

Hematopoietic stem cell transplantation: clinical use and perspectives

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ABSTRACT

Hematopoietic stem cell transplantation is the accepted therapy of choice for a variety of malignant and non-malignant diseases in children and adults. Initially developed as rescue therapy for a patient with cancer after high doses of chemotherapy and radiation as well as the correction of severe deficiencies in the hematopoietic system, it has evolved into an adoptive immune therapy for malignancies and autoimmune disorders. The procedure has helped to obtain key information about the bone marrow environment, the biology of hematopoietic stem cells and histocompatibility. The development of this new discipline has allowed numerous groups working around the world to cure patients of diseases previously considered lethal. Together with the ever growing list of volunteer donors and umbilical cord blood banks, this has resulted in life saving therapy for thousands of patients yearly. We present an overview of the procedure from its cradle to the most novel applications, as well as the results of the HSC transplant program developed at our institution since 1989.

Key words: hematopoietic, stem cells, transplantation, allogeneic

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) remains until now the only proven clinical use of stem cells. Since the discovery of this procedure in the early 1960s as a cure for hematologic cancer and both congenital and acquired diseases of the hematopoietic system (Fig. 1) (Pasquini & Wang, 2011; Thomas et al., 1975), significant progress has been made to make HSCTs safe and available to all patients with a clinical indication of the procedure.

HEMATOPOIETIC STEM CELLS (HSC) AND THE NICHE

HSC sustain blood cell production over the entire life of an individual. Initially during embryonic life HSCs develop in different anatomical places, beginning in the mesodermal germ layer which gives rise to the hemangioblasts (Huber et al., 2004). Subsequently a second short wave of erythroid progenitors originates from the yolk sac and later the liver becomes the third structure that gives rise to definitive erythroid differentiation (Gekas et al., 2005). HSCs that originate complete hematopoiesis are found initially in the aorta-gonad-mesonephros (AGM) region for a short period in a low number of cells. Subsequently the main place of HSC accumulation coming from the yolk sac and the AGM region corresponds to the fetal liver (Ema & Nakauchi, 2000). Finally, the hematopoiesis transfers to the bone marrow where it will contribute to the definitive adult hematopoietic system through the entire life of the individual.

The first demonstration of the existence of HSCs was reported in 1961 by Till and McCulloch (1961). Later the concept of the hematopoietic stem cell niche emerged, a highly specialized place where stem cells localized in the bone marrow (Schofield, 1978).

Currently the adult HSC niche is known to involve several other cell types that support HSCs including osteoblasts, osteoclasts, mesenchymal stem cells, adipocytes and neuronal

cells, among others (Doan & Chute, 2012). Also, a network of extracellular matrix proteins and surface molecules are pivotal for HSC survival, self-renewal, proliferation, differentiation and trafficking (Rettig et al., 2012).

At least 2 different niches have been described within the niche concept; the osteoblastic niche and the vascular niche, with different localizations and functions (Till & McCulloch, 1961). The former corresponds to the area where HSCs are in direct contact with the endosteal surface and the osteoblasts; evidence has shown that stem cell fate is regulated by the direct contact between HSCs and osteoblasts through Notch activation (Calvi et al., 2003; Yin & Li 2006). The vascular niche in the adult individual has been shown to be an area of HSC regulation. It has been demonstrated that *in vitro*, endothelial cells are able to expand significantly HSCs, probably through via soluble factors (Chute et al., 2002; Zhang et al., 2008). *In vivo* several studies have supported the existence of an anatomical vascular niche (Kiel et al., 2005; Lo Celso et al., 2009; Kopp et al., 2005).

The HSC-niche interactions subsequently induce the production of more differentiated precursors and finally mature blood cells which will be the components of the hematological and immune systems.

CLINICAL HSC TRANSPLANTATION

HSC transplantation (HSCT) is a procedure in which the entire hematopoiesis and immune system are replaced by the donor's cells (Copelan, 2006). HSCT can be classified according to its purpose, HSC origin and HSC donor type (Tables 1, 2 and 3). Matching in allogeneic transplantation is done by comparing alleles of the human histocompatibility locus (HLA) located in chromosome 6. HLA antigens are classified in class I (A, B, C) and class II (DRB1, DQB1, DPB1), and matching between donor and patient can be done at low, intermediate and high resolution (Petersdorf, 2008). Indications for HSC

transplantation are malignant and non-malignant diseases (Fig. 1). Most HSCT procedures are performed with autologous HSC for different forms of cancer, with multiple myeloma being the most common indication. Nevertheless, the development of equally effective and less toxic procedures is resulting in a

decreasing use of this procedure as therapy for these patients. Most allogeneic transplants are performed for patients with hematologic malignancies, mainly acute leukemias. Chronic myelogenous leukemia was the most common indication until tyrosine kinase-based therapy became available and proved to

