Cord blood stem cell transplantation in primary immune deficiencies

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Purpose of review

Umbilical cord haematopoietic stem cell transplantation for primary immunodeficiencies is examined with other developments in treatment. Cord blood biology is reviewed, and advantages and disadvantages of umbilical cord blood stem cell transplantation for primary immunodeficiencies discussed. Clinical outcome data and future developments are reviewed.

Recent findings

Cord blood T lymphocytes become tolerant to host human leukocyte antigen antigens, but retain alloreactivity to other antigens, in part due to immaturity of cord blood T lymphocytes and dendritic cells. Although naïve T lymphocytes can generate herpes virus specificity after transplantation, the risk of viral death is increased within the first 100 days. The clinical success of umbilical cord blood stem cell transplantation for primary immunodeficiencies is reviewed and new methods for expanding the stem cell number or encouraging engraftment with the use of third-party haematopoietic or mesenchymal stem cells examined.

Summary

Many advantages make umbilical cord blood an attractive source of stem cells; over 100 umbilical cord blood stem cell transplantations have been performed for primary immunodeficiencies, with low rates of significant graft vs. host disease, despite significant human leukocyte antigen mismatch. Immune reconstitution is as good as for other stem cell sources: use of nascent stem cells in young recipients may have long-term advantages. Stem cell engineering to improve engraftment will expand potential beneficiaries of umbilical cord blood stem cell transplantation to older patients.

Keywords

primary immunodeficiency, severe combined immunodeficiency, umbilical cord blood stem cell transplantation

Curr Opin Allergy Clin Immunol 7:528–534.

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Current Opinion in Allergy and Clinical Immunology 2007, 7:528–534

Abbreviations

GvHD	graft vs. host disease
HLA	human leukocyte antigen
HSC	haematopoietic stem cell
HSCT	haematopoietic stem cell transplantation
PID	primary immunodeficiency
SCID	severe combined immunodeficiency
UCBSCT	umbilical cord blood stem cell transplantation

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Introduction

Umbilical cord blood stem cell transplantation (UCBSCT) for primary immunodeficiencies (PIDs) is placed in the context of other new developments in the field. The historical reasons for the dramatic improvement in outcome after haematopoietic stem cell transplantation (HSCT) for PIDs is outlined, cord blood biology reviewed, and the advantages and disadvantages of UCBSCT for PIDs discussed, noting ready availability of the unit, lower risk of graft vs. host disease (GvHD) despite a degree of human leukocyte antigen (HLA) mismatch and higher frequency of unusual HLA types compared with bone marrow registries, naivety of lymphocytes against disseminated viral infection, prolonged immune reconstitution as well as low stem cell dose for recipients over 15 kg. Clinical outcome data and likely future developments are reviewed.

Haematopoietic stem cell transplantation for primary immunodeficiencies

Genetically inherited disorders of innate or adaptive immunity usually present in early childhood and frequently lead to severe or fatal complications. The most serious, severe combined immunodeficiencies (SCIDs), present in early infancy and without treatment are fatal by the age of 1 year. These disorders affect development and/or function of T lymphocytes, and sometime B lymphocytes and natural killer cells. Other combined immunodeficiencies such as Wiskott–Aldrich syndrome, CD40 ligand deficiency or innate system disorders, such as chronic granulomatous disease, are less immediately life threatening, but registry data indicate poor long-term outlook. At the same time, allogeneic HSCT is now more successful in curing lethal forms of immunodeficiency with long-term survivors leading normal lives, often off all medication. Thus, the range of conditions

treated by HSCT has considerably broadened. Initially only patients who had an HLA-identical relative were transplanted as HSCT using other donors was considered to carry too great a risk of fatal GvHD.

Unrelated HLA-matched donor transplants were first performed in the 1970s. The first active bone marrow donor registry (The Anthony Nolan Trust) was established in 1974. Now over 10 million volunteer stem cell donors are registered worldwide. In 1981, the introduction of T lymphocyte depletion to remove alloreactive lymphocytes from the bone marrow source enabled transplantation across HLA barriers. This meant that patients without an HLA-identical donor could receive T lymphocyte-depleted marrow from an HLA-haploidentical parent. More recent innovations such as use of granulocyte colony-stimulating factor-mobilized peripheral blood HSCs, concentration of diagnosis and treatment in specialized centres, early identification of infection using PCR techniques, more effective antiviral and antifungal treatments (including infusion of cytotoxic T lymphocytes specific for Epstein–Barr virus, cytomegalovirus and adenovirus), better treatment of GvHD, including the use of monoclonal antibodies such as infliximab and basiliximab, in combination with improved supportive care, have improved the success rate for HSCT for SCID from 40 to 80% for HLA-haploidentical transplantation.

