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Cord Blood Transplantation in Adults with Acute Leukemia

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) with some graft sources such as bone marrow (BM), mobilized peripheral blood (PB) and cord blood (CB) offers the only curative potential for many patients with high risk hematological malignancies, particularly acute leukemia. Although BM from human leukocyte antigen (HLA)-identical related donors within immediate families is a frontline graft source for this treatment, an alternative stem cell source has increasingly provided for patients lacking HLA-identical related donors. Recently, CB has been considered an acceptable alternative to source of stem cells in unrelated allogeneic HSCT for pediatric and adult patients without HLA-identical related or unrelated donors. This review focuses on clinical results of cord blood transplantation (CBT) including factors associated with transplantation outcomes and clinical comparison studies of CBT and other sources of allogeneic HSCT in adults with acute leukemia. Several strategies including a reduced intensity regimen and double CB units from different donors have been developed to overcome the limited cell dose in CBT for adults. Moreover, to reflect the current encouraging reports and potential strategies, the possibility of CB for immune therapy in the setting of allogeneic HSCT is also discussed.

More than 50 years ago in 1957, Thomas et al. reported the first experience with allogeneic bone marrow transplantation (BMT) in patients with advanced leukemia (Thomas et al., 1957) and since then allogeneic HSCT has been a curative treatment for patients with both malignant and non-malignant hematologic diseases (Appelbaum, 2007). The initial purpose of infusion of BM was rescue of the BM function against myeloablative dose of radiation and/or chemotherapy, which generates killing of leukemia cells. Thereafter, the evidence of a graft-versus-leukemia (GVL) effect, which is mediated by both host histocompatibility antigen-specific T cells, tumor antigen-specific T cells and Natural killer (NK) cells against leukemia cells, confirmed that allogeneic HSCT is also the only form of cancer immune therapy for leukemia refractory to chemotherapy (Jenq & van den Brink, 2010).

Although allogeneic HSCT was initially limited to the approximately two-thirds of patients with a suitably HLA-identical related donor, an alternative stem cell source has increasingly provided for patients lacking HLA-identical related donors. After Broxmeyer et al.

demonstrated that CB included a number of hematopoietic stem/progenitor cells that would be capable of hematopoietic reconstitution in humans (Broxmeyer et al., 1989), the first CBT was reported by Gluckman et al. in a child with Fanconi anemia using CB from his HLA-matched sister in 1988 (Gluckman et al., 1989). Since the first success of CBT, Rubinstein et al. established the first unrelated CB bank at the New York Blood Center in 1992 (Rubinstein et al., 1993, 1995). Since then, CB banks have been developed worldwide for not only related but also unrelated CBT with more than 3000 CB transplants performed annually around the world (Foeken et al., 2010). In 1996, Laporte et al. reported a first adult patient with chronic myelogenous leukemia (CML) who underwent the transplantation of CB from unrelated donor (Laporte et al., 1996). Earlier, most patients were pediatric (Kurtzberg et al., 1996; Wagner et al., 1996; Rubinstein et al., 1998) because of the relatively lower cell doses in CB grafts, followed by an increased number of adult CBT (Laughlin et al., 2001; Sanz et al., 2001), showing that CB could effectively restore hematopoiesis with acceptable incidence of severe graft-versus-host disease (GVHD). Recently, CB has been considered an acceptable alternative to source of hematopoietic stem cells (HSCs) in unrelated allogeneic HSCT for pediatric and adult patients without HLA-identical related or unrelated donors.

In comparison with other sources of allogeneic HSCT, CBT has several clinical advantages, including rapid and convenient availability because of the stored CB units in the CB bank, less stringent criteria for HLA matching for donor-recipient selection, lower incidence of GVHD without compromising GVL effects, low risk of viral transmitting and the absence of risk for donors, whereas limited cell dose remains the main disadvantage in CBT. The limited cell dose might contribute to higher incidence of graft failure and delayed neutrophil recovery, which are mostly due to higher risk of bacterial and fungal infections in the early phase after CBT (Narimatsu et al., 2005; Parody et al., 2006; Tomonari et al., 2007; Yazaki et al., 2009; Miyakoshi et al., 2007; van Burik & Brunstein, 2007; Delaney et al., 2009). Moreover, viral infections may be more common after CBT than after BMT/PBSCT, essentially attributable to delayed immune reconstitutions after CBT (Tomonari et al., 2003a, 2003b, 2004, 2005; Parody et al., 2006; van Burik & Brunstein, 2007; Delaney et al., 2009). The advantages and disadvantages of CB as a source of allogeneic HSCT are shown in Table 1.

2. Clinical results in adults with acute leukemia

2.1 Factors associated with clinical outcomes in CBT

It is known that larger total nucleated cell (TNC) dose improve faster hematopoietic recovery, decrease treatment-related mortality (TRM) and survival of CBT recipients (Rubinstein et al., 1998; Laughlin et al., 2001; Gluckman et al., 2004; Arcese et al., 2006; Barker et al., 2010). Recent New York Blood Center analysis of 1061 recipients of single-unit myeloablative CBT for leukemia or myelodysplastic syndrome (MDS) demonstrated that TNC dose and HLA-match each affected survival via their effect on TRM (Barker et al., 2010). These analysis recommended the best transplantation outcomes were in recipients of 6 of 6 units regardless of precryopreservation TNC dose (median, 4.0×10^7 cells/kg), indicating that HLA match at HLA-A and -B antigens and -DRB1 alleles, rather than high TNC dose, was the more favorable graft characteristic. Further, recipients of 4 of 6 units required a precryopreservation TNC $\geq 5.0 \times 10^7$ cells/kg to achieve comparable TRM and disease-free survival (DFS) to that of recipients of 5 of 6 units with a TNC $\geq 2.5 \times 10^7$ cells/kg. In contrast, the minimum cell dose is not clear for adults who have indications for CBT. In a

