell recovery.

Duration of Infection Prophylaxis

No data are available to guide the duration of prophylaxis for fungal, viral, and PCP/toxoplasmosis infections. Importantly, prophylaxis until the patient is off immunosuppression and has achieved some basic measures of immune recovery is appropriate (as indicated by, eg, a CD4 cell count >200/ μ L). This time period can vary widely and will be influenced by ATG-based in vivo T cell depletion and ongoing GVHD therapy. Clinically validated measures of functional immune reconstitution are needed. All patients require post-transplantation immunization with all relevant protein conjugate and live vaccines, and vaccine responses in CBT recipients have been reported [100].

MANAGEMENT OF DELAYED ENGRAFTMENT AND GRAFT FAILURE

Single-center series have reported sustained donor neutrophil engraftment rates of 95% [36] that are comparable to those seen in adult donor bone marrow transplantation. Nonetheless, CBT is associated with delayed engraftment and an increased risk of graft failure compared with transplantation with peripheral blood stem cell allografts. Because graft failure is associated with a very high risk of lethality, every effort must be made to avoid this complication through rigorous unit selection, optimized thawing, immediate post-thaw potency evaluation, and optimized conditioning and immune suppression. Access to reserved “ready to ship” backup unit(s) is prudent. Use of granulocyte colony-stimulating factor early post-transplantation to facilitate neutrophil recovery is standard (Table 1).

Prompt diagnosis of graft failure is also critical. Early evaluation can permit emergency intervention. Standard chimerism evaluation is by quantitative PCR for informative polymorphic short tandem repeat regions, and centers assess engraftment between days +21 and +28. Absence of signs of white blood cell count recovery should trigger rapid processing of chimerism assays. Donor bone marrow chimerism \geq 90% at 21 days post-CBT has been shown to be associated with a high likelihood of sustained engraftment following dCBT [101], although clinical graft failure may still occur in patients who are 100% donor chimeric, especially in the setting of severe illness. In patients without white cell recovery and lacking evidence of progressive donor engraftment in serial chimerism testing, most centers commence workup for a second transplantation at approximately day +35. Although optimal preparative regimens for a second transplantation have not been established, they usually include fludarabine or cyclophosphamide and often ATG as well. In addition, some centers prefer to use a haploidentical donor for rescue of patients with graft failure after CBT.

GVHD Diagnosis and Therapy

Whereas some studies have reported the skin is the most commonly involved organ in acute GVHD [23,102], other centers have found that the GI tract is the most frequently affected [73,103]. CBT-mediated GVHD may be more corticosteroid-responsive than that mediated by adult donor grafts and initial treatment of the skin with lower doses of prednisone or of the upper GI tract with poorly absorbed corticosteroids can be effective [73]. Lower GI acute GVHD is most likely to mediate TRM and requires prompt diagnosis and

more intensive therapy. When diarrhea is present, rapid evaluation for infection (*Clostridium difficile* or viruses) should be performed, recognizing that some patients can have both GVHD and infection. Therapy of lower GI disease must not be delayed. Interestingly, some analyses have suggested that the development of acute GVHD is not associated with a decrement in survival [104]. Multiple series have reported low incidences of moderate or severe disabling chronic GVHD [4,73,74,103] and increased corticosteroid responsiveness [105] after CBT. This represents a major advantage of this HSC source from the standpoint of quality of life and should be the subject of long-term CBT outcome analyses.

OTHER COMPLICATIONS

Pre-Engraftment Syndrome

Pre-engraftment syndrome (PES) manifests as unexplained fever $\geq 38.3^{\circ}\text{C}$ (101°F) in the absence of infection. Sometimes accompanied by an erythematous rash, PES occurs before or at neutrophil recovery (median onset approximately 9 days; range, 5 to 12 days) and is a recognized complication of both single-unit and double-unit CBT [106,107]. Because patients can develop severe capillary leak syndrome, resulting in hypoxia and renal impairment and potentially multiorgan failure, PES requires prompt recognition and therapy. PES is highly corticosteroid-responsive and a short course of i.v. methylprednisolone (eg, 1 mg/kg/day for 3 days) with or without tapering is the accepted therapy.

Autoimmune Hemolysis and Immune Thrombocytopenic Purpura

Autoimmune hemolysis and immune thrombocytopenic purpura are other reported complications of CBT that may occur at a higher rate than in adult donor allograft transplantation. Autoimmune hemolysis and immune thrombocytopenic purpura can be both abrupt in onset and life-threatening [108–110]. High rates of immune cytopenias have been reported in pediatric patients undergoing CBT in the first year of life [111]. Early intervention with corticosteroids and rituximab at diagnosis is

effective, and early rituximab administration is a corticosteroid-sparing strategy in patients with severe disease [110].