TABLE 1
Purpose of HSCT

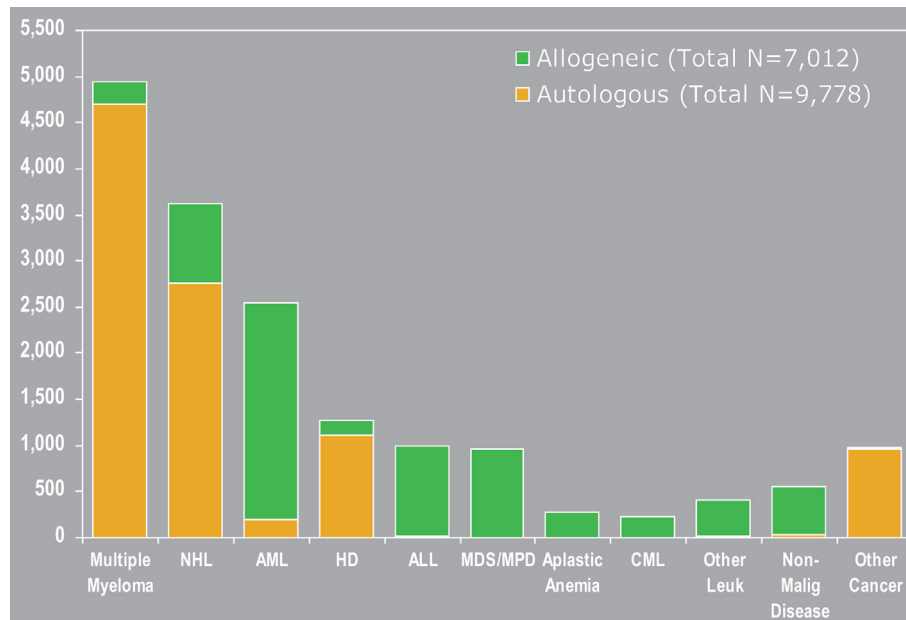
1. Rescue a patient with cancer from the toxic effects of high dose chemotherapy +/- radiation therapy (autologous or allogeneic)
2. Correct a congenital or acquired severe blood disorder by replacing the patient's with the donor's hematopoietic system (allogeneic)
3. Increase the control of a malignant disease by alloimmune effector mechanisms of the graft versus host reaction (allogeneic)
4. Reset the immune system to abolish autoimmunity (autologous or allogeneic)

TABLE 2
Donor sources in HSCT

1. Bone marrow, harvested by multiple punctures and aspiration of posterior iliac crests
2. Mobilized peripheral stem cells, obtained by leucopheresis after administration of granulocyte stimulating factor
3. Placental blood collected through the umbilical cord at the time of delivery

TABLE 3
Donor types in HSCT

1. Autologous: HSC are obtained from the patient
2. Allogeneic: HSCs are obtained from a donor
 - a. Matched related, sibling.
 - b. Mismatched related: partially matched family member. This graft usually requires graft manipulation either negative T cell selection or positive CD34 selection (haploidentical)
 - c. Matched unrelated: HSC from an unrelated donor that satisfies match criteria similar to a sibling donor
 - d. Mismatch unrelated: HSC from an unrelated donor with major or minor mismatches in HLA type



NHL: Non Hodgkin's lymphoma, HD: Hodgkin's disease, AML: acute lymphoblastic leukemia ALL: acute lymphoblastic leukemia, MDS/MPD: Myelodysplastic syndromes, CML: chronic myelogenous leukemia.

Figure 1. Indications for Hematopoietic Stem Cell Transplants in the United States, 2009. Center for International Bone Marrow transplant Research (www.cibmtr.org).

be a better alternative, particularly in older patients in the early phases of the disease. Transplantation in this group is now reserved for younger patients and when leukemia becomes resistant to tyrosine kinase inhibitors.

To engraft allogeneic HSCs successfully, a patient has to receive some form of immune ablative therapy or conditioning regimen before transplantation. In patients with hematological malignancies this is usually accomplished by the use of chemotherapy and total body radiation, which also function as anticancer therapy. Conditioning regimens are termed myeloablative when high doses of both radiation and chemotherapy are used and reduced intensity when lower doses are used. The intensity of the conditioning regimen depends on the underlying diagnosis, age of the patients and co-morbidities. Reduced intensity regimens have allowed extension of the procedure to older and sicker patients (Kassim et al., 2005).

The most limiting complication for allogeneic HSCT is graft versus host disease (GVHD), an immune rejection to host tissues mediated by donor lymphocytes which results in a skin rash, diarrhea and liver disease (Ferrara et al., 2009). This condition can become chronic and produce a systemic sclerosis-like illness which can produce scarring of the skin, gut and eyes (Horowitz & Sullivan, 2006). The most important factor that determines the incidence and severity of GVHD is HLA matching.

Transplantation failure is due to either disease relapse in patients transplanted for malignancies or to mortality related to the procedure, almost always due to infections and sometimes as a result of conditioning-induced organ damage. Infections by common and opportunistic microorganisms is a consequence of the profound immune suppression of patients and the prolonged recovery of innate and adaptive immunity (Table 4). GVHD is a contributing factor to infectious complications because of the further delay in immune reconstitution it provokes.

