Leukemia & Lymphoma, 2014; Early Online: 1–5

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2014.947980

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healthcare

REVIEW

Advances in umbilical cord blood transplant: an overview of the 12th International Cord Blood Symposium, San Francisco, 5–7 June 2014

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Abstract

From 5 to 7 June the 12th Annual International Cord Blood Symposium was held in San Francisco. The meeting was devoted to advances in umbilical cord blood research with a major focus on translational and clinical results in cord blood transplant and in regenerative medicine. Over 3 days, a comprehensive summary of the state of the art was provided. We have summarized the most important data, organized around the following themes: use of umbilical cord blood for tissue repair, new indications for umbilical cord blood unit stem cell transplant (CBU SCT), enhancing count recovery after CBU SCT, improving outcomes, product quality and financial and cost considerations.

Keywords: Umbilical cord blood, transplant, leukemia, lymphoma, regenerative medicine

Introduction

From 5 to 7 June 2014 the 12th Annual International Cord Blood Symposium was held in San Francisco (http://cordbloodsymposium.org). The meeting was devoted to advances in umbilical cord blood research with a major focus on translational and clinical results in cord blood transplant and in regenerative medicine. Over 3 days, a comprehensive summary of the state of the art was provided. Here we have summarized the most important data, organized around the following themes: use of umbilical cord blood for tissue repair, new indications for umbilical cord blood unit stem cell transplant (CBU SCT), enhancing count recovery after CBU SCT, improving outcomes, product quality and financial and cost considerations.

Umbilical cord cells for tissue repair

Umbilical cord blood cells have generated considerable interest for use in tissue repair, because of their unique properties and ready availability. A number of studies previously presented are steadily advancing or reaching completion. Most of these studies focus on acquired neurologic disease, and are based on murine data indicating the regenerative potential of glial precursors, and the ability to isolate such precursors from umbilical cord blood [1–3]. A pilot study of infusion of autologous cord blood cells in newborns with hypoxic encephalopathy has been completed [4]. The logistical problems of collecting and preparing cord blood units (CBUs) from these newborns were considerable, but overcome. Preliminary results are encouraging in that sequelae-free survival at 1 year was achieved in 74% of recipients. A group in Houston is conducting a randomized trial of infusion of bone marrow mononuclear cells versus cord blood mononuclear cells in children with cerebral palsy. Dr. Wise Young from Keck Medical School is conducting trials of CBU cell therapy in spinal cord injury. These trials are conducted in mainland China and Hong Kong. Preliminary results are encouraging and randomized trials are under way.

Less far advanced but potentially of great interest are the investigations of CBU cells as sources for other cell populations, such as mesenchymal stem cells or endothelial progenitor cells, with major proliferative potential. Potential applications of such cell populations include diseases such as bronchopulmonary dysplasia or retinopathy of prematurity [5,6]. As proposed by Fate Therapeutics (http://fatetherapeutics.com), the activation state, phenotypic profile, homing properties and clinical potential of various CBU cell types may be further enhanced by *in vitro* manipulation with, for example, prostaglandin E2.

New indications for umbilical cord blood transplant

The average age of patients referred to transplant is increasing, and their management presents a considerable challenge. Cure rates with conventional chemotherapy are exceedingly low, and transplant represents the only curative therapy for such patients. On the other hand, healthy sibling donors cannot often be found, and chronic graft-versus-host disease (GVHD) occurring after unrelated transplant is debilitating and a major deterrent. Umbilical cord blood transplant has a low incidence of chronic GVHD, and there is increasing

