STEM CELLS TRANSLATIONAL MEDICINE®

FETAL AND NEONATAL STEM CELLS

Concise Review: Umbilical Cord Blood Transplantation: Past, Present, and Future

JAVIER MUNOZ,[a,*] NINA SHAH,[b,*] KATAYOUN REZVANI,[b] CHITRA HOSING,[b] CATHERINE M. BOLLARD,[c,d,e] BETUL ORAN,[b] AMANDA OLSON,[b] UDAY POPAT,[b] JEFFREY MOLLDREM,[b] IAN K. MCNIECE,[b] ELIZABETH J. SHPALL[b]

Key Words. Umbilical cord blood transplantation • Lymphoma • Leukemia • Graft versus host disease • Hematopoietic stem cell transplantation • Transplant related mortality

ABSTRACT

Allogeneic hematopoietic stem cell transplantation is an important treatment option for fit patients with poor-risk hematological malignancies; nevertheless, the lack of available fully matched donors limits the extent of its use. Umbilical cord blood has emerged as an effective alternate source of hematopoietic stem cell support. Transplantation with cord blood allows for faster availability of frozen sample and avoids invasive procedures for donors. In addition, this procedure has demonstrated reduced relapse rates and similar overall survival when compared with unrelated allogeneic hematopoietic stem cell transplantation. The limited dose of CD34-positive stem cells available with single-unit cord transplantation has been addressed by the development of double-unit cord transplantation. In combination with improved conditioning regimens, double-unit cord transplantation has allowed for the treatment of larger children, as well as adult patients with hematological malignancies. Current excitement in the field revolves around the development of safer techniques to improve homing, engraftment, and immune reconstitution after cord blood transplantation. Here the authors review the past, present, and future of cord transplantation. STEM CELLS TRANSLATIONAL MEDICINE *2014;3:1435–1443*

[a]Department of Hematology-Oncology, Banner MD Anderson Cancer Center, Gilbert, Arizona, USA; [b]Department of Stem Cell Transplantation and Cellular Therapy, MD Anderson Cancer Center, University of Texas, Houston, Texas, USA; [c]Program for Cell Enhancement and Technologies for Immunotherapy, Children's National Hospital System, and [d]Department of Pediatrics and [e]Department of Microbiology, Immunology and Tropical Medicine, George Washington University, Washington, D.C., USA

[*]Contributed equally.

Correspondence: Nina Shah, M.D., Department of Stem Cell Transplant and Cellular Therapy, MD Anderson Cancer Center, University of Texas, 1515 Holcombe Boulevard, Unit 423, Houston, Texas 77030; USA. Telephone: 713-794-5644; E-Mail: nshah@mdanderson.org

Received July 29, 2014; accepted for publication September 19, 2014; first published online in SCTM *EXPRESS* November 5, 2014.

1066-5099/2014/$20.00/0

http://dx.doi.org/10.5966/sctm.2014-0151

INTRODUCTION

Stem cell therapy has the potential to treat several life-threatening and debilitating conditions including cancer, Alzheimer's disease, and neurological injury. Although investigation is ongoing in developing areas such as human embryonic stem cells and inducible pluripotent stem cells, hematopoietic stem cells have been clinically applied for decades now. Although these hematopoietic stem cells are perhaps more differentiated than embryonic stem cells, autologous and allogeneic sources of hematopoietic stem cells can restore the hematopoietic system in a patient with a hematologic malignancy after high-dose chemotherapy.

Hematopoietic stem cells can be readily obtained from different adult tissues such as bone marrow and peripheral blood. More recently, umbilical cord blood has become recognized as yet another source of these valuable cells. Previously disposed after childbirth, cord blood has become a precious product and valuable tool for patients with malignancies that lack a stem cell donor. The National Marrow Donor Program has approximately 23 million volunteer adult donors [1]; nevertheless many patients, particularly minorities [2], who need an allogeneic stem cell transplant do not have a suitable matched unrelated donor. Thus possibilities include mismatched related, mismatched unrelated, or cord blood donors. It has been more than 20 years since the first human cord blood transplant was performed. Methods of collection, banking, cryopreservation of cord blood, and thus clinical outcomes continue to improve worldwide for both malignant and nonmalignant conditions.

HISTORY OF CORD BLOOD TRANSPLANTATION: THE PAST

During fetal development, hematopoiesis transitions from the fetal yolk sac to the liver and finally to the adult bone marrow. Fetal liver cells as a hematopoietic stem cell source were abandoned because of poor success rates. It was then hypothesized that cord blood might be a better provider of progenitor cells because of increased availability and long-term maintenance of a higher number of stem cells [3].

The first cord blood transplant recipient was a patient with Fanconi's anemia who received a cord blood unit from his human leukocyte antigen (HLA)-identical sibling in 1988 [4]. A combination of factors triggered the use of this new technology in Fanconi's anemia, including the recently acquired

Table 1. Selected cord blood clinical trials recently reported at meetings of the American Society of Hematology, American Society of Blood and Bone Marrow Transplantation, and the American Society of Clinical Oncology

Abstract	Author	Title or description
359	Wagner et al. [37]	No survival advantage after double UCB compared with single UCB transplant in children with hematologic malignancy: Results of the BMT CTN 0501 randomized trial
10006	Collins et al. [38]	Long-term survival after alternative donor transplantation in children with acute leukemia
162	Dahi et al. [39]	Prospective evaluation of alternative donor availability in 708 patients: Improved allograft access with enlarging CB inventory for all patients including racial and ethnic minorities
161	Bachanova et al. [40]	Alternative donor transplantation for adults with lymphoma: Comparison of umbilical cord blood versus 8/8 HLA-matched donor (URD) versus 7/8 URD
295	Stiff et al. [41]	StemEx (copper chelation-based) ex vivo expanded UCBT accelerates engraftment and improves 100-day survival in myeloablated patients compared with a registry cohort undergoing double unit UCBT: Results of a multicenter study of 101 patients with hematologic malignancies
402	Vasileiou et al. [42]	Comparative analysis of cell dose and viability of cord blood units at cryopreservation and at thaw/infusion
146	Ponce et al. [43]	High day 28 ST2 biomarker levels predict severe day 100 acute graft-versus-host disease and day 180 transplant-related mortality after double-unit cord blood transplantation
381	Poon et al. [44]	Double-unit umbilical cord blood transplant for adults with acute leukemia and myelodysplastic syndrome results in comparable outcome as matched sibling or unrelated donor
345	Ghantoji et al. [45]	Characteristics and outcome of CMV infections in 95 CB transplant recipients: The MD Anderson experience
189	Barker et al. [46]	DCBT combined with haploidentical CD34+ cells results in 100% CB engraftment with enhanced myeloid recovery
196	Volodin et al. [47]	Outcomes of double-unit umbilical cord blood transplantation using fludarabine/busulfan-based reduced intensity conditioning regimen
57	Ponce et al. [48]	High disease-free survival and enhanced protection against relapse after DCBT when compared with unrelated donor transplantation

Abbreviations: BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CB, cord blood; CMV, cytomegalovirus; DCBT, double-unit cord blood transplantation; HLA, human leukocyte antigen; UCB, umbilical cord blood; UCBT, umbilical cord blood stem cell transplantation; URD, unrelated donor.

capability of prenatally diagnosing this condition via amniotic fluid sampling, improved HLA testing, and mastering the harvesting/cryopreservation/thawing of cord blood cells. The patient engrafted completely with donor cells and has remained in complete hematological remission for more than 20 years, without graft-versus-host disease (GVHD). It was hypothesized that fewer or less-developed T cells in the cord blood unit compared with bone marrow or peripheral blood would yield less GVHD. Less acute/chronic GVHD [5] and similar survival from HLA-identical sibling cord blood transplantation, albeit with delayed granulocyte/platelet engraftment, were observed in subsequent studies.

