Chapter 16

Alternative Donor Sources for Hematopoietic Stem Cell Transplantation

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Additional information is available at the end of the chapter

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1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has become a common procedure for the therapy of hematologic malignancies, immune disorders and many other blood related disorders. Over 18,000 procedures are performed yearly in the US and Europe. The donor of choice for allogenictransplantation is a fully HLA matched sibling, which is available for only 20 to 25% of patients. Alternate donor sources have been developed and in the past few years transplant using these sources have surpassed the ones from sibling donor. These alternate sources are: adult volunteer donors which have been organized in large national registries; umbilical cord blood that is stored in blood banks worldwide; and manipulated stem cells grafts from haploidentical relatives. There is a wide variation in the transplant procedures, complications and outcomes between these sources, as well as debate over which one is the best source for each given patient, with few prospective comparative trials reported or in progress to settle this issue. We review the development and present status of each alternate source along with reported comparisons of properties and outcomes.

2. Hematopoietic stem cell transplantation: Purpose and indications

HSCT is a procedure where the entire hematopoiesis and immune system are replaced by the donor's cells [1]. HSCT can be classified according to its purpose, HSC donor type and HSC origin

The purposes of HSCT are:

1. Rescue a cancer patient from the effects of high dose chemotherapy and total body radiation. The most common indications are leukemia and lymphomas, which account for more than two thirds of transplants.
2. Correct a congenital or acquired cell disorder of the hematopoietic system (i.e., severe aplastic anemia and immune deficiencies, some inborn errors of metabolism)
3. Control the proliferation of cancer cells through immune mediated mechanisms that from part of the graft versus host reaction
4. Reset the immunological system, which had proven useful in patients with severe autoimmune disorders

Donor types are autologous, where stem cells are obtained from the patient, and allogeneic where stem cells are obtained form a donor. Autologous cells are only used in the treatment of malignant disorders that do not involve the bone marrow and autoimmune diseases.

An ever growing list of malignant and nonmalignant disorders is treated with HSCT (Table 1). It has grown at a rapid pace in the past two decades. Annual procedures in the US and Europe have gone from a few hundred in the early 90´2 to over 18,000 in 2011 [2, 3](figure 1).

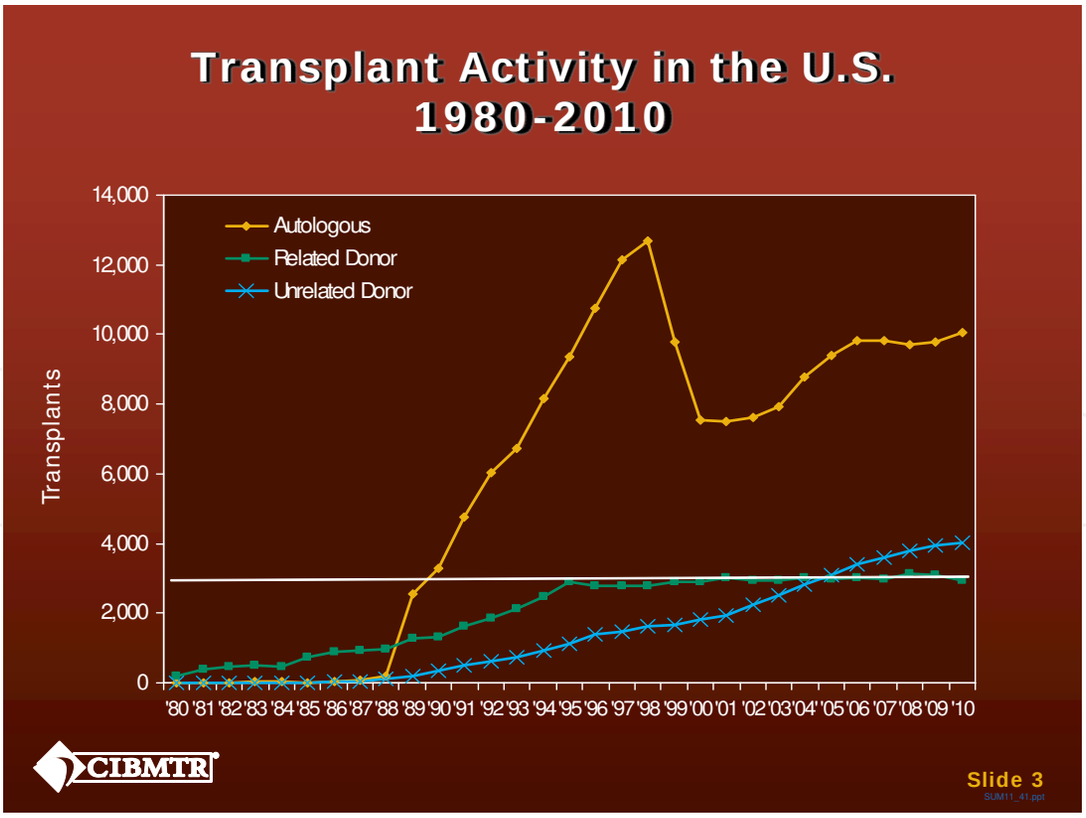

Figure 1. Transplant activity in the US, 1980 to 2010, by type of transplantation. Since 2005 unrelated donor transplants surpassed sibling donor procedures [2].