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Received 17 July 2014; accepted 20 July 2014

evidence that it may have a major role in transplant for elderly patients. Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) in patients over the age of 50 compared the outcomes of CBU stem cell transplant with unrelated donor transplant [7]. Survival after CBU SCT is comparable to that of one antigen-mismatched unrelated donor transplant. It is slightly worse than that of matched unrelated donor transplant, but the long term risk of chronic GVHD is much reduced (28% vs. 53% after unrelated donor transplant). Similar results were reported from France. They found that donor choice (matched related donor [MRD], unrelated donor [URD], CBU) had no effect on overall survival [8]. In another recent study of older adults with acute myeloid leukemia (AML), the treatment related mortality of CBU stem cell transplant was lower than that of matched sibling transplant [9]. Relevant recent studies are summarized in Table I. At the University of Colorado, the survival of CBU SCT recipients is similar to that of unrelated donor transplant recipients, but the incidence of chronic GVHD is less [10]. They therefore favor the use of CBU SCT, which can also be organized more rapidly. The excellent outcomes of CBU SCT for older patients with leukemia extends therapeutic options, particularly for patients of minority descent, as discussed by Dr. Dahi from Memorial Sloan Kettering Cancer Center (MSKCC) [11].

CBU SCT also has an increasing role in the treatment of lymphoma. Comparative analysis from both the CIBMTR [12] and from Eurocord [13] show comparable outcomes between CBU SCT and unrelated donor transplant.

Improving engraftment: expansion-homing infusion of accessory cells

Considerable effort has been spent on overcoming the delays in engraftment that constitute the major limitation of allogeneic cord blood transplant. Cord blood expansion, improvement of cord blood homing or co-administration of third party cells are all emerging technologies at various levels of development. Horwitz from Duke University presented data on a multicenter trial of nicotinamide based expansion [14]. A 3-week incubation period is required, but engraftment of white blood cells (WBCs) and platelets proceeded extremely rapidly. All patients received two grafts, an unmanipulated one and a graft treated with nicotinamide. In most cases the nicotinamide treated graft assured durable engraftment. No updates were presented on another technology which has generated considerable interest: SR1 is an aryl hydrocarbon receptor antagonist which stimulated stem cell expansion and has been investigated in a 2-week expansion system [15]. The drawback of these and competing expansion technologies [16,17] may well be the need for prolonged incubation, not always practical for the treatment of acute leukemia.

Early data on fucosylation of umbilical cord blood cells [18] and data on CBU incubation with prostaglandin E2 were also presented [14]. Both methods improve homing of stem cells, and in small studies are associated with improved engraftment. Sitagliptin, an inhibitor of dipeptidyl-peptidase, also improves homing, and is readily available as an oral medication (used for treatment of diabetes) [19]. An initial trial had disappointing outcomes, possibly because of rapid metabolism of the drug [20,21]. A follow-up trial is ongoing. Expansion of cord blood stem cells using a Notch inhibitor was one of the earliest technologies [22]. The investigators have abandoned the concept of utilizing the Notch inhibitor with patient-specific umbilical cord blood stem cells. Instead they focus on developing an off-the-shelf expanded product that may be of use to shorten neutropenia after leukemia induction or after cord blood transplant. Initial results suggest that engraftment with an off-the-shelf human leukocyte antigen (HLA) unmatched expanded product may be somewhat delayed compared with engraftment of HLA matched products [23]. Nevertheless, infection rates after use of these products were quite low.

By far the largest patient experience was presented by our group. Using a combination of third-party haploidentical cells and cord blood cells we have achieved very rapid engraftment rates. In a CIBMTR conducted case–cohort analysis we compared outcomes of 98 patients undergoing this so-called haplo-cord transplant with those of 344 patients undergoing double cord transplant. Rates of engraftment of platelets and neutrophils were much faster and survival was improved with haplo-cord transplant [24] (Table II). The device for isolating CD34-selected haploidentical cells has recently been Food and Drug Administration (FDA)-approved under a humanitarian device exemption, rendering this technology readily available in both Europe and the USA.