HISTORICAL EVOLUTION: HOW HURDLES WERE OVERCOME

Bone marrow transplantation was performed successfully as a result of the studies done by Donnall Thomas and the group

at the Fred Hutchinson Cancer Center during the 1960s. Early studies demonstrated the effect of high radiation therapy doses and chemotherapy in the bone marrow as well as the capacity to regenerate the individual's hematopoietic function by reinfusion of stored bone marrow cells from the individual or a donor (Lorenz et al., 1951; Mannick et al., 1960; Santos & Owens 1969).

To control GVHD two issues had to be dealt with: histocompatibility and post-transplant immune suppression. The first was accomplished with the continuous improvement of HLA matching from antigen to allelic typing, as well as the discovery of an ever growing list of class I and II alleles. The second was successfully dealt with by the introduction of calcineurin inhibitors, mainly cyclosporine, a potent immune suppressor developed for solid organ transplantation (Choi et al., 2010).

Infection control has improved significantly with the introduction of wide spectrum antibiotics, effective antifungals and an ever growing list of antivirals developed to curb the activation of latent or acquired disease. The use of controlled hospital environments to control the spread of airborne fungi goes in this direction (Tomblyn et al., 2009).

The second source of HSCs to enter the clinic were peripheral SC obtained from a healthy donor after mobilization with granulocyte stimulating factor and collected via leukapheresis. This avoids a painful surgical, and results in faster engraftment of granulocytes and platelets as well as improved immune reconstitution compared to bone marrow grafts (Storek et al., 2001).

The recognition of umbilical cord blood as a source of HSCs that can repopulate the marrow of a patient was reported in 1988 in a Fanconi anemia patient (Gluckman, 2009), based on previous work by Broxmeyer (2009) and Knudtzon (1974). The successful results of transplantation in children using cord blood grafts stimulated its use in adult patients. The main limitation was and remains the low cell number, with slow hematologic and immune reconstitution and initially high transplant-related mortality (Gluckman et al., 1997; Rubinstein et al., 1998). Several strategies are under evaluation to improve the results of umbilical cord blood transplantation (UCBT) in

TABLE 4

Prevalence of opportunistic infections after allogenic HSCT in the different post transplantation periods.

Phases of allogenic HSCT	Hematologic reconstitution (day +30)	Early immunologic reconstitution (day +100)	Late immune reconstitution (day +365)
Host factors	Neutropenia, lymphopenia, mucositis,	Deficiency in humoral and cellular immunity, acute GvHD	Deficiency in humoral and cellular immunity, chronic GvHD
Infectious agents	Gram negative bacteria Coagulase negative Staphylococcus Enterococci Candida spp Aspergillus spp Respiratory and enteric viruses (RSV, influenza, parainfluenza, rotavirus)		Encapsulated bacteria Adenovirus Cytomegalovirus Pneumocystis jiroveci

adults and large children. The most successful corresponds to double UCBT. Considering that most of the adult patients do not qualify for UCBT due to their weight and their minimum nucleated cell requirements, this is achieved with 2 UCB units. Several groups have published their results (Barker et al., 2003; Gutman et al., 2009; Brunstein et al., 2010). Overall, these studies have shown that myeloablative conditioning followed by double UCB graft infusion is associated with acceptable engraftment rate and long term overall survival, similar to adult graft sources. Interestingly, these studies have demonstrated the predominance of one of the 2 units shortly after transplant. The mechanisms are not fully understood but most likely are immunological in nature (Gutman et al., 2010; Ramírez et al., 2012). Large retrospective studies in Europe and the US comparing results between unrelated cord blood and adult volunteer donors have shown similar overall survival (Rocha et al., 2004; Laughlin et al., 2004). Important differences between the HSC sources are depicted in Table 5.

UNRELATED DONOR TRANSPLANTATION

Once transplantation from fully matched siblings and well matched relatives was done safely, the problem of patients without such a donor became the first priority. To this effect volunteer donor registries were started first in Europe (Anthony Nolan, UK, 1974) and later in the US (National Donor Marrow Program, 1986). These registries were quick to collaborate and large databases of donors from many registries were united (Bone Marrow Donors Worldwide). These efforts have resulted in more than 20 million donors recruited to date in all continents, providing thousands of HSC products for transplantation (WMDA) (Foeken et al., 2010). Despite this effort only 50% of the patients searching for an unrelated donor find one, and this average is widely variable among different ethnic backgrounds. The finding that umbilical cord blood was an alternative source of HSCs spurred the creation of public access cord blood banks which have meant a

TABLE 5

Comparison of the main features of UCBT and BMT (adapted from SCHOEMANS et al.)

