Transplantation and Cellular Therapy 27 (2021) 286–291

Transplantation and Cellular Therapy

journal homepage: www.tctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

Guideline

Guidelines for Adult Patient Selection and Conditioning Regimens in Cord Blood Transplant Recipients with Hematologic Malignancies and Aplastic Anemia

Leland Metheny[1,*], Ioannis Politikos[2], Karen K. Ballen[3], Andrew R. Rezvani[4], Filippo Milano[5], Juliet N. Barker[2], Claudio G. Brunstein[6], on behalf of the American Society for Transplantation and Cellular Therapy Cord Blood Special Interest Group

[1] *Stem Cell Transplant Program, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, Ohio*
[2] *Adult Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*
[3] *University of Virginia Cancer Center, Charlottesville, Virginia*
[4] *Division of Blood & Marrow Transplantation, Stanford University, Stanford, California*
[5] *Fred Hutchinson Cancer Research Center, Seattle, Washington*
[6] *Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, Minnesota*

Article history:
Received 10 November 2020
Accepted 10 November 2020

Key Words:
Cord blood transplant
Conditioning regimens
Hematologic malignancies

A B S T R A C T

For cord blood transplantation (CBT), appropriate patient and conditioning regimen selection is necessary to achieve long-term disease-free survival. This review aims to provide comprehensive guidelines on these issues using evidence from the literature and experience at dedicated CBT centers. Topics include patient and disease characteristics that make CBT a good or poor choice and a review of outcomes in commonly used conditioning regimens in CBT. This is accompanied with recommendations on regimen intensity based on disease, organ function, and patient performance status and age. In addition, the use of antithymocyte globulin in CBT is discussed, as is the choice of conditioning in aplastic anemia patients who have access to acceptable CB units.

INTRODUCTION

Cord blood (CB) is a valuable alternative graft source for patients with hematologic malignancies in need of allogeneic transplantation who lack HLA-matched adult donors [1-3]. Advancements in CB transplantation (CBT), including the development of novel conditioning regimens, have contributed to improved CBT outcomes. Multiple centers are investigating CBT after conditioning regimens of varying intensity in patients with hematologic malignancies (Table 1). Combining evidence from the literature and the practice of experienced centers, this review provides guidelines for patient selection and recommended conditioning regimens in adult CBT recipients being treated for hematologic malignancies or severe aplastic anemia (Tables 2 and 3). Special considerations in children will be included in separate guidelines specific to pediatrics.

FAQ1: In which patients may CB be an especially attractive stem cell source?

Although CB is routinely used as a graft source in dedicated centers, it may be especially attractive in specific patient populations, such as those who require very urgent transplantation given the immediate availability of publicly banked CB grafts [4]. This is of utility in patients with more common HLA haplotypes who will frequently have excellent CB grafts that can be shipped rapidly or in patients who require a backup source of hematopoietic cells if the availability of an adult donor is in doubt. Moreover, CBT is valuable for patients belonging to racial and ethnic groups in whom HLA-matched unrelated donors are difficult to find in existing registries and in those patients with uncommon haplotypes [2,5,6]. In addition, CBT has been associated with robust graft-versus-leukemia (GVL) effects and thus may be an attractive graft source in patients with high-risk diagnoses, including those with detectable minimal residual disease (MRD) at transplantation, based on some retrospective studies [7,8]. Finally, CB may be an attractive graft source when considering long-term outcomes such as graft-versus-host disease (GVHD), relapse-free survival (GRFS) [9-11]. The low

Financial disclosure: See Acknowledgments on page 288.
*Correspondence and reprint requests: Leland Metheny, Stem Cell Transplant Program, University Hospitals Seidman Cancer Center, Case Western Reserve University, 11100 Euclid Avenue, LKS 5079, Cleveland, OH 44106.
E-mail address: Leland.metheny@uhhospitals.org (L. Metheny).

https://doi.org/10.1016/j.jtct.2020.11.008
2666-6367/

Table 1
Survival after CBT for Hematologic Malignancies with Various Conditioning Regimens

