

# Hematopoietic Stem Cell Applications: Past, Present and Future

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## ABSTRACT

Hematopoietic stem cells have been at the forefront of stem cell research and its applications. Several advancements have occurred in the field of hematopoietic stem cell transplantation since this was first accepted as a treatment for otherwise incurable hematological disorders. The progress in this field is to the extent that it is unfathomable to a single person be it a scientific researcher or a practicing clinician. In this internet era, most patients are also well informed of the utility of stem cells. There is a need to bridge the gap in knowledge of this science between the scientists, physicians and the public at large. This review aims to summarize the advances in hematopoietic stem cell applications.

**Keywords:** Hematopoietic stem cells, Application, Transplantation.

## Key messages:

- Hematopoietic stem cells possess the characteristics of self renewal, differentiation, mobilization and apoptosis.
- The transfer of hematopoietic stem cells to rescue a recipient's hematopoiesis, who has received conditioning with high dose chemotherapy and/or total body irradiation, constitutes hematopoietic stem cell transplantation (HSCT).
- Hematopoietic stem cells can be obtained from the bone marrow, peripheral blood or umbilical cord blood.
- Autologous HSCT involves the infusion of one's own hematopoietic stem cells. An allogeneic HSCT involves the infusion of hematopoietic stem cells from another individual.
- Depending on the HLA match, the HSCT is of following types: Syngeneic, matched related, matched unrelated and haploidentical.
- Patient selection and the timing of transplant are the most important factors determining transplant outcomes.
- Hematopoietic stem cells and umbilical cord stem cells have applications in regenerative medicine as shown in preclinical and early clinical studies.

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## INTRODUCTION

Stem cells and its applications have been center stage of most of the biological research in the past decade or so. Its interest is so because of its widely believed potential applications to the humanity. The benefit and risks have also been an area of debate among the scientists, politicians and the public in general. However, it is up to the scientific community to educate the people about the present applications, ethics and limitations of this science. To

understand this science, it is important to define what constitutes the stem cell. Human stem cells are classified as pluripotent embryonic stem cells and multipotent tissue specific adult stem cells. Tissue specific adult stem cells are defined as clonal, self renewing, multipotent cells sustaining the homeostatic cellular requirements of a tissue or an organ for the lifetime of the host.<sup>1</sup>

Hematopoietic stem cells are characterized by the ability of self renewal and differentiation to all mature blood lineages.<sup>2</sup> These cells possess the characteristics of self renewal, differentiation, mobilization and apoptosis. Bone marrow transplantation has been the single most important application of hematopoietic stem cells till date. Depending upon the source of hematopoietic stem cells, the procedure may be called as bone marrow transplantation (BMT, when source of hematopoietic stem cells is from bone marrow), peripheral blood stem cell transplantation (PBSCT, source of hematopoietic stem cells from peripheral blood), umbilical cord stem cell transplantation (UCSCT, when source of hematopoietic stem cells is from umbilical cord). However, for all practical purposes, the better terminology is hematopoietic stem cell transplantation (HSCT). The theoretical basis for hematopoietic stem cell transplantation came from the studies of Nowell and Ford, who demonstrated that bone marrow cells infused from one mouse into a lethally irradiated mouse were capable of rescue by generating the entire repertoire of hematopoietic cells.<sup>3,4</sup> This provided the basis for Sir Donnall E Thomas to perform first, unsuccessful allogeneic transplants in 1957<sup>5</sup> and later, successful syngeneic transplants (marrow from an identical twin) in 1959<sup>6</sup> in leukemia patients following total body irradiation. His experiments with autologous transplants in canine models, technique of cryopreservation and peripheral blood as a substitute for bone marrow stem cells has paved the way for what is the current practice in this field. After initial failure in allogeneic transplantation and with the understanding of the human histocompatibility, the first matched sibling donor transplant was done by Dr Robert Good in an infant with immunodeficiency in 1968<sup>7</sup> and by Sir Thomas in a patient with leukemia in 1969.<sup>8</sup> We have come a long way since this pioneering research.

Current estimates of annual number of HSCTs are 55,000 to 60,000 worldwide. Reasons for widespread use include proven efficacy in many diseases, better understanding of the procedure, patient selection, improved

stem cell collections, conditioning strategies, better supportive care and developments in the field of matched unrelated transplants and cord blood transplants. This has led to transplants being done in older and sicker patients with lesser transplantation related morbidity and mortality.