	CB	BM/ mobilized PB
Advantages		
Availability of grafts	Rapid (less than one month)	Prolonged (a few months)
Requirement of HLA matching	4/6 or higher	6/6
Risk of severe GVHD	Lower risk	Higher risk
Risk of viral transmission	Very low risk	Low Risk
Risk of donor	No risk	Low Risk
Disadvantages		
Number of infused nucleated cells	Limited cell dose	Higher cell dose
Speed of hematopoietic recovery	Delay	Faster than CB
Risk of infection after HSCT	Higher risk than BM/PB	High risk
Possibility of donor lymphocyte infusion or second HSCT from same donor	Impossible	Possible
Potential of congenital disease transmission	Low potential	Few potential

CB indicates cord blood; BM, bone marrow; PB, peripheral blood; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation.

Table 1. Advantages and disadvantages of CB as a source of hematopoietic stem cell compared with BM or mobilized PB

Japanese study, patients receiving CB grafts containing $1-2 \times 10^7$ cells/kg were observed and four of seven low-cell-dose recipients survived with longer follow-up (Takahashi et al., 2006). Those results indicated that CB grafts containing fewer than 2×10^7 cells/kg may be useful for cases for which no grafts with higher cell doses or other stem cell sources are available. On the other hands, Wagner et al. demonstrated that a correlation between higher CD34+ cell dose and rate of engraftment in pediatric patients (Wagner et al., 2002). However, CD34+ cell measurement is not standardized between CB banks.

HLA compatibility was thought to be another key factor in CBT outcome, as with other stem cell sources. Several studies have shown that HLA mismatch at HLA-A, -B antigens and -DRB1 alleles leads to delayed engraftment, increased severity of acute GVHD, increased TRM and decreased survival (Rubinstein et al., 1998; Gluckman et al., 2004; Barker et al., 2010; Delaney & Ballen, 2010). Although increasing the number of HLA mismatching might be associated with decreased relapse risk in patients with leukemia, suggested GVL effect increased in HLA-mismatched CBT, HLA-mismatch does not offer any benefit in DFS (Barker et al., 2010). In general, recommended CB unit is ≥ 4 of 6 HLA-A, -B antigen and -DRB1 allele matched with the patient.

The role of anti-HLA antibodies in graft rejection of organ transplantations has been analyzed extensively. The majority of CBTs have HLA disparities. Takanashi et al. reported the impact that patients' pretransplantation anti-HLA antibodies have on the outcome of myeloablative CBT using single unit (Takanashi et al., 2010). Of 386 cases tested, 89 (23.1%) were anti-HLA antibody-positive. Of the 89 antibody-positive cases, 20 patients had specificity against the CB HLA. Cumulative incidence (CI) of neutrophil recovery 60 days after transplantation was 83% for the antibody-negative group, 73% for antibody-positive,

but only 32% for the positive against CB ($p < 0.0001$). These data suggested that patients' pretransplantation anti-HLA antibodies should be tested and considered in the selection of CB.

The logistics of the selection of CB grafts, including how to select double-unit grafts, for transplantation are as practiced by each centers (Shaw et al., 2009; Rocha & Gluckman, 2009; Barker et al., 2011).

2.2 Comparisons of unrelated donor cord blood and other stem cell sources

After Laughlin et al. initially reported the feasibility in adult patients receiving myeloablative CBT (Laughlin et al., 2001), two registration-based and one single-institution studies comparing both CBT and BMT from unrelated donor in adult patients with acute leukemia after myeloablative conditioning were published (Laughlin et al., 2004; Rocha et al., 2004; Takahashi et al., 2004). Selected studies are detailed in Table 2. These studies demonstrated that hematological recovery after CBT was slower when compared to unrelated BMT and that the incidence of severe acute and chronic GVHD was significantly lower after CBT than after BMT. However, the DFS rate and relapse incidence in CB recipients were not inferior to those in BM recipients. In a two meta-analysis using pooled comparative data from the above three reports, Hwang et al. reported that TRM (pooled estimate 1.04, 95% confidence interval [CI]=0.52-2.08; $p=0.91$) and DFS (pooled estimate 0.59, 95% CI=0.18-1.96; $p=0.39$) were not statistically different in adults (Hwang et al., 2007), whereas Wang et al. reported overall survival (OS) after CBT (hazard ratio [HR] 1.26, 95% CI=1.13-1.40) was statistically inferior in adults (Wang et al., 2010). Recently, Eapen et al. reported a comparative analysis of CBT from unrelated donor with BMT or peripheral blood stem cell transplantation (PBSCT) from unrelated donors in 1525 adult patients with acute leukemia after myeloablative conditioning (Eapen et al., 2010). 165 received CBT, 888 received PBSCT, and 472 received BMT. Leukaemia-free survival (LFS) in patients after CBT was comparable with that after 8/8 and 7/8 allele-matched PBSCT or BMT. However, TRM was higher after CBT than after 8/8 allele-matched PBSCT (HR 1.62, 95% CI=1.18-2.23; $p=0.003$) or BMT (HR 1.69, 95% CI=1.19-2.39; $p=0.003$). Grades II to IV acute and chronic GVHD were lower in CBT recipients compared with allele-matched PBSCT (HR 0.57, 95% CI=0.42-0.77; $p=0.002$ and HR 0.38, 95% CI=0.27-0.53; $p=0.003$, respectively), while the incidence of chronic, but not acute GVHD, was lower after CBT than after 8/8 allele-matched BMT (HR 0.63, 95% CI=0.44-0.90; $p=0.01$).