Series	Patient Characteristics	Conditioning	Survival
High-dose			
Kanda et al., 2011 [47]	n = 27 Leukemias, MDS, lymphoma Median age, 33 yr; range, 20–58 yr	Flu 160 mg/m^2, TBI 1350 cGy	2-yr OS: 58%, 2-yr PFS: 52%
Barker et al., 2015 [19]	n = 56 Leukemias, MDS Median age, 35 yr; range, 18-49 yr	Cy 120 mg/m^2, Flu 75 mg/m^2, TBI 1320 cGy	3-yr OS: 52%; 3-yr PFS: 50%
Anand et al., 2017 [48]	n = 31 Acute leukemias, MDS, lymphoma Median age, 46 yr; range, 19-65 yr	Flu 160 mg/m^2, TBI 1350 cGy, thiotepa 10 mg/kg	3-yr OS: 57%, 3-yr PFS: 51%
Intermediate intensity			
Sanz et al., 2013 [45]	n = 102 Leukemias Median age, 30 yr; range, 16-52 yr	Thiotepa 10 mg/kg, Bu 9.6 mg/kg i.v., Flu 150 mg/m^2, ATG 8 mg/kg	5-yr PFS: 34%
Milano et al., 2020 [50]	n = 130 Leukemias, MDS Median age, 45 yr; range, 0.6-65 yr	Treosulfan 42 m/m^2, Flu 150/200 mg/m^2, TBI 200 cGy	3-yr OS: 66%, 3-yr PFS: 57%
Barker et al., 2020 [8]	n = 90 Acute leukemias (68%), MDS, MPD, NHL Median age, 47 yr; range, 21-63 yr	Cy 50 mg/kg, Flu 150 mg/m^2, thiotepa 10 mg/kg, TBI 400 cGy	3-yr OS: 82%, 3-yr PFS: 76%
DeFilipp et al., 2020 [32]	n = 31 Leukemias, MDS, lymphoma Median age, 57 yr; range, 21-68 yr	Flu 180 mg/m^2, Mel 100 mg/m^2, TBI 200 cGy	2-yr OS: 53%, 2-yr PFS: 47%
Kalin et al., 2019 [58]	n = 68 Leukemias, MDS, lymphoma, aplastic anemia Median age, 57 yr; range, 20-69 yr	Flu 160 mg/m^2, Cy 60 mg/kg, TBI 400 cGy	1-yr OS: 61%, 1-yr PFS: 60%
Nonmyeloablative			
Fuchs et al., 2020 [22]	n = 186 Acute leukemias, MDS, lymphoma Median age, 58 yr; range, 20-70 yr	Cy 50 mg/kg, Flu 200 mg/m^2, TBI 200 cGy	2-yr OS: 46%, 2-yr PFS: 35%
Peffault de Lator et al., 2018 [59]	n = 26 Aplastic anemia Median age, 16 yr; range, 9-23 yr	Cy 120 mg/kg, Flu 120 mg/m^2, ATG 5 mg/kg, TBI 200 cGy	2-yr OS: 84%

Flu indicates fludarabine; Cy, cyclophosphamide; Mel, melphalan; TBI, total body irradiation; ATG, anti-thymocyte globulin.

Table 2
Suggested Indications for CBT in Hematologic Malignancies and Severe Aplastic Anemia

Disease	Stage, Risk, or Characteristic	Recommendation
Acute leukemia	High risk CR1 or CR2$^+$; MRD$^+$; not in remission	CB suitable. High- or intermediate-intensity conditioning preferred. Consider clinical trial.
Chronic myelogenous leukemia	CP1 with tyrosine-kinase inhibitor failure or intolerance; second CP; accelerated phase	CB suitable
MDS	IPSS-R [60]: intermediate risk, high risk, and very high risk	
Aggressive NHL	CR1 not suitable for other therapy; second or subsequent CR	CB suitable. High- or intermediate-intensity conditioning preferred
CLL/prolymphocytic leukemia	High-risk disease (eg, p53 mutation, relapse after autologous transplantation or BTK inhibitor, Ritcher's transformation)	CB suitable. Recommend intermediate/NMA conditioning
Multiple myeloma/ plasma cell leukemia	High-risk or advanced disease	Consider in clinical trials. Recommend intermediate/ NMA conditioning
Hodgkin lymphoma	Advanced disease in either CR/ PR.	
Follicular lymphoma/ indolent lymphoma	Failure of initial therapy in CR1$^+$ or PR1$^+$ or beyond	CB suitable. Recommend intermediate/NMA conditioning
Aplastic anemia	After failure of first immunosuppressive regimen	Consider if on clinical trial or in an experienced center
Other MPD	Advanced disease	

CP, chronic phase; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; CR, complete remission; PR, partial remission; IPSS-R, revised International Prognostic Scoring System.

