# Chapter 16
# Haplo-cord Transplantation: Overcoming the Limitations of Umbilical Cord Blood (UCB) Transplantation (UCBT)

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## 1 Introduction

Originally proposed by Fernandez et al., the infusion of umbilical cord blood (UCB) cells with CD34-selected donor stem cells from an adult typically results in rapid hematopoietic recovery from adult donor cells that are over time replaced by definitive hemato- and lymphopoiesis from the cord blood graft. Fernandez et al. reported in 2001 three patients with advanced hematologic malignancies who underwent UCB transplant (UCBT) after myeloablative conditioning supported by coinfusion of adult haploidentical CD34 cells [1]. The same group has since performed 87 such transplants and detailed results were reported in 2009 on the 55 initial patients [2, 3]. Six other groups have reported outcomes of cord blood transplant supported by coinfusion of adult, usually haploidentical cells [4–8]. The group at the University of Chicago pioneered this technology in the USA.

## 2 Initial Data on Haplo Cord—University of Chicago

Our original protocol initiated at the University of Chicago in 2005 included two cohorts with different intensity conditioning. In the intensive cohort, patients received myeloablative conditioning, consisting of thiotepa, fludarabine, and total body irradiation (TBI 200 cGy BID for 3 days). Only 13 patients were accrued, most of them with advanced hematologic malignancies. Though all engrafted rapidly, there was excessive toxicity mainly due to interstitial pneumonitis and this regimen has been abandoned. It is likely that this toxicity was related to excessive toxicity of the conditioning regimen, because similar problems were observed in recipients of related and unrelated donor transplantation [9]. The large majority of patients since then have received a widely utilized reduced intensity conditioning consisting of

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fludarabine (25 mg/m2 × 5), melphalan, (140 mg/m2 × 1 or 70 mg/m2 × 2) and thymoglobulin® (4 mg/kg × 4 doses, and more recently × 3 doses for patients over the age of 50). Posttransplant graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus (target level 5–15 ng/ml) and mycophenolate mofetil. Supportive care followed usual transplant procedure with prophylactic quinolone until engraftment, antifungal, pneumocystis, and antiviral prophylaxis. Cytomegalovirus (CMV) prophylaxis was modeled on our initial studies of CMV prophylaxis with high-dose valacyclovir in T-depleted transplant recipients; a variant of this regimen was also recently used by the Seattle group. Monitoring for Epstein–Barr virus (EBV) was not routinely performed in the initial patients.

We initially reported on 45 patients; their median age was 50, weight 80 kg, and 58 % had active disease. Neutrophil engraftment occurred at 11 days (interquartile range, IQR, 9–15) and platelet engraftment at 19 days (IQR, 15–33). In the majority of patients, early haploidentical engraftment was replaced by durable engraftment of UCB by 100 days, with regular persistence of minor host and/or haplo-hematopoiesis. Percentage of haplo chimerism at day 100 correlated with haplo CD34 dose ($p = 0.003$). Cumulative incidence of acute GVHD (aGVHD) was 25 % and chronic GVHD was 5 %. Actuarial survival at 1 year was 55 %, progression-free survival (PFS) 42 %, nonrelapse mortality (NRM) 28 %, and relapse 30 % [7]. Average duration of admission and transfusion requirements compared favorably with those reported from other institutions with double UCBT.

## 3 Modifications to the Initial Protocol

While the general treatment strategy has remained unchanged since the report on our initial patients, important modifications have been introduced as these studies were continued at the University of Chicago and at Weill Cornell Medical College in New York (WCMC). The most important ones relate to donor selection and cell dose infused.

### *3.1 Donor Selection*

Many groups have reported on the role of donor-specific human leukocyte antigen (HLA) antibodies (DSA) in graft rejection, and anecdotally we too have observed cases of graft failure associated with DSA [10–12]. We currently check for the presence of DSA in all recipients, attempt to avoid donors targeted by DSA, and, if unavoidable, attempt to reduce the burden of DSA by plasma exchange, intravenous immunoglobulin (IVIG), rituximab, and/or proteasome inhibitor [13]. UCB selection now also takes into account cord blood viability, an important determinant of cord blood engraftment [14].

