# Chapter 8
# Cord Blood Stem Cell Banking

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## Abbreviations

| | |
|---|---|
| AABB | American Association of Blood Banks |
| ALL | Acute lymphoblastic leukemia |
| AML | Acute myeloid leukemia |
| EBMT | European Society for Blood and Bone Marrow Transplantation |
| GCSF | Granulocyte colony-stimulating factor |
| GVHD | Graft-versus-host disease |
| HIE | Hypoxic-ischemic encephalopathy |
| HLA | Human leukocyte antigen |
| HSC | Hematopoietic stem cell |
| HSCT | Hematopoietic stem cell transplantation |
| MSC | Mesenchymal stem cell |
| MUD | Matched unrelated donor |
| PBSC | Peripheral blood stem cell |
| UC | Umbilical cord |
| UCB | Umbilical cord blood |
| UCB SCB | Umbilical cord blood stem cell bank |

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## 8.1 Introduction

The potential use of umbilical cord blood (UCB) was first proposed in 1982 by Edward Boyse, whereafter the first successful human leukocyte antigen (HLA)-identical UCB transplant was performed in 1988 by Gluckman and colleagues on a 5-year-old patient with Fanconi's anemia (1989). The first unrelated UCB transplant was performed in 1993 by Kurtzberg and Wagner (Kurtzberg et al. 1996; Wagner et al. 1996). Since then, UCB, previously considered a biological waste product, has been used as a source of hematopoietic stem cells (HSCs) and progenitor cells for HSC transplantation to treat individuals with sibling, related or unrelated, donor cells for a number of malignant and nonmalignant disorders as well as immune deficiency and genetic disorders.

This chapter provides a critical overview of UCB stem cell banking. The advantages and disadvantages of using UCB stem cells over the more traditionally used bone marrow or mobilized peripheral blood stem cells (PBSC) will be covered. The controversial debate surrounding public versus private UCB stem cell banks (UCB SCBs) will also be addressed. In addition, this chapter will focus on the ethical and regulatory issues surrounding UCB SCBs, the establishment of UCB SCBs in developed versus developing countries, and the use of UCB stem cells in transplantation and regenerative medicine.

### *8.1.1 Umbilical Cord Blood Versus Bone Marrow or Mobilized Stem Cells for Transplantation*

Hematopoietic stem cell transplantation (HSCT) involves the transfer of immunocompetent hematopoietic stem and progenitor cells from donors to recipients to reconstitute the marrow and restore immune function in the treatment of high-risk acquired and inherited hematologic malignancies as well as nonmalignant hematopoietic and immunological diseases. However, the availability of an adequate HLA-matched sibling remains only 25–30 % (Gragert et al. 2014), and patients rely heavily on the worldwide network of bone marrow registries to find a suitable donor. This, in itself, has limitations due to the vast majority of registered donors being Caucasian, making it difficult to obtain matched unrelated donors (MUDs) of other races.

HSCT can be used following myeloablative or reduced-intensity chemotherapy regimens. Myeloablative treatment involves the administration of high doses of chemotherapy, which destroys cancer cells and normal cells within the bone marrow prior to transplantation, while reduced-intensity conditioning involves treatment with lower doses of chemotherapy agents such as busulfan and cyclophosphamide. There are two types of HSCT, autologous and allogeneic. In autologous transplants, the donor and recipient are the same individual. In the case of allogeneic transplants, the donor and recipient may be genetically related or unrelated; however, the donor and recipient are HLA matched as closely as possible. The rate of graft failure is higher in unrelated

transplants that mismatch at one or two alleles compared to a fully HLA-matched transplant (Kanda et al. 2014). Two distinct classes of stem cells are used in HSCT. These include bone marrow or mobilized PBSC and UCB stem cells.