## CHANGING SCENARIO OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

In the 1970s, nonmalignant diseases, like aplastic anemia (40%) and immune deficiencies (15%), were the major indications for HSCT. By 1985, leukemias (70%) overtook nonmalignant diseases as an indication of allogeneic HSCT which is so till date. Aplastic anemia and immune deficiencies now account for 5% of allogeneic transplants. Multiple myeloma is the most common (48%) indication of autologous transplants. Non-Hodgkin's lymphoma (28%) and Hodgkin's lymphoma (12%) are next common. Breast carcinoma was the most frequent (40%) carcinoma treated with autologous HSCT in 1994 to 1995. However, the borderline or negative results in most randomized trials and the revelation of fraud in one positive trial<sup>9</sup> have resulted in waning of interest in treating this cancer with this approach. Solid cancers account for 10% of all autologous stem cell transplants.

## SOURCE OF STEM CELLS

The stem cell can be obtained from the following sources of the human body.

- *Bone marrow (BM)*: Till recently, all stem cell harvests were done from the bone marrow. The procedure of isolating stem cells from the bone marrow is a painful and tedious process. It is a problem with young donors where this procedure often needs to be done under general anesthesia. Currently, bone marrow is the stem cell source in about 50% of pediatric transplants and less than 15% of adult transplants.
- *Peripheral blood hematopoietic stem cells (PBSC)*: PBSC is collected from the peripheral blood by leukapheresis after stem cell mobilization using growth factors. These harvests have more progenitor cells and have been shown to have an advantage in terms of faster hematopoietic recovery. Randomized control trials (RCT) have also shown a survival advantage for PBSC compared to BM as a source for HSCT, however at the cost of increased risk of graft versus host disease.<sup>10</sup> It is due to this reason and also the ease of accessibility that there is an increasing trend to use this as a stem cell source. Currently, PBSC accounts for about 70% of related donor and 60% of unrelated donor HSCT. PBSC have been excluded from the purview of the national

organ transplant act thereby permitting its sale for transplant purposes.<sup>11</sup>

- *Umbilical cord blood (UCB)*: UCB is rich in hematopoietic precursors; however the quantity collected from one individual is inadequate to repopulate bone marrow for a normal adult. This can be overcome by double cord transplants, coinfusion of mesenchymal stem cells, direct injection of cord blood into the marrow and other *ex vivo* cell expansion techniques. UCB cells are immunologically naive and have lower number of T-cells and hence transplant can be carried out even if there is a four out of six HLA match. UCB transplants now account for up to 5% of all transplants. There is an increasing awareness of UCB banks among the public, thanks to the aggressive marketing by private banks. However, the UCB from these private banks is reserved for the same individual in contrast to public banks in some countries where they are available to all. The probability of using one's own UCB for a hematological disorder in childhood where HSCT is required, is to the tune of 1:2500 to 1:200,000.<sup>12,13</sup> This is the major drawback of private banking.

## TYPES OF TRANSPLANT

Hematopoietic stem cell transplants (HSCT) are basically of two types: Autologous and Allogeneic.

- Autologous HSCT involves the intravenous infusion of a patient's own hematopoietic stem cells to rescue the patient from severe bone marrow injury caused by high dose chemotherapy and or radiotherapy as a part of treatment for cancer. This works on the principle that dose escalation of chemotherapy to a point of irreversible myelotoxicity but tolerable due to the replacement of myeloid function with the infused hematopoietic stem cells.
- Allogeneic HSCT on the other hand involves infusion of hematopoietic stem cells from another individual. The type of transplant in common diseases is summarized in Figure 1.<sup>14</sup> Depending on the donor, allogeneic HSCT can further be subclassified as follows, summarized in Table 1.
  - *Syngeneic donor*: This involves transplant from a twin sibling. These are akin to autologous HSCT as there is a full HLA match and the least complications.
  - *HLA matched sibling donor*: Here, the hematopoietic stem cells are taken from the patient's sibling, i.e. brother or sister. Every individual has a  $1/2^{n-1}$  ( $n$  = number of siblings), i.e. about 33% chance of having a matched sibling donor. This limits to a great

extent the number of patients who can undergo transplantation.