### 3.2 Cell Dose Haplo Donor

In the initial trial, the graft cell dose was calculated based on T-cell dose. Some of the recipients received extremely high doses of CD34- selected cells, which was associated with failure of the cord blood graft. Currently we limit the dose of the haplo graft to a maximum of $5 \times 10^6$ CD34/kg recipient weight.

Since the introduction of these modifications in graft selection and cell doses, failure of the UCB unit has become rare, with only three instances among 40 patients. In two of the three cases, the failure of the cord blood graft could be attributed to technical issues.

### 3.3 Cell Dose Cord Blood Unit (CBU)

While emphasizing cord blood quality, we have deemphasized cord blood cell dose. In an ongoing study, we are systematically studying the lowest threshold for cord blood units that are associated with durable CBU engraftment. Doses as low as $0.5 \times 10^6$ nucleated cells/kg have been followed by durable CBU engraftment. Definitive conclusions are not possible yet, but at present, no adverse impact of lower cell dose on long-term engraftment has been observed. We hypothesize that the acceptance of lower UCB cell doses may ultimately result in improvement in outcomes, because often, and particularly in minorities, smaller CBU's are better matched CBU's and there is increasing evidence that better matching is associated with improved outcome in UCB transplant [15, 16].

### 3.4 Supportive Care

Because of the low incidence of chronic GVHD, GVHD prophylaxis has been tapered and mycophenolate is discontinued on day 28. Close monitoring for EBV reactivation and aggressive intervention with rituximab upon reactivation are now standard. For patients more than the age of 50, with a high incidence of EBV reactivation, the dose of antithymocyte globulin (ATG) has been reduced [17]. During 2013, pretransplant trimethoprim-sulfamethoxazole, long standard, was omitted at WCMC, and three cases of toxoplasmosis (two disseminated and one central nervous system, CNS) were observed. Polymerase chain reaction (PCR) monitoring for toxoplasma is now routinely performed for patients at WCMC [18]. Other aspects of supportive care, particularly broad spectrum azoles, posttransplant neupogen, and intensive CMV prophylaxis remain standard [19].

## 4 Comparison Between Haplo-Cord and Double Cord Transplantation

As of October 2013, 99 patients had been treated at University of Chicago and WCMC, using the same conditioning regimen. We compared our outcomes with those of 737 adults undergoing double UCBT as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) [20]. Patients undergoing haplo-cord transplant were significantly older (median age 54 vs. 48, $P = 0.0096$), more frequently were of minority ethnicity (60 % white vs. 76 % white, $p = 0.0013$) and had higher risk disease (45 % American Society for Blood and Marrow Transplantation, ASBMT, high risk vs. 23 % ASBMT high risk). In order to adjust for such imbalances, a case cohort study was performed and controls were selected based on patient age, gender, race, disease type, disease stage pretransplant, Karnofsky Performance Status (KPS), and year of transplant. One to four matched controls were identified for each patient and the final control group had 344 patients. Patient characteristics are shown in Table 16.1. The median age of the patients was 54. More than half had acute leukemia or myelodysplastic syndromes (MDS) and one-third had lymphoid disorder. A considerably higher percentage of patients in the haplo-cord group had high-risk disease, (44 % vs. 34 %, $p = 0.06$).

In multivariate analysis, engraftment of neutrophils and platelets was considerably faster after haplo-cord transplantation than after double UCBT. By day 30, 91 % of haplo-cord transplant recipients had achieved neutrophil recovery and 53 % platelet recovery vs. 72 % and 6 % of controls respectively ($P < 0.0001$ for both platelet and neutrophil recovery (Fig. 16.1 and Table 16.2). Survival was also superior at all time points ($p = 0.0069$) and the survival advantage became more apparent over time. At 4 years, 43 % of haplo-cord recipients remained alive vs. 21 % of double-cord recipients ($p = 0.0053$). These data strongly suggest a considerable advantage of haplo-cord transplant over double-cord-blood transplantation. This advantage extends from more rapid hematologic recovery to shorter duration of admission and improvement in overall survival.

