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Reviw article ■

Cord Blood Transplantation in Adult Patients With Hematological Malignancies

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SUMMARY

The purpose of this review was to show the available clinical and biological advances of umbilical cord blood allogeneic stem cell transplantation in adult patients. In adults, umbilical cord blood transplantation, due to less pronounced graft versus host disease compared to conventional approaches may, be feasible in spite of slower engraftment. The authors discussed certain attempts for improvement of umbilical cord stem cells engraftment.

Key words: **umbilical cord transplantation, unrelated stem cell transplantation**

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INTRODUCTION

Human umbilical cord blood (UCB) represents highly potential source of stem cells capable of regenerating the hematopoesis after myeloablative (1-4) or nonmyeloablative chemotherapy (5). Since the first success with related UCB transplant (6), many countries have formed the unrelated donor UCB programs and banks. Throughout the last two decades, a significant positive experience has been gathered in children (1-4) as well as in transplantation of adult patients (5, 7-10) suffering of malignant and nonmalignant hematological diseases (11). Recent meta analysis has undoubtedly confirmed the equivalent outcome and overall survival between the UCB and match-unrelated donor (MUD) bone marrow transplantation both in pediatric and adult patients (12).

In this review, the authors discuss the possibilities and limitations of umbilical cord blood as a new stem cell source in adults suffering of hematological malignancies.

Logistic and clinical advantage of UCB transplantation

Allogeneic blood and bone marrow stem cell transplantations are limited by the availability of suitably HLA-matched donors (13). Only 30% of patients have HLA-identical sibling donors through the donor registries worldwide. Nearly 75% of Caucasians, but far fewer racial minorities could find suitable HLA-matched donors through donor registries. On the contrary, the UCB donor pool offers a wide variety of HLA subtypes providing higher frequency of rare haplotypes compared to the bone marrow registries, because it is easier to target ethnic minorities (14).

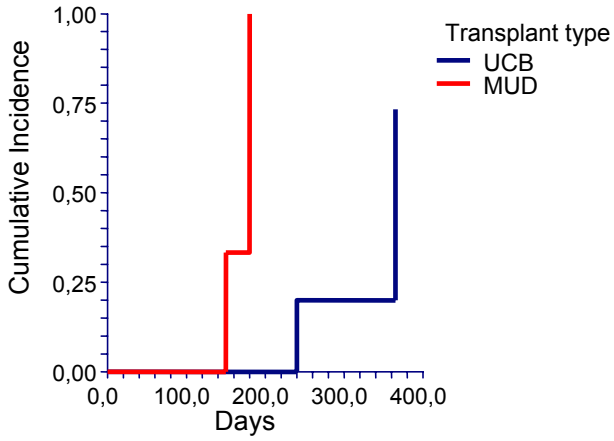

Figure 1. *Cumulative incidence of acute and chronic graft-*versus*-host disease in a small case series of Serbian patients transplanted in the centres outside Serbia that have returned to Serbia from the treatment. Abbreviations: UCB-umbilical cord blood, MUD-matched unrelated donor. Delay in appearance of GVHD in the UCB group. Probability for day +150 in the MUD group 0.3333 [CI for 95% (0.0667-1.000)]. Probability in the UCB group for day +240 0.2000 [CI for 95% (0.0346 -1.000)].*

This approach provides (i) significantly faster availability of banked cryopreserved UCB units, with patients receiving UCB transplant a median of 25-36 days earlier than those receiving an unrelated bone marrow graft; (ii) extension of the donor pool due to the tolerance of 1-2 human leukocyte antigen (HLA) mismatches out of six; (iii) lower incidence and severity of acute graft-*versus*-host disease (GVHD) (Figure 1); (iv) lower risk of transmitting infections by latent viruses, such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV); (v) lack of risk to the donor (13, 14).

The detailed extended list of advantages of the UCB transplantation is summarized in Table 1 (15).