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Leukemia and lymphomas with specific clinical or biological characteristics, including:

- Acute high risk myelogenousleukemia (AML):
  - Antecedent hematological disease (e.g., myelodysplasia (MDS))
  - Treatment-related leukemia
  - Induction failure
  - First complete remission with intermediate- or poor-risk cytogenetics or molecular markers
  - AML after relapse
  - Second complete remission and beyond
- Acute high risk lymphoblastic leukemiaincluding:
  - Poor-risk cytogenetics (e.g., Philadelphia chromosome (t(9;22)) or 11q23 rearrangements)
  - High White cell blood count ("/>30,000 - 50,000) at diagnosis in adults
  - t(11;22) in infants
  - Central Nervous system NS or testicular involvement
  - No complete remission within 4 weeks of initial treatment
  - Second complete remission and beyond
- Chronic myelogenousleukemia:
  - No hematologic or response post-tyrosine kinase inhibitor (TKI) initiation
  - Disease progression or intolerance to TKI
  - Accelerated phase or blast crisis (myeloid or lymphoid)
- Chronic lymphocytic leukemia
- Juvenile myelomonocyticleukemia
- Hodgkin lymphoma
- Non-Hodgkin lymphoma

Multiple myeloma and other plasma cell disorders

Severe aplastic anemia and other marrow failure states, including:

- Severe aplastic anemia
- Fanconianemia
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Pure red cell aplasia
- Amegakaryocytosis / congenital thrombocytopenia

SCID and other inherited immune system disorders, including:

- Severe combined immunodeficiency (SCID, all sub-types)
- Wiskott-Aldrich syndrome

Hemoglobinopathies, including:

- Beta thalassemia major
- Sickle cell disease

Hurler's syndrome and other inherited metabolic disorders, including:

- Hurler's syndrome (MPS-IH)
- Adrenoleukodystrophy
- Metachromatic leukodystrophy

Myelodysplastic and myeloproliferative disorders, including:

- Refractory anemia (all types)
- Chronic myelomonocyticleukemia
- Agnogenic myeloid metaplasia (myelofibrosis)

Familial erythrophagocyticlymphohistiocytosis and other histiocytic disorders

Other malignancies

Table 1. Current indications of allogeneic stem cell transplantation

3. Sources of hematopoietic stem cells

3.1. Bone marrow

Marrow tissue obtained by repeated bone punctures and filtered to eliminate bone particles and fat was the original source of HSC. It contains 1 to 15 % of CD34+ cells, the marker by which HSC are identified. 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 [4]. 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 himself or a donor. Bone marrow as a source continues to be widely used but it has not increased due to the inherent nature of the procedure that includes general anesthesia, results in considerable blood loss and is often followed with significant donor discomfort.

3.2. Mobilized peripheral stem cells

Donors treated with hematopoietic colony stimulating factors, mainly G-CSF, will mobilize large amounts of CD34+ cells to their peripheral blood. These cells can be recovered by leucopheresis, a procedure that circulates the blood of the patient/donor through a centrifuge, separates white blood cells and reinfuse the remaining blood back to the donor. This is the preferred source today for adult donors, which results in the harvest of large quantities of both CD34+ cells and other mononuclear cells, mainly T lymphocytes. Both hematopoietic and immune reconstitution are faster with PBSC than with bone marrow and less opportunistic infections have been reported in patients receiving them [5, 6]. In patients with leukemia, they have also been associated with higher incidence of chronic graft versus host disease and improvements in survival but direct comparisons in a single center have been few. In one of the few randomized trials comparing both stem cell sources, Storek et al reported a fourfold increase of post transplant circulating CD45RA (naïve T cell precursors) in recipients of PBSC, as well as a significant decrease in fungal an bacterial infections. In this report survival was improved in PBSC recipients. Although earlier reports found that the incidence of chronic graft versus host disease in patients receiving higher doses of CD34+ in a PBSC graft more recent studies in larger number of patients have shown an overall benefit of the CD34+ dose [7].

3.3. Umbilical cord blood

Blood obtained from the placenta at birth is rich in high quality HSCs and can reconstitute the hematopoietic function in a patient just like bone marrow or mobilized peripheral stem cells [8, 9]. These cells have to be cryopreserved right after collection and stored for latter use in liquid nitrogen. Cord blood banks have been established worldwide to provide this stem cell source (see below) Umbilical cord blood grafts contain fewer HSCs than other sources and because of this its use was initially limited in adult patients [10, 11]. Ways to circumvent this limitation have been developed using pooled cells from two cord blood units. This modality was first done by the group in University of Minnesota looking to expand a cord blood unit

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while using a second one to increase the cell dose. Patients transplanted in this fashion had quicker hematopoietic cell recovery compared to those who received a single cord blood unit and transplant related mortality was greatly reduced [12]. An intriguing result was that only one unit of cord blood was identified in the peripheral blood of the patient, a phenomenon yet to be fully explained. These early results gave way to widespread use of two cord grafts in adult patients [13, 14]

A second alternative to increase the cell dose content has been expanding the cells before use. Many studies to accomplish this are on the way but it has not yet reached clinical use [15, 16]

3.4. Donor sources for allogeneic transplantation

Donors for allogeneic HSCT are matched in 3 to 6 loci of the human major histocompability complex (HLA, see below). Matching criteria are very strict due to the risk of acute and chronic graft versus host disease, the most common complication of HSCT, which can result in significant morbidity and mortality. Based on their origin and match grade donors can be divided into:

- Fully matched relative, almost always a sibling and rarely other family members. As HLA loci are inherited in a Mendelian fashion, the chances of a patient having a matched sibling are 25% with each sibling, which determines that only 20 to 25% of the patients have this type of donor. The chances improve in larger families.
- Partially matched relative: the donor shares at least one haplotype with the patient (haploidentical). HSC grafts need to be manipulated either with positive selection of CD34+ cells o negative selection of T lymphocytes.
- Matched or partially matched unrelated donor: presently there are more than 20 million unrelated donors listed in registries worldwide (see below) which are accessible for patients needing a transplant. These include adult volunteer donors and cord blood units stored in public access blood banks. The match grade accepted for a transplant depends on the criteria of the transplant center.