Tipping the balance: modulating graft-versus-host disease and graft-versus-leukemia, preserving the immune system

Other classic transplant complications such as GVHD, immunocompromise and relapse remain considerable problems after CBU SCT. Many investigators are addressing

Table 1. Comparative outcomes* of stem cell transplant for older adults with hematologic malignancies.

			n	Age	OS	PFS	TRM at 3 years	Relapse	aGVHD	cGVHD
Weisdorf [7]	AML > 50	MUD	441	58	**43%**	**39%**	**27%**	35%	36%	53%
		MMUD	94	58	37%	34%	41%	26%	44%	59%
		CBU	205	59	30%	28%	35%	35%	59%	**28%**
Peffault de Latour [8]	AML > 50	MRD	80	58	51%		18%	33%	10%	43%
		URD	32	59	53%%		14%	29%	15%	41%
		CBU	80	59	45%		24%	43%	14%	23%
Konuma [9]	> 45	MRD	31	48	55% at 5 years		33%	17%	16%	48%
		CBU	66	49	67%		**15%**	22%	9%	46%

AML, acute myeloid leukemia; MUD, adult matched unrelated donor; MMUD, adult mismatched unrelated donor; CBU, cord blood unit; MRD, matched related donor; URD, adult unrelated donor; OS, overall survival; PFS, progression-free survival; TRM, transplant related mortality; aGVHD, acute graft-versus-host-disease; cGVHD, chronic GVHD.
*Significant differences are shown in bold.

Table II. Comparison of outcomes of haplo-cord versus double umbilical cord blood transplant (from [24]).

Event	Haplo-cord ($n = 99$), P_1 (95% CI)	dCBU ($n = 344$), P_2 (95% CI)	p-Value
ANC recovery			
30-Day	91 (84–95)%	72 (67–76)%	< 0.0001
60-Day	96 (90–98)%	86 (82–89)%	0.0001
90-Day	96 (90–98)%	87 (83–90)%	0.0001
120-Day	96 (90–98)%	87 (83–90)%	0.0001
Platelet recovery			
30-Day	53 (43–61)%	6 (4–9)%	< 0.0001
60-Day	75 (65–82)%	54 (46–59)%	< 0.0001
90-Day	79 (70–85)%	64 (59–69)%	0.0014
120-Day	80 (71–86)%	66 (61–70)%	0.0019
Overall survival			
1-Year	52 (40–60)%	44 (39–50)%	0.2277
2-Year	43 (32–54)%	38 (32–43)%	0.3846
3-Year	43 (32–54)%	33 (26–40)%	0.1219
4-Year	43 (32–54)%	21 (11–33)%	0.0053

ANC, absolute neutrophil count; CI, confidence interval; dCBU, double cord blood unit.

these issues by novel methods of cord selection, by modifying the cord blood product or by changing the conditioning regimens.

Eapen *et al.* have shown that CBUs that are matched at high resolution for HLA-A, -B, -C and -DR result in faster engraftment, fewer complications and better overall outcomes [25]. However, there is an inverse relationship between the probability of finding a large cell dose CBU and the likelihood of finding a well matching CBU. This is particularly true for ethnic minority patients, for whom one is unlikely to be able to identify a well matching, large size CBU [26–28]. Our own group is attempting to reduce GVHD and improve transplant outcomes by emphasizing HLA matching of the cord blood products over cell dose. Using the haplo-cord platform, we have accepted very small, but well matching CBUs. We have identified well-matched 8/8 units for up to 20% of our patients and at least 7/8 matched units in over 50%. Our preliminary results suggest excellent outcomes with the use of such small units.

Other methods of optimizing CBU selection may involve selection based on killer cell immunoglobulin-like receptor (KIR) phenotype, with two groups investigating slightly different KIR selection algorithms [29,30]. A group of investigators from Utrecht, The Netherlands, presented a different approach. They developed a computer algorithm that predicts for GVH reactivity of single antigen mismatched adult unrelated donors. (The mismatches are labeled PIRCHEs or "predicted indirectly recognizable HLA epitopes.") In retrospective analysis they found that a higher degree of mismatching at class I (higher PIRCHE I) was associated with a lower relapse rate. A higher number for mismatch at class II (high PIRCHE II) was associated with more chronic GVHD. This intuitive and appealing model can be implemented using software developed by the investigators. Confirmation in other studies is required, but the concept generated considerable interest. An alternative approach pioneered at M. D. Anderson consists of the transfection of hematopoietic cells with zinc-finger nucleases that target HLA class I, leading to complete elimination of class I expression [31]. In principle such cells should be universal donor cells.