Data comparing both CBT and BMT or PBSCT from related donors in adult patients is equally encouraging. We studied the outcomes of 171 adults with hematological malignancies who received unrelated CBT as a primary unrelated stem cell source ($n=100$), or BMT or PBSCT from related donors ($n=71$; 55 BMT and 16 PBSCT) followed by myeloablative regimens (Takahashi et al., 2007). Significant delays in engraftment occurred after CBT. The CIs of grades III to IV acute and extensive type chronic GVHD among CBT recipients were significantly lower than those among BMT/PBSCT recipients. Multivariate analysis demonstrated no apparent differences in TRM (9% in CBT and 13% in BMT/PBSCT), relapse (17% in CBT and 26% in BMT/PBSCT) and DFS (70% in CBT and 60% in BMT/PBSCT). Unrelated CB could be as safe and effective a stem cell source as related BM or mobilized PB for adult patients when it is used as a primary unrelated stem cell source.

Reference	Disease	HSC source: number of patients	Median age (years)	Median time to ANC≥500/ μ l (days)	Incidence of grade II- IV acute GVHD (%)	Incidence of TRM (year)	Relapse rate (year)	Probability of DFS (year)
Laughlin et al.,2004	AML ALL CML MDS	CB:150	16-60	27	41	63%	17%	23% (3)
		uBM:367		20	48	46%	23%	33% (3)
		MuBM:83		18	51	65%	14%	19% (3)
Roche et al.,2004	AML ALL	CB:98	25	26	26	44% (2)	23% (2)	33% (2)
		uBM:584	32	19	39	38% (2)	23% (2)	38% (2)
Takahashi et al.,2004	AML ALL Other	CB:68	36	22	30	9% (1)	16% (2)	74% (2)
		uBM:39	26	18	30	29% (1)	25% (2)	44% (2)
Takahashi et al.,2007	AML ALL Other	CB:100	37	22	52	9% (1)	17% (3)	70% (3)
		rBM/PB:71	40	17	52	13% (1)	26% (3)	60% (3)
Kumar et al.,2008	ALL138	CB:19	19	NA	32*	34% (3)	5% (3)	61% (3)
		rBM:90	90	NA	20*	44% (3)	26% (3)	27% (3)
		uBM:15	15	NA	10*	53% (3)	20% (3)	13% (3)
		MuBM:14	14	NA	7*	86% (3)	0% (3)	14% (3)
Atsuta et al.,2009	AML:484	CB:173	38	NA	32	30% (1)	31% (2)	36% (2)
		uBM:311	38	NA	35	19% (1)	24% (2)	54% (2)
	ALL:336	CB:114	34	NA	28	21% (1)	31% (2)	45% (2)
		uBM:222	32	NA	42	23% (1)	24% (2)	51% (2)
Eapen et al.,2010	AML ALL	CB:165	28	24	30	37% (2)	1.00**	1.00**
		uBM:332	39	19	39	22% (2)	0.85**	1.15**
		MuBM:140			46	34% (2)	0.84**	0.93**
		uPB:632	33	14	48	24% (2)	0.85**	1.12**
		MuPB:256			52	38% (2)	0.91**	0.91**

CBT indicates cord blood transplantation; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; HSC, hematopoietic stem cell; CB, cord blood; uBM, unrelated bone marrow; MuBM, mismatched unrelated bone marrow; rBM/PB, related bone marrow/ peripheral blood; uPB, unrelated peripheral blood; MuPB, mismatched unrelated peripheral blood; ANC, absolute neutrophil count; NA, information not available; GVHD, graft-versus-host disease; TRM, treatment-related mortality; DFS, disease-free survival.

* The incidence of grade III-IV acute GVHD was shown in this study.

**Results were expressed as hazard ratios (the relative rate of occurrence of the event with CB as compared with another).

Table 2. Published comparative reports of CBT and other stem cell sources in adults with acute leukemia

Another alternative option for patients lacking an HLA-matched related and unrelated donor is allogeneic HSCT from haploidentical related donors. Almost all patients will have available to them a haploidentical family member donor. However, randomized study has never been published the comparison of outcomes of haploidentical HSCT and CBT for adult patients with leukemia (Ballen & Spitzer, 2011). Clinical study comparing haploidentical HSCT to CBT are warranted.

Reports of disease-specific outcomes for adult patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) after CBT are still limited (Ooi et al., 2004, 2008, 2009; Konuma et al, 2009a). Kumar et al. studied the relative impact of donor source on

outcomes following myeloablative HSCT for 138 adult patients with ALL (Kumar et al., 2008). When compared with unrelated BMT, OS with CBT was better (relative risk [RR] 0.3, 95%CI=0.1-0.7; $p=0.01$). Recently, Atsuta et al. reported a disease-specific comparison of CBT and HLA allele-matched unrelated BMT among 484 patients with AML (AML; 173 CB and 311 BM) and 336 patients with ALL (ALL; 114 CB and 222 BM) who received myeloablative transplantations (Atsuta et al., 2009). In multivariate analyses, among AML cases, lower OS (HR 1.5, 95%CI=1.0-2.0; $p=0.028$) and LFS (HR 1.5, 95%CI=1.1-2.0; $p=0.012$) were observed in CB recipients. The relapse rate did not differ between the 2 groups of AML (HR 1.2, 95%CI=0.8-1.9; $p=0.38$). However, the TRM rate showed higher trend in CB recipients (HR 1.5, 95%CI=1.0-2.3; $p=0.085$). In ALL, there was no significant difference between the groups for relapse (HR 1.4, 95%CI=0.8-2.4; $p=0.19$) and TRM (HR 1.0, 95%CI=0.6-1.7; $p=0.98$), which contributed to similar OS (HR 1.1, 95%CI=0.7-1.6; $p=0.78$) and LFS (HR 1.2, 95%CI=0.9-1.8; $p=0.28$).