Table 3
Suggested Criteria for Conditioning Intensities

Variable	High Intensity	Intermediate Intensity	Nonmyeloablative
Age, yr	≤40	≤65	≤70
KPS score	≥90	≥80	≥70
Cardiac, %	≥50	≥50	≥40
Pulmonary, %	DLCO (Hb)/FEV_1 ≥60		DLCO (Hb)/FEV_1 ≥50 with no O_2 requirement
Renal	Creatinine clearance ≥60 mL/min	Creatinine clearance ≥50 mL/min	Creatinine clearance ≥50 mL/min
Hepatic	AST/ALT ≤3 × ULN; bilirubin ≤2 × ULN		AST/ALT ≤5 × ULN; bilirubin ≤2.5 × ULN
HCT-CI	HCT-CI should be considered in selection of conditioning intensity. However, additional data are required to determine the maximum acceptable HCT-CI score for high- or intermediate-intensity conditioning regimens.		
Exclusions	Previous autologous or allogeneic transplantation (any conditioning intensity)	Previous transplantation with high-dose conditioning	—

KPS indicates Karnofsky Performance Status; FEV_1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lungs for carbon monoxide; AST, aspartate aminotransferase; ALT, alanine transaminase; ULN, upper limit of normal.

incidence of chronic GVHD (cGVHD) after CBT can also be beneficial, given the association of cGVHD with significant disability and impaired quality of life [12].

FAQ2: What characteristics may make a patient a poor candidate for CBT?

CBT using low-cell dose grafts risks delayed or failed engraftment. Therefore, CB might not be an ideal graft source for patients with access to only smaller units and who likely will not tolerate prolonged cytopenias, especially those who have active infections, have multiple comorbidities, are refractory to platelet transfusions, or of advanced age [13-15]. In addition, standard immunoprophylaxis uses calcineurin inhibitors, and sustained therapeutic drug levels early post-transplantation are required to prevent severe acute GVHD. These medications may be difficult to administer safely in patients with significant baseline renal impairment (glomerular filtration rate <50 mL/minute) or other risk factors for renal toxicity [16]. Patients who come to transplantation without previous cytotoxic chemotherapy, such as those with myelodysplasia and myeloproliferative diseases, and patients with splenomegaly also are at increased risk of graft failure [17,18].

FAQ3: What are the common elements of successful CBT conditioning regimens that facilitate engraftment?

A successful conditioning regimen for CBT used a combination of agents with additive immunosuppressive properties that can overcome the histocompatibility barrier to engraftment of an HLA-mismatched graft. Historically, the most commonly used platform has included a combination of cyclophosphamide, fludarabine, and various doses of total body irradiation (TBI) [17,19-22]. These conditioning regimens, in combination with well-selected CB grafts, have resulted in high rates of neutrophil and platelet engraftment in recently reported CBT series (Table 1). Compared with chemotherapy only-regimens, TBI-containing regimens have been associated with enhanced engraftment, especially in the setting of HLA disparity [23].

FAQ4: Should antithymocyte globulin (ATG) be included in the conditioning regimen?

Multiple studies have now reported that ATG-based CBT performed as treatment for hematologic malignancies has been associated with increased mortality due to delayed T cell recovery [24-29]. Consequently, ATG inclusion is no longer recommended in such patients. Centers are investigating alternatives to the use of ATG that would facilitate engraftment without impairing immune reconstitution. Fludarabine-based highly immunosuppressive regimens have been associated with high rates of engraftment and robust T cell immune reconstitution in adults without the use of ATG [19,30,31]. Dose escalation of low-dose TBI has been used successfully in place of ATG, as well [32,33]. For patients undergoing CBT for hematologic malignancies who have not received recent immunosuppressive chemotherapy, low-dose fludarabine (eg, 25 mg/m^2/day for 3 doses) is now being investigated 2 to 3 weeks before admission to reduce the risk of graft rejection (Barker JN, personal communication, 2020). Another strategy that is especially relevant to patients with bone marrow failure syndromes involves administration of ATG weeks before the conditioning regimen with pharmacokinetic-guided dosing to ensure recipient immunosuppression while also ensuring that peritransplantation and post-transplantation in vivo T cell depletion is avoided [34,35].