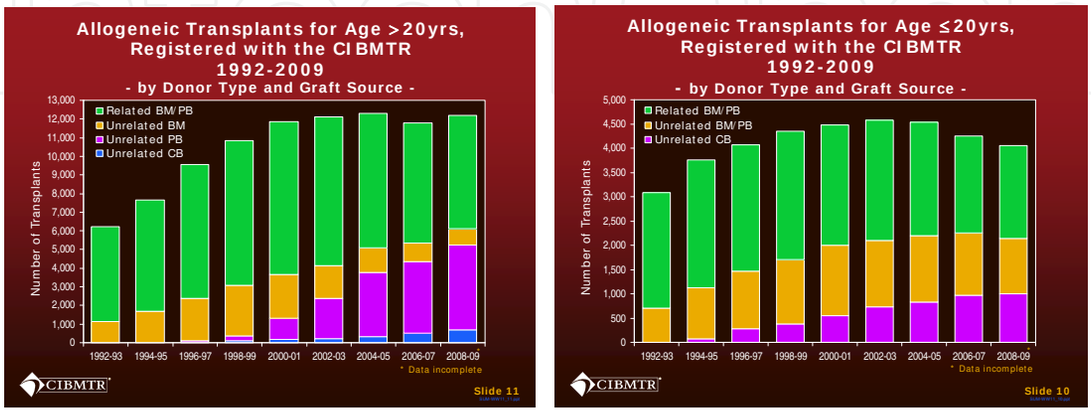

Figure 2. Stem cells sources and donor types in the US allogeneic transplantation, 1992 to 2009.

4. HLA typing in stem cell trasnplantation

The HLA system, also referred to the major histocompatibility complex, is a series of genes that expressed in the surface of immune and non immune cells represent a keystone in immune regulation and mediate graft acceptance or rejection in human allogeneic transplantation. First described in the 1950s as leukoagglutinin antibodies that appeared in the serum of pregnant women after blood transfusion, in 1967 the first nomenclature for HLA antigens was developed after initial efforts of systematization and standardization. Initially HLA antigens were described by serologic reaction with standard antibodies but as the genes encoding these antigens were sequenced, DNA techniques were adopted to increase the repertoire and further understand the polymorphic structure of the complex.

The antigens of the HLA system are encoded in genes located in the short arm of chromosome 6 (6p21.3). Their mission is to orchestrate the humoral and cellular immune responses, a basic issue in self and non-self molecular recognition. HLA antigens are localized on cell surface membranes and they form part of the antigen presenting complex with T cells receptors. The HLA/MHC region is inherited as a haplotype, which means that one person inherits 50% of the genetic information for MHC from the mother and the other half from the father, and shares a codominant expression. The most significant characteristic of this zone is its high polymorphism, which confers a huge variation between individuals.

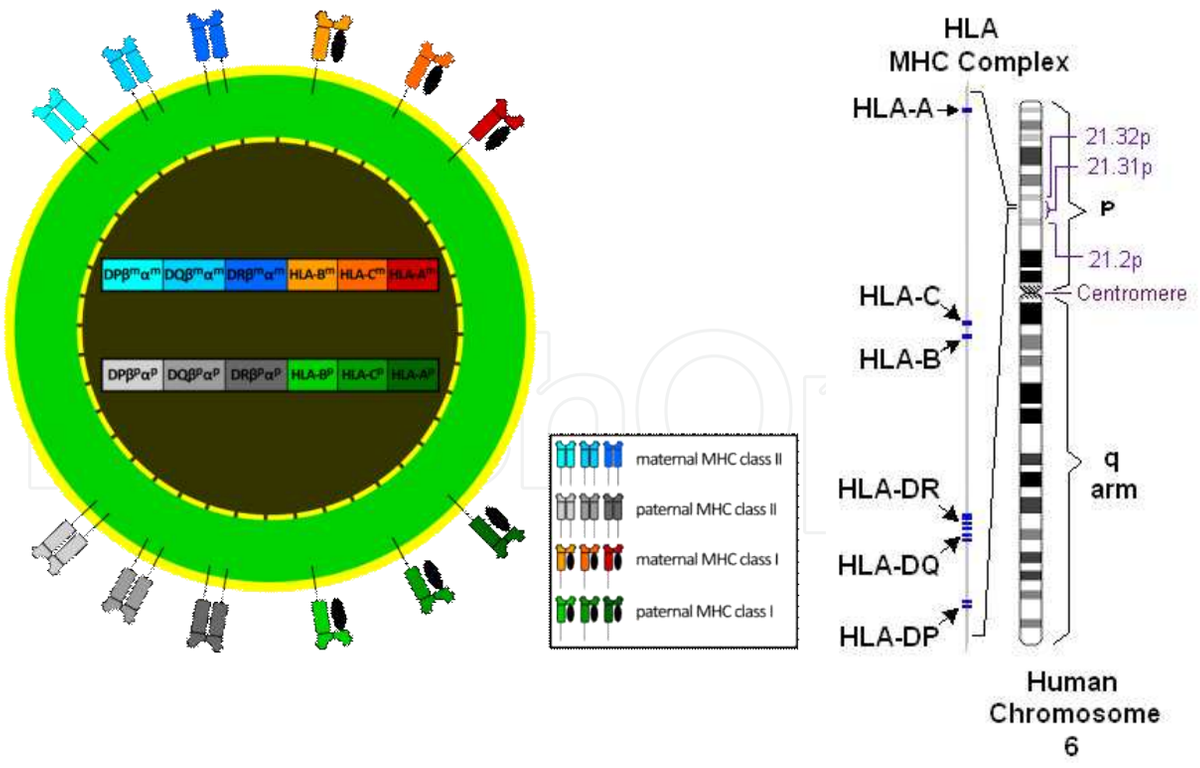

Figure 3. A Inherited MHC I and II complex antigens expressed on leucocyte membrane B. HLA encoding regions in Cr6.