Taken together, their results showed that CBT is feasible in adults when a CB unit contains a higher number of cells and when a transplant is needed urgently, and should be considered an option as an allogeneic stem cell source for patients lacking an HLA-matched unrelated donor. The results also showed that despite increased HLA disparity, CBT from unrelated donors is promising in adults with acute leukemia.

3. Improvement methods of engraftment and delay hematopoietic recovery

The relatively low number of HSCs and progenitors per one unit is a main limitation of CB instead of BM or mobilized PB as a stem cell source for HSCT, especially in adults. The low cell dose available for HSCT might contribute to higher incidence of graft failure, delayed hematopoietic recovery and delayed immune reconstitution. As a consequence, it is well known that transplanted cell dose is associated with TRM and survival after CBT. There have been several developing strategies to overcome the obstacle of low number of cell dose using CB as a stem cell source for transplantation, especially in adults.

3.1 Ex vivo expansion of cord blood

To improve limited cell dose contained in CB grafts, one attractive option is ex vivo expansion of CB which has been shown to have greater proliferative and self-renewal capacity when compared to the other sources of HSCs (Broxmeyer et al., 1992; Hows et al., 1992). Initial CB expansion attempts have used a variety of cytokines, such as stem cell factor (SCF), fms-like tyrosine kinase 3 (flt-3) ligand, thrombopoietin (TPO) and G-CSF (granulocyte colony-stimulating factor), reagents, such as polyamine copper chelator, tetraethylenepentamine (TEPA), and mesenchymal stem cells (MSCs), to cell culture. Several clinical studies were investigated, but have not achieved clinically relevant effects (Shpall et al., 2002; de Lima et al., 2008, 2010; Jarosca et al., 2003; Delaney et al., 2010; Kelly et al., 2009) (Table 3). Delaney et al. report the development of a clinically relevant Notch-mediated ex vivo expansion system for CB CD34⁺ cells and the phase I study involving transplantation of a non-manipulated unit along with CB progenitors from a second CB unit that have undergone Notch-mediated ex vivo expansion in 10 patients with acute leukemia (Delaney et al., 2010). After ex vivo expansion, there was an average fold expansion of CD34⁺ cells of 164 and an average fold expansion of total cell numbers of 562. The infused CD34⁺ cell dose derived from the expanded CB graft averaged 6×10^6 CD34⁺cells/kg versus 0.24×10^6 CD34⁺cells/kg ($p=0.0004$) from the non-manipulated CB graft. Time to absolute

neutrophil count (ANC) $\geq 500/\mu\text{l}$ was shortened significantly with a median time of 16 days (range, 7–34 days) compared with cohort of 20 patients undergoing double CBT with a median time of 26 days (range, 16–48 days; $p= 0.002$), despite loss of contribution to engraftment from the expanded cell graft. This is highly suggestive of a facilitating effect of the cultured cells in promoting engraftment from the non-manipulated CB unit. This is the first instance of rapid engraftment derived from ex vivo expanded CB stem/progenitor cells in humans.

Expansion type	Reference	Number of patients	Cytokines	Days in culture	TNC fold expansion (folds)	CD34+ fold expansion (folds)	Median time to ANC $\geq 500/\mu\text{l}$ (days)	Median time to PLT $\geq 20000/\mu\text{l}$ (days)	Incidence of each grade acute GVHD (%)	Survival (duration of follow up)
Liquid culture	Shpall et al.,2002	37	SCF,G-CSF,TPO	10	56	4	28	106	II to IV:67% III to IV:40%	32% (30 months)
	de Lima et al.,2008	10	SCF,Flt3L, G-CSF,TPO,IL-6+TEPA	21	219	6	30	48	II to IV:44% III to IV:0%	30% (180 days)
	Delany et al.,2010	10	Notch ligand,SCF, Flt3L,TPO,IL-6,IL-3	16	562	164	16	NA	II to IV:9/9 III to IV:1/9	7/10 alive (1 year)
Stromal co-culture	de Lima et al.,2010	32	SCF,Flt3L, G-CSF,TPO+ MSCs	14	40	14	15	40	II to IV:50% III to IV:16%	40% (1 year)
Continuous perfusion system	Jaroscak et al.,2003	27	PIXY321,Flt3L,EPO	12	2.4	0.5	22	71	II to IV:36% III to IV:22%	39% (41 months)

CBT indicates cord blood transplantation; CB, cord blood; SCF, stem cell factor; G-CSF, granulocyte colony-stimulating factor; TPO, thrombopoietin; Flt3L, fms-like tyrosine kinase 3 ligand; IL, interleukin; TEPA, tetraethylenepentamine; MSCs, mesenchymal stem cells; PIXY321, granulocyte-macrophage colony-stimulating factor/interleukin-3 fusion protein; EPO, erythropoietin; TNC, total nucleated cell; ANC, absolute neutrophil count; PLT, platelet; NA, information not available; GVHD, graft-versus-host disease.