- *Matched unrelated donor (MUD):* With the availability bone marrow donor registries worldwide, it is now possible to find an unrelated HLA matched donor from these registries. It usually takes 3 to 6 months to find a donor by this method. The trend for matched unrelated donor transplants is also increasing with advances in higher resolution HLA matches and better supportive care. MUD transplants now account for about half of all allogeneic transplants world over. This trend is visible in Figure 2.
- *Haploidentical transplants:* Relatives that share one HLA haplotype with the recipient and are mismatched for one or more antigens on the unshared haplotype have been tried as donors with partial success. However, this technique requires T-cell depleted grafts to reduce the possibility of life-threatening GVHD.

**INDICATIONS FOR TRANSPLANTATION**

- *Patient selection:* There has been better understanding that HSCTs done early in disease course and an appropriate time has favorable outcomes in terms of transplant related mortality and disease recurrence. Patient selection is probably the most important factor determining transplant outcomes. There is an increasing trend toward early transplant in first complete remission (CR). The median diagnosis-transplant time interval has also decreased. Patients with better performance status are most suited for transplants. The upper limits of age are also being pushed higher each year with the availability of better supportive care and use of reduced intensity or nonmyeloablative conditioning. Autologous transplants are now being conducted even beyond 70 years and allogeneic transplants beyond 60 years of age.
- *Autologous hematopoietic stem cell transplantation:* The first autologous HSCT in humans was performed in 1958

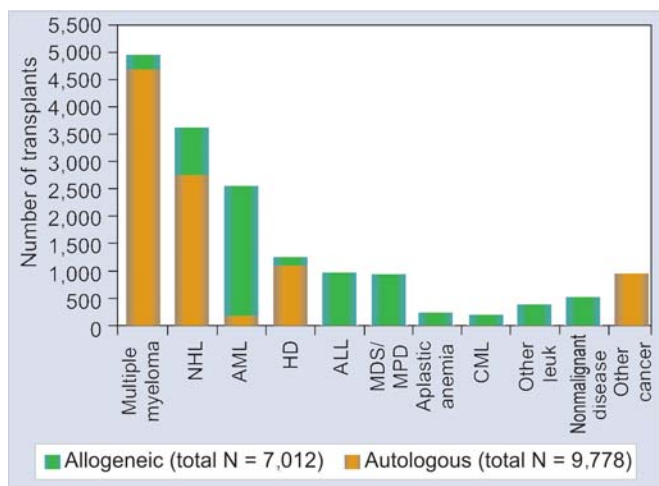


Fig. 1: Indications for hematopoietic stem cell transplantation in the United States<sup>14</sup>

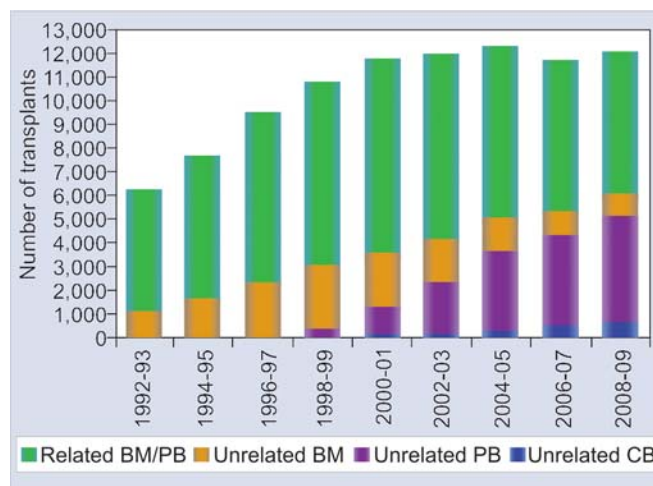


Fig. 2: Allogeneic transplants by donor type and graft source<sup>14</sup>

**Table 1:** Types of hematopoietic stem cell transplantation

Source	Type	Subtype	Donor		
Bone marrow	Allogeneic	Syngeneic	Twin sibling		
		Matched related	Sibling		
		Matched unrelated	Unrelated donor through registries		
		Haploidentical	Parents		
Peripheral blood stem cell	Autologous	Self	Self		
		Allogeneic	Syngeneic	Twin sibling	
			Matched related	Sibling	
			Matched unrelated	Unrelated donor through registries	
Umbilical cord blood	Allogeneic	Haploidentical	Parents		
		Autologous	Self	Self	
			Allogeneic	Syngeneic	Twin sibling
				Matched related	Sibling
Matched unrelated	Unrelated donor through registries				
	Autologous	Self	Self		

for teratocarcinoma and renal cell carcinoma.<sup>15</sup> Autologous HSCT involves the patient’s hematopoietic stem cells to be cryopreserved and thawed before reinfusion. However, noncryopreserved cells stored for a short duration have also been used for autologous HSCT. The following diseases are commonly treated by autologous HSCT (Table 2).