The bone marrow is located within long and flat bones and is the site at which virtually all blood stem cells reside, constituting what is defined as the stem cell niche. Bone marrow-derived HSCs can either be harvested by inserting a needle into the marrow cavity of the iliac crest or by a process known as apheresis, which enables the collection of mobilized PBSC. The growth factor granulocyte colony-stimulating factor (GCSF) facilitates the mobilization of stem cells from the bone marrow into the bloodstream. The mobilized stem cells can then be obtained from the peripheral blood, which is a less invasive procedure than acquiring stem cells from the bone and is currently the most frequently used source of HSCs. UCB is also successfully used in HSCT and is easily accessible as it is harvested from the placenta through the umbilical vein. The blood from the umbilical cord/placenta is a rich source of stem cells (Gluckman et al. 1989), and due to the immaturity of the immune cells in UCB, HLA typing is only performed for HLA-A, HLA-B (antigen level), and HLA-DRB1 (allele level) (Eapen et al. 2007), and a 4/6 to a 6/6 match is adequate for unrelated donors (Barker et al. 2010; Eapen et al. 2007). Recent studies suggest that it would be optimal to perform high-resolution (allele-level) typing for four HLA loci (HLA-A, HLA-B, HLA-C, and HLA-DRB1) for a single unit to minimize the risk of mortality after UCB transplantations (Eapen et al. 2011, 2014). Matching of the class I alleles is vital, since mismatching at these alleles is reported to increase the risk of graft failure (Petersdorf et al. 2001). Although UCB-derived stem cells have several advantages, the number of cells obtained from a single UCB unit is limited, as a result of which pediatric patients remain the primary focus. A minimum of $2–5 \times 10^7$ nucleated cells are required per kilogram body weight to be confident of a successful transplant (Welte et al. 2010). Nonetheless, the application of UCB in HSCT is being extended to treat adult patients through the use of single- or double-unit transplants.

UCB has sufficient numbers of hematopoietic progenitor cells to ensure long-term engraftment (Broxmeyer et al. 1989), and the rapid proliferative capacity of these cells makes it possible to reconstitute the entire bone marrow (Gluckman et al. 1997). Clinical observations have shown that the risk and severity of graft-versus-host disease (GVHD) is decreased in patients receiving UCB stem cells compared to cells from the bone marrow or peripheral blood. UCB stem cells differ from bone marrow and peripheral blood HSCs, in that UCB stem cells are "immunologically naive" (Wagner and Gluckman 2010). In addition, UCB T cells are phenotypically and functionally immature and are less responsive to stimulation compared to their adult counterparts, which has been suggested as a possible reason for the lower incidence of GVHD (Harris et al. 1992). UCB also contains increased numbers of natural killer cells and lower cytotoxic T-cell activity (Bensussan et al. 1994; Berthou et al. 1995). Consequently, UCB transplantations result in delayed engraftment of neutrophils and platelets and aberrant immune reconstitution.

In addition to its use in transplantation, UCB is a valuable source of cells for cellular therapies associated with tissue repair, replacement, and regeneration aimed at restoring impaired function resulting from congenital defects, disease, and trauma. The therapeutic potential of stem cells obtained from UCB is currently being investigated in over a hundred clinical trials for a wide range of disorders, including autism, diabetes, cerebral palsy, and spinal cord injury. This will be discussed in more detail in Sect. 8.1.4.

### *8.1.2 Umbilical Cord Blood Stem Cell Banks*

The successful use of UCB in HSCT has led to the establishment of UCB SCBs worldwide with various options being available for banking/storage. An UCB SCB is a facility in which donated UCB stem cells are stored for future use (Ballen et al. 2008). These UCB units are retrieved upon request from a recipient for transplantation or regenerative treatment purposes. There are a variety of UCB SCBs which are either public or privately financed organizations (Butler and Menitove 2011). More recently, hybrid UCB SCBs have come into existence, where a combination of private and publicly funded units are banked (Guilcher et al. 2014).

#### 8.1.2.1 Public Cord Blood Banks

Public UCB SCBs typically receive anonymous non-remunerated altruistic donations from willing donor families. These UCB units are subsequently made available for any histocompatible patient requiring a HSCT (Ballen et al. 2008; Brown et al. 2011; Wilson et al. 2011). Once the UCB unit is banked, it is anonymized where neither the donor nor the donor's family may retrieve it for personal use. Only in the prearranged instance of directed donation may the UCB unit be retrieved by the donor family to treat a family member (Ecker and Greene 2005; Ballen et al. 2008).

To ensure the safety of the donation, the UCB unit undergoes a series of tests prior to being banked. Should it pass and adhere to the stringent regulations and requirements (Table 8.1) set out by the American Association of Blood Banks (AABB) and NetCord Foundation for the Accreditation of Cellular Therapy (NetCord-FACT), the UCB unit is then banked and made accessible to the public (Butler and Menitove 2011). Should the unit not be eligible for banking, it is either discarded or used for research purposes (Sugarman et al. 1997; Ballen et al. 2008).