Table 3. Published clinical trials of CBT using ex vivo expanded CB

3.2 Reduced-intensity conditioning regimen

Myeloablative conditioning (MAC) regimens for allogeneic HSCT have been restricted to younger patients without comorbidities, because TRM occurs more frequently among elderly patients and those with serious comorbidities. Reduced-intensity conditioning (RIC) regimens have emerged as a novel transplantation modality for those patients with the expectation of reducing TRM and increasing survival after allogeneic HSCT. This strategy was recently expanded for quick use with stem cell sources not only from BM or mobilized PB, but also from CB (Barker et al., 2003; Miyakoshi et al., 2004; Chao et al., 2004; Misawa et al., 2006; Brunstein et al., 2007; Komatsu et al., 2007; Majhail et al., 2008; Uchida et al., 2008; Cutler & Ballen, 2009; Horwitz & Chao, 2010). Several studies have reported on CBT using RIC for adult patients with leukemia, and selected studies using mainly single CB unit are

detailed in Table 4. The University of Minnesota group initially reported unrelated CBT for adults after RIC, demonstrating that 0-2 antigen mismatched CBT was sufficient to engraft most adults after RIC and was associated with low incidence of severe acute GVHD (Barker et al., 2003). They reported the updated results of this strategy in 110 adult patients with hematological disease to confirm the suitability of this strategy (Brunstein et al., 2007). Neutrophil recovery was achieved in 92% at the median of 12 days. The incidence of grades III to IV acute GVHD was 22%. However, these studies included the results of transplantation of both single and double CB grafts, because the target cell dose for the CB graft was 3×10^7 cells/kg. Recently, same group reported the comparative efficacy of CBT after RIC relative to MAC in 119 adult patients with AML in CR (complete remission) (Oran et al., 2011). The incidence of neutrophil recovery at day +42 was higher with RIC (RIC:94% vs MAC:82%; $p < 0.1$). Incidence of grades II to IV acute GVHD was decreased (RIC:47% vs MAC:67%; $p < 0.01$). Using RIC, 3-year LFS was decreased (RIC:31% vs MAC:55%; $p = 0.02$) and 3-year relapse incidence was increased (RIC:43% vs MAC:9%; $p < 0.01$). Two-year TRM was similar (RIC:19% vs MAC:27%; $p = 0.55$). In multivariate analysis, RIC recipients and those in CR2 with CR1 duration < 1 year had higher risk of relapse and poorer LFS with no independent predictors of TRM. Further studies are warranted to establish criteria for eligible patients and optimal RIC regimens for CBT.

Reference	Number of patients	Conditioning regimen	Median TNC cell dose (/kg)	Median CD34+ cell dose (/kg)	Median time to ANC \geq 500 / μ l (days)	Incidence of grade II-IV acute GVHD (%)	Incidence of TRM (year)	Relapse rate (year)	Probability of OS (year)
Miyakoshi et al.,2004	30	Flu/Mel/TBI4 Gy	3.1	0.7	17.5	27	27% (100 days)	10%[3/30pt]	33% (1)
Chao et al.,2004	13	Flu/CY/ATG	2.1	1.3	12	40%[2/5pt]	31%[4/13pt]	46%[6/13pt]	22% (4)
Misawa et al.,2006	12	Flu/CY/TBI3 Gy	2.5	0.9	17	62.5	50%[6/12pt]	8%[1/12pt]	42% (1)
Brunstein et al.,2007*	110 (2CB:93) (1CB:17)	CY/Flu/TBI2 Gy	3.7(2CB) 3.3(1CB)	4.9(2CB) 3.8(1CB)	12	59	26% (3)	31% (3)	45% (3)
Komatsu et al.,2007	17	Flu/BU	2.6	0.7	18	0	24%[4/17pt]	41%[7/17pt]	35%[6/17pt] (13months)
Majhail et al.,2008	43	CY/Flu/TBI2 Gy	4.0	0.4	NA	49	28%(180 days)	NA	34% (3)
Uchida et al.,2008	70	Flu/Mel/TBI4 Gy	2.8	0.8	18	61	53%[37/70pt]	26%[18/70pt]	23% (2)

CBT indicates cord blood transplantation; Flu, fludarabine; Mel, melphalan; TBI, total body irradiation; CY, cyclophosphamide; ATG, antithymocyte globulin; BU, busulfan; TNC, total nucleated cell; ANC, absolute neutrophil count; NA, information not available; GVHD, graft-versus-host disease; pt, patients; TRM, treatment-related mortality; OS, overall survival.
*Some results included CBT using double unit cord blood.

Table 4. Published reports of CBT using reduced-intensity conditioning in adults

3.3 Transplantation using multiple grafts of cord blood

Double CBT (dCBT) was initially developed as a strategy to overcome the cell dose limitation preventing the number of adults transplanted with single unit CB, and has been widely used in United States and Europe. Several studies have reported on double CBT for

adult patients with acute leukemia (Barker et al., 2005; Ballen et al., 2007; Rodrigues et al., 2009; MacMillan et al., 2009a; Gutman et al., 2009; Verneris et al., 2009; Cutler et al., 2010; Rocha et al., 2010a, 2010b; Brunstein et al., 2010; Delaney et al., 2009; Stanevsky et al., 2010), and representative studies are detailed in Table 5. Several studies showed that double CBT is associated with a higher incidence of acute GVHD compared with single CBT (sCBT). Interestingly, the risk of relapse after double CBT is significantly lower compared with single CBT for patients with leukemia in remission, suggesting that a greater GVL effect due to HLA disparity for the double CB recipient (Brunstein et al., 2007, 2010; Rodrigues et al., 2009; Verneris et al., 2009). On the other hand, neutrophil engraftment and LFS were similar for recipients of single or double CB units. Recently, Roche et al. also reported the results of single (n=377) and double (n=230) CBT in adult patients with AML or ALL in remission (Rocha et al., 2010a). In patients transplanted in CR 1, there were no statistical differences in CI of neutrophil recovery (dCBT 78% vs sCBT 82%; p=0.11). Acute GVHD was higher after dCBT compared with sCBT (45% vs 27%; p<0.001). At 3 years, relapse incidence was 15% after dCBT and 25% after sCBT (p=0.03). Estimated 3 years LFS was 53% after dCBT and