After encouraging outcomes in the matched related sibling arena [3], the first unrelated mismatched cord blood transplants followed in children and adults [5–7]. Subsequently, an international cooperative cord blood bank network, the Netcord group, was established in 1998 [8]. The availability and ease of cord blood collection and banking made cord blood searching and acquisition faster [7] than the search for bone marrow stem cells. Furthermore, the appeal of cord blood increased as it became apparent that less stringent HLA matching (in comparison with bone marrow or peripheral blood progenitor cells) was required [9], perhaps because fewer activated lymphocytes are present in cord blood [10]. All those advantages brought cord blood to its present role as a prime candidate for use in hematopoietic stem cell transplantation.

Current Applications of Cord Blood Transplantation: The Present

Much progress has occurred since the pioneering of the first cord blood transplant, with more than 35,000 transplants performed to date. The indication for transplantation has now transitioned from nonmalignant to malignant diseases, and the majority of recipients are now adults lacking an HLA-matched donor.

Pediatric Patients With Malignancies

The initial positive results of cord blood transplantation in pediatric patients [11, 12] prompted the Cord Blood Transplantation study: a pivotal prospective multicenter trial of cord blood transplantation (CBT) in 191 pediatric patients with hematologic malignancies [13]. In this study, the median time to neutrophil engraftment was 27 days; the rate of acute grade 3/4 GVHD by day 100 was 19.5%, and chronic GVHD at 2 years was 20.8%. The probability of 2-year survival was 49.5% [13], that faired favorably compared with previous reports. A larger study from the Center for International Blood and Marrow Transplant Research was conducted with 503 children with acute leukemia transplanted with cord blood versus 282 children transplanted with HLA-matched unrelated donors [14]. The 5-year leukemia-free survival was similar for allele-matched bone marrow transplants and cord blood units mismatched at either one or two antigens. These data suggested that the progression-free survival was similar to allogeneic bone marrow transplantation. The decreased risk of GVHD made CBT more attractive because it allowed greater donor-recipient HLA disparity. Despite the fact that GVHD was lower, a graft-versus-leukemia effect was observed.

Pediatric Patients With Nonmalignant Diseases

Nonmalignant conditions that have been treated by cord blood transplantation include severe combined immune deficiency [15], hemoglobinopathies [16], Krabbe's disease [17], chronic

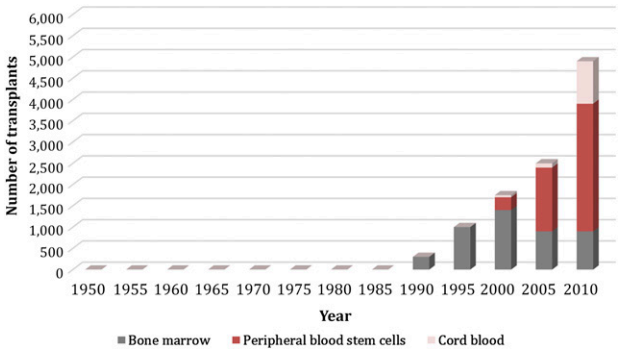

Figure 1. Approximate trends regarding transplants by hematopoietic cell source and increasing numbers of cord blood transplantations [49, 50].

granulomatous disease [18], and Hurler's syndrome [19]. Boelens et al. [20] evaluated the outcomes of transplantation using various hematopoietic cell sources in 258 children with Hurler's syndrome after myeloablative conditioning. Event-free survival after HLA-matched sibling donor and 6 of 6 matched unrelated cord blood donor was similar at 81% but lower at 68% after 5 of 6 matched cord blood donor and at 57% after 4 of 6 matched unrelated cord blood donor. Interestingly, full-donor chimerism was higher after cord blood transplantation (92% versus 69%, $p = .039$). A low progenitor cell dose is one of the major disadvantages of single-unit cord blood transplantation, resulting in slower engraftment and higher rates of graft failure. As such, CBT for other bone marrow syndromes, such as severe aplastic anemia and Fanconi's anemia, remains uncertain because of higher graft failure in this population when compared with other indications [21].

Adult Patients

Encouraging pediatric results led to the first large study of cord blood transplantation in adults in 2001. This study enrolled 68 patients with hematologic malignancies who received myeloablative conditioning. At 40 months after single-cord blood transplantation, 26% of patients remained disease-free [22]. Compared with unrelated stem cell transplantation with myeloablative conditioning, cord blood transplantation displayed similar leukemia-free survival (LFS), chronic GVHD rates, transplant-related mortality, and relapse rate in patients with acute leukemia [23]. In a subsequent study of matched unrelated, mismatched related and one- or two-HLA-antigen-mismatched cord blood transplants, there were similar rates of treatment-related mortality, treatment failure, and overall mortality [24]. Similarly, a retrospective analysis comparing unrelated bone marrow (472 patients) or peripheral blood progenitor cells (888 patients) with cord blood (165 patients) transplantation in adults with acute leukemia found that LFS after CBT was comparable with outcomes seen with 8 or 8 or 7 of 8 allele-matched peripheral blood progenitor cells or bone marrow transplantation [25]. The incidence of chronic, but not acute, GVHD was lower after CBT compared with 8 of 8 allele-matched bone marrow transplantation ($p = .01$). However, transplant-related mortality was higher after CBT when compared with 8 of 8 allele-matched peripheral blood progenitor cell recipients ($p = .003$) or bone marrow transplantation ($p = .003$) [25]. Therefore, this study encouraged the use of cord blood transplantation if no HLA-matched unrelated adult donors are available.