In the case of public UCB SCBs, the units are donated without any cost to the donor family. However, should a unit be retrieved by a recipient, the costs accrued for the banking, storage, and further preparation/testing required for release of the unit will be covered by the recipient. Even though these banks work on cost-recovery basis (not for profit), a major point of concern surrounding this type of UCB banking is the financial sustainability (Allan et al. 2013). The costs involved

**Table 8.1** Benefits and limitations of UCB SCBs (Abdullah 2011; Ballen et al. 2008; Butler and Menitove 2011; Guilcher et al. 2014; Sugarman et al. 1997; Wagner et al. 2013; Yoder 2014)

| Type of bank | Public | Hybrid | Private |
|---|---|---|---|
| Cost involved | Assumed by the bank and partially recovered from the recipient | A combination of public and private, with cross subsidization of the former by the latter | Borne by the donor |
| Cord blood owner | Bank | Bank or private donor | Private donor |
| Recipient | Unrelated transplant patients and researchers | Unrelated transplant patients, researchers, and private donors (donor or relative) | Donor or relative |
| Uses | Unrelated transplant and regenerative medicine (clinical trials and research) | Unrelated transplant and regenerative medicine (clinical trials, experimental treatments, and research) | Related transplant and regenerative medicine (experimental treatments) |
| Advantages | Unit available globally for a matching donor | Families can store units for personal use; may be made available to the public | Family has control over the stored unit |
| | Stringent quality control of units | Publically donated units available globally for a matching donor | |
| | No cost implications for the donor | Private section subsidizes the public costs | |
| | Low CBU attrition rate | | |
| Disadvantages | Opportunity to donate is not universal due to stringent quality and testing criteria | Transferring the financial cost from public subsidies like philanthropists and government to the private client is seen as a conflict of interests | Stored unit not available to public |
| | High operating costs are difficult to manage | | Donors often misinformed about the indications and efficacy of use |
| | Product is not available for family | | May be less stringent quality control |
| | | | Low retrieval rate |
| | | | Substantial financial cost to families |

include the collection, testing, and processing of the units for storage, the preservation of the UCB units, and the man power needed to maintain the facility (Ballen et al. 2008). As a result, this obstacle has prevented the establishment of many public banks and remains a reality for those currently in operation. Public UCB SCBs are funded in several ways which include federal/government funding, revenue generated through the sale of UCB units, grants, and private/philanthropic investors (Abdullah 2011; Allan et al. 2013).

#### 8.1.2.2 Private Cord Blood Banks

In a private UCB SCB, the bank receives payment from families who wish to store their UCB stem cells for autologous use or for use by next of kin (Ballen et al. 2008; Jordaan et al. 2009; Butler and Menitove 2011). Therefore, the units are stored at the cost of the donor family and also retrieved at the donor family's expense. Private banking is expensive and operates on a for-profit basis with shareholder requirements. There is an ongoing and constant debate about private banking (Sullivan 2008; Hollands and McCauley 2009; Ballen 2010). Arguments in favor of private banking include the following facts: (a) there are no medical or ethical issues related to collection (assuming that the third stage of labor proceeds unhindered) with limited risk to mother and child around material that would otherwise have been discarded—the same would be true for public banking; (b) one should have the right to exercise control over one's own body and the bank should have the economic freedom to run its own business; and (c) private banking is practiced in many countries where the demand is high, and if prohibited locally, cells would be sent to another country where banking is allowed. None of these arguments speak in favor of the potential medical benefits that could potentially be derived from the stored cells. This is one of the major issues around which arguments against private banking are constructed.

Arguments against public banking include the fact that (a) the recall rate of the stored cells is limited, albeit far greater than in private banks; (b) other sources of stem cells are adequate; (c) the indications for use of autologous UCB stem cells for transplantation are limited although their use in regenerative medicine may be easier to justify but difficult to quantify; (d) the volume of UCB/number of stem cells limits use to pediatric patients (or requires more than one unit in adults); (e) parents are driven by subjective (emotional) factors to store their children's stem cells due to an overestimation of the perceived benefit of private banking; and (f) private banking is elitist, i.e., it is not accessible to all (due to cost). Other arguments such as the fact that private banks deprive public banks of material, that there is inadequate informed consent, or that there is less stringent quality control than in public banks may apply to some private banks but certainly not to all. Several international professional bodies have expressed their views on the question of stem cell banking (European Group on Ethics in Science and New Technologies to the European Commission 2004; American Academy of Pediatrics 2007; ACOG 2008; South African Society of Obstetricians & Gynaecologists 2014). Some of these arguments will be explored in more detail below.

With regard to the limited likelihood that a stored unit will be used, it is universally accepted that the recall rate on privately stored UCB stem cells remains very low

(Sullivan 2008). This is because the current applications of stem cell therapy are limited mainly to HSCT, for which the use of autologous UCB stem cells is limited. Marketing often overestimates the immediate benefits of stem cell therapy. It is accepted that one cannot ignore the real promise that stem cell therapy might hold in the future, but at present this remains difficult to quantify (Sullivan 2008; Ballen 2010).