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There are two distinct classes of HLA molecules, named I and II; genes HLA-A, B and C encode homonym antigens (A, B and C) and conform class I molecules. They are expressed in all cells and mediate antigen recognition which triggers activation of cytotoxic lymphocytes. Class II antigens are HLA-DR, DQ and DP and its corresponding antigens. They are expressed in professional antigen presenting cells and together with the T cell receptor they form the complex that activates T helper cells.

It has been widely described that the one of the main prognostic factors in HSCT is HLA matching, which plays a significant role in engraftment, overall survival, transplant related infections, and leukemia control [17].

5. Development of donor registries and cord blood banks

Large registries of volunteer donors were the natural solution to the need of patients who lacked a matched sibling for transplantation. Because of the highly polymorphic nature of the HLA system, thousands of donors had to be recruited to find matches for a sizable population of patients. This required the development of large organizations which recruit donors, obtain all the necessary information along with blood samples for HLA typing and enter all this information in searchable registries that can identify and contact the donor in case their stem cells are required. Registries work with donor centers which perform all the necessary medical tests and, if the transplant goes through, harvest stem cells from the bone marrow or peripheral blood.

Most of this activity started around blood banks that had leucopheresis programs and volunteer donors for platelets products with HLA typing done. Most registries are national, government supported organizations that work with their transplant and donor centers. Once they became established it was also natural that international collaboration soon commenced and stem cell products traveled between countries and continents. The first successful unrelated donor transplant took place in 1973 in New York when a young boy with an inherited immunodeficiency received multiple marrow transplants from a donor identified as a match through a blood bank in Denmark. Driven by the need of a single patient with Wiskott Aldrich disease, a congenital immune deficiency that could only be cured with a transplant, the Anthony Nolan Registry was started in England in 1974. The first unrelated donor transplant for a patient with advanced leukemia was done in 1979 in Seattle and spurred the formation of the National Bone Marrow Donor Registry, which later became the National Marrow Donor Program (www.nmdp.org). NMDP has grown to recruit over 5,000,000 volunteer donors. Their vast experience in donor selection is summarized in periodical guidelines and recommendations [18]. The first transplants facilitated through these registries were done in the mid 80´s. Soon many more registries around the world would follow; increasing the donor pool from a few thousand in 1980 to over 20 million by 2012 (figure 4).

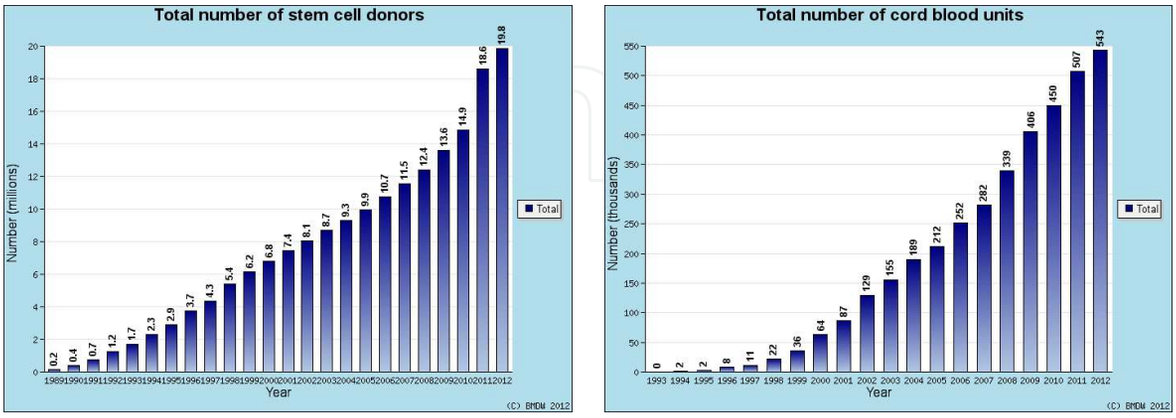

Figure 4. Stem cell donors and cord blood units listed in BMDW (www.bmdw.org)

The largest donor registries are located in the US and Europe, accounting for more than 60% of the donor pool. Based on the finding of large amounts of high quality HSC in newborn blood the first HSCT with umbilical cord blood was done in France in 1988 in a child with Fanconi Anemia who received the cord blood cells of his matched newborn sibling [19]. Since cord blood cells can be frozen and stored in liquid nitrogen for very long periods of time without losing their properties, cord blood Banks were established in the early 90s with blood units collected from the placenta at birth. HLA typing is done in these units and the cord blood bank acts as a donor registry, increasing furthermore the donor pool.

In 1988 the Europdonor Foundation was started in the Netherlands to facilitate access to donor registries around the world in a single site. Their network site, Bone Marrow Donors Worldwide (www.bmdw.org) works as a registry of registries and allows for search among all available donors. Presently BMDW lists donors from 112 registries in 50 countries.

Their mission is listed as:

- To maximize the chance of finding a stem cell donor or cord blood unit by providing access to all stem cell donors and cord blood units available in the world.
- To minimize the effort required for stem cell donor or cord blood unit searches: only registries with potential stem cell donors or cord blood units need to be contacted.

Two consequences are derived from this significant increase in the donor pool:

- Unrelated donor transplant activity has increased at a parallel pace (figure 1). Annual procedures in the US and Europe have gone from a few hundred in the early 90´2 to over 18,000 in 2011 (CIBMTR, EBMT) and in both cases have surpassed the number of sibling

donor patients transplants, which have remained constant. Despite this, and taking into account that needing a transplant and having a sibling donor are independent variables, there is room for much improvement in making this therapy available to all who need it.