Double Cord Blood Transplantation

In an effort to overcome the relatively low number of progenitor cells present in a single cord blood unit, double cord blood transplantation (DCBT) was developed. In a study of 23 adults with high-risk hematological malignancies undergoing DCBT, the median time to engraftment was 23 days [26]. Engraftment was derived from a single donor, in 76% of patients at day 21, with one predominating unit in all patients at day 100. Single-unit dominance after double-unit cord blood transplantation has been confirmed in subsequent studies [27, 28] and CD3+ cell dose is an independent factor associated with unit predominance [27]. Of note, despite higher incidence of grade 2 acute GVHD in recipients of two partially HLA-matched cord blood units, there were no detrimental effects on transplantation-related mortality at 1 year (24 versus 39%, $p = .02$) [29]. Incidence of relapse or progression was found to be 31% at 1 year with a significantly lower risk ($p = .03$) in recipients of double-unit cord blood in patients with non-Hodgkin's lymphoma ($n = 61$), Hodgkin's lymphoma ($n = 29$), and chronic lymphocytic leukemia ($n = 14$) [30]. Furthermore, a prospective study comparing single versus double cord blood transplantation confirmed a lower relapse risk after infusion of two units (30.4% versus 59.3%, $p = .045$) [31]. A study that compared double cord blood transplantation ($n = 128$) to matched-related ($n = 204$) and matched-unrelated donor transplantation ($n = 152$) for adult leukemia patients found a significantly lower risk of relapse in recipients of double cord blood (15%) compared with matched-related donor (43%) and matched-unrelated donor (37%). However, nonrelapse mortality was higher for double cord blood (34%) compared with matched-related donor (24%) and matched-unrelated donor (14%) [32].

To improve these outcomes, cord blood transplantation has been explored after reduced intensity conditioning (RIC) regimens including the fludarabine, cyclophosphamide, and low-dose total body irradiation regimen [33] and the fludarabine, melphalan, and rabbit anti-thymocyte globulin [34] regimen. Adults with acute leukemia undergoing DCBT with the RIC regimen ($n = 120$), DCBT with alternative RIC regimens (including an alkylating agent plus fludarabine plus or minus total body irradiation) ($n = 40$), and 8 of 8 ($n = 313$) or 7 of 8 HLA-matched ($n = 111$) peripheral blood progenitor cells RIC transplants demonstrated a probability of survival of 38%, 19%, 44%, and 37%, respectively. All groups showed similar outcomes with the exception of recipients of double cord-treated patients with alternative RIC regimens, who displayed higher transplant-related mortality and higher overall mortality [35]. Similarly, the Blood and Marrow Transplant Clinical Trials Network conducted two parallel multicenter phase II trials for patients without a suitable related donor [36]. The outcomes of RIC with fludarabine, cyclophosphamide, and total body irradiation with subsequent unrelated double cord versus HLA-haploidentical related donor marrow were compared in both trials. The 1-year cumulative incidence of nonrelapse mortality was higher after cord blood (24% versus 7%), although the relapse rate was higher after haplomarrow transplantation (31% versus 45%) [36]. These phase II trials endorsed the value of double cord transplantation as an alternative donor source and set the stage for a multicenter, phase III, randomized trial of RIC and transplantation of double unrelated cord blood versus HLA-haploidentical related bone marrow for patients with hematologic malignancies (BMT CTN #1101, NCT01597778).

Additional preliminary data have recently been presented to further highlight cord blood as a viable transplant option

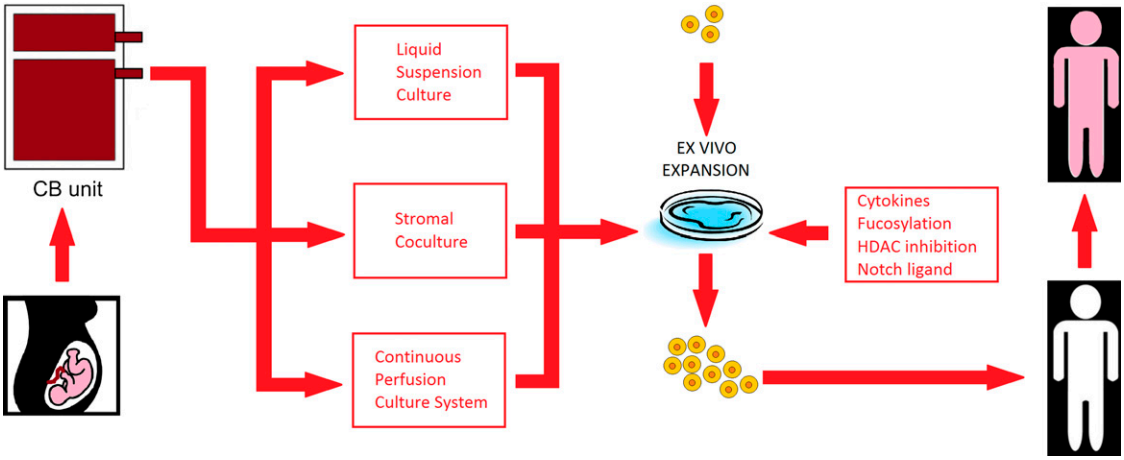

Figure 2. Schematic of ex vivo expansion techniques for cord blood transplantation (based on [55]). Abbreviations: CB, cord blood; HDAC, histone deacetylase.

Table 2. Milestones in hematopoietic cell transplantation and blood cord transplantation [68, 69]

Year	Milestones in HCT and blood cord transplantation	Reference
1868	The bone marrow is first described as blood-forming tissue.	[70]
1939	The first clinical marrow transplant is attempted, although unsuccessful.	[71]
1957	Infusions of normal marrow prevented death from marrow failure in animals after lethal doses of radiation.	[72]
1957–1959	Marrow transplantation in man after lethal whole-body irradiation.	[73–76]
1968–1969	The first successful allogeneic HCT procedures are performed in patients with severe combined immunodeficiency diseases.	[77]
1975	The first successful allogeneic HCT for leukemia is performed.	[78, 79]
1978	Successful autologous HCT for lymphoma.	[80]
1988	The first HLA identical-sibling human cord blood was performed in a patient with Fanconi's anemia.	[4]
1990	E. Donnall Thomas is awarded the Nobel Prize in Medicine/Physiology for the development of HCT as a cure for hematologic disorders.	[81]
1996	First unrelated mismatched cord blood transplant in children.	[6]
1996	First unrelated cord blood transplant in adult.	[82]
1997	The Eurocord-Netcord network was formed.	[83]
2000	Cord blood transplants in HLA identical siblings resulted in similar survival when compared with bone marrow transplants in children.	[84]
1996–2001	Demonstration that long-term leukemia-free survival is similar for cord blood and matched unrelated bone marrow transplants.	[5, 11, 21, 22, 85, 86]
2002	Transplantation of ex vivo expanded cord blood.	[87]
2004	Nonhematopoietic stem cells from cord blood as a first step for regenerative medicine.	[88]
2005–2010	Improving results with double cord blood transplants and nonmyeloablative conditioning regimens.	[26, 89, 90]
2008	Transplantation of ex vivo expanded cord blood cells using the copper chelator tetraethylenepentamine.	[82]
2010	Notch-mediated ex vivo expansion system of cord blood progenitors.	[53]
2011	In a "first-in-human" clinical trial, infusion of ex vivo expanded T regulatory cells reduced GVHD in adults transplanted with cord blood.	[64]
2012	Cord blood engraftment with ex vivo mesenchymal cell coculture.	[56]
2013	In a phase I trial, prostaglandin-modulated cord blood transplantation showed accelerated neutrophil recovery (17.5 vs. 21 days).	[63]
2014	Fucosylation with fucosyltransferase VI or fucosyltransferase VII improves cord blood engraftment.	[91]

Abbreviations: GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HLA, human leukocyte antigen.