The issue of engraftment and GVHD can also be addressed by modulating conditioning regimens, and there is considerable debate over the use of antithymocyte globulin (ATG) in conditioning regimens. Its use is recommended by the European Group for Blood and Marrow Transplantation (EBMT) after adult unrelated donor transplant because it reduces acute and chronic GVHD without affecting overall survival; to a certain degree its effect may depend on the dose administered [32–34]. We use ATG in umbilical cord blood transplant as well, and have observed excellent engraftment rates and extremely low rates of acute (20%) and particularly chronic GVHD (3%) in our haplo-cord program [35]. Epstein–Barr virus (EBV) reactivation is common, but can be controlled with monitoring and aggressive intervention.

Other groups have shied away from the use of ATG because of concern over disease recurrence and excessive immunocompromise. A French multicenter retrospective analysis found that ATG was associated with worse non-relapse mortality and worse overall survival. However, the use of ATG was strongly center-dependent, and the analysis (reported in preliminary fashion) was not adjusted for supportive care practices, which likely differed among centers [36]. A Dutch pediatric study did not find major differences in survival [37,38]. Without ATG, risks of acute and chronic GVHD and graft rejection are considerably higher. The MSKCC group reported an incidence of grade II–IV acute GVHD of 53% and grade III–IV acute GVHD of 23% [39]. Most of the acute GVHD was gut GVHD. Fifty-four percent of those surviving beyond day 100 had late GVHD, usually either late acute or overlap syndrome. They have attempted to address this by increasing the intensity of mycophenolate prophylaxis [40]. The Seattle group has addressed the issue of graft rejection by intensifying the radiation doses in their non-myeloablative conditioning regimen [41].

GVHD has also been addressed by infusion of *in vivo* expanded T-regulatory cells, which in preliminary studies have shown decreased rates of acute GVHD, but possibly increased rates of early viral infections [42,43]. Others are testing the use of *in vitro* expanded natural killer (NK) cells for prevention and treatment of relapse [44].

Quality of cord blood units

Delayed recovery of grafts or lack of recovery can be fatal, and may in some cases be caused by poor cord blood graft quality and function, which in turn may be affected by processing and cryopreservation of the cords. Assessing quality of individual CBUs remains a challenge. Dr. Regan presented the results of a CIBMTR sponsored collaborative cord blood bank study. They focused on the predictive value of CFU-GM (colony forming unit – granulocyte, macrophage) analysis performed at four cord blood banks across the USA. They did not find any predictive value to the assay. The number of CFU-GMs did not correlate with rate of neutrophil engraftment. Absence of CFU-GM growth did not correlate with recovery.

The MSKCC group analyzed predictors of engraftment in double CBU grafts. Since only one graft has durable engraftment (the dominant graft), they focused on its qualities. They found that pre-cryopreservation CD34 cell dose was

the measure best correlated with engraftment. Provenance of the CBU (Foundation for the Accreditation of Cellular Therapy [FACT] accredited bank vs. not) and standardization of the cryopreservation process (units with volume between 24.5 and 26 mL) were also associated with better outcome [45]. The Dana Farber group also analyzed the relationship between provenance of CBUs and engraftment after double CBU grafts. In multivariate analysis the small group of patients ($n = 17$) who received a red blood cell-replete graft had better day-100 and 1-year survival than 115 patients receiving at least one red blood cell-depleted graft [46]. This is somewhat surprising, since most cord blood banks favor red blood cell depletion of cord blood units in order to minimize infusion reactions, albeit that red blood cell-replete units may be more enriched in hematopoietic progenitors [47].

Cost of banking and cost of procurement of cord blood units

In an era of cost containment and declining reimbursement, pricing and costs play an increasing role in determining CBU use. Dr. Shpall summarized the results of cord blood procurement. Procurement of up to two units costs on average of $90 000. This is excessive compared to the overall cost of the transplant, particularly in developing countries.

Dr. Kurtzberg summarized the pressures on cord blood banks, which partially explain the pricing [27]. The collection process is costly, with considerable drop-off between the moment of birth, collection, transfer to the bank and cryopreservation. This attrition is due to quality and/or volume issues of the CBU. For every four units considered, only one is cryopreserved. Of the inventory, only approximately 10% are used. Attrition could be diminished by stricter volume requirements, but since African Americans tend to have smaller CBUs, such a policy would disproportionately affect minority accrual.