	UCB	BM/PBSC
Number of available donors as 07/07/2012	563,6926 units	19,585,600 donors
Major limiting factor	Fixed unit cell content	HLA match and donor attrition
Minimum number of total nucleated cells for transplant	Aprox 2,5x10 ⁷ /kg	Aprox 2.0 x 10 ⁸ /kg
Second graft or DLI	Impossible	Possible
Median speed of donor availability	1 day	3-4 months
Donor morbidity	None	Fatigue, local pain, lower back pain
EBV/CMV transmission to recipient	Negligible	Possible
Risk for transmission of congenital diseases	Theoretically possible	None
Standard HLA match requirements	Minimum 4/6	Mostly 8/8

UCB: umbilical cord blood; BM/PBSC: bone marrow/peripheral blood stem cells; DLI: donor lymphocyte infusion; EBV/CMV: Epstein Barr virus/Cytomegalovirus

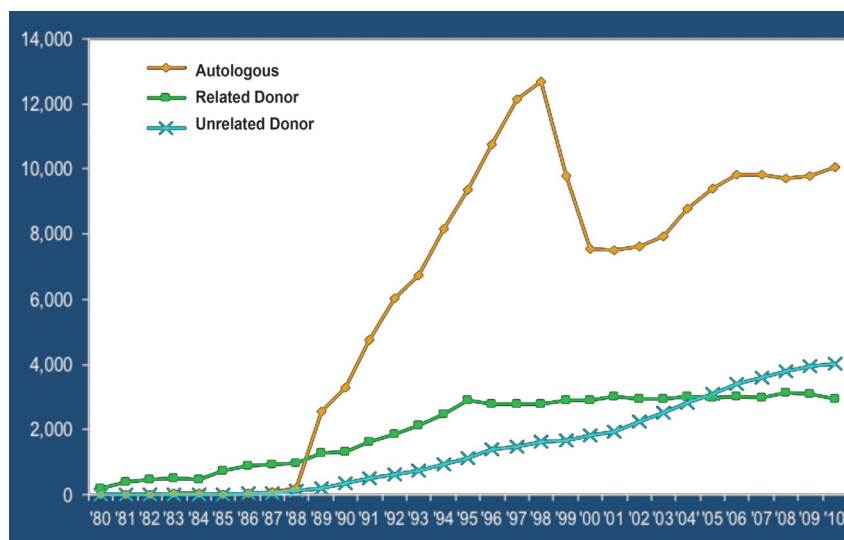


Figure 2. Transplant activity in the US 1980-2010. Center for International Bone Marrow transplant Research (www.cibmtr.org)

significant increase of the unrelated donor pool, especially for the pediatric age population. By 2012 an estimated 500,000 cord blood units have been stored globally (Bone Marrow Donors Worldwide). These banks obtain cord blood from donations; the blood is collected on delivery and white blood cells are purified, mixed with DMSO and frozen in liquid nitrogen. The units are then characterized (HLA, infectious diseases) and offered for clinical use through the multiple donor registries.

DONOR AVAILABILITY FOR UNRELATED DONOR TRANSPLANTATION

As more transplant teams are established and more donors are available worldwide, the number of allogeneic procedures has

increased by nearly 30% in the past decade both in the US (Fig. 2) (Pasquini & Wang, 2011) and in Europe (Fig. 3) (Passweg et al., 2012). Mobilized peripheral stem cells have become the fastest growing stem cell source in adult transplantation and umbilical cord blood in children (Foeken et al., 2010) (Fig. 4). The growth of adult volunteer donor registries and the establishment of large cord blood banks have increased the available donor pool for unrelated transplantation. The present number of registered donors in Bone Marrow Donors Worldwide exceeds 20,000,000, including over 500,000 stored umbilical cord blood units which represent a nearly 12-fold increase in 20 years (Figure 5). Despite all this progress, transplant activity differs widely between developed and developing countries. The World Marrow Donor Association

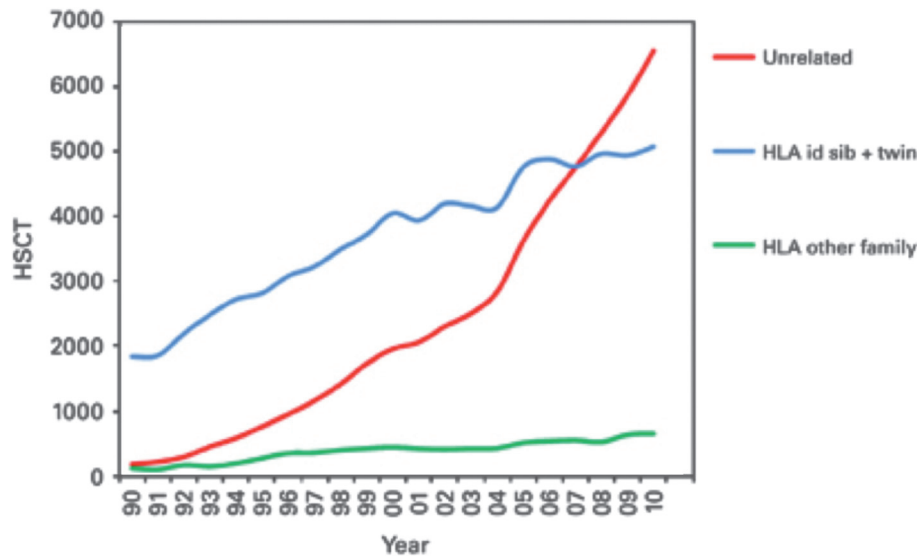


Figure 3. Allogeneic Transplant activity in Europe (EBMT) 1990 to 2010 (Passweg et al., 2012).

