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Umbilical Cord Blood Banking for Transplantation in Morocco: Problems and opportunities

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ABSTRACT

Since the success of the first umbilical cord blood (UCB) transplantation in a child with Fanconi anaemia in 1989, great interests have emerged for this source of stem cells. UCB provide an unlimited source of ethnically diverse stem cells and an alternative for bone marrow (BM) and peripheral blood (PB) hematopoietic stem cell transplantation. Thus, UCB and manipulated stem cells are now collected and banked according to international accreditation standards for listing on registries allowing rapid search and accessibility world wide. This work aims to identify problems limiting the creation of a Moroccan cord blood bank and to highlight opportunities and issues of a new legislation promoting additional applications of cell therapy.

Key words : Umbilical Cord Blood Banking, Related donor, Unrelated donor, Legislation, Morocco

INTRODUCTION

Umbilical Cord Blood transplantation (UCBT) was first reported in 1989 by Gluckman E. et al [1] and UCB is now routinely used as a source of Hematopoietic Stem Cells (HSC). The major advantage of this source is the acceptable degree of human leukocyte antigen (HLA) mismatch compared to bone marrow (BM) and is more and immediately accessible when no available BM HLA-matched donors are found [2-5]. In addition, UCB presents less risks of transmissible viral infection than maternal blood [6], and stem cells it contains present self-renewal, proliferative and immune-modulatory abilities [7].

Furthermore, although UCB contains one log less nucleated cells than BM and Peripheral Blood (PB), UCB units are now successfully used in transplantation of patients with myeloid and lymphatic leukemia, lymphoma, myelodysplasia, aplastic anaemia, hemoglobinopathies, thalassaemia, immune deficiency, autoimmune and inherited metabolic diseases, and other diseases especially in children [1,2-8]. However, allogeneic UCBT is limited by HLA-matching and many previous reports correlated outcomes in engraftments to HLA disparity after UCBT in patients [3,4,8,9].

Many other variables are influencing outcomes after UCBT in adults such as diagnosis and stage of disease, but the nucleated cell dose has been reported to be the clearly associated with the engraftment and the risk of transplant-related events [10]. To overcome this cell dose restriction, double or multiple units of UCB are used in children and adolescent [11] and in adults with a reduced intensity conditioning to benefit older patients or those for which myeloablative conditioning remains too risky [4,15-17].

As the immunologic complications of Graft Versus Host Disease (GVHD) usually offset the therapeutic benefits of unrelated BM transplants, the UCB selection criteria for unrelated transplantation were different regarding malignant and non-malignant diseases [11], and specific strategies and transplant programs are improved to better help finding of adequate grafts quality.

With the increasing therapeutic applications of related and unrelated UCB stem cells followed by the increased demand of UCB units, international organizations, registries and biobanks are created to improve good practices in UCB collection, manipulation and storage to achieve high quality for the UCB units, and to define standardized procedures for donor search and acquisition.

<http://factwebsite.org/CordSearch.aspx?&type=CordBloodBank&country=&state=>

FOCUS ON CORD BLOOD TRANSPLANTATION

Hematology disorders/ Oncology

Several studies have shown that patients with acute leukemia are the most treated with UCB units in the absence of Matched-Related Donor (MRD) or Unrelated Donor (URD). After UCB HSC Transplantation (HSCT), the incidence and severity of GVHD is less than observed with BM and PB [1,2,11]. This may be due to the functional immaturity of

infused lymphocytes with a decreased cytotoxicity, an altered cytokine profile, a decreased HLA expression and an increased regulatory T cells [12,19,20]. Other findings suggest that even if survival is similar after transplantation with MRD, URD and UCB in children with acute leukemia, occurrence of acute and chronic GVHD and relapse remain higher respectively in MRD and URD than in UCB group [21], while survival after transplantation with URD UCB units is similar to Matched URD from BM [22].

Furthermore, the outcomes of related or unrelated UCBT in children revealed the importance of the cell dose infused as a predictor of neutrophils and platelets engraftment [8,24]. In addition, the incidence of GVHD and chronic GVHD depends on the degree of HLA mismatch in both pediatric [2,3,19,21,23,25-28] and adult patients [4,11,12,14-16,29-31] as indicated in Table 1 and 2. In fact, the infusion of partially HLA-matched UCB units, neutrophils and platelets engraftment ranged from 26-32 days (Table 1) and 20-27 days (Table 2) in pediatric and adult patients respectively. The overall survival also increased in groups with rapid neutrophils engraftment.

Non oncology

Most indicated use of UCB units in non hematopoietic diseases remains the primary immune deficiencies. HSCT from an HLA-matched donor was in fact shown to correct the immune system in children [33]. As indicated in Table 3, successful and over survival after UCBT was found to be dependent on the degree of HLA disparity [34]. Other studies suggested that higher infused cell doses can partially reduce the impact of HLA disparity on survival [8].

