

# Improving the Efficacy and Availability of Stem Cell Transplant Therapies for Hematopoietic Stem Cell Transplantation

William YK Hwang<sup>1\*</sup>, Zhiyong Poon<sup>2</sup> and Sudipto Bari<sup>3</sup>

<sup>1</sup>Singapore General Hospital and Duke-NUS Graduate Medical School, Singapore

<sup>2</sup>Singapore MIT Alliance, Singapore

<sup>3</sup>Department of Pharmacy, National University of Singapore, Singapore

## Abstract

Over a million hematopoietic stem cell transplants (HSCTs) have been performed around the world for treatment of a range of cancers and hematological indications. A significant increase in transplants and transplant centers has been seen in many parts of the world, with the highest relative increase of transplant centers occurring in the Asia Pacific region, specifically in countries like China, India, Singapore and Thailand. The Bone Marrow Donors Worldwide (BMDW) register has grown to include over 20 million donors by 2013 with consequent greater ease in finding an unrelated donor for transplant. The availability of donors has been further enhanced through the use of alternate stem cell sources like cord blood and haploidentical donors. To protect donors while serving the needs of patients who are urgently seeking histocompatible donors in around the world, the World Marrow Donor Association (WMDA) has helped in establishing standards, accreditation, safety measures, shared processes and global monitoring systems for stem cell registries.

Recent developments in pre-transplant preparative regimens as well as post-transplant care have made incremental but definite improvements in post-transplant survival. Graft engineering has also helped to facilitate the removal of cells which cause graft-versus-host disease (GVHD), the eradication of cells which might cause relapse, the expansion of donor cells when there is an inadequate cell dose, and the addition of selected cells to improve graft function with augmented anti-tumor or anti-infective properties. These advances help enhance the safety, efficacy and availability of HSCT, ensuring that this modality of treatment remains an important part of the continuum of care of patients of potentially fatal cancers and blood diseases.

**Keywords:** Hematopoietic stem cell transplantation; Cord blood transplants; Stem cell expansion; Donor availability; WMDA; Cord blood expansion; Cellular therapy

## Introduction

Hematopoietic stem cell transplants (HSCT) are used to correct defects that occur in blood cells by supplanting the patient's hematopoietic stem cells with those derived from donors, so that new healthy blood cells can develop to replace the existing defective blood cells. In 2012, over 1 million HSCTs had been performed around the world by 1450 transplant centers from 72 countries in over 5 continents [1] for treatment of a range of hematological disorders such as leukemia's, lymphomas, autoimmune diseases or anemia. This statistic was derived from databases maintained by several worldwide organizations, including the Center for International Blood and Marrow Transplant Research (CIBMTR), the European Blood and Marrow Transplant Group (EBMT) and the Asia Pacific Blood and Marrow Transplant (APBMT) group. Outcomes for HSCT have been maintained by these observational databases which facilitate research in this field around the world [2,3]. This staggering number of transplants performed was facilitated by a number of factors, which include the proliferation of transplant centers around the world capable of performing this procedure, the greater ease in finding a suitable donor for HSCT with new donor sources and the improved outcomes of HSCT with the development of new drugs and techniques in transplantation.

## Increased Accessibility to HSCT Centers

A dramatic increase in transplant centers has been seen in many parts of the world, particularly in Latin America [4], the Eastern Mediterranean Region [5] and the Asia Pacific region [6]. Owing to rapid economic development in Asia over the last few decades, the

highest relative increase of transplant centers occurred in the Asia Pacific region, specifically in countries like China, India, Singapore and Thailand. Most of the transplants appear to be performed by teams which perform at least 80 transplants a year and transplant rates in each country correlated with the number of transplant teams per 10 million inhabitants (team density) [7]. As the rates of transplant per million inhabitants appeared to increase depending on the size and experience of the team, and without saturation ( $R^2=0.54$ ), this suggests that there are many places in the world that could continue to benefit from an increase in the capability and experience in performing transplants. Further development in such regions could drive the continued proliferation of transplant centers, such that this procedure could be made accessible to a greater number of patients in need of HSCT.