FAQ5: What factors should be considered when selecting conditioning intensity in CBT recipients with hematologic malignancies?

Indications for CBT are generally similar to those for other stem cell sources and according to the American Society for Transplantation and Cellular Therapy guidelines for allogeneic transplantation. The choice of conditioning intensity should be informed by the disease risk and remission status of the patient's malignancy and the patient's risk of transplantation-related mortality (TRM) or morbidity with higher-intensity regimens. Notably, CBT recipients may be at greater risk of TRM after high-intensity conditioning compared with recipients of allografts from adult donors, owing to the heavily pretreated patient population frequently selected to undergo CBT, prolonged post-transplantation neutropenia, and calcineurin inhibitor-based immunosuppression.

As with other types of allografts, the revised Disease Risk Index (rDRI) [36], which is based on diagnosis, disease status/staging, and cytogenetics, is an independent risk factor for progression-free survival (PFS) in patients undergoing CBT [37]. More specifically, in patients with acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphoblastic leukemia (ALL), important factors to consider when assessing relapse risk post-CBT include the presence of high-risk cytogenetic and molecular abnormalities [38] and the presence of MRD [7]. Although not specifically examined in CBT recipients, existing evidence supports myeloablative conditioning in patients with acute leukemia, although the benefit

of conditioning intensity in patients with MDS is less clear [39,40]. Also, patients with AML, MDS, or ALL with MRD following induction or consolidation can benefit from myeloablative CBT [7,41], especially when combined with double-unit grafts [42]. Recommended indications [3] and conditioning intensity according to diagnosis are shown in Table 2.

When judging a patient's risk of TRM after CBT, important patient characteristics to consider include age, Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), performance status, extent of previous therapy (eg, previous autologous transplantation or number of chemotherapy regimens), organ function (especially pulmonary and renal impairment) and specific comorbidities. The HCT-CI is a critically important determinant of TRM after CBT [31,43,44]. Accordingly, HCT-CI score should be considered when determining regimen intensity (Table 3).

It is important to recognize that transplantation may be futile in patients with diagnoses with a high rDRI or with disease that is not in remission, as well as patients who are also older and/or have high HCT-CI scores and thus cannot tolerate intensive conditioning. Conversely, high disease-free survival has been observed in CBT recipients with low HCT-CI scores who thus may tolerate higher-intensity regimens if necessary [31].

FAQ6: What are the commonly used high-intensity conditioning regimens in CBT?

The most widely used high-intensity TBI conditioning regimen is cyclophosphamide 120 mg/kg, fludarabine 75 mg/m^2, and TBI 1320 cGy, which has shown acceptable overall survival (OS) and PFS in phase II studies and retrospective analyses [19,21,45] (Table 1). Other regimens that have been investigated include fludarabine and TBI (fludarabine 160 mg/m^2 and TBI 1350 cGy) and fludarabine, thiotepa, and TBI (fludarabine 160 mg/m^2, TBI 1350 cGy, and thiotepa 10 mg/kg) [46-48].

FAQ7: What are the commonly used intermediate-intensity conditioning regimens?

Regimens that are neither high-intensity nor nonmyeloablative vary in intensity (Table 1). At the higher end of the spectrum are regimens that are myeloablative but lower toxicity compared with high-dose TBI conditioning. The most common of these regimens is cyclophosphamide 50 mg/kg, fludarabine 150 mg/m^2, thiotepa 10 mg/kg, and TBI 400 cGy [8,9,31,49]. This regimen has been investigated predominately in adults up to age 60 years as an alternative to high-dose TBI conditioning, and a 3-year PFS of 76% has been reported in this patient population [8]. However, there are little available data on this regimen in patients age >60 years. Increased age is associated with increased TRM, and this regimen is poorly tolerated in patients with a high HCT-CI.

A treosulfan-based regimen that includes treosulfan 42 m/m^2, fludarabine 150 to 200 mg/m^2, and TBI 200 cGy is another alternative that has been associated with a 3-year PFS of 57% [50]. Treosulfan approval in the United States is expected in the near future. In this clinical trial, a fludarabine dose of 200 mg/m^2 was used in patients deemed at greater risk of graft failure, including those patients with MDS, myeloproliferative disorders, and leukemia if the last multiagent chemotherapy was given >3 months before transplantation. In other patients, the fludarabine dose was 150 mg/m^2.