Non-Hodgkin’s lymphoma was the first hematologic malignancy treated by high dose therapy and autologous HSCT.<sup>16</sup> A prospective randomized control trial of autologous HSCT versus and standard dose therapy in relapsed NHL showed a significant difference in favor of autologous HSCT in terms of 5-year event free survival (EFS) and overall survival (OS). This study established high dose therapy and autologous HSCT as the standard treatment for relapsed aggressive (diffuse large B cell, Burkitt’s, T cell) NHL.<sup>17</sup> HSCT in Mantle cell lymphoma and other indolent NHL (follicular lymphoma) have been controversial. The German Hodgkin’s lymphoma study group<sup>18</sup> and the British National lymphoma investigation<sup>19</sup> randomized control trials in relapsed Hodgkin’s lymphoma showed an improvement in failure free survival but no difference in OS. High dose therapy followed by autologous HSCT is the current standard of care for most patients with relapsed and refractory Hodgkin’s lymphoma.

Multiple myeloma: Randomized control trials have demonstrated clear superiority of high dose therapy and autologous HSCT over standard chemotherapy.<sup>20</sup> One-third of the patients achieve a CR with a disease free progression of 10 years in a third among these. This demonstrates a potential curability of the disease. However, in the era of newer drugs with higher and deeper responses, there is no definite evidence for early transplant. Currently, myeloma is one of the most frequently treated malignancies with HSCT. Young

patient with limited AL-amyloidosis are also candidates for autologous HSCT.

Carcinomas and sarcomas: Other malignancies where autologous HSCT has been successfully tried include malignant melanomas, neuroblastoma and germ cell tumors. Besides this autologous HSCT has also been studied in autoimmune diseases, like SLE, rheumatoid arthritis and multiple sclerosis, however no recommendations can be made in the absence of well designed clinical trials.

- *Allogeneic HSCT*: The application of allogeneic transplants can be mainly divided into nonmalignant and malignant causes. Nonmalignant conditions and indications for allogeneic HSCT include the following (Table 2).

Thalassemia is one of the commonest inherited condition for which HSCT is the only curative treatment option. The life of a thalassemic patient is highly miserable with the requirement of frequent blood transfusions and complications of iron overload. All patients with HLA matched related donors should be offered HSCT at the earliest as delay in transplant reduces transplant success due to irreversible damage of iron overload. The indications for HSCT in sickle cell disease are evolving and is currently recommended in age <16 years, recurrent vaso-occlusive episodes (chest or CNS) and sickle cell nephropathy.<sup>21</sup> The success rate is among the best of all disorders offered HSCT. Despite this HSCT is not commonly performed for this disease because of parent’s unacceptability to transplant related mortality. Severe combined immunodeficiency (SCID) and Wiskott-Aldrich syndrome are some of the primary immunodeficiency states for which an allogeneic HSCT is life saving. In the absence of a matched sibling donor, alternative donor sources include cord blood, unmodified matched unrelated or T-cell depleted HLA-haplotype/disparate parental grafts in that order. The success

**Table 2:** Indications of hematopoietic stem cell transplantation

Category		Condition	Autologous	Allogeneic
Nonmalignant	Inherited	Thalassemia		++
		Sickle cell anemia		++
		Primary Immunodeficiency		++
	Acquired	Inborn errors of metabolism		++
		Aplastic anemia		++
		Paroxysmal nocturnal hemoglobinuria		++
Malignant		Myelodysplastic syndrome		++
		Chronic myeloid leukemia		++
		Acute myeloid leukemia	+	++
		Acute lymphoblastic leukemia	+	++
		Chronic lymphocytic leukemia	+	++
		Non-Hodgkin’s lymphoma	++	
		Hodgkin’s lymphoma	++	
		Multiple myeloma	++	
		Neuroblastoma	++	
		Germ cell tumor	++	

rate even with the latter donors has reached up to 70%.<sup>22</sup> The current management of storage disorders (inborn errors of metabolism) includes comprehensive strategies like newborn screening, enzyme replacement therapy, substrate depletion with HSCT limited to some patients and centers. The future in this group of disorders lies in gene transfer and embryonic stem cells therapy.

