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Review

Enhancing the efficacy of engraftment of cord blood for hematopoietic cell transplantation

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ABSTRACT

Clinical cord blood (CB) hematopoietic cell transplantation (HCT) has progressed well since the initial successful CB HCT that saved the life of a young boy with Fanconi anemia. The recipient is alive and well now 28 years out since that first transplant with CB cells from his HLA-matched sister. CB HCT has now been used to treat over 35,000 patients with various malignant and non-malignant disorders mainly using HLA-matched or partially HLA-disparate allogeneic CB cells. There are advantages and disadvantages to using CB for HCT compared to other sources of transplantable hematopoietic stem (HSC) and progenitor (HPC) cells. One disadvantage of the use of CB as a source of transplantable HSC and HPC is the limited number of these cells in a single CB collected, and slower time to neutrophil, platelet and immune cell recovery. This review describes current attempts to: increase the collection of HSC/HPC from CB, enhance the homing of the infused cells, *ex-vivo* expand numbers of collected HSC/HPC and increase production of the infused CB cells that reach the marrow. The ultimate goal is to manipulate efficiency and efficacy for safe and economical use of single unit CB HCT.

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1. Introduction

Hematopoietic cell transplantation (HCT) is a life-saving procedure for treatment of malignant and non-malignant disorders, and is usually a last resort for those whom there is no other treatment available [1,2]. The life-saving cells necessary to establish a new hematopoietic system to replace the damaged or malignant cells are hematopoietic stem (HSC) and progenitor (HPC) cells [3–5]. These cells give rise to all the blood forming elements. Their production is regulated by various proteins, such as cytokines and chemokines, other growth regulatory molecules, the in vivo microenvironmental niche composed of various stromal cells and the extracellular matrix, and the hypoxic atmosphere within the niche [6,7].

HSC and HPC are found in various tissues, including bone marrow (BM) which is the major site of production of blood cells in the adult. HSC/HPC are also found circulating in the blood but their numbers in blood under normal steady state conditions are low, unless these cells are mobilized from the BM with chemotherapy, growth modulating proteins such as granulocyte colony stimulating factor (G-CSF), or smaller molecules (macrophage inflammatory protein (MIP)-1α or GRO-β), including synthetic ones (AMD3100/Plerixafor) [3,6]. HSC and HPC can also be found in umbilical cord blood (CB), at the birth of a baby [1,2]. Currently the three main clinical sources of HSC and HPC for HCT are BM, mobilized peripheral blood (mPB), and CB. Each has been used successfully and has advantages and disadvantages.

The advantages of CB for HCT include the ease of collection of the CB at the birth of the baby, with no problems for the mother or baby, the ability to store CB collections immediately after cryopreservation in either a public CB bank for use by others after HLA-typing, or in a family bank for future use by the baby donor or perhaps for a family member. At present, CB has been used to transplant over 35,000 recipients with success rates equivalent to those done with BM or mPB [1,2]. One outstanding advantage of CB, besides the almost immediate availability of the cells for transplant, is the documented lower graft vs. host disease (GVHD) associated with the use of CB, in comparison to that of BM or mPB [1,2]. This lowered level of resultant GVHD associated with CB as the donor cell population of HSC and HPC has allowed CB to be used in situations of increased HLA-disparity compared to that of BM or mPB, opening up the opportunity for transplants that cannot be performed safely with equivalent partially HLA-mismatched BM or mPB. Thus, there is great optimism for use of CB as a source of HSC and HPC for HCT. However, there are disadvantages to using CB compared to BM and mPB, including the more limited numbers of cells collected at the birth of the baby, which is a one-time only collection, and the slower time to engraftment for neutrophils, platelets, and immune cell reconstitution [1,2]. Being able to successfully address these two concerns would make CB an even more desirable source of transplantable HSC and HPC, and would likely greatly enhance the clinical use of these cells for HCT. Moreover, in addition to use of CB, BM or mPB for transplantation, another treatment has more recently emerged, that of haploidentical HCT, which seems to also have the advantage of increased use in an HLA-disparate setting, lowered GVHD, and with enhanced time to engraftment [8]. However, haplo-identical transplantation is not without its own inherent problems, including enhanced relapse rates over time. Which source of cells will be best for which situation will "play-out" in time. In the meantime, efforts are on-going by numerous research and transplant investigators to find ways to enhance the numbers of HSC/HPC from CB, and to accelerate the time to engraftment with CB. Results are promising, and hopefully efforts in this important endeavor will continue to move forward.

2. Background to the field

The first CB HCT was performed in October 1988 at the Hopital St. Louis, in Paris under the direction of Eliane Gluckman, M.D., with an HLA-matched sibling CB collection that was processed, frozen and then hand-delivered to Dr. Gluckman by my laboratory [9]. The initial scientific studies suggesting CB as a source of transplantable HSC and HPC [10–14], as well as this first [9] and a number of subsequent HLA-matched sibling CB transplants that started the field of CB HCT came from my laboratory and from our first proof-of-principle CB bank [15–19]. These first CB HCT efforts have been described [9,20–22]. Many of the first HCT advantages and disadvantages first noticed by us and our clinical collaborations still persist to this day, 28 years after the first transplant. While better clinical procedures have enhanced HCT outcome with HLA-matched and partially matched allogeneic transplants, there is much room for improvement. Efforts toward this outcome by our group and others are described below.

3. Ongoing experimental laboratory and clinical efforts to enhance CB HCT

Clinical efforts for, and the status of, CB HCT have been described in detail in several of our recent review articles [1,2]. Present efforts to enhance the efficacy of CB HCT include: (A) more effective means to manage high quality and quantity collections of CB that maximize numbers of functional HSC; (B) efforts to increase the homing capacity of HSC, since only a small portion of the HSC infused intravenously (i.v.) during HCT actually reach and/or engraft in the BM, a necessary site of eventual lodgment for HSC in order for their maintenance, expansion and differentiation to mature blood cells; (C) the capacity to expand numbers of collected HSC and HPC outside the body (*ex-vivo*); and (D) determine how best to enhance the production of the cells that eventually reach (home to) the BM, as part of the actual engraftment procedure.