Intermediate-intensity conditioning also includes chemotherapy-only myeloablative regimens. Of those, the combination of fludarabine with myeloablative doses of busulfan was limited by high rates of graft failure in adults [51,52]. However, improved outcomes have been observed with intensified busulfan-based regimens incorporating additional immunosuppressive chemotherapeutic agents or TBI [45,46,51,53,54]. Of those, the regimen of fludarabine 150 mg/m^2, thiotepa 5 mg/kg/day for 2 days, and i.v. busulfan 3.2 mg/kg/day for 3 days is commonly used by European centers, although this is typically in combination with ATG [45,46], which is no longer recommended.

Less intensive conditioning regimens include melphalan 140 mg/m^2 and fludarabine 180 mg/m^2. This regimen frequently been accompanied by in vivo T cell depletion with ATG [55]. Owing to the delay in immunologic recovery, ATG may be replaced with TBI or higher doses of melphalan to ensure engraftment [32,56].

Finally, at the lower end of the spectrum of intermediate intensity, the HOVON group has investigated a regimen based on the Minnesota nonmyeloablative (NMA) platform but with intensified TBI dosing (cyclophosphamide 60 mg/kg, fludarabine 160 mg/m^2, TBI 400 cGy). This HOVON regimen is associated with reliable engraftment, lack of autologous recovery, and promising disease control without excessive TRM [57,58].

FAQ8: What is the most commonly used NMA conditioning regimen?

The cyclophosphamide 50 mg/kg, fludarabine 200 mg/m^2, and TBI 200 cGy Minnesota regimen is the most well established NMA conditioning regimen (Table 1) [17,20,22]. Notably, the fludarabine dose is been reduced from the originally reported 200 mg/m^2 to 150 mg/m^2 by some investigators to mitigate the risk of neurotoxicity. Patients who are appropriate for NMA conditioning are older patients, patients with significant comorbidities, and patients with extensive previous treatment (eg, prior autologous transplantation) (Tables 2 and 3).

FAQ9: What conditioning regimens have been used in patients with severe aplastic anemia undergoing CBT?

CBT has been successful in the treatment of aplastic anemia, and most experience is in pediatrics. For adults, CBT can be considered, depending on transplantation center experience. In a phase II study, 26 patients with aplastic anemia (median age, 16 years; range, 9 to 23 years) who had an available CB unit with a cell dose of at least 4×10^7 total nucleated cells/kg underwent conditioning with cyclophosphamide 120 mg/kg, fludarabine 120 mg/m^2, ATG 5 mg/kg, and TBI 200 cGy. The 2-year OS was 84% [59] (Table 1). For other bone marrow failure syndromes or diseases of hematopoiesis, CBT should be limited to research trials or very experienced centers.

FUTURE CONSIDERATIONS

Although innovative intermediate-intensity regimens have demonstrated excellent clinical outcomes in dedicated CBT centers, it remains to be seen whether these regimens will have similar outcomes, and thus wider applicability, in programs that do not routinely perform CBT. Furthermore, composite outcomes, such as GRFS and patient quality of life, have become important factors in HCT. These outcomes have yet to be prospectively explored in CBT; multicenter trials are needed to address these questions.

ACKNOWLEDGMENTS

Financial disclosure: The authors have no financial conflicts of interest to disclose.

Conflict of interest statement: There are no conflicts of interest to report.

REFERENCES

1. Warlick ED, Peffault de Latour R, Shanley R, et al. Allogeneic hematopoietic cell transplantation outcomes in acute myeloid leukemia: similar