The use of UCBSCs for HSCT needs evaluating in this context. The first UCBSCT was performed in 1988 for Fanconi's anaemia [1]. International bone marrow donor registries are increasingly holding data on donated cord blood. A cord blood bank was established in 1993 in New York; currently more than 200 000 cord blood units are stored in 37 cord blood banks.

Cord blood biology

Whilst solid organ transplant recipients require lifelong immunosuppression to prevent graft rejection, HSCT grafts usually become tolerant of recipients, eliminating the need for long-term immunosuppression. When tolerance does not develop fully, however, acute or chronic GvHD ensues. Cord blood T lymphocytes seem to become more readily tolerant to host HLA antigens than bone marrow T lymphocytes, which may reduce the risk and severity of GvHD for a given degree of HLA mismatch following UCBSCT. Cord blood T lymphocytes remain tolerant to the host despite retaining alloreactivity to third-party cells [2].

Increased tolerance associated with functional immaturity of dendritic cells

Initiation of acute GvHD is mediated by $CD8^+$ T lymphocytes dependent on residual host antigen-presenting cells, but intensified by donor antigen-presenting cells, such as dendritic cells. $CD4^+$ T lymphocytes are particularly important in chronic GvHD. There are fewer plasmacytoid dendritic cells and myeloid dendritic cells in cord blood, and they are more likely to express an immature or tolerogenic phenotype characterized by low expression of major histocompatibility II and costimulatory molecules. Interferon-α and tumor necrosis factor-α production is diminished in cord blood immature myeloid dendritic cell and plasmacytoid dendritic cells, and immature dendritic cells from cord blood are also potent inducers of $CD4^+$ T regulatory cells [3••].

Functional immaturity of umbilical cord blood lymphocytes

Activated UCB lymphocytes produce lower amounts of cytokines after stimulation compared with activated adult T lymphocytes, including lower amounts of interferon-γ and tumor necrosis factor-α, important inducers of GvHD. UCB lymphocytes produce less interleukin-2 and -4 as well as demonstrating less antigen-specific cytotoxicity. There are lower levels of expression in genes activated by the nuclear factor of activated T lymphocytes pathway, many of which are responsible for cellular activation and differentiation [4].

Telomere length changes

Telomere length critically determines the replicative lifespan of dividing cells as telomeres shorten with every mitotic division. When telomeres reach a critical length the cells become senescent. Studies with HSCs have shown a consistent correlation between telomere length and cell or organism age, with shorter telomeres in senescence. Telomere lengths in donor and recipient haematopoietic cells after marrow and peripheral blood HSCT show an accelerated rate of shortening after transplant compared to age-matched controls corresponding to roughly 8–60 years of normal aging, with measurable immune dysfunction and telomere attrition in long-term allogeneic transplant recipients [5]. The time for donor telomeres to reach critical length that induces senescence would be expected to be greater in recipients of young HSCs than recipients of older HSCs. This may not matter for older patients but for young children, in particular, their likely lifespan may exceed that of the transplanted HSCs, as predicted by telomere shortening. Whilst transplanted cord blood mononuclear cells have a significant net decrease in telomere length compared with the cord blood donor, they retain their initial significantly longer telomere length compared to transplanted peripheral blood HSCs from adult donors [6••].

Engraftment

After collection and storage, the nucleated cell count of a cord blood unit correlates closely with $CD34^+$ count. Cord bloods collected from male infants have a higher content of $CD34^+$ cells. $CD34^+$ count increases with

birth weight, particularly when this exceeds 3000 g. There is a trend towards increased $CD34^+$ cell content in cord blood from Caucasian mothers [7•].

