Cord blood transplantation for bone marrow failure syndromes: state of art

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Abstract: Hematopoietic stem cell transplantation (HSCT) and immunosuppressive therapy (IST) represent the milestones of the treatment algorithm for idiopathic and inherited bone marrow failure (BMF) disorders. However, patients lacking a suitable donor or failing IST still have a poor prognosis. Cord blood transplantation (CBT) has extended the possibility of HSCT for many patients in case of the absence of an eligible donor, and although in the last years, this procedure is less used in several hematological diseases, it remains an option for the treatment of patients with BMF syndromes. Nevertheless, optimization of conditioning regimen and cord blood unit selection is warranted to reduce the risk of graft failure and transplant-related mortality. This review summarizes the state of art of CBT in the field of BMF diseases, focusing on historical and recent issues in idiopathic aplastic anemia and inherited disorders.

Keywords: Cord blood transplantation (CBT); bone marrow failure (BMF); severe aplastic anemia (SAA); Fanconi anemia (FA)

Introduction

Bone marrow failure (BMF) disorders are rare diseases, which can occur in children and adults, as a consequence of idiopathic [aplastic anemia (AA)] or inherited disorders [such as Fanconi anemia (FA), Diamond-Blackfan anemia (DBA), dyskeratosis congenita (DC), and others]. Hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-matched sibling donor (MSD) using bone marrow (BM) as stem cell source, represents the first-line treatment option for all patients aged less than 40 with either inherited or acquired BMF (1-4). Appropriate classification and diagnosis of patients is mandatory, because of its impact on clinical management, choice of stem cell source and preparative regimen in case of HSCT, estimated risk for complications, including future cancers, genetic and medical counselling as well as follow-up of patients and

family members (5).

Immunosuppressive therapy (IST) is the treatment of choice in case of lack of a sibling donor and for patients diagnosed with idiopathic BMF over 40 years of age (2,6). Growth factors, corticosteroids, and androgens represent the main alternative, non-transplant therapies for inherited BMF but results are often heterogeneous (5,7-12).

In historical cohorts, the use of alternative donors increased the risk of poor outcomes (4,13,14). However, more recently, with advances in HLA typing and a better choice of conditioning regimens as well as the improvement in supportive care, long-term survival after an HSCT from unrelated donors, has significantly improved (15,16). Therefore, in case of a lack of a suitable BM donor or failure of first-line IST, other alternative stem cell sources and donors can be considered. In this setting, cord blood

(CB) offers an alternative, rapidly available, source of hematopoietic stem cells (HSC).

In this special issue, we have reviewed outcomes and results of principal studies concerning cord blood transplantation (CBT) in the setting of both idiopathic and inherited BMF disorders, addressing particular attention to FA.

First proof of concept

The first data on the infusion of CB cells in humans (17) arose from a partnership among three teams: E Gluckman from Hospital Saint Louis in Paris (France) who was working on the importance of attenuated dose conditioning regimens for FA patients (18); AD Auerbach from the Rockefeller University in New York (USA), who designed a method for prenatal diagnosis in FA (19); HE Broxmeyer from Indiana University in Indianapolis (USA), who studied hematopoietic progenitors in CB (20). Thus, the first CBT was performed at Saint Louis Hospital of Paris on a 5-year-old boy diagnosed with a BMF secondary to FA (17). Graft consisted of cryopreserved CB cells from the unaffected HLA-identical sister. The patient, conditioned with low-dose cyclophosphamide (Cy) and limited-field thoraco-abdominal irradiation, developed no major complication after CBT and reconstituted a month later with complete donor chimerism, maintaining a full immunological and hematological reconstitution 30 years after CBT (21,22). This was the first proof of concept that the CB of a single newborn is sufficient to reconstitute the host lympho-hematopoietic compartment definitely. After this first success, CB banks (CBB) arose all around the world for the gathering and cryopreservation of CB for allogeneic purposes (23).

The principal pragmatic advantages of using CB as stem cells source are the absence of risks for donors (and mothers), the reduced risk of transmitting infections, the relative prompt availability for immediate use (due to the ability to preserve fully tested and HLA-typed stem cell grafts in the frozen state). The Eurocord experience reported several studies focusing on outcomes of CBT in BMF since the late 1990s (24,25).

CBT in acquired severe AA (SAA)

Significant progress on the management of SAA has largely improved outcomes of patients who failed or relapsed after IST.