## Enhancing Donor Availability

An important pre-requisite for performing a successful HSCT is to find a suitable human leukocyte antigen (HLA)-matched donor source of hematopoietic stem cells (HSCs) with sufficient cell dosage. To increase the chances of finding a donor, the Bone Marrow Donors Worldwide (BMDW), a collation system which collects the phenotypes

**\*Corresponding author:** William YK Hwang, Singapore General Hospital and Duke-NUS Graduate Medical School, Singapore, Tel: 6563214855; E-mail: [william.hwang.y.k@sgh.com.sg](mailto:william.hwang.y.k@sgh.com.sg)

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of donors from all participating registries in the world, was established in 1988 [8]. The BMDW register, which had 155,000 donors in 1989, grew to include 12 million donors by 2009 [9] and over 20 million donors by 2013 [10]. Given the current world population (7 billion), it can be estimated that there is one donor for every 350 individuals. This rapid growth is attributed to the efforts of registries such as the US National Marrow Donor Program (NMDP), which seeks to maintain a registry that is large in number and ethnically diverse in order to ensure access to HSCT for all patients [11]. Often, HLA frequency data has been used to evaluate optimal registry size and composition [12].

With growth in transplant activities and the donor pool, there has been a need to protect donors while serving the needs of patients who are urgently seeking histocompatible donors in around the world. This has been the goal of the World Marrow Donor Association (WMDA), which has helped in establishing standards and accreditation of stem cell registries [13], regulations regarding the quality and safety of stem cell products, global monitoring of donor safety [14], guidance on donor medical suitability and many other recommendations. These activities have culminated in an increase in unrelated donor transplantation to more than 20,000 a year with about half of these being shipments of stem cell products from a donor in one country to a patient in another part of the world.

## Improving HSCT Outcomes

### Novel preparative regimens and supportive care

Before healthy HSCs are transplanted, patients are subjected to a period of myeloablative or reduced intensity conditioning with chemotherapy and/or radiotherapy to provide adequate immunosuppression to prevent early rejection of transplanted cells, to eradicate malignant cells prior to transplant and to ablate the recipient bone marrow tissue of hematopoietic cells to make room for the donor cells [15]. Such myeloablative conditioning regimens can potentially lead to a high incidence of transplant related complications that may result in patient mortalities. However, in the last two decades, there has been a significant reduction in transplant related mortality (TRM), largely because of the use of less toxic, yet effective, preparative regimens as well as improvements in supportive care [16]. Traditional conditioning regimens have been enhanced by the incorporation of newer drugs that target specific hematopoietic cells (like rituximab) as well as other drugs with less toxicity and higher anti-tumor effects like treosulfan [17], thiotepa [18] and radiolabelled antibodies [19]. In post-transplant care, a common complication is the development of bacterial, fungal or viral infections in the period following myelosuppression and re-establishment of a new hematopoietic system. Here, the availability of a whole new armamentarium of anti-fungal [20] and anti-viral [21] drugs have increased our ability to treat and prevent such infections. New medications such defibrotide have also been introduced to deal with other common post-myeloablative complications such as veno-occlusive disease [22]. The use of post-transplant granulocyte colony stimulating factor (G-CSF) has accelerated blood count recovery following autologous transplants [23]. Furthermore, post-transplant vaccination programs, have been implemented in most centers in order to boost the immunity of the transplant patients, and have been shown to be important and cost effective [24]. Together, such developments over the years have made incremental but definite improvements in post-transplant survival.

In future, the potential wide scale implementation of a robust biomarker analysis platform for early identification of transplant patients who are likely to relapse or non-responsive to the conventional

graft-versus-host-disease (GvHD) prophylaxis would provide physicians sufficient time to take appropriate medical intervention to reduce TRM [25,26].