Antigen-specific T lymphocyte function

Naïve T lymphocytes present in cord blood are capable of generating T lymphocytes with specificity for herpes viruses within the first 100 days after transplantation. Standard immunosuppression (cyclosporin and steroids) does not appear to interfere with development of antigen specific T lymphocytes. As cord blood does not contain antigen-specific memory T lymphocytes, the antigen-specific T lymphocytes detected during the first 12 months after cord blood are most likely derived from the naïve T lymphocytes infused at the time of transplantation [8••].

Infectious complications

Infection is a risk during three phases of HSCT:

- Pre-engraftment: bacterial and fungal infection due to neutropenia, lymphopenia, mucositis, central venous catheters and acute GvHD.
- After engraftment: viral reactivations occur, particularly cytomegalovirus and adenovirus.
- After day +100: relatively immature cellular and humoral immunity mean varicella zoster virus and pneumococcal infections are a risk.

In the first 100 days post-UCBSCT, the risk of bacterial infection is diminished compared to other HSCT, but the risk of viral death is increased, even when compared to recipients of T cell-depleted marrow. This is perhaps unsurprising, as despite in-vitro data showing that UCB T lymphocytes develop antiviral responses, unlike T lymphocytes from adult donors, UCB T lymphocytes will not have encountered viruses such as Epstein–Barr virus, cytomegalovirus and adenovirus, so in-vivo responses will be poor in the first 100 days post-UCBSCT. There is a significantly higher risk of needing two or more courses of ganciclovir to treat cytomegalovirus reactivation after cord blood compared to other HSC sources. Human herpes virus 6 viraemia is most notable during weeks 2 and 3 following transplantation, and infection is more frequently observed among cord blood recipients with prior primary infection and higher viral load. UCBSCT recipients are more likely to die of viral infection in the first 100 days than recipients of T lymphocyte-depleted marrow. After day 100 there is no excess in infective deaths in UCBSCT recipients and no significant difference in the incidence of severe fungal infection regardless of HSC sources. The risk of serious infection among children receiving cord blood grafts is comparable to that of unmanipulated marrow and is lower than that of a T lymphocyte-depleted stem cell source. Among adult patients, despite an overall higher incidence of serious infections after cord blood compared with unrelated donor grafts, nonrelapse mortality and overall survival were not significantly different between HSC sources [9••].

Advantages and disadvantages of umbilical cord blood transplantation

There are a number of advantages of UCBSC over other HSC sources, but also some disadvantages.

Advantages

Advantages are listed in Table 1 and include the following.

Rapid access to the donor unit

Whilst a matched unrelated donor needs to be identified, assessed and harvested, a cord blood unit is already cryopreserved and can be at the transplant centre within a matter of days. The median time from search to availability for cord blood was 13.5 days (range 2–387 days) compared with 49 days (range 32–293 days) for a bone marrow donor in one study [10]. Rapid identification of a donor is important when transplanting infected immunodeficient patients, particularly those with SCID.

Ease of arranging date for transplantation

As the cord blood unit is readily available, the transplantation date and conditioning protocol is easily planned without reference to donor or harvest list availability.

No medical risk to the donor

The risk of bone marrow harvest to the donor is very small but finite, whereas there is no risk to donating UCBSC.

Lower risk of latent viral transmission

There is a lower risk of latent viral transmission from the donor to the recipient because most neonates are virologically naïve.

Table 1 Advantages and disadvantages of umbilical cord blood as a stem cell source for transplantation

Advantages
Rapid access to the donor unit
Ease of arranging date for transplantation
No medical risk to the donor
Lower risk of latent viral transmission
Lower risk of graft vs. host disease
Higher frequency of rare HLA haplotypes compared to bone marrow registries
Stem cell nascence
Disadvantages
Lack of availability of the donor for a boost haematopoietic stem cell transplantation
Lack of viral specific cytotoxic T lymphocytes
Slower engraftment
Reduced stem cell dose
Risk of transmitting unidentified genetic disease

HLA, human leukocyte antigen.

Lower risk of graft vs. host disease
There is a lower risk of GvHD and it is possible to perform transplants with two or three HLA antigen mismatches.

Higher frequency of rare HLA haplotypes compared to bone marrow registries
There is a higher frequency of rare HLA types represented on the cord blood registries as individuals from ethnic minorities carrying these types are more likely to donate UCBSC than bone marrow. This is particularly helpful in PIDs where there is an excess of ethnic minority patients due to consanguinity.