(Table 1). Collins et al. [38] documented long-term durability of cord blood grafts in children with acute leukemia with an 8-year probability of overall survival of 78% compared with 81% with HLA-matched and 68% with HLA-mismatched bone transplantation. Of note, there were differences in transplant characteristics because the patients that received cord blood transplants were more likely to have received a non-irradiation-containing conditioning regimen [38]. Bachanova et al. [40] explored alternative donor

Table 3. Selected published translational studies on cord blood-derived ex vivo stem cell expansion

Authors, journal, and year	Title or description	Cytokines or agents used	Reference
Durand et al. (Leuk Lymphoma, 1993)	Long-term generation of colony-forming cells from CD34+ human umbilical cord blood cells	SCF, IL-3, EPO, G-CSF	[92]
Kurata et al. (Hematol Pathol, 1995)	Ex vivo expansion of hematopoietic progenitor cells in human cord blood: An effect enhanced by cord blood serum	SCF, IL-3, CBS, FCS	[93]
Bertolini et al. (Br J Haematol 1995)	The effect of interleukin-12 in ex vivo expansion of human hematopoietic progenitors	SCF, IL-3, IL-11, IL-12	[94]
Siena et al. (Exp Hematol, 1995)	Massive ex vivo generation of functional dendritic cells from mobilized CD34+ blood progenitors for anticancer therapy	SCF, GM-CSF, TNF-α	[95]
DiGiusto et al. (Blood, 1996)	Hematopoietic potential of cryopreserved and ex vivo manipulated umbilical cord blood progenitor cells evaluated in vitro and in vivo	SCF, IL-3, IL-6	[96]
Scaradavou et al. (Blood, 1997)	A murine model for human cord blood transplantation	SCF, IL-3, IL-6	[97]
Ohmizono et al. (Leukemia, 1997)	Thrombopoietin augments ex vivo expansion of human cord blood-derived hematopoietic progenitors in combin ation with stem cell factor and flt3 ligand	SCF, IL-3, IL-6, IL-11, TPO, FL	[98]
De Bruyn et al. (J Hematother, 1997)	Ex vivo expansion of CD34 + CD38− cord blood cells	SCF, IL-3, IL-6, GM-CSF, anti-TGF-β	[99]
Piacibello et al. (Blood, 1997)	Extensive amplification and self-renewal of human primitive hematopoietic stem cells from cord blood	SCF, IL-3, IL-6, GM-CSF, G-CSF, EPO, TPO, FL	[100]
Kögler et al. (Bone Marrow Transplant, 1998)	The effect of different thawing methods, growth factor combinations and media on the ex vivo expansion of umbilical cord blood	SCF, Flt3-L, IL-3, EPO, GM-CSF	[101]
Kögler et al. (Bone Marrow Transplant, 1998)	An eightfold ex vivo expansion of long-term culture-initiating cells from umbilical cord blood in stirred suspension cultures	SCF, Flt3-L, IL-3	[102]
Köhler et al. (Stem Cells, 1999)	Optimum results for ex vivo expansion of cord blood cells were reached by a combination of SCF, Flt3-L at 300 ng/ml and IL-3 at 50 ng/ml	SCF, Flt3-L, IL-3	[103]
Nakamura et al. (Blood, 1999)	The first in vitro demonstration of the precursor of CD34(+) cells in the human CD34(−) cell population	SCF, FCS, G-CSF, IL-3, IL-6	[104]
McNiece et al. (Exp Hematol, 2000)	Increased expansion and differentiation of cord blood products using a two-step expansion culture	SCF, G-CSF, MGDF	[105]
Lewis et al. (Blood, 2001)	The first demonstration that ex vivo culture in stroma-noncontact and stroma-free cultures maintains long-term engrafting cells	SCF, IL-7, FL, TPO	[106]
Pecora et al. (Bone Marrow Transplant, 2000)	Durable engraftment in two older adult patients using ex vivo expanded and unmanipulated unrelated umbilical cord blood	PIXY321, FL, EPO	[107]
Broxmeyer et al. (Proc Natl Acad Sci USA, 2003)	Stem cells from human cord blood cryopreserved for 15 years	SCF, EPO, IL-3, GM-CSF	[108]
Jaroscak et al. (Blood, 2003)	Aastrom Biosciences developed an automated continuous perfusion culture device (AastromReplicell System) for expansion of hematopoietic stem cells	FBS, HS, PIXY321, Flt3-L, EPO	[109]
Peled et al. (Blood, 2003)	Cord blood-derived progenitor cell graft expanded ex vivo with cytokines and the polyamine copper chelator tetraethylenepentamine	SCF, TPO, IL-6 and Flt3-L	[110]
Serrano et al. (Blood, 2006)	Differentiation of naive cord-blood T cells into CD19-specific cytolytic effectors for posttransplantation adoptive immunotherapy	FCS, other	[111]
Robinson et al. (Exp Hematol, 2012)	Ex vivo fucosylation improves human cord blood engraftment in NOD-SCID IL-2Rγ(null) mice	SCF, Flt3-L, TPO, G-CSF	[61]
Shah et al. (PLoS One, 2013)	Antigen presenting cell-mediated expansion of human umbilical cord blood yields log-scale expansion of natural killer cells	IL-2	[65]
Chaurasia et al. (J Clin Invest, 2014)	Epigenetic reprogramming with the HDAC inhibitor valproic acid induces the expansion of cord blood stem cells	SCF, FBS, Flt3-L, TPO, IL-3	[112]

Abbreviations: anti-TGF-β, anti-transforming growth factor-β antibody; CBS, cord blood serum; EPO, erythropoietin; FBS, fetal bovine serum; FCS, fetal calf serum; FL, flt3 ligand; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDAC, histone deacetylase; HS, horse serum; IL, interleukin; MGDF, megakaryocyte growth and development factor; SCF, stem cell factor; TNF, tumor necrosis factor; TPO, thrombopoietin.