- The larger donor pool coupled to improvement in HLA typing with identification of a growing number of alleles allow for much better matching between donor an patient and this likely accounts for the improvement in transplant results. A recent CIBMTR report showed that the difference in one year survival of patients transplanted for leukemia or myelodysplasia comparing those with a sibling donor to an unrelated one was reduced from 20% to less than 10% in the past two decades [2, figure 4]. We cannot rule out an effect of improved transplant center experience in this result, but other smaller reports have confirmed that donor source (sibling vs. unrelated) is less relevant to outcome.

In 1990 the World Marrow Donor Association was born to help coordinate international searches and transplant of hematopoietic stem cells, keeping track of all the products facilitated inside participating countries and those exported to other countries. According to their 2010 annual report [20], 15,256 patients were transplanted during that year with stem cells form unrelated donors. Of those, 7183 stem cells products (45,7%) were imported to the country where the patient received their transplant, that is, every day 20 stem cell products travel from one country to another. 12,237 products were obtained from adult donors and 3028 were cord blood grafts (19,4%) making cord blood the fastest growing stem cell source, even though it only represents 2,5% of the donor pool. The reasons favoring this are a shorter search time, immediate availability and less strict HLA match requirements. Also, more centers are become familiarized with this type of transplant procedure, accounting for its increased use.

A general overview at the global map displayed by CIBMTR, EBMT and WMDA immediately highlights the large difference of access and activity of stem cell transplantation among different regions of the world. In general the size of the national registries mirrors the transplant activity for each region. By far, Europe and North America have the larger registries (16,2 million donors) and account for the highest transplant activity (18,500 in 2010), followed by some countries in Asia. South America and Africa lag behind. The top 5 countries shipping marrow or peripheral stem cells products are Germany, USA, Japan, United Kingdom and China, accounting for 83% of shipments. The registries recruiting the largest amount of donors in that year were REDOME (Brazil), NMDP (USA), ZKRD (Germany), CMDP (China) and CRIR (USA), accounting for 79% of the donors recruited. The five largest suppliers of cord blood units were USA, Japan, Spain, France and Italy.

6. Haploidentical stem cell transplantation

Haploidentical stem cell transplantation consists in the use of a graft from a related donor, usually parents or siblings, with whom the patient shares at least 50% (up to 80%) of the MHC

alleles. The graft itself can be collected by apheresis or bone marrow aspiration and it has to be manipulated to allow for engraftment and prevent graft versus host disease.

Two main advantages of transplantation from a full haplotype mismatched family member are evident:

1. Most, if not all, patients have an HLA-partially matched relative who is available to serve as a donor. In fact most patients will have more than one donor, allowing the possibility of switching to another relative if more than one graft is required [21, 22].
2. More frequent than not the best donor can be chosen between many candidates. The graft is immediately available once the best candidate is chosen, as is the case in sibling transplantation

Haploidenticaltransplantation has been limited by historically high rates of graft rejection, GVHD, TRM, and poor immune reconstitution, resulting in a high incidence of serious opportunistic infection. Both myeloablative and reduced intensity conditioning transplant strategies have been attempted looking for better outcomes, with diverse results. The first attempts of HLA-non identical stem cell transplantation were reported in 1985 by Beatty et al [23], who described the problems and adverse effects derived from unmanipulatedhaploidentical grafts using myeloablative conditioning regimens. This study reported non permissive toxicity and mortality with type II HLA mismatch as well as higher rates of GVHD with class I antigen mismatch. It also set the stage for graft manipulation, which has improved outcomes. Some of the strategies involved are:

1. Ex vivo T cell depletion, that resulted in improving acute and chronic GVHD, overall and event free survival [24].
2. Ex vivo positive selection of CD34+ cells resulting in a T cell reduced graft [25].
3. In vivo immune suppression with anthymocyte globulin and post transplant high dose cyclophosphamide [26]
4. Ex vivo induction of alloantigen specific anergy by coculturing host and donor BM mononuclear cells with either CTLA-4-IG or anti–B-7.1 and B7.2 antibodies [27]

Delayed immune reconstitution after haploidentical HSCT is the main contributor to morbidity and mortality of this technique. The reasons for this are T cell depletion of the graft, thymic dysfunction induced by pretransplant chemotherapies and conditioning regimens, and GVHD occurrence and its treatment [28].The other major challenge for haploidentical HSCT is the high relapse rate, and several strategies are been developed like the use of tumor specific T cells and the use of NK from the donor as shown below.

Intense pretransplant conditioning and graft manipulation to rid of T lymphocytes is associated with delayed hematological and immune recovery, resulting in an increased rate of infection. To circumvent this drawback, large doses of CD34+cells have been used to improve the speed of hematological recovery with success [29]. To hasten immune recovery and also make the procedure tolerable to older patients, less intense or reduced conditioning regimens have been tried [30] but the effect on improving immune recovery have been modest.

Perhaps the most disturbing side effect of T cell depletion to allow a haploidentical graft is the abolition of the graft versus tumor effect with the increased rate of post transplant recurrence of leukemia. This was observed in the first attempts with haploidentical grafts. Despite this a substantial graft versus tumor effect has been attributed to the infusion of natural killer (NK) cells, which are not depleted with T lymphocytes [31]. The best described element regarding NK cell activity is the inhibitory killer cell immunoglobulin-like receptor (KIR), which helps prevent NK cells from damaging host tissues, [32]. KIRs are expressed by NK cells from the donor and interact with host HLA class I epitopes (HLA-C) in the recipient. If the KIR-HLAC is mismatched, the inhibitory action of the receptor fails and the alloreactive NK cell is activated against the host cell. KIR mismatch between donor and recipient has been associated with improved survival after HSCT in AML, appearing to promote engraftment, reduce GVHD and decrease leukemic relapse [33, 34].