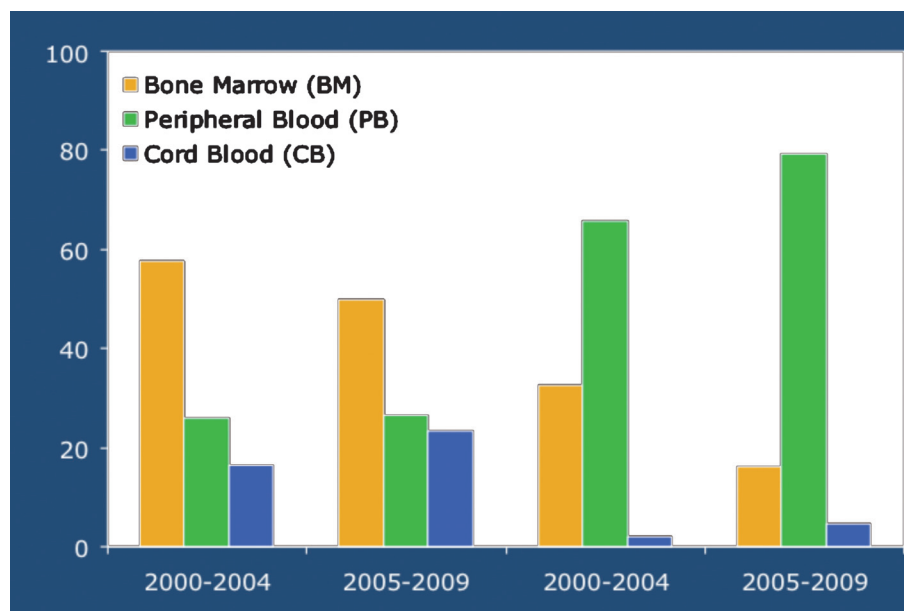


Figure 4. Allogeneic Stem Cell Sources by Recipient Age 2000-2009 (Pasquini and Wang et al., 2011).

reported in 2010 the rate of unrelated donor transplants. Procedures per 10 million habitants in developed countries ranged from 82 (Spain) to 224 (Germany) while the reported activity in South America in that same period was 6 to 14 transplants per 10 million. This reflects the high level of medical infrastructure and human resources needed to implement this procedure successfully.

The use of T lymphocyte-depleted HSC grafts from haploidentical family donors has also gained acceptance in many groups trying to overcome donor shortage. This procedure is directed towards eliminating T alloreactive cells in the graft and avoiding GVHD; many centers have improved its efficacy and safety, resulting in a slow gain of acceptance.

ALLOGENIC TRANSPLANTATION FOR HEMATOLOGICAL MALIGNANCIES

Acute and chronic leukemia constitute the most common indications for allogeneic HSCT. The mechanisms by which HSCT can cure leukemia are twofold: the high doses of chemotherapy and radiation the patients receives before infusion of the HSC graft (conditioning or preparatory regimen); and the immune-mediated graft *versus* leukemia reaction which mirrors GvHD. The relative importance of each is not well defined, and as the graft *versus* leukemia GVL reaction is better understood, more patients are being prepared with less intense doses of chemotherapy and radiation, favoring engraftment but reducing toxicity and transplant-related mortality.

Long term results in malignant diseases have classically depended on patient age, donor source (matched versus mismatched, related versus unrelated) and stage of disease. Patients in early clinical remission fare much better than patients who have experienced multiple relapses or are no longer responsive to chemotherapy. Because of this many centers will omit transplanting a patient with active disease outside a clinical trial.

ALLOGENIC TRANSPLANTATION FOR NON-MALIGNANT DISEASES: EXPANDING INDICATIONS

Allogeneic HSCT not only plays an important role in the treatment of children and adolescents with malignant diseases but it is also an effective therapy for a wide range of non-malignant diseases including hemoglobinopathies (thalassemia, sickle cell disease), congenital or acquired bone marrow failure syndromes, primary immunodeficiencies and inherited metabolic disorders. In each of these diseases, donor-derived cells have the ability to correct the underlying defect, either by direct repopulation of the hematopoietic and immune systems or by indirect delivery of the missing enzymes or other critical building blocks across the cell membranes. Contrary to what is emerging in HSC transplants for malignant diseases, the best results are still obtained with the use of identical sibling donors, which only applies to 20% of these patients. Thus the number of transplants using unrelated donors (cord blood and adult peripheral blood or bone marrow) has increased in recent years, with variable results that depend on the donor, number of cells, degree of mismatches, co-morbidity of the patient and time of transplantation. The European Group for Blood and Marrow Transplantation published the recommendation for the use of HSCT in non-malignant diseases; in some entities the transplant is considered the standard of care and in other cases this option of treatment must be considered in relation to the condition of the patient and the decision of the team and the family (Ljungman et al., 2010).

