

# The view for cord blood is “cup half full” not “cup half empty”

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In this issue of the journal, Kindwall-Keller and Ballen present a targeted overview of the advantages, disadvantages, and milestones of cord blood transplantation over the past 30 years.<sup>1</sup> First they highlight the advantages of cord blood as a source of donor cells for hematopoietic transplantation, including off the shelf availability, increased tolerance for HLA mismatching, lower incidence of acute and chronic GvHD, lower risk of infectious disease transmission, and improved protection against leukemic relapse in high risk patient populations. They also make several important points about the limitations of cord blood in transplantation, highlighting slower engraftment, delayed immune reconstitution, and cost amongst others. Overall, the report is somewhat pessimistic about the overall outlook of this novel graft source.

More than 4 decades ago, Hal Broxmeyer showed that cord blood (CB), the baby's blood left over in the placenta after birth and usually discarded as medical waste, was enriched for hematopoietic stem and progenitor cells (HSCs).<sup>2</sup> He further demonstrated that CB cells had a higher proliferative capacity and higher ratios of stem to progenitor cells compared with adult bone marrow (BM) confirming the old saying that “*younger is better.*” Broxmeyer led a group of investigators in NYC to develop techniques to collect and cryopreserve CB with the goal of performing a transplant in which CB was substituted for BM as the source of HSCs. The first transplant, performed by Eliane Gluckman in Paris, France, in 1988 using HLA-identical sibling CB to treat a 5-year-old boy with Fanconi anemia, was a success.<sup>3</sup> What an amazing phenomenon of nature, allowing recycling of otherwise discarded material to potentially save lives!

Subsequent CB transplants between siblings demonstrated a 10-fold decrease in the incidence of acute Graft-vs-Host Disease (GvHD),<sup>4</sup> and this led to the hypothesis that CB could substitute for BM as a donor for HSC transplant (HSCT) without complete HLA matching. Pablo Rubinstein and colleagues set up the first unrelated donor CB bank in the US in 1991. The results of the first 25 unrelated

donor cord blood transplants (UCBT), performed between 1993-1996, were reported by my group in 1996.<sup>5</sup> This was followed by additional reports of UCBT outcomes, all demonstrating that CB could be cryopreserved and banked, that CB conferred durable myeloid and lymphoid engraftment (albeit at a slower rate, increasing treatment-related mortality than other sources of HSCs), and that CB was transplantable without full HLA matching without increasing the incidence of GvHD, thereby providing donors for patients unable to identify donors in their families or the adult unrelated registries.<sup>6-8</sup> Over the subsequent decade, hundreds of cord blood banks, both public and private, were established worldwide. Internationally, an inventory approaching 800 000 units has been accrued to public cord blood banks. In the US, federally sponsored legislation, the C.W. Bill Young Cell Transplantation Program's National Cord Blood Inventory, which subsidizes banking of high quality cord blood units, was established in 2006. Of note, CB is the only HSC source that is licensed by the US Food and Drug Administration (FDA). Guidance for FDA licensure of public CB banks was issued in 2011 and finalized in 2014 and, to date, there have been 8 public CB banks licensed in the US.

The cell dose of the CB unit used in a transplant was established as a critical attribute for a successful transplant, and the minimum cell dose was set at 25 million cells/kg based on the pre-cryopreservation count. This led to the successful use of CB as a donor for children in need of HSCT for malignant or non-malignant conditions. In the early days of UCBT, it was assumed that a CB unit would not have enough cells to transplant most adults. Also, the size of the baby was determined to predict the size of a CB unit and since babies can only be so big, increasing the volume of collected CB was not going to solve this problem.<sup>9</sup> In 2005, Juliet Barker and John Wagner showed that the dose of cells could be increased by utilizing 2 CB units for a single patient's transplant.<sup>10</sup> Interestingly, only one CB donor would ultimately engraft, but the other unit appeared to serve a helper function that improved outcomes; yet, a landmark pediatric study conducted