In young patients without MSD, current recommendations are to perform HSCT after the failure of one course of IST, if a fully matched unrelated donor (MUD) is available (26-29). In adults, an alternative donor HSCT is a considerable option as second-line therapy, for patients who fail one or two courses of IST (24,28).

Unlikely, for many patients, especially those from minority ethnic groups or more heterogeneous populations, it is impossible to identify a suitable BM unrelated donor. The possibility of an unrelated CBT (UCBT), as alternative graft option, has been thrivingly explored in patients with hematologic malignancies (30-35). However, only a few series are reported for SAA and other BMF. In primary reports incidence of graft failure was incredibly high and survival outcomes extremely poor (25), whereas since 2000 successful UCBTs for SAA have been reported only by few small series and case reports (36-38).

In 2008 the Japanese group reported on a cohort of 31 patients with a 2-year overall survival (OS) of 41% (39).

In a retrospective analysis from Eurocord on 71 patients diagnosed with SAA [9 with paroxysmal nocturnal hemoglobinuria (PNH)] who received a single UCBT (n=57, 80%) or double UCBT (n=14, 20%) the 3-year OS was 37% and 43% after double UCBT (40). In multivariate analysis, the only factor influencing engraftment and survival was pre-freezing total nucleated cell (TNC) dose ($>3.9\times10^7$/kg, P=0.05).

A more recent survey of the Japan Society for Hematopoietic Cell Transplantation compared results of UCBT (n=69) to 8/8 (n=101), 7/8 (n=65) or 6/8 (n=37)-matched unrelated bone marrow transplantation (UBMT) from 2002 to 2012 (41). This study showed similar survival rates for adults less than 40 years of age in each of four groups and worst results for UCBT in patients older than 40 (47%, 64%, 64% and 75% of 3-year OS for UCBT, 8/8, 7/8 and 6/8 UBMT respectively), suggesting that the choice of UCBT for older adults should cautiously be considered in case of lacking an 8/8, or 7/8 matched adult donor. Those studies justify the use of double UCBT if necessary in the setting of SAA. However, graft failure remains a major concern in this particularly high-risk population and it is highly recommended to achieve the adequate cell dose threshold when considering CB units.

Results of a prospective phase II study (NCT01343953, APCORD Trial), evaluating the efficacy and safety of UCBT in refractory SAA patients, have been recently published on behalf of Francophone Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) (42). Twenty-six patients were analyzed (out of 29 included).

The conditioning regimen consisted of fludarabine (Flu) 30 mg/m^2 from day –6 to day –3, Cy 30 mg/kg from day –6 to day –3, anti-thymocyte globulin (ATG) 2.5 mg/kg from day –3 to day –2, 2-Gray total body irradiation (TBI) on day –2. An injection of anti-CD20 at the dose of 150 mg/m^2 was given at day +5 for prophylaxis of Epstein Barr virus (EBV) reactivation. Graft versus host disease (GVHD) prophylaxis was performed with cyclosporine A (CsA) alone. The median age at CBT was 16 years [interquartile range (IQR), 9.3–23.4 years]. All patients received at least 1 course of IST before transplantation (2 courses, n=5–11) with a median time between diagnosis and transplantation of (12 months; IQR, 8.7–17.8 months). Median follow-up was 38.8 months (IQR, 29.9–53.8 months). One-year survival rate was 88.5% [95% confidence interval (CI), 69.8–97.6%]. One-year treatment-related mortality was 11.5% (95% CI, 2.4–30.2%). Three patients died before 1 year due to infections arising from non-engraftment (n=2) and GVHD (n=1), and a further patient died of severe chronic GVHD at 13.9 months, leading to a 2-year survival rate of 84.6% (95% CI, 71–100%).

The graft failure and the unacceptable risk of severe infections have been major pitfalls of UCBT in refractory SAA patients (39,40). The key role of TNC doses (>3.9×10^7/kg) in umbilical transplants as well as the use of a Flu/low-dose TBI-based conditioning regimen to improve engraftment and survival outcomes, was suggested by retrospective studies (40), The APCORD study prospectively confirmed the importance of controlling these factors (42).