## 5 Experience in Other Groups

Two groups in Spain have also extensively studied cord blood transplantation supplemented by third party donor cells as has a group from the Netherlands, investigators from the National Institute of Health (NIH) and recently from Memorial Sloan Kettering Cancer Center in New York [4–7]. All of them confirmed rapid hematologic recovery, long-term dominance of the UCB graft, and most also described a low incidence of acute and chronic GVHD. The Spanish group has the largest experience using myeloablative conditioning. Their GVHD prophylaxis consisted of calcineurin inhibitors combined with steroids. In their series, there were six cases of grade III–IV acute GVHD out of 55 recipients. There were also three cases of extensive chronic GVHD. Despite this low incidence of severe GVHD, the relapse rate was only 17 % at 1 year. The incidence of opportunistic infections particularly CMV disease was

**Table 16.1** Characteristics of haplo-cord recipients and CIBMTR matched double cord transplant recipients

| Variable | Control ($N = 344$) | Case ($N = 99$) | $P$ |
|---|---|---|---|
| Age, med (range) Y | 51 (19–80) | 54 (19–73) | 0.6483 |
| Male | 202 (58 %) | 61 (62 %) | 0.6053 |
| Race | | | |
| White | 225 (65 %) | 59 (60 %) | 0.5192 |
| Black | 70 (20 %) | 25 (25 %) | |
| Others | 49 (14 %) | 15 (15 %) | |
| Disease type | | | |
| AML | 191 (56 %) | 54 (55 %) | 0.9839 |
| ALL | 45 (13 %) | 12 (12 %) | |
| CLL/Other | 15 (4 %) | 3 (3 %) | |
| CML | 11 (3 %) | 4 (4 %) | |
| MDS/MPS | 41 (12 %) | 12 (12 %) | |
| Other AL | 6 (2 %) | 1 (1 %) | |
| NHL | 24 (7 %) | 9 (9 %) | |
| HL | 11 (3 %) | 4 (4 %) | |
| Disease stage | | | |
| Early | 147 (43 %) | 34 (34 %) | 0.1520 |
| Intermediate | 80 (23 %) | 21 (21 %) | |
| Advanced | 117 (34 %) | 44 (45 %) | |
| KPS | | | |
| 60–80 % | 71 (21 %) | 21 (21 %) | 0.9015 |
| 90–100 % | 273 (79 %) | 78 (78 %) | |
| Year of TX | | | |
| 2007–2009 | 79 (23 %) | 19 (19 %) | 0.4254 |
| 2010–2013 | 265 (77 %) | 80 (81 %) | |

*AML* acute myeloid leukemia, *ALL* acute lymphocytic leukemia, *CLL* chronic lymphoid leukemia, *CML* chronic myelogenous leukemia, *MDS* myelodysplastic syndromes, *KPS* Karnofsky Performance Status, *TX* treatment, *CIBMTR* Center for International Blood and Marrow Transplant Research, *MPS* Myeloproliferative syndrome, *AL* acute leukemia, *NHL* non-Hodgkin's lymphoma, *HL* Hodgkin Lymphoma

considerable in their studies and seemingly higher than we identified in our studies. This may reflect differences in infection prophylaxis, and in GVHD prophylaxis and treatment. The routine use of steroids for GVHD prophylaxis as utilized in Spain may result in an increased propensity for infectious complications. Incidence of EBV reactivation and EBV posttransplant lymphoproliferative disorder (PTLD) was similar to what we observed in our series.

In our own studies, the source of adult donor cells has been restricted to haploidentical related donors. The Spanish group used mismatched unrelated donors in a substantial proportion of their patients; this allows additional opportunity for occasional patients who lack access to family donors. It is also possible that characteristics of the adult donor graft such as HLA type and killer immunoglobulin-like receptors (KIR) type further modulate gamma-Valerolactone (GVL) and Graft versus Host (GVH) occurrence. The ability to select from a large pool of unrelated donors based provides further opportunities to prospectively study the impact of such parameters on transplant outcome.