Primary immunodeficiencies are inherited disorders characterized by impairment of innate or adoptive immunity, commonly leading to lethal complications. Allogeneic HSCT can cure most of the lethal forms of immunodeficiencies, including severe combined immunodeficiency (SCID), several T-cell immunodeficiencies, Wiskott-Aldrich syndrome, phagocyte disorders such as leukocyte adhesion deficiency and chronic granulomatous diseases, haemophagocytic syndromes such as familial lymphohistiocytosis, Chediak-Higashi

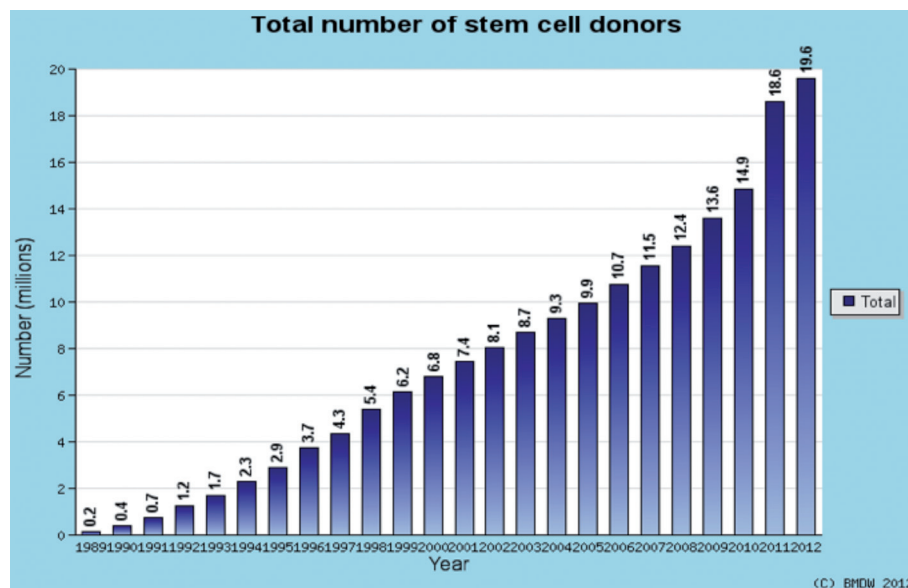


Figure 5: Unrelated stem cell donors registered with Bone Marrow Donors Worldwide 1989 to 2012 (www.bmdw.org).

syndrome, Griscelli's disease and X-linked lymphoproliferative syndrome. Treatment by HSCT is increasingly successful and is indicated from both HLA-identical and alternative donors. Patients with severe congenital immunodeficiencies need to be grafted as soon as possible. An allogeneic HSCT results in a survival rate of more than 90% when carried out shortly after birth. Prognostic factors are age, type of SCID, clinical state at the time of diagnosis, in particular the presence of a lung infection and degree of HLA histocompatibility (Wachowiak et al., 2008; Slatter & Cant, 2012). Allogeneic HSCT with an HLA-identical family donor is the treatment of choice for children with acquired severe aplastic anemia (Muñoz Villa et al., 2008). The use of alternative donors is restricted to patients who have failed other forms of therapy, and in these patients transplant-related mortality remains a significant problem mainly due to late or non engraftment (Maury et al., 2007). Children with Blackfan–Diamond anemia having a matched sibling should be transplanted if they do not respond to steroids or if they become dependent on them (Vlachos & Muir, 2010). Children with Fanconi anemia should be transplanted when they develop severe hematological disease if they have an HLA-identical sibling donor or a well-matched unrelated donor.

Allogeneic HSCT is the only currently available clinical treatment for many inherited metabolic diseases that lack effective enzyme replacement therapy, such as lysosomal and peroxisomal storage disorders (adrenoleukodystrophy, certain mucopolysaccharidoses and sphingolipidoses). Allogeneic HSC can correct these disorders in part by differentiation into monocyte macrophage cells such as microglia in the brain, Kupffer cells in the liver and alveolar macrophages in the lungs. These can induce long-term metabolic correction and ameliorate neurocognitive and functional problems (Krivit, 2004). Moreover, donor-derived cells induce 'cross-correction', a phenomenon by which the close proximity of normal cells can correct the biochemical consequences of enzymatic deficiency within the neighboring cells. Evidence of extensive distribution of donor cells in the blood vessels, peri-ventricular tissues, cerebral white matter, cerebellum, choroid plexus and forebrain parenchyma have been described (Krivit, 2004). Recent reports of large series have underlined the importance of transplantation in the early stages of the disease before significant organ and tissue damage occur (Prasad et al., 2008).