For patients with SAA, CBT from an unrelated donor should be considered only in the setting of clinical trials, when a suitable BM donor is not available and after the failure of IST. To avoid the risk of graft failure due to an allogeneic immunization, donor-specific antibodies should be screened before transplantation (43-45). One or two CB units may be used in SAA to reach at least 4×10^7 cryopreserved nucleated cells/kg with less than 2 of 6 HLA mismatches between the unit and the patient. Furthermore, particular attention should be paid to patient cytomegalovirus (CMV) status since CMV seronegativity is generally easier to manage. The importance of preventing infections and the availability of high-quality supportive care platforms are key elements for the success of this type of procedure, which should only be carried out in experienced centers.

CBT in inherited BMF syndromes

FA

FA is a rare inherited disorder characterized by congenital abnormalities and genomic instability responsible for progressive BMF, predisposition to solid and hematological malignancies, including acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and squamous cell carcinoma (SCC) (46,47). Although phenotypically different, most FA patients develop hematologic abnormalities within the natural history of their disease. Those abnormalities may range from mild hematologic changes not requiring therapeutic intervention, to the development of severe BMF or myeloid neoplasia, needing HSCT to restore the normal hematopoiesis (46). During the last decades, improvements of FA-HSCT conditioning regimens and advances in transplant procedures (e.g., more accurate HLA typing, graft manipulation, better supportive care, etc.) have drastically ameliorated the prognosis of FA patients (48,49). Reduction of radiation and chemotherapy doses, with the ideation of new reduced-intensity conditioning regimens (46,48), incorporation of Flu to preparative regimens (49,50), *in vivo* and/or *ex vivo* T cell depletion of allografts (51), were able to decrease the treatment-related mortality enhancing the engraftment and improving survival (48).

European Group for Blood and Marrow Transplantation (EBMT) retrospectively analyzed results of UCBT in 93 FA patients transplanted worldwide between 1994 and 2005 (14). The median age at transplantation was 8.6 years. The majority of patients received an HLA mismatched CBT (one mismatch in 35 cases and more than two mismatches in 45 cases). Sixty-one percent of patients received Flu within the conditioning regimen. The cumulative incidence function (CIF) neutrophil recovery was 60%±5% at day +60. The CIF of acute and chronic GVHD was 32.5% and 16%, respectively. The 2-year OS was 40%±5%. In the multivariate analysis Flu, a high number of TNC and negative recipient CMV serology were associated with favorable outcomes (14).

More recent reports, principally on small single-center experiences, show dismal results, namely high risk of graft failure, especially due to an incomplete HLA matching (52-54).

MacMillan *et al.* analyzed outcomes of 130 FA patients

undergoing alternative donor HSCT (99 receiving BM and 31 receiving CB as graft source) (55). In this study conditioning regimens changed over the time, but since 2006, irrespective of graft source, all patients (48 out of 130) received TBI (300 cGy), Cy (10 mg/kg/day for 4 days), Flu (35 mg/m^2/day for 4 days) horse ATG (30 mg/kg/day for 5 days), with CsA and mycophenolate mofetil (MMF) for GVHD prophylaxis. For the entire cohort, the probability of OS was 63% (95% CI, 54–71%) at 1 year and 58% (95% CI, 49–59%) at 5 years. The CIF of neutrophil recovery was 90% (95% CI, 84–95%) at day +30 and the use of CB was associated with a lower probability of engraftment compared with BM MUD, however, this outcome was strongly influenced by the type of conditioning regimen. For 46 recipients of the Flu/TBI 300 cGy-based conditioning regimen, neutrophil recovery was similar in recipients of BM and CB. The CIF of grade II–IV and grade III–IV acute GVHD was 20% (95% CI, 13–27%) and 9% (95% CI, 4–14%), with a similar likelihood for patients receiving a mismatched unrelated BM donor 7/8 HLA-matched T-cell-depleted BM and 4–6/6 HLA-matched CB.

To date, the outcomes of FA patients undergoing CBT versus BMT have not formally compared yet. However, the evidence is that the use of Flu is associated with better survival in spite of stem cell source (14,49), suggesting that this molecule acts as an immune suppressive agent, and enhances the engraftment without increasing extra-medullary toxicity.

In most reports, the use of CB unit with two or more HLA disparities in FA is associated with a lower probability of neutrophil recovery, decreased survival, or unacceptable rate of GVHD (14,52). For this reason, in this context, only one CB unit with no more than one mismatch is recommended (28).

Thus, UCBT, using a specific conditioning regimen disease-adapted, is indicated in FA patients who lack an HLA-matched unrelated BM donor. However, CB unit should be carefully selected, basing on HLA matching and TNC.