Reference	Number of patients	Conditioning regimen	Median time to ANC≥500/ μ l (days)	Incidence of grade II-IV acute GVHD (%)	Incidence of TRM (year)	Relapse rate (year)	Probability of DFS (year)
Barker et al.,2005	23	CY/TBI13.2Gy	23	65	22%(6months)	NA	57% (1)
Brunstein et al.,2007	93	Flu/CY/TBI2 Gy	12*	62	26%(3)*	31%(3) *	39% (3)
Ballen et al., 2007	21	Flu/Mel/ATG	20	40	19%(6months)	14% [3/21pt]	67% (1)
Rodrigues et al.,2009	26	MAC,RIC	17	32	31% (1)	13% (1)	57% (1)
MacMillan et al.,2009a	185	MAC42%,RIC 58%	NA	58%	24%(1)	NA	NA
Gutman et al.,2009**	31	CY/TBI12Gy/Flu	NA	81	21% (2)	3% (2)	76% (2)
Verneris et al.,2009	93	CY/TBI13.2Gy	25	48	29%(1)	19%(5)	51% (5)
Cutler et al.,2010	32	Flu/Mel/ATG	21	9	34%(2)	34%(2)	31%(2)
Rocha et al.,2010a	230	RIC53%	CR1:78%*** CR2<:85%***	CR1:45 CR2<:33	CR1:32%(3) CR2<:34%(3)	CR1:15%(3) CR2<:31%(3)	CR1:53%(3) CR2<:35%(3)
Brunstein et al.2010	128	CY/TBI12Gy/Flu	26	60	34 % (5)	15% (5)	51% (3)

CBT indicates cord blood transplantation; CB, cord blood; CY, cyclophosphamide; TBI, total body irradiation; Flu, fludarabine; Mel, melphalan; ATG, antithymocyte globulin; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; ANC, absolute neutrophil count; NA, information not available; CR, complete remission; GVHD, graft-versus-host disease; TRM, treatment-related mortality; pt, patients; DFS, disease-free survival.

*Some results included CBT using single unit cord blood.

** This study included 27 patients received two units (six of whom had one of the two units CD34+ selected and ex vivo expanded) and four received single units.

***Results were expressed as cumulative incidence of neutrophil recovery.

Table 5. Published reports of CBT using double units CB in adults

39% after sCBT ($p=0.09$). However, in patients transplanted in CR2 and CR3, estimated 3 years LFS was 35% after dCBT and 31% after sCBT ($p=0.48$). These data concluded double CBT has extended the use of CBT for patients otherwise not eligible for single CBT and importantly is associated with better outcomes in adults with acute leukemia transplanted in early phase of the disease. Brunstein et al. reported 536 patients with leukemia who underwent transplantation with an HLA allele-matched related donor (MRD, $n=204$), HLA allele-matched unrelated donor (MUD, $n=152$) or 1-antigen-mismatched unrelated adult donor (MMUD, $n=52$) or 4-6/6 HLA matched double CB (dCB, $n=128$) graft after myeloablative conditioning (Brunstein et al., 2010). All patients received MAC with cyclophosphamide (CY) 120 mg/kg and total body irradiation (TBI) 12 to 13.2 Gy with the addition of fludarabine (Flu) 75 mg/m² in recipients of dCBT. LFS at 5 years was similar for each donor type (dCB 51%, MRD 33%, MUD 48%, MMUD 38%). The risk of relapse was lower in recipients of dCB (15%) compared with MRD (43%), MUD (37%) and MMUD (35%), yet nonrelapse mortality was higher for dCB (34%), MRD (24%), and MUD (14%). They conclude that LFS after double CBT is comparable with that observed after MRD and MUD transplantation. Although clinical experience using double CBT is progressing as described above, 1 CB unit ultimately dominates and confers durable engraftment, but little is known about the mechanism of the determinants of durable engraftment by 1 CB unit after double CBT. More recently, Avery et al. demonstrated that indicators of CB unit potency including TNC dose, colony-forming unit (CFU), CD3+, and viable CD34+ cell content, predict the dominating unit, but HLA matching does not appear to play a role in unit dominance (Avery et al., 2011).

3.4 Co-transplantation with third party donor

Fernandez et al. have developed the strategy of single unit CBT with co-infusion of a limited number of mobilized HSC (MHSC) from an HLA-mismatched third party donor (TPD) (Fernández et al., 2003; Magro et al., 2006; Bautista et al., 2009). They reported the updated results of this strategy in 55 adult patients with high-risk hematological malignancies (Bautista et al., 2009). The median CB cell dose of 2.37×10^7 cells/kg (the median CB CD34+ cells of 0.11×10^6 cells/kg) and the median TPD-MHSC CD34+ cells of 2.4×10^6 cells/kg were transplanted. The median time to recovery of neutrophils and CB derived neutrophils as well as to complete CB chimerism was 10, 21 and 44 days. Finally, TPD-MHSC derived hematopoiesis disappeared completely. The 5 years OS and DFS were 56 % and 47%, respectively. This strategies suggested that transient hematopoiesis from TPD-MHSC might reduce the incidence of neutropenia-related serious infection, thus leading to the possibility of decreased TRM early after CBT in adult patients.