Table 4. Selected single and double-unit cord blood transplantation studies at ClinicalTrials.gov (search included only open studies and excluded studies with unknown status; accessed December 30, 2013)

Identifier	Title
NCT01163201	T-regulatory cell and CD3 depleted double umbilical cord blood transplantation in hematologic malignancies
NCT00881933	Study of fludarabine + cyclophosphamide + TBI conditioning regimen for double units CBT in SAA
NCT01015742	Unrelated double umbilical cord blood units transplantation
NCT01464359	T-cell-depleted double UCB for refractory AML
NCT01408563	Reduced intensity double umbilical cord blood transplantation
NCT01745913	Randomized HaploCord blood transplantation vs. double umbilical cord blood transplantation for hematologic malignancies
NCT01597778	Double cord versus haploidentical (Blood and Marrow Transplant Clinical Trials Network #1101)
NCT01471067	Cord blood fucosylation
NCT00862719	Sitagliptin umbilical cord blood transplant study
NCT00890500	Safety and efficacy of ProHema modulated umbilical cord blood units in subjects with hematologic malignancies
NCT01690520	Donor umbilical cord blood transplant with or without ex vivo expanded cord blood progenitor cells in treating patients with AML, ALL, CML, or MDS
NCT00412360	Single versus double umbilical cord blood transplantation in children with high risk leukemia and myelodysplasia (BMT CTN 0501)
NCT00880789	Safety, toxicity and MTD of one intravenous IV injection of donor CTLs specific for CMV and adenovirus (ACT-CAT)
NCT01923766	Cytotoxic T cells to prevent virus infections

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT CTN, Blood and Marrow Transplant Clinical Trials Network; CBT, cord blood transplantation; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; CTL, donor-derived cytotoxic T lymphocyte; MDS, myelodysplastic syndrome; MTD, maximum tolerated dose; SAA, severe aplastic anemia; TBI, total body irradiation; UCB, umbilical cord blood.

transplantation for 1,593 adults with advanced non-Hodgkin and Hodgkin lymphoma and compared cord blood versus 8 of 8 HLA-matched unrelated donor versus 7 of 8 unrelated donor. They found similar results in a multivariate analysis among the 3 groups in 3-year relapse/progression, progression-free survival, and overall survival [40]. Although clinical outcomes continue to be optimized, the development of CBT has expanded the use of allogeneic transplantation to patients who were previously unable to find a suitable donor. Dahi et al. [39] recently reported on the decline in the percentage of non-Europeans with no available graft, in part because of the availability of cord blood as a source. Increasing experience with cord blood transplant has thus changed the landscape in hematopoietic cell sources for patients undergoing allogeneic hematopoietic stem cell transplantation (Fig. 1).

Single Versus Double CBT in Pediatric Patients

In the pediatric population, the use of two partially HLA-matched cord blood units has not been shown to be superior to a single unit, if the unit contains a sufficient number of hematopoietic stem cells. In a randomized study of 224 pediatric patients with hematologic malignancies by Wagner et al. [37], there was no difference between single-unit versus double-unit cord blood transplant in the overall rate of engraftment (89% versus 86%), chronic GVHD (28% versus 31%), risk of relapse at 1 year (12% versus 14%), or disease-free survival (68% versus 64%) [51]. Economically, the use of two units would be justifiable in the pediatric setting only when one unit does not contain enough number of progenitor cells. There are no randomized data of single versus double CBT in adult patients.

Novel Clinical Trials of Cord Blood Transplantation: The Future

Novel strategies to improve cord blood transplantation outcomes include improving cord blood engraftment by the transplantation of ex vivo expanded cord blood cells. A potential advantage of expansion is the ability to use smaller cord blood units, which could in turn increase the number of available allografts. Expansion techniques currently reported include using the copper chelator tetraethylenepentamine [52], notch ligand-based cultures [53], and coculture of cord blood cells with bone marrow-derived mesenchymal stem cells [54] (Fig. 2). Expansion with notch ligand and the mesenchymal stem cell-based cocultures have resulted in rapid engraftment of neutrophils in a median of 15 days [53, 56]. Other strategies to improve engraftment include the direct intrabone injection of unrelated cord blood cells [57], supportive coinfusion from an HLA-haploidentical third party donor [58, 59], and the use of agents to enhance the homing of cord blood to the marrow via fucosylation [60, 61] or by prostaglandin E2 modulation [62, 63].

Ongoing clinical trials are also evaluating cord blood-derived immune cells to improve the rate of GVHD and antitumor efficacy. Expanding cord blood regulatory T cells, a subset of CD4+ T cells, may potentially represent a novel cell-based approach for reducing the risk of GVHD [64]. Antigen presenting cell-mediated expansion of human cord blood natural killer cells as an antitumor cellular therapy is being explored as well [65].

Delayed immune reconstitution after cord blood transplantation remains one of the most daunting obstacles to the widespread use of cord blood transplantation. As such, the expansion of cytotoxic T-cell lymphocytes from cord blood has been instituted to target the most common viral infections in this setting: cytomegalovirus, Epstein-Barr virus, and adenovirus [66]. It has also been suggested that combining haploidentical donors with cord blood transplantation can lead to faster immune reconstitution with rapid B-cell and delayed T-cell recovery [67].

Despite the numerous milestones achieved in hematopoietic cell transplantation (Table 2) and ex vivo cord blood stem cell expansion (Table 3), many questions remain unanswered in the field of cord blood transplantation. Fortunately, answers may be forthcoming from numerous ongoing clinical trials (Table 4): ex vivo

expanded stem cells (NCT01221857), fucosylation prior to infusion (NCT01471067), and inhibition of CD26 peptidase using sitagliptin to enhance engraftment (NCT00862719). Other novel trials include ACTCAT (NCT00880789) and ACTCAT2 (NCT01923766), which use modified cytotoxic T-lymphocytes to prevent or treat cytomegalovirus, adenovirus, and/or Epstein Barr Virus reactivation or infection after cord blood transplant [113, 114].

Conclusion: Umbilical Cord Transplantation Coming of Age

The future for stem cell transplantation forecasts a combination of supportive care optimization and advances in conditioning chemotherapy and immunotherapy to increase survival and decrease morbidity. Cord blood transplantation as a source of stem cells has the potential to fill the gap of a growing population of patients who do not have a fully matched donor but need allogeneic hematopoietic stem cell transplantation. Our experience in this field has evolved from initial single-unit cord blood transplantation for a few diseases in children to double-unit cord blood transplantation for multiple hematologic malignancies in adults. In addition, cord blood provides countless hematopoietic and nonhematopoietic stem cells whose full potential in stem cell biology and regenerative medicine has yet to be fully uncovered.

Acknowledgment

C.M.B. and E.J.S. have been funded by NIH Program Project Grant P01CA148600.

Author Contributions

J.M., N.S., and E.J.S.: collection and/or assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript; K.R., C.H., C.M.B., B.O., A.O., U.P., J.M., and I.M.: data analysis and interpretation; final approval of manuscript.

Disclosure of Potential Conflicts of Interest

N.S. is a compensated consultant with Sanofi and has compensated research funding from Celgene.

References

1 Ballen KK, King RJ, Chitphakdithai P et al. The national marrow donor program 20 years of unrelated donor hematopoietic cell transplantation. Biol Blood Marrow Transplant 2008;14(suppl):2–7.