Hemoglobinopathies, such as thalassemia, sickle cell disease (SCD) and other complex defects, can cause major morbidity, poor quality of life and early death from the combined effects of anemia, hemolysis, iron overload and ineffective erythropoiesis. Early transplantation from a suitable donor prevents and reverses many of these problems. Because of different natural histories, the specific questions regarding the time of transplantation, criteria for patient selection and supportive care guidelines differ for patients with thalassemia and SCD. However, limitations of donor availability and risks of potentially serious toxicities have prevented HSCT from becoming the standard of care. To help define the patient selection criteria in thalassemia and an individual patient's risks from transplantation, Lucarelli et al. developed a scoring system on the basis of chelation therapy (regular or irregular), hepatomegaly and liver fibrosis, which predicted the risks of transplantation in patients with beta thalassemia (Lucarelli et al., 1993). This score has helped in the selection of both patients and donors for transplantation. Developments of conventional therapy have improved both the quality and the duration of

life for patients with sickle cell disease (SCD). For this reason, HSCT from an HLA-identical sibling is offered only to a subset of patients at high, life-threatening risk or to patients who cannot receive adequate support (Shenoy, 2011).

THE HSC TRANSPLANT PROGRAM AT THE PONTIFICAL CATHOLIC UNIVERSITY OF CHILE

Our institution commenced this program in late 1989 and its evolution has paralleled the challenges and advances in the field. 475 transplant procedures have been performed in children and adults since its inception. Initially, autologous and matched sibling transplants were performed in standard risk patients with malignant and non-malignant diseases. Allogeneic transplantation quickly became the center of our effort as indications widened during the 90's. Having safely established the sibling donor program we began to perform unrelated cord blood transplants in 1996, shortly after the first reports of its use were published (Rubinstein, 1998). During that period adult volunteer registries were restricted to centers outside the US and Europe, making this donor source unavailable. Unrelated cord blood, despite being the last source to be developed, bridged the gap that allowed us to solve the problem of patients lacking a family donor. Ten years later we started to procure grafts from adult donor registries after the National Marrow Donor Program launched an initiative to widen the use of unrelated transplantation worldwide. Nowadays our search process is initiated through Bone Marrow Donors Worldwide and registries with potential donors are contacted after the initial search. From 1989 through 2011, 268 patients have received an allogeneic transplant. Figure 6 depicts our program's allogeneic transplant activity in 4-year periods since 1989, showing that in the last period the number of unrelated donor transplants surpassed those of siblings, in accordance with the global tendency.

Indications for allogeneic transplants in our program have mirrored those reported by CIBMTR (Table 6). Most patients are transplanted for hematological malignancies, mainly acute leukemia (68%), and most of them have received myeloablative conditioning including total body irradiation. 150 patients (71%) transplanted for malignancy had early disease (acute leukemia in first or second complete remission, chronic myelogenous leukemia in chronic phase, untreated myelodysplasia). 58 patients have been transplanted for non-malignant disorders, 45 of them children (77%) and 26 (40%) with the diagnosis of severe aplastic anemia have been almost all children. 170 patients received a graft from a sibling or well matched relative (63%), and 98 from an unrelated donor (86% cord blood).

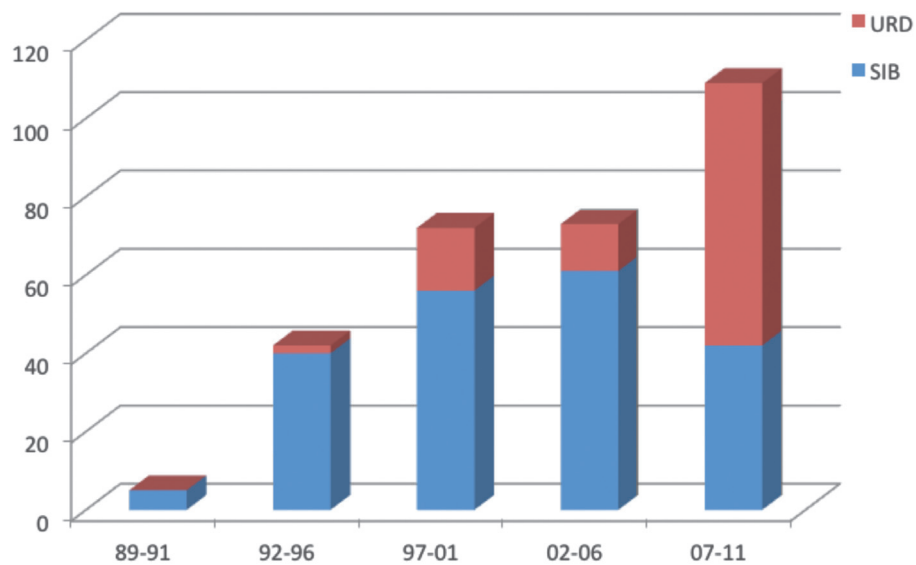
5-year overall survival for patients with malignancies was 48%. We analyzed risk factors for overall survival during the period 1997-2007, when the unrelated donor program started. The only predictive factor for survival was disease stage (early 58%, advanced 12%, $p < 0.001$, Fig. 7). For patients with early disease no differences were seen comparing patient age (<18 years, 43%; 18 or more 51%), donor source (related 62%; unrelated 59%), nor study period (1997 to 2005, 57%; 2006 to 2011 63%).

