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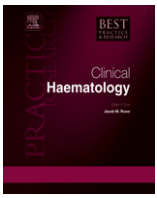

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Cord blood transplantation in children with haematological malignancies

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Umbilical cord blood transplantation (UCBT) is largely used to treat children affected by haematological malignant disorders. In comparison to bone marrow transplantation (BMT), advantages of UCBT include lower incidence and severity of graft-versus-host disease, easier procurement and prompter availability of cord blood cells, and the possibility of using donors having HLA disparities with the recipient. The large experience accumulated so far has shown that UCBT offers to children a probability of cure at least comparable to that of patients transplanted with bone marrow cells. Since it has been demonstrated that an inverse correlation between the number of nucleated cord blood cells infused per kg recipient body weight and the risk of dying for transplantation-related causes exists, recently developed strategies aimed at increasing the number of cord blood progenitors and at favouring stem cell homing could further optimize the outcome of children with leukemia or other malignancies receiving UCBT.

Introduction

Since the first successful human allograft of umbilical cord blood haematopoietic progenitors cells, performed more than 20 years ago in a child with Fanconi Anaemia [1], cord blood banks have been established worldwide for the collection and cryopreservation of cord blood cells to be employed for

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allogeneic haematopoietic stem cell transplant (HSCT). This network of cord blood banks and their collaboration with transplant centers has rendered possible that more than 400,000 cord blood units have been collected and stored and more than 20,000 umbilical cord blood transplantations (UCBT) have been performed worldwide [2]. Recent surveys estimate that, after 1998, worldwide 20% of stem cell transplants performed in young patients (i.e. <20 years old) are UCBT and, in Japan, nowadays, approximately 50% of HSCTs from unrelated donors are being performed with cord blood cells [2]. In particular, allogeneic UCBT has been largely employed for treating children affected by haematological malignancies in need of HSCT [2,3].

In comparison to bone marrow transplantation (BMT), advantages of UCBT include ease and safety of haematopoietic stem cell collection, reduced likelihood of transmitting infections, particularly human cytomegalovirus (HCMV), prompt availability of haematopoietic stem cells when an unrelated donor is employed, and reduced incidence and severity of both acute and chronic graft-versus-host disease (GvHD) [3,4]. In this regard, it must be underlined that the use of umbilical cord blood has extended the possibility to perform HSCT in HLA mismatched situation, due to peculiar immunological characteristics of placental blood lymphocytes, which display a lower alloreactive potential than bone marrow or peripheral blood lymphocytes [3–6].

The advantages of UCBT mentioned above have been demonstrated in several published reports, which have compared the outcome of UCBT and BMT from both related and unrelated donors [7–12]. In all these studies, recipients of UCBT received 1-log less nucleated cells, had delayed neutrophil and platelet recovery and showed reduced incidence of GvHD as compared to children given BMT. In particular, the first unambiguous demonstration that GvHD incidence and severity is reduced when cord blood cells are used instead of bone marrow was provided by a CIBMTR-Eurocord analysis, comparing pediatric BMT and UCBT from HLA-identical siblings [7]. While more protected than BMT recipients from GvHD-related mortality, patients given UCBT are exposed to an increased risk of dying for other, early transplant-related complications, especially of infectious origin. This increased risk of early fatalities is particularly evident in patients given a low number of cord blood cells. In this respect, in all previously published studies on UCBT, the most important factor unfavourably affecting patient outcome and limiting the success rate of the procedure has resulted to be the cell dose infused per kilogram recipient body weight, expressed either as total nucleated cells or as number of $CD34^+$ cells, which was found to correlate with engraftment, frequency of adverse transplant-related events and survival [6–14]. Indeed, as a higher number of cells infused per kilogram recipient body weight predicts a better outcome, it is now recommended that UCB units with at least $2.5–3 \times 10^7$ nucleated cells/kg recipient body weight before thawing be selected [15,16].

Although as mentioned above UCBT offers the possibility of using donors HLA mismatched with the recipient, the precise influence of HLA disparities in the donor/recipient pair on the outcome of unrelated UCBT is controversial and not fully established. The reason for the difficulties of establishing, from available data, guidelines for donor choice based on HLA incompatibilities is related to the heterogeneity of the patient population, as well as of the regimen used for GvHD prophylaxis, to the lack of accuracy of HLA typing and to the frequent absence of high-resolution molecular typing. It is also evident that cell dose and number of HLA mismatches mutually interact influencing the probability of engraftment and other outcomes. Indeed, a higher cell dose in the graft could partially overcome the negative impact of HLA for each level of HLA disparity [9]. Moreover, so far, there are no sound data for predicting which type of HLA disparity could have the most detrimental impact on outcome; however, matching for HLA-DRB1 appeared to be privileged for patients receiving a unit with two HLA incompatibilities.

Related donor UCBT for children with haematological malignancies

Few studies have reported outcomes of patients with malignant disorders after related UCBT [6,7,17–20]. The most focused analyses on the outcome of children with haematological malignancies transplanted with cord blood cells of a relative were performed by Eurocord. The first one, published more than 10 years, reported risk factors for outcomes in 102 children with acute leukemia who received UCBT either from a related donor ($n = 42$, including 12 with HLA-mismatched donors and 30 with HLA-identical donors) or unrelated donor ($n = 60$) [18]. In this study, it was clearly shown that