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by the BMT-CTN failed to demonstrate an advantage of double cord blood transplantation over single cord blood transplantation in pediatric patients with leukemia.<sup>11</sup> Alternative approaches to expand CB cells prior to transplantation have been under investigation for more than a decade, and in the past few months, Nicord (Omidubicel), expansion of CD133 cells in nicotinamide, manufactured by Gamida Cell Ltd in Jerusalem, achieved the primary endpoint of accelerating neutrophil engraftment in a phase III registration trial and is under consideration for licensure from the US FDA. This is an exciting advance for the CB field, because it provides the opportunity to utilize the current public inventory of banked units for patients of all sizes and to shorten times to engraftment and length of hospitalization and to improve overall outcomes.

Despite the slower engraftment and increased transplant-related mortality (TRM) associated with UCBT, overall outcomes focused on relapse-free, GvHD-free survival are equivalent or superior to those seen with other HSC sources. This is because the increased TRM is out competed by the decreased acute and chronic GvHD and improved protection against relapse in patients with hematological malignancies. Recent studies have shown a benefit for UCBT in adult patients with high-risk hematological malignancies, where it is clear that graft vs leukemia (GVL) effects are preserved without increased GvHD.<sup>12</sup> CB is also an ideal graft source for newborns and infants where cell dose is relatively higher and engraftment is rapid. In addition, because CB is essentially an “off-the-shelf” product, it is readily available as a donor source for infants diagnosed with congenital leukodystrophies or immune deficiency syndromes requiring transplantation in the first 1-2 months of life. With more and more of these diseases being diagnosed through newborn screening, the need for CB as the donor source for transplantation will increase. Furthermore, for some genetic diseases, collection of autologous cord blood to be used as the source of HSCs for transplantation provides an ideal, non-invasive source of cells for this technology. In sickle cell disease, where maintenance of expression of the gamma gene is a novel approach to gene therapy, cord blood, where the gamma gene is biologically still “on” is the ideal source of HSCs for this approach.

The ability to identify a fully matched donor for a patient in need of an unrelated donor for transplant is decreasing and over the next 1-2 generations, with additional mixing of races and ethnicities, expected to be even more difficult. Despite 22 million volunteer donors registered with the National Marrow Donor Program's Be the Match Registry and despite more than 32 million volunteer donors worldwide, full matching is becoming more and more challenging; therefore, a readily available source of donor cells that can be used without full matching but still capable of engrafting, causing minimal GvHD, and controlling leukemic relapse is highly desirable. Over the past 3-5 years, the use of haplo-identical related donors has emerged as a potential solution to this problem, but haplo transplants have increased relapse rates in some patients with blood cancers and increased rejection rates in some patients with genetic diseases, so haplo is not the perfect solution either.

Finally, CB banks have developed unique expertise in GMP manufacturing of cellular products. They have created infrastructure to recruit donors, procure CB and birthing tissues, determine donor eligibility, test, process, cryopreserve, ship and thaw qualified CB units for transplantation. In addition, they have the expertise and regulatory bandwidth to procure, harvest and store birthing tissues which can be utilized to manufacture cell therapies for use in regenerative medicine. Highly effective immunotherapies including allogeneic CAR-NK and cytotoxic T-cells (CTLs) have been manufactured from cord blood and are in development for commercialization.<sup>13,14</sup> Derivatives of cord blood CD14 monocytes are in clinical trials for treatment of hypoxic and demyelinating diseases<sup>15-18</sup> and cord blood is being investigated as a therapy for children with autism spectrum disorder, a severely disabling disease with increasing prevalence in our society.<sup>19,20</sup> Finally cord and placental tissues are robust sources of mesenchymal stromal cells which are undergoing testing in many diseases as immune modulators and suppressors of pro-inflammatory states,<sup>21</sup> including as a treatment for complications of COVID-19.<sup>22</sup>

So I'm not giving up on cord blood and products from related birthing tissues. The CB industry was the first to enter the regulated cell therapy environment, but its experience and progress to date can be leveraged for the development of many promising and exciting therapies to come.

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