Inherited BMF other than FA

Until recently, outcomes of HSCT in other type of inherited BMF syndromes, such as in the context of DC, Shwachman-Diamond syndrome (SDS), DBA, etc. have been discouraging because of the high risk of transplant-related morbidity, including graft failure, GVHD, infectious complications and the propensity to develop organ toxicity

(26,56-58).

In 2011, Eurocord reported on an analysis of 64 patients diagnosed with inherited BMF disorders other than FA receiving related (n=20) CBT and non-related (n=44) CBT (59). Diagnoses were DBA (21 patients), congenital amegakaryocytic thrombocytopenia (16 patients), DC (8 patients), SDS (2 patients), severe congenital neutropenia (16 patients) and unclassified (1 patient). The group who received the related CBT engrafted at day 60 in 95% of cases. The median number of TNC infused was 5×10^7/kg. Only two patients had grade II–IV acute GVHD, while the 2-year CIF of chronic GVHD was 11%, and the 3-year OS rate was 95%. In contrast, among patients who received grafts from unrelated donors, the CIF of neutrophil recovery was 55% at day 60 although the median number of infused TNC was 6.1×10^7/kg. Also, the 100-day CIF of grade II–IV acute GVHD was 24%, and the 2-year CIF of chronic GVHD was 53%, for a 3-year OS rate of 61%. In this group age less than 5 years (P=0.01) and more than 6.1×10^7/kg TNC (P=0.05) were factors associated with a better OS.

Generally speaking, HSCT from MSD remained the preferred choice, and very sporadic series are reported for each disease category to make any general recommendation. However, although retrospective, Eurocord studies provide evidence that in these particularly high-risk patients, related CBT can be associated with excellent results, while UCBT outcomes may be improved by an increasing of TNC dose and better HLA matching.

Specific situations: CBT from a matched related donor for children with BMF

Eurocord analysed, in partnership with Severe Aplastic Anemia Working Party (SAAWP) of the EBMT, the outcomes of 117 children and young adults diagnosed with acquired and inherited BMF, receiving a related HLA-identical CBT (60).

In this series, 82 patients received a single CB unit and 35 received a mixed graft (CB and BM cells from the same donor). The median age at transplantation was 6.7 years.

The CIF of neutrophil recovery (day 60) was 88.8% (95% CI, 83.1–94.9%) with a median time to engraftment of 21 days (range, 7–105 days). The 100-day CIF of acute grade II–IV GVHD was 15.2% (95% CI, 9.8–23.6%) and the 7-year CIF of chronic GVHD was 14.5% (95% CI, 8.6–24.2%).

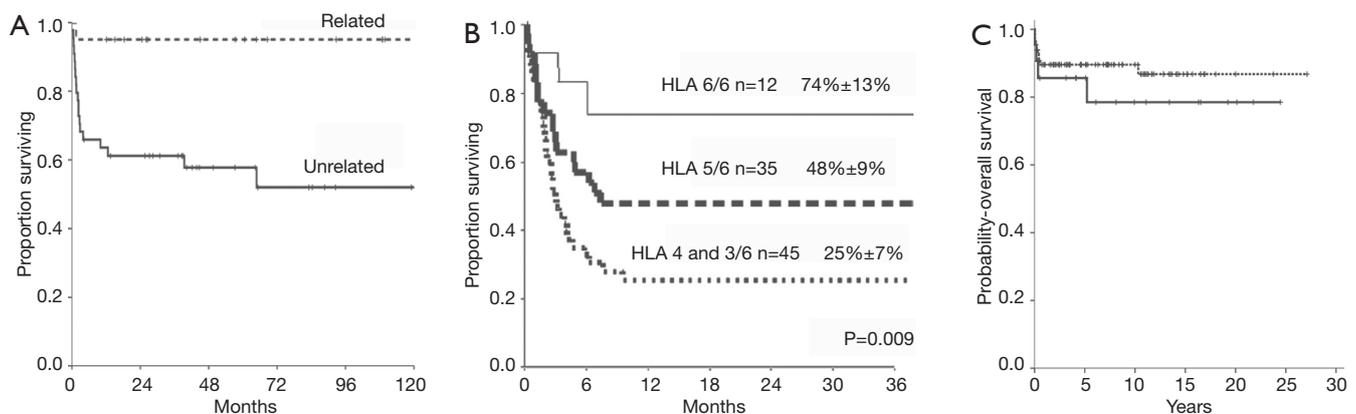With a median follow up of 7.2 years (1.5 months to

Figure 1 Survival outcomes of BMF patients receiving CBT. (A) OS of patients with inherited BMF other than Fanconi anemia receiving a related or an unrelated CBT (29); (B) OS of patients with Fanconi anemia receiving an unrelated CBT (23); (C) OS of patients with inherited (dotted line) and acquired (solid line) BMF receiving a related CBT (60). HLA, human leukocyte antigen; OS, overall survival; BMF, bone marrow failure; CBT, cord blood transplantation.