outcomes regardless of donor type. *Biol Blood Marrow Transplant*. 2015;21:357–363.
2. Barker JN, Byam CE, Kernan NA, et al. Availability of cord blood extends allogeneic hematopoietic stem cell transplant access to racial and ethnic minorities. *Biol Blood Marrow Transplant*. 2010;16:1541–1548.
3. Kanate AS, Majhail NS, Savani BN, et al. Indications for hematopoietic cell transplantation and immune effector cell therapy: guidelines from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow Transplant*. 2020;26:1247–1256.
4. Barker JN, Krepski TP, DeFor TE, Davies SM, Wagner JE, Weisdorf DJ. Searching for unrelated donor hematopoietic stem cells: availability and speed of umbilical cord blood versus bone marrow. *Biol Blood Marrow Transplant*. 2002;8:257–260.
5. Barker JN, Boughan K, Dahi PB, et al. Racial disparities in access to HLA-matched unrelated donor transplants: a prospective 1312-patient analysis. *Blood Adv*. 2019;3:939–944.
6. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the US registry. *N Engl J Med*. 2014;371:339–348.
7. Milano F, Gooley T, Wood B, et al. Cord-blood transplantation in patients with minimal residual disease. *N Engl J Med*. 2016;375:944–953.
8. Barker JN, Devlin SM, Naputo KA, et al. High progression-free survival after intermediate intensity double unit cord blood transplantation in adults. *Blood Adv*. 2020;4:6064–6076.
9. Sharma P, Purev E, Haverkos B, et al. Adult cord blood transplant results in comparable overall survival and improved GRFS vs matched related transplant. *Blood Adv*. 2020;4:2227–2235.
10. Baron F, Labopin M, Ruggeri A, et al. Impact of donor type in patients with AML given allogeneic hematopoietic cell transplantation after low-dose TBI-based regimen. *Clin Cancer Res*. 2018;24:2794–2803.
11. Zheng CC, Zhu XY, Tang BL, et al. Clinical separation of cGvHD and GvL and better GvHD-free/relapse-free survival (GRFS) after unrelated cord blood transplantation for AML. *Bone Marrow Transplant*. 2017;52:88–94.
12. Fatobene G, Storer BE, Salit RB, et al. Disability related to chronic graft-versus-host disease after alternative donor hematopoietic cell transplantation. *Haematologica*. 2019;104:835–843.
13. Konuma T, Tsukada N, Kanda J, et al. Comparison of transplant outcomes from matched sibling bone marrow or peripheral blood stem cell and unrelated cord blood in patients 50 years or older. *Am J Hematol*. 2016;91:E284–E292.
14. Peffault de Latour R, Brunstein CG, Porcher R, et al. Similar overall survival using sibling, unrelated donor, and cord blood grafts after reduced-intensity conditioning for older patients with acute myelogenous leukemia. *Biol Blood Marrow Transplant*. 2013;19:1355–1360.
15. Tanaka M, Miyamura K, Terakura S, et al. Comparison of cord blood transplantation with unrelated bone marrow transplantation in patients older than fifty years. *Biol Blood Marrow Transplant*. 2015;21:517–525.
16. Gutgarts V, Sathick IJ, Zheng J, et al. Incidence and risk factors for acute and chronic kidney injury after adult cord blood transplantation. *Biol Blood Marrow Transplant*. 2020;26:758–763.
17. Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, Miller JS, Wagner JE. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. *Blood*. 2003;102:1915–1919.
18. Yuasa M, Yamamoto H, Kageyama K, et al. Splenomegaly negatively impacts neutrophil engraftment in cord blood transplantation. *Biol Blood Marrow Transplant*. 2020;26:1689–1696.
19. Barker JN, Fei M, Karanes C, et al. Results of a prospective multicentre myeloablative double-unit cord blood transplantation trial in adult patients with acute leukaemia and myelodysplasia. *Br J Haematol*. 2015;168:405–412.
20. Brunstein CG, Barker JN, Weisdorf DJ, et al. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplantation outcomes in 110 adults with hematologic disease. *Blood*. 2007;110:3064–3070.
21. Barker JN, Weisdorf DJ, DeFor TE, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. *Blood*. 2005;105:1343–1347.
22. Fuchs EJ, O'Donnell PV, Eapen M, et al. Double unrelated umbilical cord blood versus HLA-haploidentical bone marrow transplantation (BMT CTN 1101). *Blood*. 2021;137(3):420–428. https://doi.org/10.1182/blood.2020007535. accessed January 2021.
23. Nakasone H, Fuji S, Yakushijin K, et al. Impact of total body irradiation on successful neutrophil engraftment in unrelated bone marrow or cord blood transplantation. *Am J Hematol*. 2017;92:171–178.
24. Brown JA, Stevenson K, Kim HT, et al. Clearance of CMV viremia and survival after double umbilical cord blood transplantation in adults depends on reconstitution of thymopoiesis. *Blood*. 2010;115:4111–4119.
25. Brunstein CG, Weisdorf DJ, DeFor T, et al. Marked increased risk of Epstein-Barr virus-related complications with the addition of antithymocyte globulin to a nonmyeloablative conditioning prior to unrelated umbilical cord blood transplantation. *Blood*. 2006;108:2874–2880.