Michael Boo, JD, discussed utilization and the cost issue from the National Marrow Donor Program (NMDP) point of view. CBU use in the USA has declined somewhat in the past 3 years. It is stable in most European countries but increasing in Japan, France, China and the UK. The cost of CBU procurement and particularly of double CBU procurement definitely plays a role in limitation of its use. Several alternative scenarios of pricing of CBUs were discussed, including a uniform price across the country, reduction in prices for second units and so on. None of these options were thought to be either practical or consistent with current regulations.

The costs of banking are closely related to the costs of regulation. Michael Boo presented a survey of the costs of the FDA-imposed licensing process for cord blood banks. On average, costs for a bank to become licensed ranged from $250 000 to $1.5 million. While the licensing process has definite advantages, it has also imposed considerable burdens on the centers. The licensing process is modeled on the process designed for the pharmaceutical industry, where production batches can be inspected. This is impractical for the cord blood banking industry, where every single CBU represents a unique batch. A plea was made to adjust the regulatory process to take into account the unique features of the cord blood industry and its products. Also, consistency in interpretation of the regulations was requested. Dr. Mercy Quagraine discussed the regulations from the standpoint of the FDA.

Lastly, Ari Giniger, PhD, from Israel discussed the Israeli model for funding cord blood banks. Private and public cord blood banks face the same regulations (in contrast to the USA where private cord blood banks are less regulated) and costs of public cord blood banks are borne in part by their integration with private banks.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

References

[1] Goldman SA, Nedergaard M, Windrem MS. Glial progenitor cell-based treatment and modeling of neurological disease. Science 2012;338:491–495.

[2] Tracy ET, Zhang CY, Gentry T, et al. Isolation and expansion of oligodendrocyte progenitor cells from cryopreserved human umbilical cord blood. Cytotherapy 2011;13:722–729.

[3] Tracy E, Aldrink J, Panosian J, et al. Isolation of oligodendrocyte-like cells from human umbilical cord blood. Cytotherapy 2008; 10:518–525.

[4] Cotten CM, Murtha AP, Goldberg RN, et al. Feasibility of autologous cord blood cells for infants with hypoxic-ischemic encephalopathy. J Pediatr 2014;164:973–979.

[5] Prasain N, Meador JL, Yoder MC. Phenotypic and functional characterization of endothelial colony forming cells derived from human umbilical cord blood. J Vis Exp 2012;(62): pii: 3872.

[6] Broxmeyer HE, Lee MR, Hangoc G, et al. Hematopoietic stem/progenitor cells, generation of induced pluripotent stem cells, and isolation of endothelial progenitors from 21- to 23.5-year cryopreserved cord blood. Blood 2011;117:4773–4777.

[7] Weisdorf D, Eapen M, Ruggeri A et al. Alternative donor transplantation for older patients with acute myeloid leukemia in first complete remission: a center for international blood and marrow transplant research-eurocord analysis. Biol Blood Marrow Transplant 2014;20:816–822.

[8] 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.

[9] Konuma T, Kato S, Ooi J, et al. Comparable long-term outcome of unrelated cord blood transplantation with related bone marrow or peripheral blood stem cell transplantation in patients aged 45 years or older with hematologic malignancies after myeloablative conditioning. Biol Blood Marrow Transplant 2014;20:1150–1155.

[10] Gutman JA, Myint H, Lee CK, et al. Chronic graft versus host disease and immunosuppression burden is significantly lower following adult cord blood transplantation versus matched unrelated donor transplantation. Biol Blood Marrow Transplant 2014;20(Suupl. 2):S35.

[11] Dahi PB, Ponce D, Byam C, et al. Prospective evaluation of alternative donor availability in 708 patients: improved allograft access with enlarging CB inventory for all patients including racial and ethnic minorities. Blood 2013;122(Suppl. 1): Abstract 162.