Table 1. *Advantages of umbilical cord blood (UCB) as hematopoietic stem cells for allogeneic transplantation (15)*

1. Umbilical cord blood is an abundantly available source of stem cells, which can be harvested at no risk to the mother or infant.
2. Since collection occurs after birth of a full term normal infant, UCB is not associated with current ethical concerns raised in use of embryonic stem cells.
3. Ethnic balance in a cord blood repository can be maintained automatically in heterogeneous populations or can be controlled via collection from birthing centres representing targeted minority populations.
4. There is low viral contamination of UCB including cytomegalovirus and Epstein-Barr virus.
5. UCB, cryopreserved and banked, is available on demand particularly for patients with unstable disease, eliminating delays and uncertainties that now complicate marrow collection from unrelated donors.
6. To date, no malignant transformation of infused UCB has been observed in any transplant recipient.
7. The amplification of allogeneic responses including Th1-associated cytokine production by neonatal T lymphocytes has been shown to be less than that of adult T cells, which may underlie UCB reduced graft-versus-host reactivity compared with adult-derived marrow grafts.
8. Frozen UCB can be easily shipped and thawed for use when needed, compared to freshly donated bone marrow, which has a limited shelf-life, necessitating coordination between harvesting physicians, transportation personnel, and transplantation teams.
9. There is an undistorted accumulation of HLA genotypes acquired in a UCB bank because stored UCB suffers no attrition except by clinical use, unlike volunteer

unrelated adult donor registries in which donors are lost due to advancing age, new medical conditions, or geographic relocation.

10. As yet to be determined, although intriguing given the emerging understanding of age-dependent telomerase activity and important contributions of genetic HSC regulation with advancing age of the donor to hematopoietic and immune function in the recipient, pediatric patients transplanted with newborn HSC would expectedly maintain normal hematopoietic and immune function during advancing decades, compared with HSC grafts received from adult donors.

Limitations of UCB transplant approach

The main problem of using UCB for transplantation is the low number of hematopoietic progenitor and stem cells (Figure 2) in UCB compared with bone marrow or mobilized peripheral blood stem cells, which translates into increased risk of graft failure, delayed hematopoietic engraftment (Figures 3 and 4) and delayed immune reconstitution (2, 4, 7).

Figure 2. *Umbilical cord blood prepared for infusion. Picture clearly shows the small amount of umbilical blood available.*

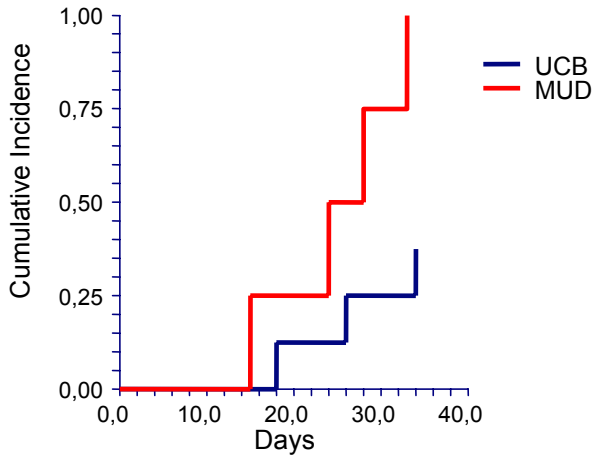

Figure 3*. Cumulative incidence of neutrophil engraftment after stem cell transplant. Data from discharging lists of Serbian patients transplanted in the centres outside Serbia that have returned to Serbia from the treatment. Median engraftment in MUD group was +23,5 (15-33) days after stem cell infusion. Estimated probability of neutrophil recovery in MUD group for day +28 was 0,75 [CI, 95% (0,4259-1,0000)]. Median neutrophil recovery in UCB group was 26 (18-44). Estimated probability for day +28 in UCB group was 0.25 [CI 95% (0,0753-0,8302)].*
Abbreviations: UCB-umbical cord blood, MUD-matched unrelated donor.