NEW TECHNOLOGIES

Extensive investigation of strategies to enhance myeloid engraftment is underway [112,113]. Expansion methods that are currently in clinical trials include ex vivo expansion of stem/progenitor cells using culture in the presence of Notch ligand [114], a mesenchymal coculture system [115], and culture with the addition of small molecules (eg, nicotinamide [116], StemRegenin-1 [117], UM171 [118]). Preclinical expansion systems that await evaluation in the clinical setting include an endothelial-based expansion system [119]. Concerns that real-time expansion of the graft could cause undue delay in transplantation has led to investigation of the provision of “off-the-shelf” previously expanded CB-derived myeloid progenitors [114]. The addition of a third-party CD34⁺ cell-selected myeloid bridge [120,121] is another alternative, although in vivo T cell depletion appears to be necessary to promote a myeloid bridge [122]. Enhanced homing is an alternative approach, and fucosylation is currently under investigation [123]. Along with enhancing myeloid recovery, strategies to prevent and treat viral infections in CBT recipients through the provision of cytotoxic T cells are also under development [113,124]. The infusion of third-party CB-derived T regulatory cells is being investigated as a novel GVHD prophylaxis [125], and third-party EBV-specific cytotoxic T lymphocytes can be effective therapy for EBV-PTLD [126].

CONCLUSIONS

CBT is an established therapy for the treatment of patients with hematologic malignancies. Recognition of commonly encountered complications of CBT will further improve the success rate of CBT. Importantly, the goal of reducing TRM is realistic given the increasing global CB inventory and center experience, as well as efficient management of donor searches to include early recognition of poor or futile URD searches and optimized unit selection. Further

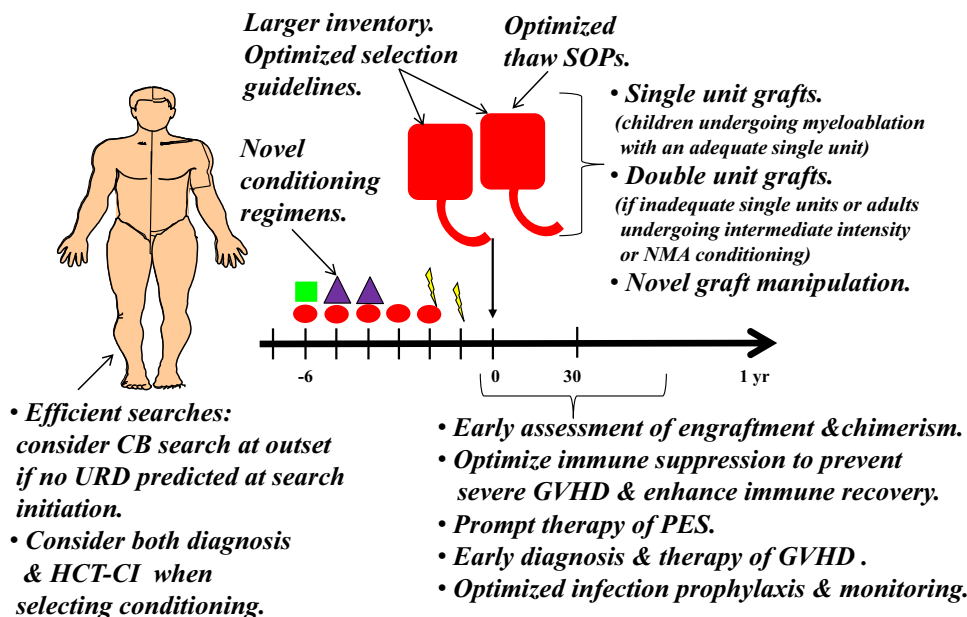


Figure 7. Summary of the current measures to optimize CBT in patients with hematologic malignancies. The emphasis is on patient and unit selection, conditioning intensity, GVHD prophylaxis, transplantation day management, and early post-transplantation care.

improvement has been realized with the development of novel conditioning regimens tailored to patient diagnosis and comorbidities, multiple new strategies to speed engraftment, augmented GVHD prophylaxis, prompt GVHD diagnosis and therapy, and improved early treatment of opportunistic infections (Figure 7). Although the cost of CB grafts and supportive care early after transplantation remain a source of concern for many centers, graft costs should be placed in perspective. All alternative donor allograft strategies for patients with hematologic malignancies are expensive, and true cost comparisons must take into account long-term patient care, including, for example, the cost of management of severe chronic GVHD, the cost of relapse, and the cost of relapse prevention measures, such as the addition of post-transplantation maintenance or cellular therapies. Only long-term outcome analyses with quality of life measures will be able to determine the value and cost of CBT compared with other therapies. In addition, improved graft availability, informed graft selection, and emerging techniques to enhance engraftment are likely to improve outcomes and decrease the costs associated with CBT. Finally, collaborative multicenter studies, information exchange among centers worldwide, and efforts of special interest groups will hasten progress in optimizing the care of CBT recipients.

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