5-year overall survival for patients with non-malignant disorders in the pediatric age group was 62%. Due to the wide diversity of diseases in this group we sought to identify prognostic factors that could apply to all of them. Three such

TABLE 6

Patient and donor characteristics of the HSCT program at the Catholic University of Chile

Indications	Children < 18	Adults
Malignant		
Acute lymphoblastic leukemia	44	34
Acute myelogenous leukemia	23	35
Chronic Leukemia, myelodysplasia	17	34
Lymphoma	3	7
Other tumors	4	1
Early disease	66	84
Late disease	24	24
Non malignant		
Severe aplastic anemia	13	10
Histiocytosis	4	
Congenital		
Marrow failure syndromes	9	1
Immunodeficiency	11	
Hemoglobinopathy		1
Metabolic disorders	8	
Sibling or other related donors	76	91
Unrelated donors	66	32
Cord blood	60	26
Adult volunteer	6	6

**Figure 6.** Evolution of donor types in the HSCT program at the Catholic University of Chile. Number of patients transplanted in different age periods. SIB: sibling or other related. URD: unrelated donor.

factors emerged; donor source (sibling versus unrelated), the immune status of the patient (lymphopenic versus non-lymphopenic) and the presence of significant co-morbidities which were disease-related (active infections, severe iron overload and poor performance status). A worse prognosis was associated with the use of unrelated donors, with patients that had normal lymphocyte counts at transplantation and the presence of co-morbidities. When all three factors were scored together a powerful prognostic index was identified which allowed us to identify a group with a high risk of failure (5 year overall survival of 87% versus 26%. $p < 0.001$, Fig. 8).

CONCLUSIONS

HSC transplantation has developed into a mature field of medicine, reaching an ever growing number of patients worldwide thanks to improvements in transplantation techniques, center experience and donor availability. Our

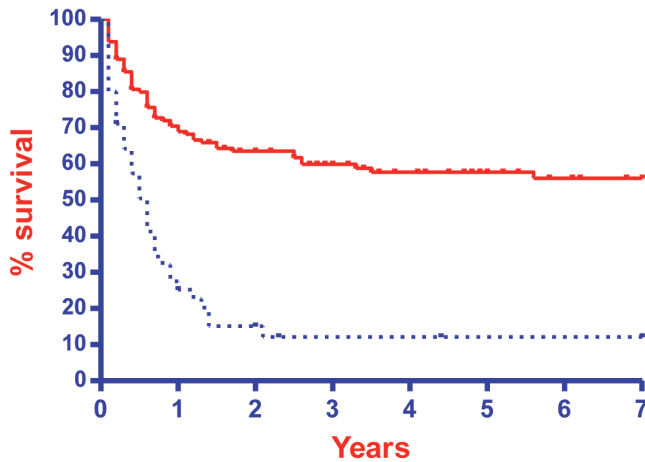


Figure 7. Allogenic HSCT results for patient with malignant diseases

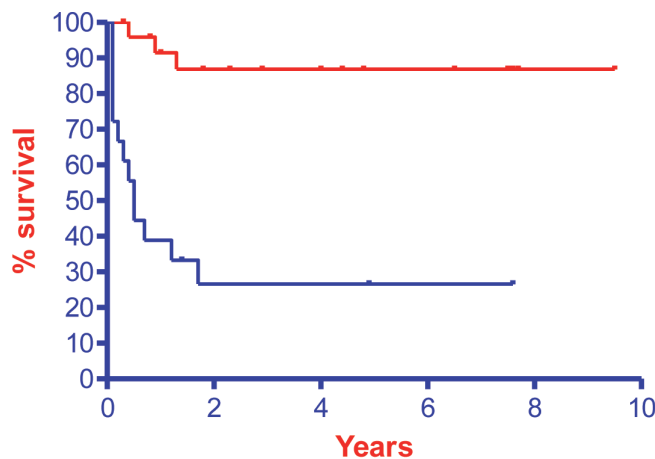


Figure 8. Allogenic HSCT results in children with non malignant diseases. Prognostic score (PS): related donor: 0; unrelated donor: 1; lymphopenic patient: 0; nonlymphopenic: 1; without comorbidities:0; with comorbidities

experience as well as that of many other centers has shown that patients with malignant diseases in need of transplantation should be evaluated and performed as soon as a donor is identified to avoid progression of their illness. Careful patient and donor selection will optimize results in patients with non-malignant disorders. Finally, continued improvements in the transplant process, in the understanding of the biology of hematopoietic stem cells and the ability to manipulate the immune system to develop a safer transplant procedure will help to benefit more patients without other realistic hope for a cure.

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