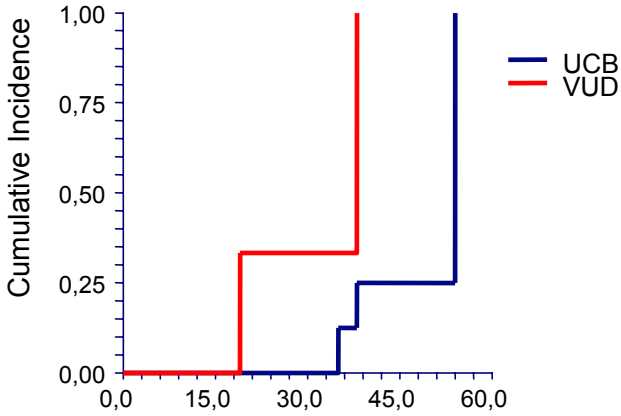

Figure 4. *Cumulative incidence of platelet engraftment after stem cell transplant. Data from discharging lists of Serbian patients transplanted in the centres outside Serbia that have returned to Serbia from the treatment. Median engraftment of platelets in UCB group was for day +47 (38-54) and for MUD +35 days (19-38). Cumulative incidence for day +35 in UCB group was 0,125 [CI for 95% (0,020-0,781)] while for the same day in MUD group was 0,333 [CI for 95% (0,067-1,000)].*
Abbreviations: UCB-umbilical cord blood, MUD-matched unrelated donor

The limited cell content of UCB units results in delayed engraftment, with consequent effects on early post-transplant survival, a practical limitation that does not exist with bone marrow (BM) or peripheral blood hematopoietic stem cell sources.

In that sense, a CD34 cell dose $<1.7 \times 10^5$ /kg was found to be associated with increased transplant mortality (4). Therefore, some centres have established a total cell nuclear dose (TCN) of cells $>2 \times 10^7$/kg pre-cryopreservation that allows minimal requirements for UCB transplantation (9, 16). Gluckman et al. have reported linear-logarithmic dependence of cell dose and engraftment probability. Data reported that the mononuclear cell dose of $>3.7 \times 10^7$/kg is necessary for consistent engraftment (17). This approach is not applicable for adult patients since a cell dose of over 3×10^7/kg could be difficult to achieve from a single unit of UCB. Moreover, if the level of HLA compatibility is not satisfactory, cell nuclear dose higher than 2.5×10^7/kg could

not be sufficient to minimize transplant related mortality (TRM)(18). Subsequent New York Blood Centre analyses reinforced the combined effect of HLA and TNC. For 5/6 match CB units, pre-cryopreservation TNC doses $>2.5\times10^7$/kg would lead to overall survival above 50%. However, for a similar survival rate, a higher TNC dose would be required ($>5\times10^7$/kg) when 4/6 match grafts were used (18). Based on these studies, it was recommended to use UCB units with ≤2 mismatch and a TNC $>2.5\text{-}3.0\times10^7$ cells/kg (19, 20). These recommendations reflect a clear emphasis on TNC, given the higher TRM with the low cell doses, rather than on HLA matching.

It is generally considered that higher level of HLA compatibility could overcome the risks that could emerge in the low cell dose setting (21).

The current standards for UCB selection are based on HLA matching at low-intermediate resolution for HLA-A and -B and high resolution (allele-level) matching for HLA-DRB1. As a result, UCB graft match level is referred to as 6/6, 5/6, or 4/6 match with 0, 1, or 2 mismatches with the recipient, respectively. Clearly, the number of HLA mismatches affects the transplantation outcome (2, 3, 13). Thus, the selection of an optimal UCB graft must consider both cell dose and HLA match. Balancing these two critical graft characteristics remains controversial and possible "permissive" mismatches for UCB grafts have not yet been identified. Therefore, guidelines for UCB unit selection are not yet firmly established.