3.5 Intrabone transplantation

To improve efficient engraftment possibly due to better stem cell homing to the bone marrow, Frassoni et al. reported the phase I/II study of direct intrabone transplantation of single unit CB in 32 patients with acute leukemia (Frassoni et al., 2008). Although the median transplanted cell dose was 2.6×10^7 cells/kg (range, 1.4-4.2), the median time to recovery of neutrophils in 28 patients and platelets in 27 patients was 23 days (range, 14-44) and 36 days (range 16-64), respectively. All patients with hematopoietic recovery showed complete donor engraftment from 30 days after CBT. No patient developed grades III to IV acute GVHD. This preliminary data suggest that direct intrabone CBT overcomes the

problem of graft failure even when low numbers of single unit unrelated HLA-mismatched CB are transplanted in adults and need to be confirmed in a larger number of adult patients.

3.6 Improvement of homing capacity

The interaction of stromal-derived factor-1 (SDF-1)/CXCL12 with CXCR4 mediates the homing of HSCs to the BM. CD26, a surface serine dipeptidylpeptidase IV (DPPIV), cleaves the amino-terminal dipeptide from some chemokines, including SDF-1. Diprotin A, which is inhibitor of CD26 peptidase activity, enhances engraftment of HSCs from CB into nonobese diabetic/severe combined immunodeficiency (NOD/SCID) mice (Campbell et al., 2007). Based on these data, the clinical trial to look the efficiency of CB engraftment using Diprotin A is now warranted. Moreover, several clinical trials should be investigated to answer the efficacy of co-infusion of haploidentical MSCs for the enhancement of engraftment and prevention of graft failure in CBT (Macmillan et al., 2009b; Gonzalo-Daganzo et al., 2009; Bernardo et al., 2011).

4. Immune therapy using cord blood

4.1 Immune reconstitution after CBT

Infection-related mortality is the primary cause of death early after CBT, with most deaths occurring in the first 3-6 months after transplant. Komanduri et al. reported prolonged T lymphopenia, impaired T cell functional responses to superantigens and cytomegalovirus (CMV), thymopoietic failure were important causes of delayed immune reconstitution after CBT in adult (Komanduri et al., 2007). For several months, until recovery of the thymus is restored to support de-novo T cell generation, protective antiviral immunity depends on the activity of postthymic T cells infused within the CB grafts. However, almost all T cells in CB grafts are naïve lymphocytes that have been functionally altered by placental factors to provide a protective environment during pregnancy. T cells in CB grafts need to undergo in-vivo priming, T helper (Th)1/T cytotoxic (Tc)1 maturation, and peripheral expansion before they can afford immunologic protection. Remarkable immunophenotypic changes are notable already in the first 2-3 weeks after CBT. These changes result from apparent 'homeostatic' peripheral T cell expansion in the lymphopenic environment (Szabolcs & Niedzwiecki, 2007; Szabolcs & Cairo, 2010).

4.2 Cellular therapy for viral infection or leukemia after CBT

One of the major limitations of CBT is the lack of donor cells available for posttransplantation donor leukocyte infusions (DLI) to boost immunity for severe viral infection or induce GVL activity for leukemia relapse, because the initial donor is unavailable. Although there was no obvious available source for adoptive cell therapy in the setting of CBT, several researches suggest that adoptive immune therapy using CB immune cells have the potential to improve the outcomes after CBT (Hanley et al., 2010).

4.2.1 Cytotoxic T lymphocytes

Ex vivo generation of T cells from CB naïve T cells has been achieved in several methods using CD3/CD28 costimulation, interleukin (IL)-2, and IL-7 (Mazur et al., 2008; Davis et al., 2010). Moreover, several researchers successfully have generated antigens-specific cytotoxic T lymphocytes (CTLs) from CB. Park et al. developed a protocol to in-vitro-prime and

expand CMV-specific CTLs from CB (Park et al., 2006). Recently, Hanley et al. reported the generation of single cultures of CTLs from CB that are specific for CMV, Epstein-Barr virus (EBV) and adenovirus (Adv) (Hanley et al., 2009). The CB CTLs recognized multiple viral epitopes, including CD4-restricted Adv-hexon epitopes and immunosubdominant CD4- and CD8-restricted CMVpp65 epitopes. A clinical trial using CB derived multivirus specific CTLs for prevention and treatment of these virus infection in CB transplant is now underway. To generate CB derived T cells recognizing B-lineage ALL because GVT effects are largely mediated by CTLs, several researchers developed CB derived T cells are expanded and genetically modified to express CD19 chimeric antigen receptors (Serrano et al., 2006; Micklethwaite et al., 2010). The genetically modified T-cell clones revealed an ability to lyse CD19+ leukemic cells specifically and repetitively.

4.2.2 NK cell

NK cells are a subset of lymphocytes with functions associated with innate immunity. NK cells also have been found to substantially contribute to GVT effects. Adoptive immune therapy with NK cells to treat malignancy is actively being investigated in early phase clinical trials. Ruggeri et al. reported the PB derived NK cell alloreactively is capable of preventing relapse of AML in the setting of killer immunoglobulin-like receptor (KIR) ligand-mismatched haploidentical HSCT (Ruggeri et al., 2002). Two retrospective studies on the effects of KIR ligand-mismatching in CBT for leukemia have result in conflicting results. Willemze et al. reported that a favourable effect of KIR ligand-mismatching on relapse rate and survival (Willemze et al., 2009), whereas Brunstein et al. reported no effect on relapse (Brunstein et al., 2009). The impact of KIR ligand-mismatching on relapse after CBT remains to be determined. NK cells are present at the similar percentages in both CB and PB. However, CB NK cells express a relatively higher percentage of inhibitory receptors, such as CD94/NKG2A and KIR (Verneris & Miller, 2009). The expanded CB NK cells exhibit anti leukemic activity in mouse model (Xing et al., 2010). Based on these data, the efficiency of CB NK cells to treat leukemia relapse is now underway.