With regard to the volume of UCB/number of stem cells required for a successful transplant ($2–5 \times 10^7$ nucleated cells or $2 \times 10^5$ CD34+ cells per kilogram body weight (Welte et al. 2010)), there is a direct correlation between the success of HSC engraftment following transplantation and the number of cells used to treat the patient. With UCB stem cells, there is a limitation to the size of the patient that can be treated which is dependent on the number of stem cells recovered after thawing. This limitation may be overcome when stem cell expansion becomes a routine procedure in the future.

With regard to the availability of other types of stem cells, there are a number of other sources which include (a) adult stem cells—HSCs (bone marrow, peripheral blood) and mesenchymal stem cells (MSCs; from a variety of sources including the bone marrow and adipose tissue)—and (b) pluripotent stem cells (induced pluripotent stem (iPS) cells and embryonic stem (ES) cells derived by various techniques). While the therapeutic potential of pluripotent stem cells remains to be demonstrated, the value of adult stem cells (and in particular HSCs) is beyond doubt.

With regard to informed consent, not only must individuals be empowered with the necessary knowledge to make decisions for themselves, but an individual's autonomy to make decisions must be respected. Informed consent and all communication in printed and electronic media should include the current statistics of the chances of a newborn or its family ever needing the banked stem cells. In addition, provision could be made for a cooling-off period after birth during which the stem cell banking contract must be confirmed by the parents. It is therefore important for regulatory authorities to enforce a high standard of informed consent.

With regard to marketing, perhaps one of the biggest marketing inaccuracies in the private banking business is to list the great potential of stem cells and then to infer that this is what can be done with autologous UCB. While much of the potential of autologous UCB may be realized at some point in the future, at present this is not the case and is difficult to quantify. Support for private stem cell banking is therefore often based on an overestimation of the benefits of stem cell therapy. The argument that the public may be exploited by unrealistic promises about stem cell therapy is certainly valid. It remains, however, that this is a period of emotional vulnerability and that despite adequate informed consent, prospective parents may not make decisions that are entirely rational. It has been argued that the enforcement of a high standard of informed consent could partially rectify this problem. However, to ignore the real promise that stem cell therapy holds would also be dishonest.

With regard to the elitist nature of private banking in which the service remains inaccessible to many because of the cost factor, it should also be appreciated that equality will not be achieved by denying everyone a benefit because it is currently only available to some. Objections to private stem cell banking based on elitism would be better addressed by thinking of constructive ways to increase access by the entire population to stem cell banking and related therapies, as in the case of public or hybrid banking (Jordaan et al. 2009).

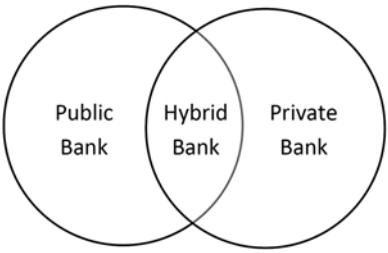


**Fig. 8.1** Representation of hybrid banking

#### 8.1.2.3 Hybrid Cord Blood Banks

Hybrid UCB SCBs are an amalgamation of public and private UCB SCBs (Fig. 8.1). In this setting, a UCB unit is stored and can be retrieved for personal or public use (Guilcher et al. 2014). There are currently two modes of storing UCB units in hybrid UCB SCBs, which are either sequential or splitting. The sequential mode is when a family stores the UCB unit for private future use, but if required can be used by someone else, with the family's consent. In the splitting mode, units are divided in two, where one part is stored for private purposes and the other is made available to the public (Wagner et al. 2013). Hybrid UCB SCBs, therefore, leverage funds obtained from the private section to subsidize the public section of the bank (Guilcher et al. 2014).

#### 8.1.2.4 Global Policies and Legislation

The objectives of regional, national, or international policies and legislation are (a) to protect the individual from harmful and unethical practices and (b) to respect the individual's right to determine how to use her/his own stem cells. Provision should be made for all who might benefit from stem cells for therapeutic purposes, and everyone should be given an equal opportunity to benefit from the advances in medical science. In addition, policy and legislation should not be unduly restrictive so as to avoid stifling basic and clinical research and biotechnological innovation.