[12] Brunstein C, Burns LJ, Wang T et al. Alternative donor transplantation for adults with lymphoma: comparison of umbilical cord blood versus 8/8 HLA-matched donor (URD) versus 7/8 URD. Blood 2013;122(Suppl. 1): Abstract 161.

[13] Rodrigues CA, Rocha V, Dreger P, et al. Alternative donor hematopoietic stem cell transplantation for mature lymphoid malignancies after reduced-intensity conditioning regimen: similar outcomes with umbilical cord blood and unrelated donor peripheral blood. Haematologica 2014;99:370–377.

[14] Horwitz ME, Chao NJ, Rizzieri DA, et al. Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment. J Clin Invest 2014;124:3121–3128.

[15] Wagner JE, Brunstein CG, McKenna D, et al. Safety and exploratory efficacy of ex vivo expanded umbilical cord blood (UCB) hematopoietic stem and progenitor cells (HSPC) using cytokines and stem-regenin 1 (SR1): interim results of a phase 1/2 dose escalation clinical study. Blood 2013;122(Suppl. 1): Abstract 698.

[16] de Lima M, McMannis J, Gee A et al. Transplantation of ex vivo expanded cord blood cells using the copper chelator tetraethylenepentamine: a phase I/II clinical trial. Bone Marrow Transplant 2008;41:771–778.

[17] de Lima M, McNiece I, Robinson SN, et al. Cord-blood engraftment with ex vivo mesenchymal-cell coculture. N Engl J Med 2012;367:2305–2315.

[18] Robinson SN, Thomas MW, Simmons PJ, et al. Fucosylation with fucosyltransferase VI or fucosyltransferase VII improves cord blood engraftment. Cytotherapy 2014;16:84–89.

[19] Broxmeyer HE, Hoggatt J, O'Leary HA, et al. Dipeptidylpeptidase 4 negatively regulates colony-stimulating factor activity and stress hematopoiesis. Nat Med 2012;18:1786–1796.

[20] Velez de Mendizabal N, Strother RM, Farag SS, et al. Modelling the sitagliptin effect on dipeptidyl peptidase-4 activity in adults with haematological malignancies after umbilical cord blood haematopoietic cell transplantation. Clin Pharmacokinet 2014;53: 247–259.

[21] Farag SS, Srivastava S, Messina-Graham S, et al. In vivo DPP-4 inhibition to enhance engraftment of single-unit cord blood transplants in adults with hematological malignancies. Stem Cells Dev 2013;22:1007–1015.

[22] Delaney C, Heimfeld S, Brashem-Stein C, et al. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. Nat Med 2010;16:232–236.

[23] Delaney C, Milano F, Heimfeld S, et al. Dose dependent enhancement of neutrophil recovery by infusion of notch ligand ex vivo expanded cord blood progenitors: results of a multi-center phase I trial. Blood 2013;122(Suppl. 1): Abstract 297.

[24] van Besien K, Artz A, Zhang M-J, et al. Haplo+cord transplantation: rapid neutrophil and platelet recovery and improved long-term survival compared to double umbilical cord blood (UCB) transplantation—a case-cohort analysis. J Clin Oncol 2014;32(5 Suppl.): Abstract 7004.

[25] Eapen M, Klein JP, Ruggeri A, et al. Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy. Blood 2014;123:133–140.

[26] Gragert L, Maiers M, Williams E, et al. Modeling effective patient-donor matching for hematopoietic transplantation in United States populations. Hum Immunol 2010;71(Suppl.):S114.

[27] Page KM, Mendizabal A, Betz-Stablein B, et al. Optimizing donor selection for public cord blood banking: influence of maternal, infant, and collection characteristics on cord blood unit quality. Transfusion 2014;54:340–352.

[28] Cairo MS, Wagner EL, Fraser J et al. Characterization of banked umbilical cord blood hematopoietic progenitor cells and lymphocyte subsets and correlation with ethnicity, birth weight, sex, and type of delivery: a Cord Blood Transplantation (COBLT) study report. Transfusion 2005;45:856–866.

[29] Venstrom JM, Pittari G, Gooley TA, et al. HLA-C-dependent prevention of leukemia relapse by donor activating KIR2DS1. N Engl J Med 2012;367:805–816.