4.2.3 Regulatory T cell

Regulatory T cells (Tregs) are a suppressive subset of the naturally occurring T cells characterized by their constitutive expression of CD4 and the IL-2 receptor α chain (CD25). Tregs are also characterized by high levels of the forkhead box protein 3 (FoxP3). Tregs can abrogate GVHD in murine models of major histocompatibility complex (MHC) mismatched allogeneic HSCT through suppression of alloreactive effector T cells. In contrast to Tregs from PB, Tregs are readily purified from CB. CB Tregs have greater expansion potential when compared to PB Tregs (Tolar et al., 2009). Brunstein et al. reported that infusion of ex vivo expanded Tregs from CB reduced the incidence of grades II to IV acute GVHD in CBT recipients compared with historical controls without Tregs (Brunstein et al., 2011).

4.2.4 MSCs

MSCs were initially described as a BM-derived mononuclear cell population adhered to plastic with a fibroblast-like morphology, when cultured ex vivo. Thereafter, MSCs can also be isolated from CB (Tolar et al., 2009). These cells are capable of differentiation into multiple lineages, including bone, cartilage and adipocyte cells in particular. The functional aspects of MSCs include tissue repair, hematopoietic engraftment support, immune

modulation. Clinical trial studying the effects of BM derived MSCs for the treatment of standard therapy-resistant severe GVHD has been initiated recently with promising results (Le Blanc et al., 2008). However, whether CB derived MSCs have similar beneficial effects for the treatment of severe GVHD is unknown.

5. Problem of donor cell leukemia

Donor cell-derived hematological malignancy is a rare complication after allogeneic HSCT. Previous studies reported that 0.12-5% of patients developed donor cell leukemia (DCL) after allogeneic HSCT (Hertenstein et al., 2005; Flynn & Kaufman, 2007; Wiseman, 2010). Several reports demonstrated that donor cell-derived hematological malignancy occurred in patients after CBT (Matsunaga et al., 2005; Fraser et al., 2005; Ando et al., 2006; Sevilla et al., 2006; Mitsui et al., 2007; Nagamura-Inoue et al., 2007; Hamaki et al., 2008; Konuma et al., 2009b; Crow et al., 2010; Castleton et al., 2010; Ballen et al., 2010; Wang et al., 2011). Ballen et al. reported the occurrence of donor-derived hematological malignancies after double CBT (Ballen et al., 2010). Sixteen patients developed a second hematological malignancy (both cases of MDS/myeloproliferative diseases (MPD) and 14 of the lymphomas) at a median of 134 days after double CBT. The mechanism for causing DCL after allogeneic HSCT is not well understood. The presence of preleukemic clones found only rarely in CB samples might contribute to the development of DCL after CBT (Mori et al., 2002). Moreover, various factors including impaired tumor surveillance, chronic antigenic stimulation by differences between donor and recipient cells, perturbations within the host BM microenvironment, premature aging of the donor cells, and the associated chromosomal instability might contribute to the development of DCL after allogeneic HSCT (Flynn & Kaufman, 2007; Wiseman, 2010). It has been hypothesized that donor cell-derived hematological malignancy may be substantially more frequent with a CB source of stem cells (Greaves, 2006). Further research and the increasing number of reports will improve understanding of the clinical implications of the donor cell-derived hematological malignancies after CBT.

6. Conclusion

Clinical results of CBT for acute leukemia have improved recently in adult patients. In addition to the potent HSCs in CB, multiple populations of stem cells with stem cell properties have been identified from CB and have led to the idea that CB can be used for regenerative therapies. In fact, clinical trials are now underway in type 1 diabetes, cerebral palsy and peripheral vascular disease. Moreover, recent studies demonstrated that it is possible to generate induced pluripotent stem (iPS) cells from human CB (Giorgetti et al., 2009; Haase et al., 2009; Hu et al., 2011; Broxmeyer et al., 2011). These data offer CB derived iPS cells are also considered an ideal source for future regenerative therapies.

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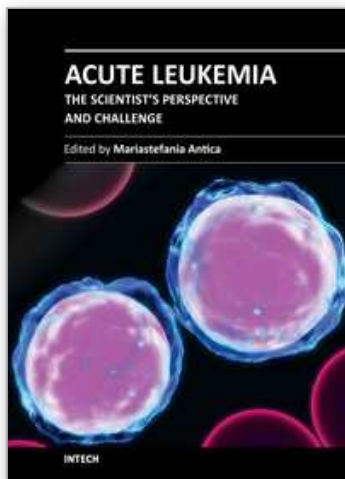
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This book provides a comprehensive overview of the basic mechanisms underlying areas of acute leukemia, current advances, and future directions in management of this disease. The first section discusses the classification of acute leukemia, taking into account diagnoses dependent on techniques that are essential, and thankfully readily available, in the laboratory. The second section concerns recent advances in molecular biology, markers, receptors, and signaling molecules responsible for disease progression, diagnostics based on biochips and other molecular genetic analysis. These advances provide clinicians with important understanding and improved decision making towards the most suitable therapy for acute leukemia. Biochemical, structural, and genetic studies may bring a new era of epigenetic based drugs along with additional molecular targets that will form the basis for novel treatment strategies. Later in the book, pediatric acute leukemia is covered, emphasizing that children are not small adults when it comes to drug development. The last section is a collection of chapters about treatment, as chemotherapy-induced toxicity is still a significant clinical concern. The present challenge lies in reducing the frequency and seriousness of adverse effects while maintaining efficacy and avoiding over-treatment of patients.

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