Several general recommendations have been put forward by a number of professional bodies which include working and research groups, healthcare providers, and UCB SCB representatives for consideration with the banking and retrieval of UCB units (Armson 2005; Ballen et al. 2008; Petrini 2013). These can be summarized as follows:

1. Balanced and accurate information must be provided on the advantages and disadvantages of UCB banking including the remote chance that the unit will ever be used.
2. Perinatal healthcare providers should be informed about the clinical potential and the indications that can effectively be treated with UCB stem cells based on scientific evidence. UCB donation should be discouraged when UCB stored in

a bank is to be directed for later personal or family use, because most conditions that might be helped by UCB stem cells already exist in the infants' UCB (i.e., premalignant changes in stem cells).
3. UCB storage for personal use should only be considered by a family where a sibling or parent possesses a disorder or disease that can be treated with the autologous HLA-matched UCB—directed donation.
4. UCB should not be stored for personal use if an allogeneic transplantation is the treatment of choice for a child or family member that does not have an HLA-identical sibling or a well-matched family member.
5. Allogeneic UCB should be considered in adolescents and young adults with hematologic malignancies because of the advantage of the graft-versus-leukemia effect.
6. Donation of UCB for altruistic purposes to a public UCB SCB and subsequent allogeneic transplantation should be encouraged when UCB banking is being considered by expecting families and their healthcare providers.
7. Because there is limited scientific data at the present time to support autologous UCB SCB and given the difficulty of making an accurate estimate of the need for autologous transplantation and the ready availability of allogeneic transplantation, private storage of UCB as "biological insurance" should be discouraged.
8. Public, hybrid, and private UCB SCBs should strictly adhere to the regulations and requirements indicated for the safety and efficacy of the UCB units.
9. Recruitment of UCB donors should be fair and noncoercive.
10. Testing for maternal infectious and genetic diseases must be discussed.
11. Private UCB SCBs should be regulated to ensure that promotional marketing and financial costs are fair.
12. Parents and healthcare providers must understand and acknowledge the differences between autologous and allogeneic donations and the differences between private and public UCB SCBs.

Standards and regulations should be developed by perinatal facilities to educate the expecting family regarding the need for UCB in the public and private UCB SCB industry.

### *8.1.3 Cord Blood Banking in Developed Versus Developing Countries*

Due to the high costs involved in establishing and maintaining UCB SCBs, it is in the developed nations of the world that the collection, banking, and utilization of UCB are most prevalent. Countries primarily involved in UCB banking include the United States, the United Kingdom, as well as those in Western Europe and Australasia.

The first public UCB SCB was established in New York, USA, in 1992, and the first private UCB SCB in 1995, also in the United States. Since then numerous pub-

lic and privately owned UCB SCBs have been established that are actively involved around the world in collecting, processing, testing, and cryopreserving UCB for potential future use.

With the increased interest in UCB-related therapeutics and the need for effective and reliable banking come the attending problems of regulation, standardization, and the protection of donors, recipients, and the public as a whole. Therefore registries and regulatory bodies are formed to establish standard protocols and provide guidelines for standard and good practice in all that pertains to UCB collection, banking, and usage. These national regulatory agencies and transplant centers are aware of the need for global standards whose major objective is to promote quality throughout all phases of UCB SCB with the goal of achieving consistent production of high-quality units for transplantation. This covers collection of UCB stem cells, regardless of the methodology or site of collection; screening, testing, and eligibility determination of the maternal and infant donor according to applicable laws; and all phases of processing and storage including qualitative testing and characterization of the unit.

Considering the rigors and financial implications involved in the establishment of registries and regulatory bodies, as would be expected, all the well-known registries and regulatory bodies are domiciled in developed countries, although some have member UCB SCBs in developing countries (Brazil, Iran, Saudi Arabia, and the United Arab Emirates).

Establishment and maintenance of an UCB SCB is financially intensive with costs including tissue typing, infectious disease testing, and also the annual cost of cryopreservation. However, these costs have in no way reduced the growth of UCB SCBs as there are over 150 public and 200 private UCB SCBs worldwide; however, the majority of these are found in the developed countries.

Hemoglobinopathies are inherited disorders which result in life-threatening noncommunicable diseases in children. The most common of these are β-thalassemias and sickle cell disease which are often associated with many of the developing countries of the world such as sub-Saharan Africa, the Indian subcontinent, Bangladesh, Myanmar, and Southeast Asia (Weatherall 2010; Faulkner et al. 2013).