In aplastic anemia, trials have shown a clear survival benefit with allogeneic HSCT compared to immunosuppressive therapy in patients less than 40 years of age (73 vs 68%).<sup>23</sup> A time interval from diagnosis to transplantation is the single most important factor determining transplant outcomes. So, aplastic anemia should be looked as a medical emergency and transplant option given to all those who are eligible at the earliest. For those without matched sibling donors, a search for an unrelated donor should begin within 4 months of failure of immunosuppressive therapy. The options for paroxysmal nocturnal hemoglobinuria associated aplastic anemia remain the same. Allogeneic HSCT are also recommended in high risk Myelodysplastic syndromes, where a suitable donor is available.<sup>24</sup>

### TIMING OF TRANSPLANT

The timing of transplant is the most important factor in the outcome of HSCT in malignant conditions. In acute myeloid leukemia, there is evidence that allogeneic HSCT in patients younger than 55 years with high risk cytogenetics has survival benefit. It is also the favored option for patients in second complete remission. However, for those without a matched sibling donor, an autologous HSCT is an option in CR2, though it is not curative.<sup>25</sup> Myeloablative allogeneic HSCT is recommended for all adult acute lymphoblastic leukemia risk subgroups in CR1 and CR2. An autologous HSCT can be performed in the absence of a matched donor.<sup>26</sup> In children, the recommendations are to perform an allogeneic HSCT in CR1 for induction failure and in CR2 for early marrow relapse.<sup>27</sup> In the era of tyrosine kinase inhibitors, allogeneic HSCT is reserved for accelerated and blastic phases of chronic myeloid leukemia and for treatment failures due to proven TKI resistance. Transplant is restricted to high-risk patients (17p del/p53 mutation) or relapsed/refractory chronic lymphocytic leukemia.<sup>28</sup> HSCT for solid cancers is limited by the fact that graft versus tumor effects are not robust. The safety and efficacy also needs to be confirmed in larger RCTs.

### NONHEMATOLOGICAL APPLICATIONS OF HEMATOPOIETIC STEM CELLS

Hematopoietic stem cells were believed to have the property of plasticity, i.e. the ability to dedifferentiate into

parenchymal cells of the tissue into which they were transplanted. It was assumed that they would have a role in tissue regeneration and this was the reason for their interest in regenerative medicine. HSC probably act by secreting various cytokines and chemokines stimulating proliferation of endogenous native tissue stem cells, inhibiting apoptosis and promoting angiogenesis. However, this has not translated into clinical success. The results with intravenous or intracoronary injections of autologous hematopoietic stem cells (mononuclear cells) in ischemic heart disease have not been up to the expectations,<sup>29</sup> probably because the process of regeneration involving HSC is a very slow process. Cord blood is being studied for these applications too. UCB has been shown to contain unrestricted somatic stem cells (USSCs), mesenchymal stem cells (MSC) and endothelial colony forming cells (ECFC). The bone marrow is also a source of some of these stem cells like mesenchymal stem cells. These stem cells have osteogenic, chondrogenic, and adipogenic differentiation potential. These cells have been shown to have applications in regenerative medicine involving traumatic and skeletal diseases, plastic surgery, type 1 diabetes mellitus, cardiovascular (ischemic heart disease, cardiomyopathies) and neurological diseases (Parkinson's disease, strokes, motor neuron disease, spinal trauma) in preclinical studies. As the ethics in the use of embryonic stem cells is highly debated, *ex vivo* expansion of cord blood may replace embryonic stem cells for these applications in the future.<sup>30,31</sup> It is for these reasons that it is important to advocate public banking of UCB.

### CONCLUSION

The progress in the field of hematopoietic stem cell transplantation has been enormous. The results are getting better with each passing year. Despite this, the cure rates for most diseases are only slightly superior to that was seen in the past. The future lays in enhanced stem cell selection and amplification strategies. We are still far from an ideal, all purpose universal donor cell line, but this goal does not seem impossible.

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