Further attempts to "engineer" the graft has been made to improve results. Handgretinger [24] developed a protocol based on animal models, using NK cell enriched CD3+ depleted stem cells, with either myeloablative or reduced intensity conditioning regimens, plus anti CD-20 for in vivo B cell depletion. Assessment of immune reconstitution by flow cytometry showed a faster recovery of CD4+, CD56+ and thymic precursors measured by TREC analysis. The protocol reported significant reduction in transplant related mortality as well as incidence of cytomegalovirus and adenoviral infections,

7. Donor search algorithms

It is widely recognized that the HLA matching level is the most important factor for transplant outcome [16, 35, 36]. Thus, fully matched siblings are the best source of HSC for transplantation, also due to their immediate availability, lower transplant related complications and mortality, and reduced costs in obtaining stem cells. Nevertheless a fully matched HLA graft also implies a reduced alloreactive effect of donor T cells against tumor cells in patients transplanted for malignant diseases and this can reflect on a higher rate of relapse, which has to be weighed against the reduced transplant related mortality.

Several aspects can be taken into consideration when choosing an unrelated donor among the different alternatives and they all come into play simultaneously. A very important one is center experience, which in itself accounts for most of the improvement in outcome [37]. Large transplant programs usually have preferences regarding the donor chosen based in their experience. The search process, stem cell procurement, and previous results weigh in their policy. Some programs only use one source of stem cells (i.e. adult donor or cord blood) and establish search and procurement protocols based on this choice. Programs with a preference for cord blood grafts will consider using less compatible cord blood units (4/6 match) or resource to double cord blood grafts for adult patients [11,12, 38, 39] before considering an adult donor with a single high resolution HLA mismatch. Other programs with no cord blood transplant experience will either resource to a partially matched donor or forfeit transplantation altogether. Perhaps the most center-dependent modality is haploidentical transplantation.

Few centers have the infrastructure and professional teams trained in T cell depletion or CD34+ enrichment and despite its obvious appeal and having been around for a long period of time the procedure has not reached wide acceptance. The total number of haploidentical transplants reported to EBMT in the past decade has remained almost unchanged [3].

Despite different preferences in donor selection some points are generally agreed upon in the transplant community, which rely in overall experience and careful review of multiple published reports [40].

1. The best alternate donor for unrelated transplantation in a patient who can wait for the search process to be completed is a fully matched adult with at least 8 high resolution (i.e. 4 digit or similar) matched alleles [34, 41]. Some centers will require a 10/10 match, usually including DQB1, for donor acceptance. Unfortunately, and despite the massive recruitment of donors worldwide, we are still far from securing a fully matched donor for every patient. A 2004 report by the National Marrow Donor Program in the US, with over 4 million recruited donors, projected that only white and hispanic patients would have an over 50% chance for a fully matched donor by 2007, with other ethnic groups faring much worse [42]. When more than one fully matched donor is available other secondary aspects can be taken into consideration: younger age, male sex, CMV serology referred to the patient, ABO compatibility, larger weight and rapacity. Despite this, only HLA matching and donor age affect patient survival [17].

2. If no such donor is available or the patient cannot wait, most centers will opt for fully matched or single mismatched cord blood unit (6/6 or 5/6; HLA-A and B in low resolution and DRB1 in high resolution), provided it reaches a total nucleated cell dose of at least 3,0 x 10^7 per kg of the patient [43]. This is readily available for most children up to 40 kg. [44]but can be difficult for large adults. In this situation most programs recur to a double cord blood unit graft, a modality that has gained wide acceptance [37,38]. If no highly matched cord blood units are available the options mentioned are either an adult donor with a single major locus mismatch or a single or double 2 mismatched cord blood unit (4/6). This situation is generally decided upon center experience and bias towards one or the other graft source.

3. It has been difficult to place haploidentical transplantation in donor selection algorithms since most of these procedures are done in few highly specialized centers that have the facilities and trained staff for it. Recently, new approaches to avoid graft rejection and GVHD by in vivo T cell depletion with potent immune suppression and chemotherapy have been tried with reported results that are similar to the use of double cord blood grafts [45]. In general transplant related mortality in haploidentical transplantation has been reportedly lower than using cord blood but this advantage has been offset with the higher risk of relapse, which makes this source less recommendable for patients with high risk disease. Longer follow up will be needed to address the question of which particular patient benefits from which particular donor.

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	Adult donor	Cord blood	Haploidentical
Donor availability adults	Fully matched 50% One mismatch 70%	5/6 or 6/6 : 85% * 4/6: 100% *	80%
Donor availability pediatric	Fully matched 50% One mismatch 70%	5/6 or 6/6: 90% 4/6: 100%	100%
Average time from search to transplant	3 months (0,5-6)	21 days (7-60)	7 days
Target CD34+ dose /kg	> 2 x 106	> 0,1 x106	>10x106
Graft manipulation	Not required	Not required	Required
T cells in the graft	Replete (PBSC "/> BM)	Partially depleted	Depleted
T cell immune reconstitution	3 months	6-9 months	6-9 months
Acute Graft versus host	Higher depending on mismatch	Less depending on mismatch	Rare
Chronic graft versus host	Higher depending on match	Similar depending on match	Rare
Relapse risk	Similar to less	Similar to less	Higher
CMV reactivation **	Similar	Frequent	Frequent
Post transplant cell infusion	Possible	Not possible	Possible

*single or double unit graft

**depends on the donor and patient serology results

Table 2. Comparison between alternative donor sources

8. Transplant outcomes: Comparison among donor sources

Large registries have tracked the progress of HSCT results in the past decades. The information obtained from them allows comparing in an extensive number of patients the impact of disease type and stage, the donor source and donor type in transplant outcomes. Analysis of the data from CIBMTR has shown that transplant results in young patients with hematological malignancy in early stages of the disease comparing related unrelated donors have improved consistently in the past 20 years, reducing a 20% difference in one year survival to less than 10% (figure 5). This data strongly supports the use of a matched adult volunteer donor as the first choice when one is available, and this is something most centers will agree upon. The challenge and controversy comes from selecting between a cord blood graft, a mismatched unrelated adult donor or ahaploidentical donor [46]. Several studies have addressed this issue for different graft sources in patients with different diseases, both in adults and in children, based on registry data or comparing published reports using a single donor source. Very few clinical trials have attempted to compare graft sources and none have been randomized [44]. Center preference and the difficulty involved in search logistics will make very unlikely that a randomized trial will ever be accomplished.