### Better graft selection

The choice of a good graft is a key prognostic factor in the outcome of HSCT. Good donor grafts can reduce the incidence of transplant related complications such as GvHD, graft rejection, inefficient immune reconstitution and the development of serious infections [27]. Graft quality is largely contingent upon the degree of HLA-matching and source (bone marrow, peripheral blood or cord blood). Related donors offer the best chances for an identical HLA-matched graft; this is the ideal HSC source for good transplant outcomes. If a suitable related donor is not found, it is often possible to find a suitable donor in a matched unrelated donor (MUD), and this process has been greatly facilitated over the last two decades by the emergence of bone marrow donor registries as reviewed above. For patients who do not have a matched sibling donor or a optimally matched MUD for transplantation, other graft sources have been used, including and umbilical cord blood (CB) and mismatched haploidentical related donors, where patients can receive donor cells from siblings or parents who are only half-matched with them. The initial clinical experience with haploidentical HSCT indicated the need for strategies to deal with the significantly higher incidence and severity of GvHD in patients receiving such transplants [28]. Recently, however, safer methods of performing haploidentical transplants [29], involving the use of in vitro and in vivo depletion of donor T-cells before transplantation or the induction of donor-host alloantigen anergy [30] using techniques like post-transplant cyclophosphamide, have successfully reduced GvHD complications following these transplants.

Cord blood (CB) is a particularly interesting source of cells for transplantation as it has demonstrated equivalent survival outcomes compared with unrelated donor bone marrow despite greater donor-recipient HLA disparity [31]. Further increases in the size and diversity of CB inventories may realize the potential of every patient having access to at least a 5/6 matched CB unit of adequate cell dose (70-fold relative value for each CB unit banked versus each BM donor recruited) [32]. Compared to bone marrow or mobilized peripheral blood progenitor cells (PBPCs), CB transplantations (CBTs) are associated with a greater ease of HSC collection, prompt availability (from over 500,000 CB units stored in public cord blood banks worldwide), lower risk for transmission of infections, greater tolerance across HLA barriers and a lower incidence of GvHD [33,34]. For these reasons, there is a great deal of interest in employing CBTs for adult patients who need allogeneic HSCT but do not have access to a HLA-matched donor. This is relevant in approximately 40% of Caucasians, and up to 55-80% of non-Caucasian patients will not be able to find an 8/8 HLA-A,-B,-C, and -DR MUD. These groups comprise over 5000 patients each year, who are candidates for a CBT [35], especially when other donor sources are unavailable or deemed to be unsuitable by the transplant physician.

### Enhancing cord blood transplants

Although CBTs have been used successfully in pediatric patients, there are significant challenges to their use in adult patients. The characteristically slower rate of hematopoietic recovery after CBT in adults, relative to bone marrow or PBPC, is a consequence of a lower HSC and progenitor content for sustaining transplantation as well as intrinsic functional cellular deficiencies related to engraftment in CB grafts [36]. Median neutrophil and platelet engraftment times, which

are early measures of the success of a transplant, are more than 25 days and 45 days, respectively, for unmanipulated CB grafts versus a median of less than 20 days and 24 days, respectively, for BM grafts or PBPCs. Reconstitution times for other immune cells such as T cells, B cells and NK cells, which typically occurs later (>3 months) than neutrophil and platelet recovery, are delayed more significantly after CBT due to the relatively immature immune status of CB cells [37]. The weak engraftment kinetics increases the risk for graft failure and the prolonged period of cytopenia (neutrophils, platelets, T cells and B cells) exposes the patient to opportunistic bacterial and viral infection, which are the major contributing factors in greater than 40% of deaths following CBT [38].

To overcome the limitation of cell dose, infusion of two partially HLA-matched cord units has been adopted [39] although whether interactions between the CB units are cooperative or competitive is not so clear [40]. This approach has also not reliably demonstrated a reduction in time to donor engraftment, with reported median neutrophil and platelet engraftment times ranging widely between 12-32 days and 41-105 days, respectively [41]. Current clinical trials are exploring new strategies such as co-infusion of haplo-identical CD34 stem cells in the setting of a conventional single or double cord blood unit transplantation (DCBT) [42] to achieve initial rapid neutrophil engraftment from the haploidentical cells, which eventually get rejected while the CB graft gradually takes over hematopoiesis.