27.1 years), 7-year OS for the whole population was 87.9% (95% CI, 80.8–92.6%), 89% for inherited and 81% for acquired (P=0.66).

This study confirmed that CBT from an HLA-identical sibling donor could be a good option for patients with BMF since it is associated with excellent survival outcomes and low risk of GVHD and graft failure. In this setting collecting CB unit at the birth of a new sibling, especially in case of inherited BMF, should be strongly recommended.

Table 1 summarizes the main retrospective and prospective studies on CBT in BMF whereas figure 1 shows principal survival outcomes.

Emerging strategies and ongoing trials

The last EBMT activity survey, based on 2017 data and describing the status of HSCT in Europe and affiliated countries, reported on general decreasing use of CBT, mainly because of a growing number of haploidentical HSCT (61).

Of interest, in BMF, the whole number of patients receiving an allogeneic HSCT is slightly decreasing, and the number of CBT performed is very low (14 in 14 transplant centers). Such a change may be explained by the use of thrombopoietin (TPO) analogs in refractory AA patients. In spite of these changing trends in transplant activities a number of clinical trials, concerning the use of CB in patients diagnosed with BMF are ongoing and still recruiting patients, particularly in the setting of SAA (NCT02838992, NCT02745717, NCT00604201,

NCT03173937, NCT01553461, NCT01586455).

Improving engraftment and promoting immune reconstitution are the main goals of new promising techniques, which are now entering clinical trials. Several strategies are in fact, object of study in order to increase the HSC dose of CB grafts.

Methods to enhance the homing to stem cell niches in the marrow have been variously investigated and still require extensive studies (62,63). In this setting, intra-bone infusion of CB cells may be beneficial in some contexts (64,65), even if this technique is far to be recommended.

Another evolving concept to promote CB engraftment is the expansion of HSCs by *ex vivo* or *in vivo* manipulations, concerning, for instance, the use of cytokines and growth factors in order to increase the progenitor compartment present in CB (66-68).

Earlier approaches concerned the use of culture media enriched with several cytokine combinations including TPO, granulocyte colony-stimulating factor (G-CSF), stem cell factor (SCF), erythropoietin (EPO), interleukin (IL)-3, IL-6, Fms-related tyrosine kinase 3 ligand (Flt-3L) (69-74). New strategies including insulin-like growth factor binding proteins, pleiotrophin, angiopoietin-like proteins, or novel combinations of mitogens are in the preclinical phase of study and need further refining before the development of clinical trials (75-77). Of interest, recently, a computerized modelling approach has been developed to select the optimal cytokine mix for the *ex vivo* expansion of CB stem cells (78).