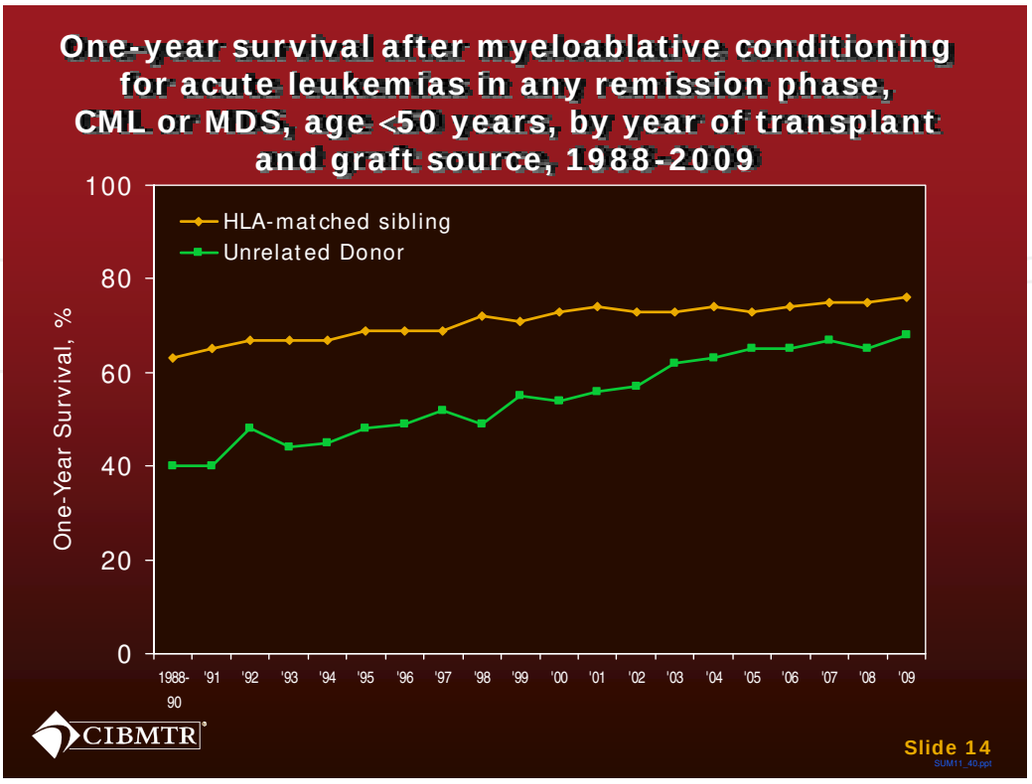

Figure 5. Improvement in one year survival of HSCT from related and unrelated donors in patients with hematological malignancies.

Several large studies have compared umbilical cord blood with mismatched unrelated donors in patients with hematologic malignancies:

Laughlin et al compared results of a single cord blood unit graft versus a 7/8 HLA matched unrelated donor in 233 patients from the databases of CIBMTR and the National Cord Blood Program in New York and found similar outcomes when measuring transplant related mortality, event free survival and overall survival. Survival was a sobering 26% to 20% in cord blood versus mismatched donor, and did not reach significance [47].

Eapen published in 2007 the results in a large group of children with acute leukemia transplanted with a single cord blood unit, a fully matched unrelated donor or a mismatched unrelated donor [48]. The measured outcome was leukemia free survival, also assessing the relative effect of cell dose and HLA matching in the outcome of cord blood transplants. The study included 785 patients younger than 16 years at transplantation with acute lymphoblastic or acute myeloid leukemia who received either a single-unit cord-blood or a bone-marrow graft from an HLA-matched or HLA-mismatched unrelated donor in the USA. The comparisons were made between six groups: HLA-matched cord blood, one-antigen mismatched high-cell-dose cord blood, one antigen mismatched low cell dose cord blood, two antigen mismatched cord blood (any dose), allele-mismatched bone marrow, and allele-matched bone marrow. Early transplant related mortality was significantly less in patients who received fullymatched marrow and cord blood, or a high dose one antigen mismatched cord. This

advantage was offset by a higher incidence of relapse in the first group with similar leukemia free survival among all groups analyzed. These data support the use of HLA-matched and one- or two-antigen HLA-mismatched umbilical cord blood in children with acute leukemia who need transplantation. The higher risk of non-relapse mortality associated with unrelated bone marrow and cord blood transplantation raises anxiety among pediatric oncologists when considering these donor sources for their patients. Nevertheless, the ever growing number of donor registries and cord blood banks will improve the chances of finding the best suited donor.

Another study by Eapen et al in 2010 [49] reported the outcome on 1525 adult patients transplanted for acute leukemia with unrelated matched or mismatched donors comparing them to single cord blood unit recipients. Transplant related mortality, leukemia free survival and overall survivals were almost identical among cord blood recipients and mismatched unrelated donor recipients. Overall survival 43-44%, a significant improvement from previous studies.