Table 1 : Umbilical Cord Blood Transplantation in Children with hematopoietic malignancies

Reference	Number	Age or median	Degree of HLA match	Neutrophil engraftment median or %	Platelet engraftment median or %	Acute GVHD I-II (%)	Acute GVHD III-IV (%)	Chronic GVHD	Overall survival %
Rocha et al. 1990-1997 (19)	113	5 (<1-15)	6/6	26 days	44	29/107 patients	2/107 patients	5/93 surviving	46 (2-3 years)
Wagner et al. 1994-1995 (23)	13	2,7 (0,1-21,3)	6/6 , 1-2/6, 3/6 or more	24 (16-53)	54 (39-130)	16	11	na	65 at 6 months
Dalle et al. 1996-2002 (3)	30	7,5 (0,1-19,5)	6/6, 1-2/6	28 (16-49)	43 (18-59)	3/36 (6 without hematopoietic malignancies)	11	3/36 surviving	59 (2-3 years)
Rocha et al. 1994-1998 (2)	99	6 (2,5-10)	6/6 , 1-2/6, 3/6 or more	32 (11-56)	81 (16-159)	38	21	5/43 patients	35
Kutzberg et al 2008 (25)	191	7,7		27	174	Na	42	21% at 2 years	51 (1 year)
Smith et al. 2009 (26)	21	4,2		95%	na	Na	1,2	0,8 (relative risk 95% CI)	43 (5 years)
Yoo KH et al. 1996-2003 (27)	236	na		18	45	Na	41,1 (Grade II-IV)	36,10%	47,5 (5 years)
Kato et al. 2011 (28)	332	5		89% day 90	na	na	46	19%	38 (5 years)
Yi E.S et al 2005-2010 (21)	41	9,1 (0,9-18,7)		19	51	Na	24 (Grade II-IV)	9%	na

Na : not available CI : confidence Interval

Table 2 : Umbilical Cord Blood Transplantation in Adults with heamatopoietic malignancies

Reference	Number	Age or median	Degree of HLA match	Neutrophil engraftment median or %	Platelet engraftment median or %	Acute GVHD I-II (%)	Acute GVHD III-IV (%)	Chronic GVHD	Overall survival %
Rocha et al. 1998-2002 (29)	98	24,5 (15-55)	6/6, 2/6, 3/6	26 (14-80)	na	13	13	18/16 surviving	63 (2-3 years)
Wagner et al. 1994-2001 (8)	65	7,4 (0,2-56,9)	6/6, 2/6, 3/6	23 (9-54)	86 (29-276)	51/63 patients	17	9/59 patients	58 (1 year)
Langhlin et al. 1996-2001 (30)	150	16-60	2/6	27 (25-29)	60 (54-71)	In 150 patients Grades II, III, IV : 41		35/69	19 (2-3 years)
Barker et al. 2000-2003 (4)	23	24 (13-53)	Double UCB trial : 4-6/6 matched each cord and the recipient	23 (15-41)	na	52	13	5/23 patients	57 (1 year)
Ballen et al 2003-2005 (15)	19	49 (24-63)	Double UCB trial : 4-6/6 matched to each other and to the recipient	20 (15-34)	41 (21-55)	53	5	5/16 patients	71 (1 year)
Brunstein et al. 2001-2005 (16)	106	51 (17-69)	Double UCB trial : 4-6/6 matched to each other and to the recipient	12 (0-32)	49 (0-134)	37/110 patients (4 without hemato malignancies)	22/110	23/110	45 (3 years)
Takahashi et al. 2007 (12)	100	38 median		85%	na	Na	52 (Grade II-IV)	71%	70 (3 years)
Kumar et al. 2008 (31)	173	38 median		Na	na	Na	32 (Grade II-IV)	28%	36 (2 years)
Astuta et al. 2009 (13)	114	34 median		Na	na	Na	28 (Grade II-IV)	27%	45 (2 years)
Brunstein et al. 2010 (17)	351	37 median		0,5(0,42-0,6)	na		0,55 (0,42-0,72)(Grade II-IV)	1,36% (0,99-1,88)	0,97 (0,92-1,35)

Na : not available

Table 3 : Umbilical Cord Blood Transplantation in Patients with non hematopoietic malignancies

Reference	Disease	Number	Age or median	Neutrophil engraftment median or %	Chronic GVHD	Overall survival %
Prasad et al. 2008 (32)	Inherited metabolic disorders - Hurler Syndrome - Metachromatic Leukodystrophy - Krabbe Diseases - Sanfilipo Syndrome - Adrenoleukodystrophy	159 45 15 36 19 13	na	Na	na	77 (1 year) 65 (1 year) 74 (1 year) 79 (1 year) 77 (1 year)
Frangaul H. et al 1999-2003 (33)	Primary immune Deficiencies	364	0,2-7,8	58% (day 42)	na	63 (1 year)
Bizzetto et al 2011 (34)	Hereditary BM failure	64	na	95% of R CBT 86% of UR CBT	Acute GVHD II-IV : 2/20 Chronic 11% (2 years) Acute GVHD II-IV : 24% (day 100) Chronic GVHD 53% (2 years)	95 (3 years) 61 (3 years)

Na : not available

R CBT : Related Cord Blood Transplantation

UR : Unrelated Cord Blood Transplantation

STATE OF THE ART OF UCB BANKING: Public or Private?