The use of several molecules such as nicotinamide

Table 1 Principal studies reporting patients receiving a CBT for BMF

Author; type of study	Patients, n	Type of BMF	Median age, years (range)	Graft source (–/6 HLA)	Conditioning regimen	Survival	CIF PNN engraftment	CIF acute and chronic GVHD
Gluckman et al. NEJM 1997; retrospective (25)	N=147 all hematological diseases; N=26 BMF	N=7 SAA; N=16 FA; N=1 DC; N=2 BDA	6 (0.2–45)	All diseases: N=65 UCBT/N=78 rCBT; BMF: N=9 UCBT/N=17 rCBT	Heterogeneous	1-year OS rCBT: 63% (all diseases); 1-year OS UCBT: 29% (all diseases)	At 60 days: rCBT: 79%; UCBT: 87%	9% rCBT, 50% UCBT aGVHD
Lau et al. JHSCR 2001; retrospective (36)	2	SAA	17, 18	UCBT (4/6 HLA)	(I) Cy 50 mg/kg/d (day –1); ATG: 5 mg/kg (day –5 to –1); (II) Flu 1 mg/kg/d (day –5 to –1); ATG 5 mg/kg (day–5 to –1)	Both patients alive (fup 6 months)	Day 44 and day 37	No GVHD events
Mao et al. EJH 2005; retrospective (37)	9	SAA	24 [15–37]	Single and double UCBT (4/6, 5/6 or 6/6)	Cy 20 mg/kg/d day –6 to –4; ALG 40 mg/kg/d day –3 to –1	2-year OS 77% (7/9 patient alive, median fup 32 months)	88% at day 15	22% cGVHD. No aGVHD
Yoshimi et al. BBMT 2008; retrospective (39)	31	SAA	28 (0.9–72.3)	Single and double UCBT (4/6, 5/6 or 6/6)	Heterogeneous	2-year OS 41%	55% at day 30	17% grade II–IV aGVHD; 20% cGVHD
Gluckman et al. BBMT 2007; retrospective (14)	93	FA	8.6 [1–45]	Single and double UCBT (3/6, 4/6, 5/6 or 6/6)	Heterogeneous (61% Flu based)	2-year OS 40%	60% at day 60	32% grade II–IV aGVHD; 16% cGVHD
Peffault de Latour et al. BBMT 2011; retrospective (40)	71	SAA (N=61), PNH (N=9)	13 [2–68]	Single and double UCBT (3/6, 4/6, 5/6 or 6/6)	Heterogeneous	3-year OS 38%	51% at day 60	20% grade II–IV aGVHD; 18% cGVHD
Ayas et al. BBMT 2012; retrospective (53)	26 (N=19 UBMT and N=7 UCBT)	FA	7.8 (1.4–12.9)	Single and double UCBT (4/6, 5/6 or 6/6)	Cy 5 mg/kg/d (day –5 to –2); Flu 30 mg/m2/d (day –6 to –2); rATG 5 mg/kg/d (day –5 to –2)	2/7 patients alive at 19 months	3/7 engrafted at day 30	1/7 grade II aGVHD, 1/7 cGVHD
Jaing et al. JPHO 2014; retrospective (54)	3	FA	2 (0.8–4.3)	Single UCBT (5/6 or 6/6)	Flu 30 mg/m2/d (day –10 to –5); Cy 60 mg/kg/d (day –6 to –5); rATG 2.5 mg/kg/d (day –4 to –1)	5-year OS 100% (median fup 64 months)	100% at day 30	3/3 grade II aGVHD; 2/3 limited cGVHD

Table 1 (continued)

Table 1 (continued)

Author; type of study	Patients, n	Type of BMF	Median age, years (range)	Graft source (-/6 HLA)	Conditioning regimen	Survival	CIF PNN engraftment	CIF acute and chronic GVHD
MacMillan et al. Blood 2015; prospective (55)	130 (N=99 UBMT and N=31 UCBT)	FA	9 [1–48]	Single and double UCBT (4/6, 5/6 or 6/6)	Cy 10 mg/kg/d (day −6 to −3); hATG 30 mg/kg/d (day −6 to −1); TBI (3, 4.5 or 6 Gy in 1 day) + Flu 35 mg/m²/d (day −6 to −2) in 107 patients	1-year OS 63% (entire cohort)	90% at day 40 (entire cohort)	20% grade II–IV aGVHD; 10% cGVHD (entire cohort)
Kuwatsuka et al. BBMT 2016; retrospective (41)	272 (203 UBMT and 69 UCBT)	SAA	49 for UCBT	203 UBMT; 69 single UCBT (4/6, 5/6 or 6/6)	Heterogeneous (mainly Flu/Mel or Flu/Cy based) rATG only in 3 patients	3-year OS for UCBT 69%	68% at day 28	32% grade II–IV aGVHD; 21% cGVHD
Peffault de Latour et al. Blood 2018; prospective (42)	26	SAA	16 (9.3–23.4)	Single and double UCBT (4/6, 5/6 or 6/6)	Flu 30 mg/m2/d (day −6 to −3); Cy 30 mg/kg/d (day −6 to −3); rATG 2.5 mg/kg/d day −3, −2; TBI (2 Gy day −2)	1-year OS 88.5%	88% at day 60	1/26 aGVHD; 1/26 cGVHD
Bizzetto et al. Hematologica 2011; retrospective (59)	64	Inherited BMF non FA (N=21 DBA, N=16 CAT, N=8 DC, N=2 SDS, N=16 CN, N=1 unclassified)	5 (0.3–26)	N=20 rCBT; N=44 UCBT	Heterogeneous	3-year OS rCBT: 95% UCBT: 61%	At day 60: rCBT: 95%; UCBT: 55%	rCBT: 10% II–IV aGVHD and 11 cGVHD UCBT: 24% II–IV aGVHD; 53% cGVHD
Pagliuca et al. BBMT 2017; retrospective (60)	117 (inherited and acquired BMF, related HLA identical CBT)	N= 20 SAA; N=48 FA; N=2 SDS; N=3 DC; N=5 CAT; N=27 DBA; N=4 CN; N=8 unclassified	6.7 [1–16]	N=82 single rCBT; N=35 rCBT + rBMT	Heterogeneous	7-year OS: 87.9%	84.2% at day 60	14%: II–IV aGVHD; 14.5% cGVHD