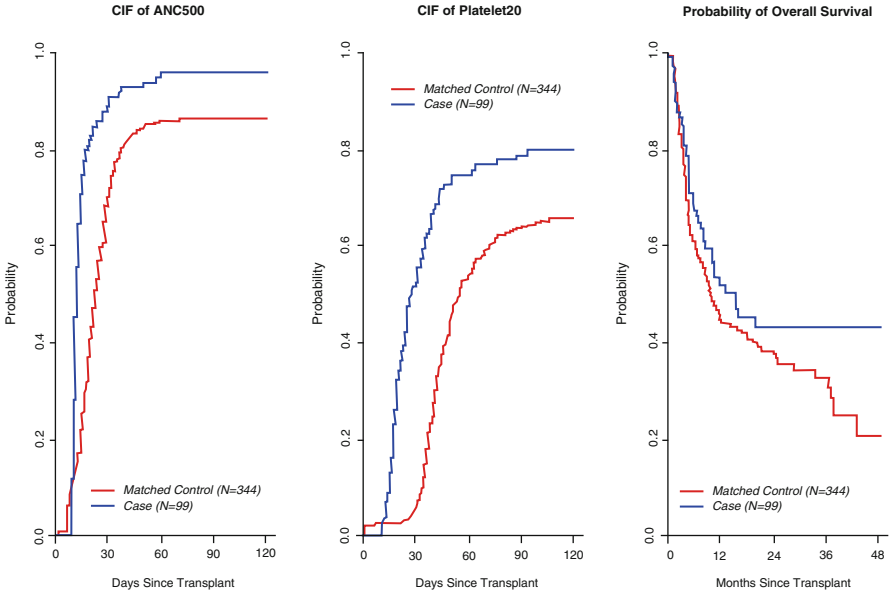


**Fig. 16.1** Haplo-cord transplant vs. matched CIBMTR DCBT controls. **a** Neutrophil engraftment ($p < 0.0001$). **b** Platelet engraftment ($p < 0.0001$). **c** Overall survival, $p = 0.07$. *CIBMTR* Center for International Blood and Marrow Transplant Research, *DCBT* double umbilical cord blood transplant, *ANC* absolute neutrophil count, *CIF* Cumulative Incidence function

**Table 16.2** Multivariate analysis comparing haplo-cord transplant vs. CIBMTR double UCBT (dUCBT)-matched controls

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

*ANC* absolute neutrophil count, *CIBMTR* Center for International Blood and Marrow Transplant Research, *dUCBT* double umbilicical cord blood transplant

The group from Madrid addressed occasional graft failures of the UCB unit by infusion of a second UCB unit, which tended to engraft and outcompete the residing adult graft. More recently they have analyzed the patterns of early chimerism, and found that the day 14 or day 21 detection of UCB T-cell chimerism was predictive of long-term CBU engraftment [21]. Absence of early CBU-derived T-cell chimerism could thus be used to guide treatment decisions.

The groups from the Netherlands and Spain have utilized haplo-cord transplant in pediatric patients and also as a way to expedite engraftment after transplant of a low cell dose CCR5−graft in HIV patients [22].

The group from NIH has focused on patients with aplastic anemia, a disease in which outcomes of cord blood transplantation were previously poor. In their series, 11 of 12 heavily transfused patients engrafted and had durable responses [5]. In a recent abstract, they provide preliminary evidence that natural killer (NK)-cell-mediated reactions between haplo and cord blood grafts due to KIR incompatibility may provide yet another mechanism of graft failure/rejection [23]. If confirmed, KIR incompatibility between different donors may need to be avoided.

Lastly, the group from Memorial Sloan Kettering Cancer Center (MSKCC) has recently presented preliminary data introducing yet another variant of the procedure [8]. They combined double UCB Stem Cell Transplant (SCT) with a haploidentical graft. The rationale for using two UCB units was threefold: (1) allowing comparison with their own historical data in double UCB SCT, (2) avoiding graft failure due to poor quality of occasional UCB units, and (3) exploiting potential GVL effects from infusion of two UCB units. As opposed to the other groups, they do not utilize ATG, for concern over excessive immunosuppression. They again confirm rapid hematopoietic reconstitution with a time to discharge that is much shorter than in their previous experience with double UCBT. The long-term benefit of a triple graft remains to be demonstrated.