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 Broxmeyer HE, Douglas GW, Hangoc G et al. Human umbilical cord blood as a potential source of transplantable hematopoietic stem/progenitor cells. Proc Natl Acad Sci USA 1989;86:3828–3832.

4 Gluckman E, Broxmeyer HA, Auerbach AD et al. Hematopoietic reconstitution in a patient with Fanconi's anemia by means of umbilical-cord blood from an HLA-identical sibling. N Engl J Med 1989;321:1174–1178.

5 Wagner JE, Rosenthal J, Sweetman R et al. Successful transplantation of HLA-matched and HLA-mismatched umbilical cord blood from unrelated donors: Analysis of engraftment and acute graft-versus-host disease. Blood 1996; 88:795–802.

6 Kurtzberg J, Laughlin M, Graham ML et al. Placental blood as a source of hematopoietic stem cells for transplantation into unrelated recipients. N Engl J Med 1996;335: 157–166.

7 Barker JN, Krepski TP, DeFor TE et al. 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.

8 Hakenberg P, Kögler G, Wernet P. NETCORD: A cord blood allocation network. Bone Marrow Transplant 1998;22(suppl 1):S17–S18.

9 Petersdorf EW, Gooley TA, Anasetti C et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and recipient. Blood 1998;92:3515–3520.

10 Garderet L, Dulphy N, Douay C et al. The umbilical cord blood alphabeta T-cell repertoire: Characteristics of a polyclonal and naive but completely formed repertoire. Blood 1998; 91:340–346.

11 Locatelli F, Rocha V, Chastang C et al. Factors associated with outcome after cord blood transplantation in children with acute leukemia. Blood 1999;93:3662–3671.

12 Michel G, Rocha V, Chevret S et al. Unrelated cord blood transplantation for childhood acute myeloid leukemia: A Eurocord Group analysis. Blood 2003;102:4290–4297.

13 Kurtzberg J, Prasad VK, Carter SL et al. Results of the Cord Blood Transplantation Study (COBLT): Clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies. Blood 2008;112:4318–4327.

14 Eapen M, Rubinstein P, Zhang MJ et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: A comparison study. Lancet 2007;369:1947–1954.

15 Fernandes JF, Rocha V, Labopin M et al. Transplantation in patients with SCID: Mismatched related stem cells or unrelated cord blood? Blood 2012;119:2949–2955.

16 Kamani NR, Walters MC, Carter S et al. Unrelated donor cord blood transplantation for children with severe sickle cell disease: Results of one cohort from the phase II study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). Biol Blood Marrow Transplant 2012;18:1265–1272.

17 Escolar ML, Poe MD, Provenzale JM et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med 2005;352:2069–2081.

18 Bhattacharya A, Slatter M, Curtis A et al. Successful umbilical cord blood stem cell transplantation for chronic granulomatous disease. Bone Marrow Transplant 2003;31:403–405.

19 Staba SL, Escolar ML, Poe M et al. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. N Engl J Med 2004;350:1960–1969.

20 Boelens JJ, Aldenhoven M, Purtill D et al. Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. Blood 2013;121:3981–3987.

21 Rubinstein P, Carrier C, Scaradavou A et al. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. N Engl J Med 1998;339:1565–1577.

22 Laughlin MJ, Barker J, Bambach B et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. N Engl J Med 2001;344:1815–1822.

23 Rocha V, Labopin M, Sanz G et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Engl J Med 2004;351:2276–2285.

24 Laughlin MJ, Eapen M, Rubinstein P et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N Engl J Med 2004;351: 2265–2275.

25 Eapen M, Rocha V, Sanz G et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: A retrospective analysis. Lancet Oncol 2010;11:653–660.

26 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.

27 Ramirez P, Wagner JE, DeFor TE et al. Factors predicting single-unit predominance after double umbilical cord blood transplantation. Bone Marrow Transplant 2012;47:799–803.

28 Gutman JA, Turtle CJ, Manley TJ et al. Single-unit dominance after double-unit umbilical cord blood transplantation coincides with a specific CD8+ T-cell response against the non-engrafted unit. Blood 2010;115:757–765.

29 MacMillan ML, Weisdorf DJ, Brunstein CG et al. Acute graft-versus-host disease after

unrelated donor umbilical cord blood transplantation: Analysis of risk factors. Blood 2009;113: 2410–2415.

30 Rodrigues CA, Sanz G, Brunstein CG et al. Analysis of risk factors for outcomes after unrelated cord blood transplantation in adults with lymphoid malignancies: A study by the Eurocord-Netcord and lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol 2009;27:256–263.

31 Kindwall-Keller TL, Hegerfeldt Y, Meyerson HJ et al. Prospective study of one- vs two-unit umbilical cord blood transplantation following reduced intensity conditioning in adults with hematological malignancies. Bone Marrow Transplant 2012;47:924–933.

32 Brunstein CG, Gutman JA, Weisdorf DJ et al. Allogeneic hematopoietic cell transplantation for hematologic malignancy: Relative risks and benefits of double umbilical cord blood. Blood 2010;116:4693–4699.

33 Barker JN, Weisdorf DJ, DeFor TE et al. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. Blood 2003;102:1915–1919.

34 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.

35 Brunstein CG, Eapen M, Ahn KW et al. Reduced-intensity conditioning transplantation in acute leukemia: The effect of source of unrelated donor stem cells on outcomes. Blood 2012;119:5591–5598.

36 Brunstein CG, Fuchs EJ, Carter SL et al. Alternative donor transplantation after reduced intensity conditioning: Results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. Blood 2011;118:282–288.

37 Wagner JE, Eapen M, Carter SL et al. No survival advantage after double umbilical cord blood (UCB) compared to single UCB transplant in children with hematological malignancy: Results of the blood and marrow transplant clinical trials network (BMT CTN 0501) randomized trial. Available at https://ash.confex.com/ash/2012/webprogram/Paper48413.html. Accessed September 2, 2014.

38 Collins CL, Ahn KW, Wang Z et al. Long-term survival after alternative donor transplantation in children with acute leukemia. J Clin Oncol 2013;31(suppl):10006a.

39 Dahi PB, Ponce DM, 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. Available at https://ash.confex.com/ash/2013/webprogram/Paper60210.html. Accessed September 2, 2014.

40 Bachanova V, Brunstein C, Burns LJ 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. Available at https://ash.confex.com/ash/2013/webprogram/Paper57320.html. Accessed September 2, 2014.

41 Stiff PJ, Montesinos P, Peled T et al. StemEx (copper chelation based) ex vivo expanded umbilical cord blood stem cell transplantation (UCBT) accelerates engraftment and improves 100 day survival in myeloablated patients compared to a registry cohort undergoing double unit UCBT: Results of a multicenter study of 101 patients with hematologic malignancies. Available at https://ash.confex.com/ash/2013/webprogram/Paper61421.html. Accessed September 2, 2014.