Table 1 (continued)

Table 1 (continued)

Author; type of study	Patients, n	Type of BMF	Median age, years (range)	Graft source (-/6 HLA)	Conditioning regimen	Survival	CIF PNN engraftment	CIF acute and chronic GVHD
Ochi et al. BBMT 2019; retrospective (38)	6	SAA	38.5 [32–45]	Single and double UCBT (4/6, 5/6 or 6/6)	Flu 30 mg/m^2 day –6 to –2; Cy 60 mg/kg day –6 to –5; TBI 4 Gy day –1	1-OS 100%	100% at day 40	3/6 grade II aGVHD (no III–IV grade); 2/6 cGVHD

CIF, cumulative incidence function; BMF, bone marrow failure; UCBT, unrelated cord blood transplantation; rCBT, related cord blood transplantation; rBMT, related bone marrow transplantation; OS, overall survival; aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease; PNN, neutrophil; CB, cord blood; BM, bone marrow; UBMT, unrelated bone marrow transplantation; Cy, cyclophosphamide, Flu, fludarabine, Mel, melphalan; TBI, total body irradiation; rATG, rabbit anti-thymoglobulin, hATG, horse anti-thymoglobulin; FA, Fanconi anemia, DC, Dyskeratosis congenita, DBA, Diamond Blackfan anemia, CN, congenital neutropenia; SAA, severe aplastic anemia; PNH, paroxysmal nocturnal hemoglobinuria; fup, follow-up; CAT, congenital amegakaryocytic thrombocytopenia.

(Nicord), copper chelator tetraethylenepentamine (TEPA), UM729 (a pyrimidoindole derivative), StemRegenin-1 (SR1), Notch ligand, valproic acid or even carbon nanotubes are under development and demonstrated to inhibit HSC differentiation or promote their self-renewal (79-86).

The co-culture of CB cells with mesenchymal stem cells (MSCs) is a strategy whose basic principle is to simulate the physiological microenvironment of the BM (87,88), and co-transplantation of those two constituents has demonstrated to promote hematopoietic engraftment in patients undergoing UCBT transplantation (87,89).

Other approaches using genetically modified feeder cells are also under development (90).

Conclusions

In conclusion, in the absence of a suitable BM donor, CBT is an option for the treatment of patients with idiopathic and inherited BMF syndromes, especially if a sibling CB donor is used.

A better selection of the CB units (privileging units with more than 4×10^7 nucleated cells/kg) and an adaptation of the conditioning regimens can be able to overcome the risk of rejection.

In case of idiopathic context 1 or 2 CB units may be used with no more than 2 of 6 HLA mismatches between the unit and the recipient. In patients with inherited BMF, particularly in the setting of FA, the current recommendation is to choose a donor with no more than one HLA mismatch because of the risk of unacceptable toxicity,

For patients with FA and other inherited BMF only 1 CB is recommended with no more than one mismatch.

Donor specific antibody screening should be performed in every patient to minimize the risk of rejection. *Ex-vivo* CB expanding strategies aiming to better engraftment are under investigation.

When the cryopreserved CB unit from the HLA identical sibling does not contain enough cell dose, add-back of BM cells at the time of transplant, could be feasible with excellent results and no increase in GVHD (60,91).

A Flu-Cy-TBI-ATG conditioning regimen (APCORD trial) can be effective and safe in refractory SAA patients receiving a single or double UCBT (42), whereas limited data are available in inherited context, although retrospective evidence suggests to reduce chemotherapy and radiation doses, integrating Flu and T-depletion, especially in FA patients.

Organ toxicity remains problematic for most inherited BMF, and prospective international clinical trials are urgently needed to improve engraftment and GVHD-free survival.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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