Trying to address the question whether a more mismatched stem-cell source will give better disease control due to a potential increased graft versus leukemia effect, Zhang 50 et al compared leukemia free and overall survival among 348 children with leukemia registered with CIBMTR who were transplanted with unrelated donor bone marrow, unrelated cord blood and HLA-matched sibling bone marrow. 3-year leukemia free survival was comparable among all groups, despite higher risks of acute and chronic GVHD after unrelated donor transplantation and higher non relapse mortality after mismatched unrelated donor BM and cord blood transplantation. The pattern of treatment failure differed by donor type. Whereas nonrelapse mortality was higher after unrelated donor transplantation, they observed a higher, but not statistically significant, risk of relapse after HLA-matched sibling donor transplantation. A logical conclusion to this and other reports is that as transplant related mortality is curbed with better control on infections, a more mismatched graft may be better for high risk leukemia. Similar results were published previously by Minnesota group [51]comparing single center transplant outcomes by HSC source for children less than 18 years with ALL in second complete remission. In a more limited sample of patients, their results also suggest that transplant outcomes are remarkably similar in recipients of matched sibling, matched unrelated or umbilical cord donor grafts.

Very few studies have compared outcomes of unrelated donors with haploidentical transplantation. Most reports come from single center studies and they are difficult to interpret due to the different techniques employed for haploidentical donor selection and graft manipulation. A recent study compared the results of two large parallel clinical trials: one, using haploidentical donors with in vivo treatment of the recipient with post transplant high dose cyclophosphamide ; two, using a double 0 to 2 antigen mismatched cord blood graft [44]. One year survival in both groups was similar around 50%. Nevertheless large differences in outcome were noted: non relapse mortality was higher in the cord blood group (24% vs. 7%) but relapse was lower (31% vs. 45%).

Different considerations apply for patients with nonmalignant disease. The emphasis is put on engraftment, quick immune recovery and avoidance of graft versus host disease. In this

regard most patients can wait and receive alternative therapy until a suitable donor is found and therefore the search process can be prolonged as much as needed. In some cases the transplant has to proceed more urgently to avoid organ damage, chronic blood transfusion or repeated infections. As most patients with nonmalignant diseases are children a well matched cord blood unit is usually available for almost every patient. The challenge of cord blood transplantation in children with nonmalignant diseases is that with the exception of severe immune deficiencies, the rate of graft failure is much higher than those with leukemia, making strict HLA matching more necessary [52]. A plausible explanation is that children with leukemia almost always receive chemotherapy to induce a remission before transplantation so their immune system is greatly impaired before they start the transplant conditioning regimen. Total body radiation is also extensively used in transplantation for malignancy resulting in complete lymphodepletion in this patient population. Moreover patients with nonmalignant disease usually receive either anti thymocyte globulin or as part of their conditioning regimen to prevent graft versus host procedure. An approach that would merit consideration is the delivery of chemotherapy which in itself prolongs or hampers immune reconstitution.

9. Donor search in Chile: Progress in a developing country

Several shortcomings apply to the development of transplant programs in developing countries. Lack of resources, shortage of trained staff and poor understanding of the benefits of transplantation by the medical community all play into this reality. In 2010 WMDA reported that out of the 4054 unrelated cord blood units that were shipped worldwide, 2706 were provided by Europe, Australia and North America, 1324 by all Asia, and only 24 by South America and none by Africa. Only 206 were transplanted in South America, a continent that harbors more than 300 million inhabitants.

In Chile our transplant program was started in 1989 with sibling donors. As we were able to successfully treat patients, the problem of those without a family match became compelling. Our initial efforts to conduct searches for unrelated donors in the international registries were hampered by the difficulty of implementing high quality HLA typing in our country, the relatively small size of the donor pool and the restrictive policy of most international registries in Europe and the US to work with transplant centers outside their network. This reality changed in 1996 when Cord Blood Banks were implemented and the first procedures using this source were done worldwide. Despite the initial small number of cord units started at that time, we were able to find one or two antigen mismatched cord blood units for most of our patients and through collaboration with the National Cord Blood Program in New York the first procedures were done in 1997. Discouraged by poor results and high transplant related mortality mainly caused by infection we decided to consider 0 to 1 antigen mismatched cord blood units only. Initially we could only find such a donor for 50% of our patients [53], but that percentage increased steadily during the next years. Cord blood transplantation gave us the initial experience we needed and in 2009 our program started to recur to unrelated adult donors facilitated first through NMDP and latter by registries and cord blood banks in the US,

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Germany, Spain, France, Italy, Netherlands, Australia among others. In the last 4 years the proportion of unrelated donor transplants doubled the matched sibling procedures. A recent review of our data showed that out of 108 completed unrelated donor searches we were able to identify a fully matched adult donor in 18 patients, and a 0 to 1 antigen mismatched cord blood unit with > 3x 10^7 cells /kg in 73 patients (84% of the total). In only 9 patients we were not able to find a suitable donor, most of them adults. In summary, despite our mixed native American and Spanish ascent almost all our patients in Chile are able to identify an unrelated donor for stem cell transplantation.

10. Conclusion

Substantial biases in donor selection are the result of center preference and it is not forthcoming that controlled clinical trials will be conducted to demonstrate superiority of one source above the other. On the other hand much work is being carried to improve the donor pool in all three donor sources:

1. As registries continue to expand the chances for patients with uncommon HLA alleles to find a donor will improve steadily, especially for those from ethnic communities under-represented in the registries
2. Work in expanding cord blood cells and understanding and manipulating their homing properties will result in safer transplantation of larger amounts of cells and faster hematopoietic reconstitution.
3. Groups developing haploidentical transplantation have worked hard in graft manipulation testing strategies of adding back alloreactive lymphocytes to reduce the risk of relapse while maintaining a low incidence of graft versus host disease.

In this scenario transplant physicians will be confronted with multiple choices when they plan a procedure in a patient lacking a sibling donor, especially when they are able to find highly matched adult volunteers, cord blood units of high quality and ever better matched with the patient, and the infrastructure and experience to perform haploidentical transplantation. In an ideal world where all of them are available, the disease and stage, the age of the patient and the perceived or proven risk for a prolonged or partial immune reconstitution will come into play.

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