42 Vasileiou S, Baltadakis I, Panitsas F et al. Comparative analysis of cell dose and viability of cord blood units at cryopreservation and at thaw/infusion for unrelated stem cell transplantation in adult recipients. Available at https://bmt.confex.com/tandem/2014/webprogram/Paper4069.html. Accessed September 2, 2014.

43 Ponce DM, Hilden P, Mumaw C et al. High day 28 ST2 biomarker levels predict severe day 100 acute graft-versus-host disease and day 180 transplant-related mortality after double-unit cord blood transplantation. Available at https://ash.confex.com/ash/2013/webprogram/Paper60713.html. Accessed September 2, 2014.

44 Poon ML, Linn YC, Lim Z et al. Double unit umbilical cord blood transplant for adults with acute leukemia and myelodysplastic syndrome results in comparable outcome as matched sibling or unrelated donor transplant only after myeloablative conditioning but not reduced intensity conditio. Biol Blood Marrow Transplant 2014;20(suppl):S247.

45 Ghantoji SS, Goddu S, Sreenivasula S et al. Characteristics and outcome of cytomegalovirus (CMV) infections in 95 cord blood transplant (CBT) recipients: The MD Anderson experience. Biol Blood Marrow Transplant 2014;20(suppl): S223–S224.

46 Barker JN, Ponce DM, Dahi P et al. Double-unit cord blood (CB) transplantation combined with haplo-identical CD34+ cells results in 100% CB engraftment with enhanced myeloid CD34+ recovery. Biol Blood Marrow Transplant 2014; 20(suppl):S138–S139.

47 Volodin L, Beitinjaneh A, Salman H et al. Outcomes of double unit umbilical cord blood transplantation using fludarabine/busulfan based reduced intensity conditioning regimen. Biol Blood Marrow Transplant 2014;20(suppl):S142.

48 Ponce DM, Devlin S, Lubin M et al. High disease-free survival and enhanced protection against relapse after double-unit cord blood transplantation (DCB-T) when compared to unrelated donor transplantation (URD-T) in patients with acute leukemia, MDS and CML. Biol Blood Marrow Transplant 2014;20(suppl):S58–S59.

49 National Marrow Donor Program. Adult Allogeneic HCT, by Transplant Type, Cell Source. Available at https://bethematchclinical.org/resources-and-education/hct-presentation-slides/adult-allogeneic-hct,-by-transplant-type,-cell-source/. Accessed August 30, 2014.

50 Appelbaum FR. Hematopoietic-cell transplantation at 50. N Engl J Med 2007;357: 1472–1475.

51 Oran B, Shpall E. Umbilical cord blood transplantation: A maturing technology. Hematology (Am Soc Hematol Educ Program) 2012; 2012:215–222.

52 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.

53 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.

54 Robinson SN, Ng J, Niu T et al. Superior ex vivo cord blood expansion following co-culture with bone marrow-derived mesenchymal stem cells. Bone Marrow Transplant 2006;37: 359–366.

55 Kelly SS, Sola CB, de Lima M et al. Ex vivo expansion of cord blood. Bone Marrow Transplant 2009;44:673–681.

56 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.

57 Frassoni F, Gualandi F, Podestà M et al. Direct intrabone transplant of unrelated cord-blood cells in acute leukaemia: A phase I/II study. Lancet Oncol 2008;9:831–839.

58 Bautista G, Cabrera JR, Regidor C et al. Cord blood transplants supported by co-infusion of mobilized hematopoietic stem cells from a third-party donor. Bone Marrow Transplant 2009;43:365–373.

59 Fernández MN, Regidor C, Cabrera R et al. Unrelated umbilical cord blood transplants in adults: Early recovery of neutrophils by supportive co-transplantation of a low number of highly purified peripheral blood CD34+ cells from an HLA-haploidentical donor. Exp Hematol 2003;31:535–544.

60 Xia L, McDaniel JM, Yago T et al. Surface fucosylation of human cord blood cells augments binding to P-selectin and E-selectin and enhances engraftment in bone marrow. Blood 2004;104:3091–3096.

61 Robinson SN, Simmons PJ, Thomas MW et al. Ex vivo fucosylation improves human cord blood engraftment in NOD-SCID IL-2Rγ(null) mice. Exp Hematol 2012;40:445–456.

62 Hoggatt J, Singh P, Sampath J et al. Prostaglandin E2 enhances hematopoietic stem cell homing, survival, and proliferation. Blood 2009; 113:5444–5455.

63 Cutler C, Multani P, Robbins D et al. Prostaglandin-modulated umbilical cord blood hematopoietic stem cell transplantation. Blood 2013;122:3074–3081.

64 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.

65 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.

66 Hanley PJ, Cruz CR, Savoldo B et al. Functionally active virus-specific T cells that target CMV, adenovirus, and EBV can be expanded from naive T-cell populations in cord blood and will target a range of viral epitopes. Blood 2009;114:1958–1967.

67 Jain N, Liu H, Artz AS et al. Immune reconstitution after combined haploidentical and umbilical cord blood transplant. Leuk Lymphoma 2013;54:1242–1249.

68 American Society of Hematology. 50 years in hematology: Research that revolutionized patient care. Available at http://www.hematology.org/About-ASH/50-Years.aspx. Accessed August 30, 2014.

69 Gluckman E, Ruggeri A, Volt F et al. Milestones in umbilical cord blood transplantation. Br J Haematol 2011;154:441–447.

70 Cooper B. The origins of bone marrow as the seedbed of our blood: From antiquity to the time of Osler. Proc (Bayl Univ Med Cent) 2011; 24:115–118.

71 Osgood EE, Riddle MC, Mathews TJ. Aplastic anemia treated with daily transfusions and intravenous marrow: Case report. Ann Intern Med 1939;13:357–367.

72 Congdon CC. Experimental treatment of total-body irradiation injury: A brief review. Blood 1957;12:746–754.

73 Thomas ED, Lochte HL Jr., Cannon JH et al. Supralethal whole body irradiation and isologous marrow transplantation in man. J Clin Invest 1959;38:1709–1716.

74 Thomas ED, Lochte HL Jr., Lu WC et al. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N Engl J Med 1957;257:491–496.

75 Thomas ED, Lochte HL Jr., Ferrebee JW. Irradiation of the entire body and marrow transplantation: Some observations and comments. Blood 1959;14:1–23.

76 Thomas E, Storb R, Clift RA et al. Bone-marrow transplantation (first of two parts). N Engl J Med 1975;292:832–843.

77 Gatti RA, Meuwissen HJ, Allen HD et al. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. Lancet 1968;2:1366–1369.

78 Graw RG Jr., Lohrmann HP, Bull MI et al. Bone-marrow transplantation following combination chemotherapy immunosuppression (B.A.C.T.) in patients with acute leukemia. Transplant Proc 1974;6:349–354.

79 Bleyer WA, Blaese RM, Bujak JS et al. Long-term remission from acute myelogenous leukemia after bone marrow transplantation and recovery from acute graft-versus-host reaction and prolonged immunoincompetence. Blood 1975;45:171–181.