HSCT is the only recognized cure for thalassemia and sickle cell anemia and is increasingly becoming more cost-effective as the cost of a transplant is comparable to a few years of supportive care for these individuals (Leelahavarong et al. 2010). Although unrelated HSCT has been used successfully, most patients with these hemoglobinopathies belong to ethnic groups that are underrepresented in donor registries. It is therefore unlikely that these individuals will be able to find a suitable donor and often cannot proceed with the transplant (Faulkner et al. 2013).

Information reported to date regarding UCB banking in developing countries is limited. However, the establishment of not-for-profit public UCB SCBs in these countries would service a large unmet need in increasing patients' chances of finding suitable donors as well as supplying a source of stem cells for applications in regenerative medicine that could potentially be used toward improving health in these countries.

Developing countries often have to prioritize providing basic healthcare needs to their populations while also addressing epidemic rates of communicable and non-communicable diseases and other health issues. Although there is an increase in the need for HSC transplants, most developing countries have a limited number of transplantation centers which also limit the use of UCB units in these countries. This shortage of transplantation centers needs to be addressed in parallel with the establishment of UCB banks. The cost of UCB unit processing can escalate in countries where there is an increased burden of microbial and viral infections. Evidence of microbial infection or positive serological tests prevents a UCB unit from being eligible for storage. Despite these costs, it remains critical that UCB SCBs meet global accreditation or quality standards as outlined by international organizations such as NetCord-FACT and AABB to ensure high and uniform quality of all UCB units available to patients requiring HSCT.

Although public UCB SCBs generally find it challenging to maintain financial viability, some developing countries have successfully managed to fund the operation of UCB SCBs with help from university-affiliated medical centers, charitable institutes, regional governments, or national support as well as revenue from exporting UCB units to transplant centers (Roh et al. 2014). The establishment of UCB SCBs should be supported in developing countries as they would service a large unmet need in these countries as well as the corresponding diaspora.

### *8.1.4 Cord Blood Stem Cells in Transplantation and Regenerative Medicine*

HSCT is a globally accepted form of therapy for the treatment of malignant and nonmalignant hematological conditions. These therapies generally aim to reconstitute the hematopoietic system in patients who have undergone chemotherapy. Despite its benefits, the use of UCB is mostly used as a last resort when no HLA-matched bone marrow donors are available. Having said this, over 35,000 UCB

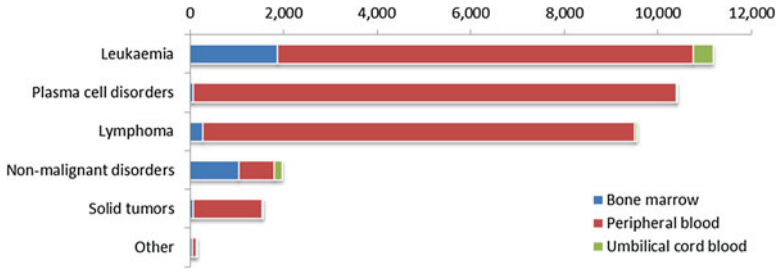


**Fig. 8.2** Number of patients receiving hematopoietic stem cell transplantations in Europe in 2013

transplants have been performed to date, and there are over 700,000 and four million units stored globally in public and private UCB SCBs, respectively.

The most recent report by the European Society for Blood and Bone Marrow Transplantation (EBMT) indicates that nearly 35,000 patients received HSCTs (bone marrow, PBSC, and UCB) in European and affiliated centers in 2013 (Passweg et al. 2015), which is approximately half of all HSCTs performed globally (Niederwieser and Baldomero 2014). The hematological malignancies continue to be the most frequently treated indications, accounting for 90 % of all HSCTs (Fig. 8.2).

Figure 8.2 further indicates the source of HSCs used for each patient treated, which reveals that the minority were collection from UCB (2 %, $n = 673$). Additionally, these UCB-derived HSCs were all predominantly used to treat patients with leukemia—mostly acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL). The nonmalignant conditions treated mostly with UCB transplantations are primary immune disorders, inherited disorders of metabolism, and severe aplastic anemia. Importantly, of the 737 UCB units transplanted in 2013, 90 % were from unrelated allogeneic donors, while the remainder were either from HLA-identical or nonidentical family members (also allogeneic, $n = 69$) and autologous banked units ($n = 2$).

Given the low volume and hence limited cell dose obtained from an UCB unit, the use of these cells is generally limited to the pediatric setting. Adults are indeed treated with UCB units, but it is often the case that a second or third unit is required, which is cost prohibitive in most cases. However, with the increase in use of haploidentical donors for both pediatric and adult indications, there has been a notable decrease in the use of UCB transplantations over the last 2–3 years (Passweg et al. 2015). The clinical benefit of using haploidentical units over UCB is, however, still to be demonstrated.