[30] Cooley S, Weisdorf DJ, Guethlein LA, et al. Donor selection for natural killer cell receptor genes leads to superior survival after unrelated transplantation for acute myelogenous leukemia. Blood 2010;116:2411–2419.

[31] Torikai H, Reik A, Soldner F, et al. Toward eliminating HLA class I expression to generate universal cells from allogeneic donors. Blood 2013;122:1341–1349.

[32] Ruutu T, Gratwohl A, de Witte T et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. Bone Marrow Transplant 2014;49:168–173.

[33] Baron F, Labopin M, Blaise D, et al. Impact of in vivo T-cell depletion on outcome of AML patients in first CR given peripheral blood stem cells and reduced-intensity conditioning allo-SCT from a HLA-identical sibling donor: a report from the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 2014;49:389–396.

[34] Van BK. Allogeneic transplantation for AML and MDS: GVL versus GVHD and disease recurrence. Hematology Am Soc Hematol Educ Program 2013;2013:56–62.

[35] Liu H, Rich ES, Godley L, et al. Reduced-intensity conditioning with combined haploidentical and cord blood transplantation results in rapid engraftment, low GVHD, and durable remissions. Blood 2011;118:6438–6445.

[36] Pascal L, Tucunduva L, Ruggeri A, et al. Impact of rabbit anti-thymocyte globulin-containing reduced-intensity conditioning regimens on outcomes of adults undergoing unrelated cord blood transplantation for hematological malignancies. Blood 2013;122 (Suppl. 1): Abstract 412.

[37] Ballen KK. ATG for cord blood transplant: yes or no? Blood 2014;123:7–8.

[38] Lindemans CA, Chiesa R, Amrolia PJ, et al. Impact of thymoglobulin prior to pediatric unrelated umbilical cord blood transplantation on immune reconstitution and clinical outcome. Blood 2014;123:126–132.

[39] Ponce DM, Gonzales A, Lubin M, et al. Graft-versus-host disease after double-unit cord blood transplantation has unique features and an association with engrafting unit-to-recipient HLA match. Biol Blood Marrow Transplant 2013;19:904–911.

[40] Ponce D, Harnicar SJ, Devlin S, et al. Intensified mycophenolate mofetil (MMF) dosing every 8 hours is safe from the standpoint of engraftment and may ameliorate severe acute graft-versus-host disease (GVHD) after double-unit cord blood transplantation (CBT). Blood 2013;122(Suppl. 1): Abstract 4600.

[41] Salit RB, Milano F, Utman JA, et al. Umbilical cord blood transplant patients at high risk of graft rejection achieve early full donor chimerism when 300cGy is used in the reduced intensity conditioning regimen. Blood 2013;122(Suppl. 1): Abstract 697.

[42] Brunstein CG, Miller JS, Cao Q, et al. Infusion of ex vivo expanded T regulatory cells in adults transplanted with umbilical cord blood: safety profile and detection kinetics. Blood 2011;117:1061–1070.

[43] Brunstein CG, Blazar BR, Miller JS, et al. Adoptive transfer of umbilical cord blood-derived regulatory T cells and early viral reactivation. Biol Blood Marrow Transplant 2013;19:1271–1273.

[44] Shah N, Martin-Antonio B, Yang H, et al. Antigen presenting cell-mediated expansion of human umbilical cord blood yields log-scale expansion of natural killer cells with anti-myeloma activity. PLoS One 2013;8:e76781.

[45] Purtil D, Smith K, Meagher R, et al. Analysis of 402 cord blood units to assess factors influencing infused viable CD34 + cell dose: the critical determinant of engraftment. Biol Blood Marrow Transplant 2014;20(Suppl. 2):S59.

[46] Nikiforow S, Li S, Liney D, et al. Impact of umbilical cord unit banking conditions on clinical outcomes in double cord transplant recipients. Blood 2013;122(Suppl. 1):Abstract 695.

[47] Young W. Plasma-depleted versus red cell-reduced umbilical cord blood. Cell Transplant 2014;23:407–415.