CB cells have also been grown in *ex vivo* cultures, through the use of hematopoietic growth factor and cytokine combinations (e.g. SCF, TPO, FLT-3, IL-3) [43] or mesenchymal stromal cell (MSC) feeder layers, to increase the numbers of blood stem cells in an attempt to reduce post-transplant mortality by accelerating the recovery rate of blood cells [44,45]. The expansion of one CB unit while another different CB unit is concomitantly infused has been safely employed in both mouse studies and clinical trials in order to ensure that the unexpanded unit serves as a back-up source of stem cells should expansion result in loss of "true" long term stem cells [46]. The expanded CB unit also tends to have faster engraftment kinetics, which is likely a result of their much increased cell numbers. In clinical studies involving dual CB unit transplantation following expansion on MSC feeder layers, the median neutrophil engraftment from the expanded unit is ~16 days and this serves to overcome peri-transplant related risks prior to the gradual dominance of the unmanipulated graft in the long-term [44,47].

To date only one clinical *ex vivo* expansion protocol used in a double cord blood transplant setting, has demonstrated both early median neutrophil recovery (13 days) and long term hematopoiesis from the expanded CB unit [48]. In this dual CBT study, the investigators expanded the stem/progenitor cells from a single unit in presence of a sirtuin 1 (SIRT1) inhibitor, nicotinamide, and infused these cells and its non-cultured T cell fraction along with a conventional unmanipulated unit. Such accelerated hematopoietic engraftment observed in early phase studies suggest tremendous potential for this modality of treatment for patients needing CB transplant but with inadequate cell doses in otherwise histocompatibility suitable units [44,47].

Co-infusion of CB grafts with bone marrow derived mesenchymal stromal/stem cells (BM-MSCs) [49]; or pre-treating the CB grafts with bio-molecules such as 16,16-dimethyl prostaglandin (dmPGE2) [50] and fucosyltransferase VI [51] are examples of adjuvant approaches that have shown to enhance the homing of CB cells to the bone marrow as well as the rate of their hematopoietic reconstitution. Such approaches appear to have the potential to improve transplant outcomes by shortening the period to neutrophil recovery after CB

transplants [52]. The capacity of MSCs to immunosuppress, secrete supportive hematopoietic factors and promote tissue repair, makes them interesting candidates as accessory cells for augmenting HSCT (particularly CBT), and several clinical investigations have been conducted or are underway at this point in time [53,54].

Finally, in contrast to systemic delivery of CB grafts, the direct injection of CB cells into the bone marrow of recipients (intrabone administration) has been studied as a method to facilitate engraftment of donor cells through better initial placement of the infused cells with good safety, tolerability and promising results shown in initial phase I/II studies [55,56].

### Adoptive and Cellular immunotherapy

Various techniques have been developed to engineer the hematopoietic stem cell graft to enable it to perform its task more effectively. These techniques include the removal of cells which cause GvHD, the eradication of cells which might cause relapse, the expansion of donor cells when there is an inadequate cell dose, and the addition of selected cells to improve graft function [57]. The development of adoptive immunotherapy mainly in the form of donor lymphocyte infusion (DLI) following transplants have shown to negate post-transplant relapses mainly via the "graft-versus-tumor" (GvT) effect [58,59]. Through the efforts of many researchers, cellular therapy has extended beyond the mere transplantation of HSC and now includes modulation or enhancement of immunity using *ex vivo* expanded T cells, NK cells [60], cytokine induced killer cells [61], mesenchymal cells [62] and various cellular subsets to selectively enhance and or suppress immune reactions. For example, preclinical models have demonstrated that regulatory T cells could alleviate the symptoms of xenogeneic GvHD [63,64]. These new cell therapies are being intensively studied and have been used to enhance the power and precision of hematopoietic cell therapy.

### The Future of HSCT

HSCT therapies are likely to remain an important part of the continuum of care. Proliferation of transplant centers, expansion of the worldwide donor network and use of unconventional donor sources will likely lead to continued global growth of HSCT. However, in order for the field to remain relevant and resilient for the future, continued exploration into safer preparative regimens and peri-transplant supportive care will be necessary to ensure that HSCT is at least as safe as other therapies. Further advances in hematopoietic stem cell expansion and cellular immunotherapy are also pivotal for this field to be a vital and vibrant component of patient care.

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