

# Umbilical cord-derived stem cell transplants – what's changed in three years?

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**ABSTRACT** Umbilical cord-derived haemopoietic stem cells (UCDSCs) were first shown to be capable of supporting sustained engraftment approximately 30 years ago, but their role as a transplant source has been slow to develop. Recent work, however, suggests an increasing future use of UCDSCs in both children and adults. The transplantation of UCDSCs is feasible, and concerns around cell dose and poor engraftment have been partly addressed with the use of double-cord donation. Other developments in this area include the potential for *ex vivo* expansion of UCDSCs and, intriguingly, the direct transplantation of UCDSCs into the marrow cavity. Clinical studies have confirmed the utility of UCDSCs and suggest that they have a particular role in patients who do not have an available sibling or fully matched unrelated donor. Given the potential availability of UCDSCs and the less stringent requirements for human leukocyte antigen matching to the recipient, the use of UCDSCs is likely to increase. This could, in theory, allow near-universal access to allogeneic transplantation for those patients who may benefit from the procedure.

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Although umbilical cord-derived stem cells (UCDSCs) have been available to clinicians for nearly three decades, the role of UCDSC transplants in the management of patients with either haematological malignancies, bone marrow failure syndromes or other disorders amenable to blood- or bone marrow-derived stem cell transplants has remained unclear. Early work in the area established that the stem cell dose was critical for engraftment; this limited the availability of sufficient CD34-positive stem cells, which therefore meant that the technique was largely confined to paediatric populations.

Two seminal papers published in the *New England Journal of Medicine* in 2004 confirmed the feasibility of the use of UCDSCs in adult patients.<sup>1,2</sup> These and other studies confirmed that the first choice source of stem cells for patients requiring allogeneic transplantation should be a human leukocyte antigen (HLA)-matched blood- or bone marrow-derived stem cell transplant from a sibling or unrelated donor, but that UCDSCs could be a reasonable alternative source of stem cells for adults who did not have recourse to a fully HLA-matched sibling or unrelated donor.

Two recent publications have further defined the role of UCDSCs in haematological malignancy. Eapen and colleagues reported on the outcome of transplantation using UCDSCs or bone marrow in children with acute leukaemia.<sup>3</sup> This large study of more than 500 patients allowed a comparison of the outcomes of UCDSC transplants versus those using bone marrow-derived stem cells but also provided data on the effects of an

HLA mismatch in both the UCDSC- and bone marrow-transplanted populations. The leukaemia-free survival of patients given UCDSCs, who were mismatched for either one or two HLA antigens, was similar to that of the fully allele-matched bone marrow transplant population. In the two antigen-mismatched UCDSC groups there was a higher transplant-related mortality, but this was balanced by a decrease in leukaemia relapse rates. The data support the use of HLA-matched and one or two antigen HLA-mismatched UCDSC transplants in children with acute leukaemia who require transplantation. Even in the paediatric group, however, it is clear that good HLA matching and a higher cell dose are associated with better outcomes, and cord blood banks should therefore be expanded to meet this need.

In a further recent study from Karolinska University Hospital the outcome of adult patients transplanted with either UCDSCs or mismatched unrelated volunteer donor stem cells was compared.<sup>4</sup> This is an important study which, although based on small patient numbers, informs the debate regarding the best source of stem cells for patients in whom an HLA-matched donor is not available. This study confirmed that delayed engraftment is a significant feature of UCDSC transplants in adults. Acute graft versus host disease remained a significant risk in both transplant groups, but it appeared (although the numbers were small) that chronic graft versus host disease might be less common in the UCDSC group. Transplant-related mortality remains a concern, with 30% of patients dying of transplant-related complications in the UCDSC group and 50% in the mismatched unrelated

donor cohort. Notwithstanding this, the actuarial three-year survival in the UCDCS group was 66%, which was significantly better than the unrelated donor group at 14%. The authors conclude that although delayed engraftment and graft versus host disease remain a significant problem in UCDCS transplantation in adults, the data support the use of UCDCSs rather than mismatched unrelated donor stem cell sources in this context.

Given that UCDCSs have a role as an alternative stem cell donor source for patients without recourse to fully allele-matched blood or bone marrow stem cell donors but that stem cell numbers are critical, has any progress been made recently in overcoming this constraint on the wider use of UCDCSs in adults?

Work has continued on the *ex vivo* expansion of UCDCSs, and there are now available combinations of cytokines that facilitate UCDCS expansion, particularly when allied with manipulations of artificial cell stroma to promote UCDCS growth.<sup>5</sup> None of these techniques are yet routinely available for clinical use, but this remains an area of ongoing research. In animal models the *ex vivo* expansion of UCDCSs does appear to be feasible, although concerns remain about the long-term repopulating ability of *ex vivo* expanded cell populations.

A novel approach to this area involves the direct introduction of UCDCSs into bone marrow via the intra-medullary administration of cells. A recently reported study from Italy assessed the safety and efficacy of this technique in 32 adult patients with acute leukaemia.<sup>6</sup> UCDCSs were obtained from single unrelated cord blood units mismatched for either one or two HLA alleles. The cord blood cells were concentrated into 5-ml dose syringes and injected into the superior posterior iliac crests of recipients under general anaesthetic. This study is remarkable in that of 27 evaluable patients all showed complete reconstitution of haemopoiesis from the cord blood cells and no patient had secondary graft failure. No patients developed significant acute graft versus host disease and the survival rate, at the time of publication, was 45% at one year. If this technique holds out its apparent promise, then this potentially affects the entire current practice of haemopoietic stem cell transplantation.

These remain exciting times for practitioners in the field of haemopoietic stem cell transplantation. A better understanding of the role of the immune system in the control of haematological malignancy has allowed conventionally conditioned transplants to be superseded by reduced intensity programmes without loss of therapeutic efficacy but with reduced transplant-related mortality in selected patient groups.

Stem cell source remains an area of intense research with sibling donor transplantation having been joined by unrelated blood and peripheral blood stem cell transplantation and now by UCDCS as a potential source of haemopoietic reconstitution. The demonstration that UCDCS transplantation is effective and feasible in both children and adults is important. Similarly, the demonstration that UCDCS transplantation may be preferable to mismatched blood- or bone marrow-derived stem cell sources also moves this field forward. Finally, renewed interest in either the expansion of UCDCSs or the novel administration of this source of stem cells opens up potentially wide therapeutic avenues.

#### KEY POINTS

- The first choice source of stem cells for patients requiring allogeneic transplantation should be a human leukocyte antigen-matched blood- or bone marrow-derived stem cell transplant from a sibling or unrelated donor, but umbilical cord-derived stem cells can be a reasonable alternative source of stem cells for adults who do not have recourse to these.
- Delayed engraftment and graft versus host disease remain significant problems in umbilical cord-derived stem cell transplantation in adults.
- Combinations of cytokines that facilitate umbilical cord-derived stem cell expansion are now available, but not yet for routine clinical use. A novel approach to this area involves the direct introduction of umbilical cord-derived stem cells into bone marrow.
- Umbilical cord-derived stem cell transplantation may be preferable to mismatched blood- or bone marrow-derived stem cell sources.

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