Recently, there has been an increase in the use of UCB units for the treatment of a variety of indications that are of non-hematopoietic origin and regenerative in nature. The utility extends beyond using a traditional preparation of mononuclear cells derived from UCB and further includes the use of ex vivo expanded MSCs from either UCB or Wharton's jelly/umbilical cord (UC). Given the current limitation of UCB related to cell dose, the option to expand MSCs from UCB/UC is both feasible and an attractive solution for UCB SCBs. It is well recognized however that the spectrum of diseases that can be treated using these two sources of stem cells is quite different and, in the case of MSCs, still needs to be established from clinical trials.

In light of this, a list of currently registered non-hematopoietic- and regenerative-type clinical studies is provided in Table 8.2 to illustrate the scope of alternative indications being explored. The table is further structured to illustrate indication grouping and the cell therapy used. According to this registry (derived from ClinicalTrials.gov), 91 clinical trials have been registered to date, of which more than half make use of UC-derived MSCs (UC-MSCs). Forty different indications have been targeted for treatment, which can be grouped into over 15 different specialties. The broad range of conditions include, among others, cardiomyopathy, muscular dystrophy, spinal cord injury, autism, liver cirrhosis, and HIV/AIDS.

**Table 8.2** Number of registered clinical studies using UCB and UC-derived cells for non-hematopoietic and regenerative medicine indications (Abdullah 2011; Ballen et al. 2008; Butler and Menitove 2011; Guilcher et al. 2014; Sugarman et al. 1997; Wagner et al. 2013)

| Indication grouping | Indication | UCB | UC-MSC | UCB-MSC | Total |
|---|---|---|---|---|---|
| Autoimmune | Autoimmune hepatitis | – | 1 | – | 1 |
| | Epidermolysis bullosa | 3 | – | – | 3 |
| | Lupus erythematosus | 1 | 2 | – | 3 |
| Cardiovascular | Cardiomyopathy | – | 2 | 1 | 3 |
| | Hypoplastic left heart syndrome | 1 | – | – | 1 |
| | Myocardial infarction | – | 1 | – | 1 |
| Circulatory | Critical limb ischemia | 2 | 1 | – | 3 |
| | Ischemic stroke | 2 | – | – | 2 |
| Dermatological | Wounds (burn) | – | 1 | – | 1 |
| Endocrine | Diabetes—type 1 | 3 | 3 | – | 6 |
| | Diabetes—type 2 | – | 2 | – | 2 |
| Gastrointestinal | Ulcerative colitis | – | 1 | – | 1 |
| Hematological | Aplastic anemia | – | 1 | – | 1 |
| Hepatic | Liver cirrhosis | – | 9 | – | 9 |
| | Liver failure | – | 2 | – | 2 |
| Immunological | Graft-versus-host disease | – | 2 | 1 | 3 |
| | Organ transplantation (kidney) | – | 1 | – | 1 |
| Infectious diseases | HIV/AIDS | – | 1 | – | 1 |
| Musculoskeletal | Duchenne muscular dystrophy | – | 1 | – | 1 |
| | Osteoporosis | 3 | – | – | 3 |
| | Cartilage defects/injuries | – | – | 1 | 1 |
| Neurological | Alzheimer's disease | – | 1 | 1 | 2 |
| | Amyotrophic lateral sclerosis | – | 1 | – | 1 |
| | Ataxia | – | 2 | – | 2 |
| | Autism | 2 | 2 | – | 3 |
| | Cerebral palsy | 9 | 1 | – | 10 |
| | Global developmental delay | 1 | – | – | 1 |
| | Hypoxic-ischemic encephalopathy | 3 | 1 | – | 4 |
| | Multiple sclerosis/neuromyelitis optica | – | 1 | – | 1 |
| | Spinal cord injury | 2 | 2 | – | 4 |
| | Traumatic brain injury | 1 | – | – | 1 |
| Oncology | Myelodysplastic syndrome | – | 1 | – | 1 |
| | Leukemia | – | – | 1 | 1 |
| Reproductive | Premature ovarian failure | – | 1 | – | 1 |
| Respiratory | Bronchopulmonary dysplasia | – | 1 | 2 | 3 |
| Rheumatic | Ankylosing spondylitis | – | 1 | – | 1 |
| | Osteoarthritis | – | – | 1 | 1 |
| | Rheumatoid arthritis | – | 2 | – | 2 |
| Other | Hearing loss | 1 | – | – | 1 |
| | Preterm neonates | 1 | – | – | 1 |
| TOTAL | | 35 | 48 | 8 | 91 |