26. Admiraal R, van Kesteren C, Jol-van der Zijde CM, et al. Association between anti-thymocyte globulin exposure and $CD4^+$ immune reconstitution in paediatric haemopoietic cell transplantation: a multicentre, retrospective pharmacodynamic cohort analysis. *Lancet Haematol*. 2015;2:e194–e203.
27. Pascal L, Mohty M, Ruggeri A, et al. Impact of rabbit ATG-containing myeloablative conditioning regimens on the outcome of patients undergoing unrelated single-unit cord blood transplantation for hematological malignancies. *Bone Marrow Transplant*. 2015;50:45–50.
28. Ballen K, Logan BR, Chitphakdithai P, et al. Unlicensed umbilical cord blood units provide a safe and effective graft source for a diverse population: a study of 2456 umbilical cord blood recipients. *Biol Blood Marrow Transplant*. 2020;26:745–757.
29. Pascal L, Tucunduva L, Ruggeri A, et al. Impact of ATG-containing reduced-intensity conditioning after single- or double-unit allogeneic cord blood transplantation. *Blood*. 2015;126:1027–1032.
30. Politikos I, Lavery JA, Hilden P, et al. Robust $CD4^+$ T-cell recovery in adults transplanted with cord blood and no antithymocyte globulin. *Blood Adv*. 2020;4:191–202.
31. Ponce DM, Sauter C, Devlin S, et al. A novel reduced-intensity conditioning regimen induces a high incidence of sustained donor-derived neutrophil and platelet engraftment after double-unit cord blood transplantation. *Biol Blood Marrow Transplant*. 2013;19:799–803.
32. DeFilipp Z, Li S, Avigan D, et al. A phase II study of reduced-intensity double umbilical cord blood transplantation using fludarabine, melphalan, and low-dose total body irradiation. *Bone Marrow Transplant*. 2020;55:804–810.
33. Salit RB, Milano F, Gutman JA, et al. Umbilical cord blood transplant patients at high risk of graft rejection achieve early full donor chimerism when 300 cGy is used in the reduced intensity conditioning regimen. *Blood*. 2013;122:697.
34. Admiraal R, Lindemans CA, van Kesteren C, et al. Excellent T-cell reconstitution and survival depend on low ATG exposure after pediatric cord blood transplantation. *Blood*. 2016;128:2734–2741.
35. Admiraal R, Boelens JJ. Antithymocyte globulin: steps toward individualized dosing. *Biol Blood Marrow Transplant*. 2018;24:633–634.
36. Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. *Blood*. 2014;123:3664–3671.
37. Paviglianiti A, Ruggeri A, Volt F, et al. Evaluation of a disease risk index for adult patients undergoing umbilical cord blood transplantation for haematological malignancies. *Br J Haematol*. 2017;179:790–801.
38. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129:424–447.
39. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35:1154–1161.
40. Kröger N, Iacobelli S, Franke GN, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: a prospective randomized phase III study of the EBMT (RICMAC trial). *J Clin Oncol*. 2017;35:2157–2164.
41. Oliver DC, Cassaday RD, Ermoian RP, Dahlberg A, Delaney C, Milano F. Myeloablative cord blood transplantation yields excellent disease free survival in patients with acute lymphoblastic leukemia. *Blood*. 2016;128:4693.
42. Balligand L, Galambrun C, Sirvent A, et al. Single-unit versus double-unit umbilical cord blood transplantation in children and young adults with residual leukemic disease. *Biol Blood Marrow Transplant*. 2019;25:734–742.
43. Salit RB, Oliver DC, Delaney C, Sorror ML, Milano F. Prognostic value of the Hematopoietic Cell Transplantation Comorbidity Index for patients undergoing reduced-intensity conditioning cord blood transplantation. *Biol Blood Marrow Transplant*. 2017;23:654–658.
44. Adachi Y, Ukai S, Sagou K, Fukushima N, Ozeki K, Kohno A. Promising outcome of umbilical cord blood transplantation in patients with multiple comorbidities. *Biol Blood Marrow Transplant*. 2018;24:1455–1462.
45. Sanz J, Wagner JE, Sanz MA, et al. Myeloablative cord blood transplantation in adults with acute leukemia: comparison of two different transplant platforms. *Biol Blood Marrow Transplant*. 2013;19:1725–1730.
46. Sanz J, Boluda JC, Martín C, et al. Single-unit umbilical cord blood transplantation from unrelated donors in patients with hematological malignancy using busulfan, thiotepa, fludarabine and ATG as myeloablative conditioning regimen. *Bone Marrow Transplant*. 2012;47:1287–1293.
47. Kanda J, Rizzieri DA, Gasparetto C, et al. Adult dual umbilical cord blood transplantation using myeloablative total body irradiation (1350 cGy) and fludarabine conditioning. *Biol Blood Marrow Transplant*. 2011;17:867–874.
48. Anand S, Thomas S, Corbet K, et al. Adult umbilical cord blood transplantation using myeloablative thiotepa, total body irradiation, and fludarabine conditioning. *Biol Blood Marrow Transplant*. 2017;23:1949–1954.
49. Sharma P, Pollyea DA, Smith CA, et al. Thiotepa-based intensified reduced-intensity conditioning adult double-unit cord blood hematopoietic stem cell transplantation results in decreased relapse rate and improved survival compared with transplantation following standard reduced-intensity conditioning: a retrospective cohort comparison. *Biol Blood Marrow Transplant*. 2018;24:1671–1677.