Overcoming the limitations of UCB transplantation

Double UCB Transplantation

Method that has shown the most promissing results in overcoming the low cell dose limitation is based on infusion of two diiferent compatible UCB units (10, 14, 22, 23). Whitin the first month, in this setting when two units were used, only one could be seen to establish hematopoesis. Neither of known factors such as total nuclear cell dose, CD3 dose, CD34 dose or HLA mismatch could be identified to determine which of those units would eventualy become dominant and reconstitute hematopoesis (16).

There is a growing interest in this strategy for the treatment of adult patients with hematologic malignancies in both the ablative and RIC settings. The double UCB platform is now the basis to investigate newer strategies to improve engraftment and outcomes.

Intra - Bone Marrow Injection

The rationale of intra-bone approach was to enhance neutrophil recovery by delivering the hematopoetic stem cell directly into the bone marrow space, reducing systemic "wasting" of an already limited number of progenitors. Animal studies showed that intraosseal application of UCB could improve homing and shorten period of cell recovery (24, 25).

In that manner, the study of Frassoni et al. showed that this method of application is safe and applicable (26). Median egraftment of neutrophiles was 23 days (14-44) and for platelets 36 days (16-64). Satisfactory level of transplant engraftment was observed even in patients with low number of stem cells ($1{,}4\times10^7$/kg), and with considerable HLA/mismatch (2/6 or even 3/6) (26). Comparable studies in patients with intravenous application have shown similar results (8, 9).

Frassoni et al. observed a reduced incidence of acute GVHD, but all patients received anti-thymocyte globulin (ATG), which may have favourably influenced the risks of GVHD. Nevertheless, considering the cell doses infused, their results with this approach were encouraging.

The University of Minnesota group studied this technique for 2 UCB units (27). Brunstein et al. (27) randomly assigned one of the UCB units to be delivered by intra-bone injection, whereas the other was infused intravenously. The endpoints of this study were safety and feasibility and also to determine whether the intra-BM injection unit would have a repopulation advantage over the intravenously injected unit, leading to faster neutrophil recovery. However, after enrolling 10 eligible patients, the study was closed early based on projected statistical futility. The median time to neutrophil recovery did not differ from the institution historical controls receiving 2 UCB units intravenously, and the intra-BM injection predominated only half of the time.

Other approaches to overcoming cell dose limitation

Certain attempts were made to enhance UCB engraftment by using reduced intensity regimes (28). Among other successful approaches, the co-infusion of purified $CD34^+$ progenitors showed to shorten the time to neutrophil recovery (29). Fernandez et al. (30, 31) reported the co-infusion of large numbers of highly purified $CD34^+$ progenitors from haploidentical donors in the setting of myeloablative transplantation with 1 UCB unit. The median time to neutrophil recovery was 10 days. Although haploidentical cells were detected in early time points, long-term hematopoiesis was derived from the UCB grafts.

Another promising approach is the using the co-cultures of UCB-derived CD34+CD38- precursors in the method of ex vivo expansion. Most recent activation of adhesion pathways using diprotin or complement fragment 3a are also being intensively investigated.

CONCLUSION

Umbilical cord blood transplant represents successful alternative to other transplant modalities for

patients without matched donor. Low cell dose and HLA mismatch are principal limitations for UCB transplantation. Recent data have already shown successful strategies to overcome those limitations setting this method of treatment as a standard care for adult patients.

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TRANSPLANTACIJA UMBILIKALNIH MATIČNIH ĆELIJA HEMATOPOEZE KOD ODRASLIH BOLESNIKA SA MALIGNIM HEMOPATIJAMA

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Sažetak

Transplantacija matičnih ćelija hematopoeze iz umbilikalne krvi se u proteklim godinama pokazala kao uspešna alternativna metoda lečenja odraslih bolesnika sa malignim i nemalignim hematološkim bolestima, koji nisu imali podudarnog davaoca.

Postoji iskrena nada da će prenesena iskustva doprineti da se ova metoda transplantacije na našim prostorima počne primenjivati i kod odraslih, ne samo kod pedijatrijskih hematoloških bolesnika.

Ključne reči: **transplantacija umbilikalne krvi, transplantacija od nesrodnog davaoca**