*UCB* umbilical cord blood, refers to the number of studies using a traditional mononuclear cell preparation, *UC-MSC* umbilical cord-derived mesenchymal stem cells, *UCB-MSC* umbilical cord blood-derived mesenchymal stem cells

The treatment of neurological diseases is by far the most active area of research (Iafolla et al. 2014). The rationale for this interest stems from the fact that UCB is known to contain a unique combination of stem and progenitor cells, including MSCs (Kang et al. 2006), embryonic-like stem cells (Zhao et al. 2006), endothelial progenitor cells (Hildbrand et al. 2004), and unrestricted somatic stem cells (Kogler et al. 2004). Additionally, the beneficial effects of these cells have been demonstrated in the preclinical setting, which indicate enhanced tissue repair and cognitive improvement (Geissler et al. 2011), as well as a stimulation of neural stem cell production (Wang et al. 2012).

Cerebral palsy and hypoxic-ischemic encephalopathy (HIE) are the indications being explored most, for which 12 clinical trials making use of a traditional UCB preparation (red cell depleted, mononuclear cells) have been registered to date. Of these studies, nine are still active and/or currently recruiting, with three having been completed. Important to note is that of the 12 registered studies, six make use of autologous therapies and hence make a case for privately banked UCB units. Sun et al. (2010) reported on the safety of using autologous UCB units in 184 children with neurological disorders (140 with cerebral palsy) and found that 1.5 % experienced hypersensitivity reactions during the autologous UCB infusion. Furthermore, no additional adverse events have been reported in these patients in 3 years of follow-up, indicating a favorable safety profile. The authors indicated that the quality of UCB units recalled from private UCB SCBs was inferior to the publicly banked units that were accessed—a situation that would need to be improved if autologous UCB therapies are to become a reality. In a separate study on children with cerebral palsy, significantly improved cognitive and motor function was reported (vs. a control group) when UCB and erythropoietin were administered (Min et al. 2013). With regard to HIE, a recent report of a Phase I study demonstrated safety of autologous UCB infusion in critically ill neonates, as well as positive preliminary data with regard to functional improvements and survival. Data from each of these early phase studies are promising, and sufficient evidence of safety is provided. The next steps are thus to further demonstrate efficacy in larger Phase II and III studies before these therapies are to become accessible in routine practice.

Promising findings have also been reported in studies on liver cirrhosis (Zhang et al. 2012; Xue et al. 2015). In contrast to the treatment of cerebral palsy and HIE, the experimental therapies recorded for liver cirrhosis make use of UC-MSCs exclusively. Large-scale pivotal studies are similarly required to demonstrate evidence of benefit. Contrary to the positive reports discussed above, little to no benefit from the use of UCB in type 1 diabetes has been reported. This was the case in two independent studies, both of which made use of autologous UCB transplantation in pediatric patients with type 1 diabetes (Haller et al. 2011; Giannopoulou et al. 2014).

There is no doubt that there will be a continued interest and investment in this area of research, which may result in approved UC and UCB-derived cellular therapies for non-hematopoietic and regenerative purposes. A further broadening of the scope of treatment is also anticipated, particularly given the potential clinical benefits of ex vivo expanded MSCs. However, if these experimental therapies are ever to become part of routine clinical practice, careful study design

based on rational principles will be essential. Notably, each and every indication and cell therapy will require specific consideration with regard to the cell source, preparation conditions, cell dose, and route of administration. Given the rise of haploidentical transplantation practices and in light of the fact that there are nearly five million UCB units stored globally (public and private combined), the industry and its stakeholders are watching this space with great anticipation.

## 8.2 Summary

The characteristics of UCB make it a suitable alternative to bone marrow and peripheral blood-derived stem cells for cell-based therapies. UCB is harvested at birth and stored in public, private, or hybrid facilities for future use. There are a number of unresolved ethical debates regarding the storage options of UCB, mainly due to the extremely low probability of the cells being retrieved for use from private banks. The majority of published sources have recommended that storage should primarily take place in a public UCB SCB, with the exception of a directed donation.

Most of the UCB SCBs worldwide are in developed countries due to the substantial costs involved in establishing and maintaining such facilities. Despite the costs, developing countries could benefit from establishing UCB SCBs as they could service an unmet need for donor-recipient matched units both in local populations and in the diaspora. With the ever-increasing number of clinical trials aimed at using UC and UCB-derived cellular therapies for non-hematopoietic and regenerative medicine, the need for readily available UCB units is likely to increase globally.

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