Advances in cord blood transplants in adults
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\begin{abstract}
Umbilical cord blood is an acceptable source of hematopoietic stem cells for patients with malignant diseases but has limitations in its use. In this review, we will discuss these limitations and the recent advances in cord blood transplants that may enable cord blood to become more widely available as an alternative stem cell source for adults for the treatment of malignant diseases and for use in regenerative medicine.
\end{abstract}

\section{Introduction and context}
High-dose chemotherapy with hematopoietic stem cell (HSC) rescue is a potential cure for patients with hematologic diseases, but only one-third of patients will have suitable matched related donors. Because of this limitation, alternative stem cell sources such as cord blood have been studied [1,2]. Umbilical cord blood was introduced as an alternative source of allogeneic HSCs after the success of cord transplantation in a child with Fanconi’s anemia [3]. Since then, over 8000 cord blood transplantations have been performed internationally. We will highlight key studies of cord blood transplants in adults.

The selection for the best cord blood unit is based on human leukocyte antigen (HLA) matching 6/6 and a nucleated cell dose of more than $3 \times 10^6$ cells per kilogram [4]. Because this cell dose is difficult to achieve in adults by using a single cord unit, two cord blood units rather than one partially HLA-matched unit has been studied and shown to have a median engraftment of 23 days and have disease-free survival at 1 year in 57\% of patients but carries an increased risk of acute graft-versus-host disease (GVHD) [5]. The increased risk of GVHD is associated with three risk factors: (a) the use of two units compared with one unit, (b) a nonmyeloablative preparative regimen compared with myeloablative regimens, and (c) the lack of antithymocyte globulin in the preparative regimen [6]. Because of the risk of acute GVHD, dual-cord transplants result in higher early transplant-related mortality compared with single-cord transplants but have less transplant-related mortality at 1 year and may have greater graft-versus-leukemia effect [7,8]. To clarify these issues, randomized studies of dual-cord versus single-cord transplants in pediatric populations are under way. To date, however, the role of dual-cord versus single-cord transplants in adults remains unclear.

Because myeloablative conditioning regimens in cord blood transplants result in high transplant-related mortality, nonmyeloablative regimens have been studied to determine whether reliable engraftment can be achieved with less toxicity [9-11]. These nonmyeloablative regimens in cord blood transplantations have yielded similar results for safety, engraftment, and survival when compared with matched sibling donors [12,13]. In a recent review, Cutler and Ballen [14] discussed these issues in more detail. Based on these studies, nonmyeloablative conditioning regimens have been shown to be a feasible alternative for patients who otherwise would not have been able to tolerate myeloablative regimens.

\section{Recent advances}
In this section, we will discuss the use of cord blood transplantations in regenerative medicine and evaluate...
novel methods for \textit{ex vivo} expansion of HSCs. The purpose of using stem cells in regenerative medicine is to restore normal or improved physiology to damaged organs. Embryonic stem cells, fetal tissue stem cells, adult tissue stem cells, and umbilical cord blood stem cells have been evaluated for these studies [15]. Of these stem cells, cord blood stem cells carry several advantages since they are readily available and pose no risk to donors for collection. In preclinical studies, cord blood stem cells have been shown to form long-lasting blood vessels \textit{in vivo} (thus holding potential in wound-healing models), form cardiomyocytes in acute myocardial ischemia models, and reduce neurologic deficits in stroke injury models [16-18]. While these studies hold promise, they have not been translated into prospective clinical studies due to the high toxicity of immune suppression and high transplant-related mortality.

To overcome the limitation of low cell dose and delayed engraftment in cord blood transplants, \textit{ex vivo} expansion of HSCs in cord blood has been extensively studied and recently reviewed [19,20]. Initial studies were disappointing with the expansion of committed rather than primitive HSCs. Co-culture of HSCs with early-acting cytokines such as stem cell factor, FMS-related tyrosine kinase, and thrombopoietin yields the greatest expansion, with the most prolific expansion reported to be 146,000-fold [21]. One of the first clinical studies to evaluate the safety and feasibility of using \textit{ex vivo} expansion of cord blood cells with cytokines in patients with hematologic malignancies and breast cancer demonstrated a 100% neutrophil engraftment but resulted in an increased risk of acute grade III-IV GVHD compared with patients who had received unmanipulated blood [22,23]. At this time, additional clinical studies are required before cellular expansion can be done routinely.

Implications for clinical practice

The innovative use of dual-cord blood units and the feasibility of nonmyeloablative regimens to treat patients allow more patients to undergo transplantation with the hope of achieving a cure. It has already been shown that cord blood transplants have similar disease-free survival and transplant-related mortality when compared with matched unrelated bone marrow transplants in children and adults [24,25]. For now, it is still to be determined whether cord blood should be preferred over matched unrelated donor or partially matched donor cells. Also, specific diseases and disease stages for which cord blood is preferred over these other cell sources are still unknown. With the growing number of adult patients receiving cord blood transplants, we hope to be able over the next few years to clarify when cord blood is the best donor cell choice for allogeneic transplantation.

Abbreviations

GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HSC, hematopoietic stem cell.

Competing interests

The authors declare that they have no competing interests.

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