80 Appelbaum FR, Herzig GP, Ziegler JL et al. Successful engraftment of cryopreserved autologous bone marrow in patients with malignant lymphoma. Blood 1978;52:85–95.

81 Thomas ED. The Nobel Lectures in Immunology: The Nobel Prize for Physiology or Medicine, 1990. Bone marrow transplantation: Past, present and future. Scand J Immunol 1994;39:339–345.

82 Laporte JP, Gorin NC, Rubinstein P et al. Cord-blood transplantation from an unrelated donor in an adult with chronic myelogenous leukemia. N Engl J Med 1996;335: 167–170.

83 Gluckman E, Rocha V, Boyer-Chammard A et al. Outcome of cord-blood transplantation from related and unrelated donors. N Engl J Med 1997;337:373–381.

84 Rocha V, Wagner JE Jr., Sobocinski KA et al. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. N Engl J Med 2000;342:1846–1854.

85 Cairo MS, Wagner JE. Placental and/or umbilical cord blood: An alternative source of hematopoietic stem cells for transplantation. Blood 1997;90:4665–4678.

86 Sanz GF, Saavedra S, Planelles D et al. Standardized, unrelated donor cord blood transplantation in adults with hematologic malignancies. Blood 2001;98:2332–2338.

87 Shpall EJ, Quinones R, Giller R et al. Transplantation of ex vivo expanded cord blood. Biol Blood Marrow Transplant 2002;8:368–376.

88 Kögler G, Sensken S, Airey JA et al. A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. J Exp Med 2004;200:123–135.

89 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.

90 Rocha V, Crotta A, Ruggeri A et al. Double cord blood transplantation: Extending the use of unrelated umbilical cord blood cells for patients with hematological diseases. Best Pract Res Clin Haematol 2010;23:223–229.

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

92 Durand B, Eddleman K, Migliaccio AR et al. Long-term generation of colony-forming cells (CFC) from CD34+ human umbilical cord blood cells. Leuk Lymphoma 1993;11:263–273.

93 Kurata H, Takakuwa K, Tanaka K. Ex vivo expansion of hematopoietic progenitor cells in human cord blood: An effect enhanced by cord blood serum. Hematol Pathol 1995;9:73–78.

94 Bertolini F, Soligo D, Lazzari L et al. The effect of interleukin-12 in ex-vivo expansion of human haemopoietic progenitors. Br J Haematol 1995;90:935–938.

95 Siena S, Di Nicola M, Bregni M et al. Massive ex vivo generation of functional dendritic cells from mobilized CD34+ blood progenitors for anticancer therapy. Exp Hematol 1995;23:1463–1471.

96 DiGiusto DL, Lee R, Moon J et al. Hematopoietic potential of cryopreserved and ex vivo manipulated umbilical cord blood progenitor cells evaluated in vitro and in vivo. Blood 1996;87:1261–1271.

97 Scaradavou A, Isola L, Rubinstein P et al. A murine model for human cord blood transplantation: Near-term fetal and neonatal peripheral blood cells can achieve long-term bone marrow engraftment in sublethally irradiated adult recipients. Blood 1997;89:1089–1099.

98 Ohmizono Y, Sakabe H, Kimura T et al. Thrombopoietin augments ex vivo expansion of human cord blood-derived hematopoietic progenitors in combination with stem cell factor and flt3 ligand. Leukemia 1997;11:524–530.

99 De Bruyn C, Delforge A, Bron D et al. Ex vivo expansion of CD34 + CD38- cord blood cells. J Hematother 1997;6:93–102.

100 Piacibello W, Sanavio F, Garetto L et al. Extensive amplification and self-renewal of human primitive hematopoietic stem cells from cord blood. Blood 1997;89:2644–2653.

101 Kögler G, Callejas J, Sorg RV et al. The effect of different thawing methods, growth factor combinations and media on the ex vivo expansion of umbilical cord blood primitive and committed progenitors. Bone Marrow Transplant 1998;21:233–241.

102 Kögler G, Callejas J, Sorg RV et al. An eight-fold ex vivo expansion of long-term culture-initiating cells from umbilical cord blood in stirred suspension cultures. Bone Marrow Transplant 1998;21(suppl 3):S48–S53.

103 Köhler T, Plettig R, Wetzstein W et al. Defining optimum conditions for the ex vivo expansion of human umbilical cord blood cells. Influences of progenitor enrichment, interference with feeder layers, early-acting cytokines and agitation of culture vessels. STEM CELLS 1999;17:19–24.

104 Nakamura Y, Ando K, Chargui J et al. Ex vivo generation of CD34(+) cells from CD34(−) hematopoietic cells. Blood 1999;94:4053–4059.

105 McNiece I, Kubegov D, Kerzic P et al. Increased expansion and differentiation of cord blood products using a two-step expansion culture. Exp Hematol 2000;28:1181–1186.

106 Lewis ID, Almeida-Porada G, Du J et al. Umbilical cord blood cells capable of engrafting in primary, secondary, and tertiary xenogeneic hosts are preserved after ex vivo culture in a noncontact system. Blood 2001;97:3441–3449.

107 Pecora AL, Stiff P, Jennis A et al. Prompt and durable engraftment in two older adult patients with high risk chronic myelogenous leukemia (CML) using ex vivo expanded and unmanipulated unrelated umbilical cord blood. Bone Marrow Transplant 2000;25:797–799.

108 Broxmeyer HE, Srour EF, Hangoc G et al. High-efficiency recovery of functional hematopoietic progenitor and stem cells from human cord blood cryopreserved for 15 years. Proc Natl Acad Sci USA 2003;100:645–650.

109 Jaroscak J, Goltry K, Smith A et al. Augmentation of umbilical cord blood (UCB) transplantation with ex vivo-expanded UCB cells: Results of a phase 1 trial using the AastromReplicell System. Blood 2003;101: 5061–5067.

110 Peled T, Mandel J, Goudsmid RN et al. Pre-clinical development of cord blood-derived progenitor cell graft expanded ex vivo with cytokines and the polyamine copper chelator tetraethylenepentamine. Cytotherapy 2004; 6:344–355.

111 Serrano LM, Pfeiffer T, Olivares S et al. Differentiation of naive cord-blood T cells into CD19-specific cytolytic effectors for posttransplantation adoptive immunotherapy. Blood 2006;107:2643–2652.

112 Chaurasia P, Gajzer DC, Schaniel C et al. Epigenetic reprogramming induces the expansion of cord blood stem cells. J Clin Invest 2014;124:2378–2395.

113 Bart T, Boo M, Balabanova S et al. Impact of selection of cord blood units from the United States and swiss registries on the cost of banking operations. Transfus Med Hemother 2013;40:14–20.

114 Delaney C, Bollard CM, Shpall EJ. Cord blood graft engineering. Biol Blood Marrow Transplant 2013;19(suppl):S74–S78.