Stem cell nascence
The HSC telomere length is longer in patients who have received UCBSCs than in those who have received peripheral blood stem cells from older donors. UCBSCs may have greater self-renewing capacity and longevity than those derived from an adult donor. As many transplanted PID patients are infants or young children, giving HSCs with a greater proliferative lifespan is theoretically more attractive. Long-term studies will determine whether this is clinically relevant.

Disadvantages

Disadvantages to use of UCBSCs are listed (Table 1) and include the following.

Lack of availability of the donor for a boost haematopoietic stem cell transplantation
Low-intensity conditioning regimens are increasingly employed in patients with significant organ damage at time of transplant; whilst transplant-related mortality may be reduced, donor chimerism may decrease over time and rescue strategies including infusion of further mature T lymphocytes or stem cells from the original donor can rescue and reverse this decrease in chimerism. Once UCBSCs have been transplanted, further HSCs cannot be obtained from the original donor, except perhaps when a family relative was the donor.

Lack of viral-specific cytotoxic T lymphocytes
Whilst viral naivety of the neonate reduces the risk of transmitting virus from the donor to the recipient, it also means there are no activated virologically competent antigen-specific T lymphocytes within the cord to immediately neutralize disseminated viral infection in the transplant recipient. As many PID patients come to transplantation with disseminated infection, the time to clearance of virus is thus delayed and may result in a poor outcome.

Reduced stem cell dose
A $CD34^+$ stem cell dose of 1.7×10^5/kg is recommended for transplant, as lower doses are associated with slower, poor engraftment. UCBSC units contain finite cell counts; in one study, the median $CD34^+$ cell count would be satisfactory for a 12-kg individual [7•].

Slower engraftment
Engraftment tends to be slower in patients who have received cord blood related to the lower stem cell dose. This may have disadvantages in terms of effective immunity against infection, but may be preferable where there is widespread mycobacterial disease or inflammation, e.g. maternofoetal engraftment or Omenn syndrome where slower engraftment with more naïve, less readily activated cells may lead to less inflammation at the time of engraftment and therefore improved patient survival.

Risk of transmitting unidentified genetic disease
There is a theoretical risk of transmitting a genetic disease to the recipient if it has not been identified in the donor.

Umbilical cord blood haematopoietic stem cell transplantation for primary immunodeficiency

There are now many papers from a large number of centres describing UCBSCT for PIDs. There are detailed reports of 30 UCBSCTs for SCID with 77% survival and GvHD incidence of 30% (17% in six of six HLA matches) (Table 2).

There are detailed reports of 60 UCBSCTs for other PIDs, with 85% survival and GvHD incidence of 38% (3% in six of six HLA matches) (Table 3). There is incomplete information on a number of other patients [19•]. A variety of conditioning regimens have been used successfully, including myeloablative and reduced intensity conditioning protocols. Severe (grade III/IV) GvHD was uncommon, occurring in only 6% of patients. Two deaths were associated with GvHD and three patients experienced chronic GvHD; 100% donor chimerism and normal immune reconstitution is normally achieved. Mortality was due to various factors including infection ($n = 3$), veno-occlusive disease ($n = 1$) and chronic lung disease ($n = 3$). In our own practise, 20 children have received UCBSCT (13 SCID). Sixteen were six of six HLA-matched – no grade III/IV GvHD was experienced. All patients engrafted. Overall survival was 70%. There was 100% B lymphocyte function in evaluable patients. We prefer UCBSCs to T cell-depleted haploidentical HSCT in SCID patients and will accept a five of six HLA match. For larger patients with pre-existing viral infection, the choice is more difficult and UCBSC are used less often.