50. Milano F, Gutman JA, Deeg HJ, et al. Treosulfan-based conditioning is feasible and effective for cord blood recipients: a phase 2 multicenter study. *Blood Adv*. 2020;4:3302–3310.
51. Mehta RS, Di Stasi A, Andersson BS, et al. The development of a myeloablative, reduced-toxicity, conditioning regimen for cord blood transplantation. *Clin Lymphoma Myeloma Leuk*. 2014;14:e1–e5.
52. Horwitz ME, Morris A, Gasparetto C, et al. Myeloablative intravenous busulfan/fludarabine conditioning does not facilitate reliable engraftment of dual umbilical cord blood grafts in adult recipients. *Biol Blood Marrow Transplant*. 2008;14:591–594.
53. Yamamoto H, Uchida N, Yuasa M, et al. A novel reduced-toxicity myeloablative conditioning regimen using full-dose busulfan, fludarabine, and melphalan for single cord blood transplantation provides durable engraftment and remission in nonremission myeloid malignancies. *Biol Blood Marrow Transplant*. 2016;22:1844–1850.
54. Abedin S, Peres E, Levine JE, Choi S, Yanik G, Couriel DR. Double umbilical cord blood transplantation after novel myeloablative conditioning using a regimen of fludarabine, busulfan, and total lymphoid irradiation. *Biol Blood Marrow Transplant*. 2014;20:2062–2066.
55. Cutler C, Stevenson K, Kim HT, et al. Double umbilical cord blood transplantation with reduced intensity conditioning and sirolimus-based GVHD prophylaxis. *Bone Marrow Transplant*. 2011;46:659–667.
56. Ballen KK, Spitzer TR, Yeap BY, et al. Double unrelated reduced-intensity umbilical cord blood transplantation in adults. *Biol Blood Marrow Transplant*. 2007;13:82–89.
57. Somers JA, Braakman E, van der Holt B, et al. Rapid induction of single donor chimerism after double umbilical cord blood transplantation preceded by reduced-intensity conditioning: results of the HOVON 106 phase II study. *Haematologica*. 2014;99:1753–1761.
58. Kalin B, ter Borg M, Wijers R, et al. Double umbilical cord blood transplantation in high-risk hematological patients: a phase II study focusing on the mechanism of graft predominance. *Hemasphere*. 2019;3:e285.
59. Peffault de Latour R, Chevret S, Jubert C, et al. Unrelated cord blood transplantation in patients with idiopathic refractory severe aplastic anemia: a nationwide phase 2 study. *Blood*. 2018;132:750–754.
60. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120:2454–2465.