## 6 Long-term Immune Reconstitution

The Spanish group as well as the Chicago group studied long-term immune reconstitution [24]. The Chicago group assessed lymphocyte subsets, T-cell diversity, Cylex Immuknow assay (a measure of T-cell responsiveness), and serological response to pneumococcal vaccination [25]. NK-cell and B-cell reconstitution were rapid at 1 month and 3 months, respectively. T-cell recovery was delayed with gradual increase in the number of T cells, starting around 6 months posttransplantation, and was characterized by a diverse polyclonal T-cell repertoire. Recovery of immunoglobulins and responsiveness to pneumococcal vaccination was observed. T-cell spectratype was often remarkably diverse. They concluded that immune reconstitution after haplo-cord transplantation was similar to that seen after cord blood transplantation, despite infusion of much lower cord blood cell doses.

The Spanish group previously reported similar observations in their patients [26]. NK and B cells recovered to normal values by the 6th and 9th months respectively. This was somewhat slower than in the Chicago series, possibly because of routine use

of posttransplant steroids for GvHD prophylaxis. Recovery of T cells was slower, naive cells lagging behind those of memory and effector cells. Serial analyses of signal joint T cell receptor (TCR) excision circles showed a general pattern of very low levels by the 3rd month after CBT, followed by recovery to levels persistently similar or higher than those observed before transplantation and in normal controls. In both the Chicago and Madrid series, early T-cell recovery derives from the adult donor followed by gradual replacement by cells of UCB origin. It is likely that most of the early B cells after haplo-cord transplant are also UCB derived. Of interest, the NIH group observed immediate UCB-derived T-cell reconstitution, without detectable adult donor-derived T cells at any moment. This strikingly different kinetic profile of immune reconstitution may be due to the use of a different formulation of ATG. Nobody has evaluated the origin of NK and B cells.

## 7 Conclusion and Perspectives

The cumulative experience with this approach corroborated by us and others indicates that for the large majority of patients, hematopoietic recovery of both myeloid and megakaryocytic lineages is rapid and that this is an efficient and tolerable procedure. Our matched control comparison with double cord blood transplantation strongly suggests that this enhanced recovery results in improved survival. Increasing experience has allowed us to address certain issues of supportive care and have raised intriguing possibilities for further development. Traditionally cord blood transplantation has been limited by the necessity of a large CBU infusate and has therefore been more extensively utilized in children. In adults, cell dose barriers resulted in ineligibility of many patients. Those undergoing transplant often had prolonged admissions and delayed recovery, increasing the risk and expense of the procedure. These barriers to transplant have been largely overcome by haplo-cord transplantation. While many centers limit dUCB SCT to patients below a certain age limit or weight, no such barriers have been used in our programs.

In contrast to experience with single or double UCBT, the umbilical cell cord dose does not correlate with time to neutrophil or platelet recovery after haplo-cord transplant. Even very low CBU doses of $< 1 \times 10^6$ Nucleated blood cells (NBC)/kg have reliably engrafted after initial recovery was provided by the haplo graft. The ability to reduce the CBU dose may in fact constitute one of the greatest advantages of the haplo-cord procedure. The lower UCB threshold dose effectively increases the cord blood inventory by several folds and this may allow one to identify appropriately matched units for a higher percentage of recipients. This may be especially important for African American patients since UCB units of AA descent, presumably on average better matched, tend to have considerably lower cell content. Ongoing studies are attempting to identify the lowest acceptable dose of UCB cells that can be used in this setting. For patients with access to multiple UCB units, choice between donors may no longer be guided by cell dose, but by desirable UCB characteristics such as KIR type or National Integrated Medical Association (NIMA) matching [24].

Numerous options now exist for patients lacking a matched related donor. The largest experience has been accrued with transplantation from adult unrelated donors and this remains the de facto standard. But preliminary data suggest that haplo-cord transplantation may represent an equally effective alternative. The Spanish group compared the outcomes of allogeneic transplantation using haplo-cord transplant with that of those undergoing unrelated donor transplant and found similar survivals [27]. Preliminary analysis of outcomes at our own center in patients over 50 finds outcomes with haplo-cord transplant that are at least similar and likely superior to those with adult unrelated donor transplant. The low rates of chronic GvHD, combined with low rates of disease recurrence after cord transplantation, may indeed have their highest impact in older patients who often have high-risk leukemia and are particularly vulnerable to the ravages of chronic GVHD. Prospective studies are required to address this issue.

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