Future developments

The place of UCBSCT for PIDs is now well established. Strategies to overcome the disadvantages of using

Table 2 Cord blood transplantation for severe combined immune deficiencies

Diagnosis	Antigen match	No. patients	Conditioning	Graft vs. host disease grade II or greater	Partial/normal immune reconstitution	Survival (%)	References
Common γ chain	6/6	3	3	0	3	100	[11,12•,13,14,15•] (Slatter, personal communication)
	5/6	3	2	3	3	100	
	>5/6	3	2	1	2	67	
Janus-associated kinase 3	>5/6	1	1	0	1	100	[16]
T lymphocyte-negative, B lymphocyte-negative	6/6	1	0	0	1	100	[17]
Adenosine deaminase deficiency	6/6	5	1	2	2	40	[18] (Slatter, personal communication)
Other	6/6	7	5	3	5	29	[16,18,19•,20–22,23•] (Slatter, personal communication)
	5/6	5	5	0	4	80	
	<5/6	2	2	0	2	100	
Total		30	21	9	23	77	

UCBSCs are now being developed to widen the potential use (Table 4). The low stem cell dose and the associated risk of poor engraftment is the greatest challenge. Double or multiple UCBSC unit infusion has shown early, promising results with quicker engraftment [50,51•]. Ex-vivo expansion of UCB-derived T lymphocytes, whilst retaining a naïve and/or central memory phenotype with polyclonal T cell receptor diversity, may augment cord blood transplantation and improve rate and extent of immune reconstitution [52••]. A phase I trial in humans has demonstrated safety, although there was no change in time to engraftment [53]. Phase II studies are underway.

Coinfusion of purified HSCs [54,55•] or mesenchymal cells [56•,57•] derived from cord blood or third parties is currently being studied. This may improve engraftment and reduce GvHD. Other potential developments include the ex-vivo development of UCB-derived regulatory T cells [58••] and viral antigen-specific T lymphocytes.

Table 3 Cord blood transplantation for other immune deficiencies

Diagnosis	Antigen match	No. patients	Conditioning	Graft vs. host disease, grade II or greater	Partial/normal immune reconstitution	Survival (%)	References
Wiskott–Aldrich syndrome	6/6	2	2	0	2	100	[15•,18,24–26,27•,28]
	5/6	5	5	2	4	80	
	<5/6	2	2	1	2	100	
	UK	15	15	7	UK	80	
X-Linked lymphoproliferative disease	6/6	2	2	0	2	100	[29–31]
	5/6	2	2	0	2	100	
Haemophagocytic lymphohistiocytosis	6/6	1	1	0	1	100	[32–35]
	5/6	3	3	1	3	100	
Omenn syndrome	6/6	3	3	1	2	67	[15•,18,21,36–38]
	5/6	4	4	3	4	100	
Other T cell primary immune deficiencies	6/6	1	1	0	1	100	[16,31,39]
	5/6	2	2	1	2	100	
	<5/6	2	2	1	1	50	
Immune dysfunction, polyendocrinopathy, enteropathy, X-linked	6/6	2	2	0	2	100	[18,40•,41•]
	5/6	1	1	1	1	100	
Chronic granulomatous disease	6/6	1	1	0	1	100	[18,19•,42•]
	5/6	1	1	1	1	100	
	<5/6	1	1	0	1	100	
Severe congenital neutropenia	6/6	1	1	0	1	100	[39,43]
	5/6	1	1	0	0	0	
Shwachman–Diamond syndrome	6/6	1	1	1	1	100	[44,45]
	5/6	3	3	2	2	100	
Other non-T cell primary immune deficiencies	6/6	1	1	0	1	100	[46–49]
	5/6	1	1	0	1	100	
	<5/6	2	2	1	1	50	
Total		60	60	23	39	85	

UK, unknown.

Table 4 Future developments

Ex-vivo expansion of umbilical cord blood progenitor cells
Cotransplantation of umbilical cord blood stem cells and culture expanded mesenchymal stem cells
Cotransplantation of partially matched peripheral blood $CD34^+$ cells
Isolation and expansion of viral antigen-specific T lymphocytes
Coinfusion of umbilical cord blood-derived T regulatory lymphocytes
Coinfusion of umbilical cord blood-derived natural killer cells

Conclusion

UCBSCs are an alternative HSC source for PID patients and for some have a clear advantage. Overall, GvHD is less likely with HLA mismatches, but more than one HLA mismatch can still lead to GvHD and may compromise engraftment. Effective ways of increasing the stem cell count or improving engraftment by multiple cord infusion, ex-vivo expansion of UCBSCs or coinfusion of mesenchymal stem cells will open up UCBSCT to older, sicker patients, for whom it is least useful at present.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 590–591).

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