Public banks are for non-profit and financed by public funds. They are involved in collecting from anonymous consent donors after baby's delivery, processing and conserving UCB units in a registry for allogenic use. For inclusion in the registry, samples are screened based on volume, cell number, tissue types, health history and infectious diseases status. The units are then made available to suitably matched recipients. A great societal benefit is obtained from this UCB altruist donation especially for populations with ethnic minorities. Registries of these units in public banks has become a mandatory instrumental tool for hematopoietic transplantation or applications in regenerative medicine. Reports from the Bone Marrow Donors worldwide at April 2013 indicate that there were 571,318 unrelated UCB units banked from 31 countries. To date, more than 10,000 patients have received an UCB transplant worldwide.

In parallel to these public banks, an entire industry has developed. These private (for-profit) banks improve, for a fee, collection of blood samples and cryopreservation of UCB units for a future use in the child or a related family member for related or allogenic transplantation. While public banks use well established criteria for UCB units storage, private banks generally store all collected units, leading to a less quality parameter than in public banks [35].

To meet the increasing demand in therapeutic use of UCB, the number of Public UCB banks is growing. There are now nearly 142 public banks versus 134 private banks actively involved around the world with more than 780,000 units [36]. The total number of UCB units in private banks exceeds largely the number conserved in the public ones. Conversely, the units from the former are the mostly used for transplantation. In addition, the probability for a child to be transplanted by his own cells ranges from 1:2,500 to 1:200,000 if these are not available for his family members [37]. Indeed, more than 180 autologous UCBT has been successfully reported by private banks for non-malignant diseases (Cord Blood Registry in USA), the use of UCB units in malignant conditions being unlikely limited by the presence of pre-leukemic cells [38]. Also, the success rates of sibilid UCB transplants from a family member are well defined than of transplants from a public donor's UCB and this is more important for ethnic populations [39].

Many ethical debates have sparked regarding conflicting interests between private banks and the public ones and this public-private divide appears to have arisen because of the economic challenges of the UCB banks. Private banks encourage parents to store their child's UCB as a form of biological insurance for the child himself or a family members. In these companies, communication and marketing efforts are made to open up this use to a large part of population. Therefore, these banks are first created over the uncertainly future potential use of preserved own's child stem cells and the state of scientific knowledge [40]. The likelihood that collected cells will be used in HSCT for established therapeutic indications is very low. Autologous UCB cells couldn't be used for genetic diseases because they carry the same genetic

disease, and when required HSC are largely harvested from BM or PB [42, 36].

Meanwhile, the current development of public sector policies regarding stem cells manipulation and with the increasing evidence for more therapeutic use of UCB stem cells outside of transplantation (as in regenerative medicine or in immune modulation) arise attractiveness to the private banks [43,44] and approaches to accommodate between public banks and personal interest in cord blood are unlikely to be achieved.

Even if private banks have developed extent procedures for collection and storage, and benefit rapidly from advanced biotechnology, their emergence create disagreements about the future lack of UCB units in public banks to provide treatments of some malignant diseases such as leukemia and lymphoma, and more especially about health care systems democratization and ownership of human tissues. Moral questions about how designing a health care system ensuring wellbeing, commitment of generational and social fairness, social solidarity with developing these emerging tissue economies should have answers [45].

Hybrid banks are gaining popularity in some countries, and companies are collecting UCB units for family personal use and at the same time other units for unrelated use (national). Many private banks now offer UCB to matched family members of a child and include them in research projects. So, the line between private and public banks is likely to be blurred. seem to be a functional model ensuring therapeutic and economic challenges [43].

LEGISLATION AND BIOETHICS

Most experts agree that public UCB banking is the only option to obtain a suitable transplant to a vast number of people specifically for heterogeneous populations. These public banks are typically funded in part or entirely by public funds and their primary goal being the creation of an inventory of UCB units for unrelated use. They are envisaged either for solidarity and fair access to healthcare treatment purposes.

The USA and the European Union have not only regulated the therapeutic use of UCB for cell therapies and regenerative medicine, but also the banking of UCB units and the manufacture of manipulated stem cells. At the European level, cell therapy products are considered as medicinal products or as industrially produced medicinal products according to drug registration of innovative therapies system (MTI). They can also be considered as cell therapy preparations implemented in cell therapy units without the status of pharmaceutical establishment. Most of these countries have published statements on UCB and specific documents from the competent health authority, such as "l'Agence de biomédecine in France" or the FDA (Food and Drug Administration). Standards and specific international accreditations are drawn for all the process (from the collection to the distribution for transplantation). Since 2004, the main firms of biotechnology launched in applications on muscular dystrophy, bone damage, cartilage, type I diabetes, mesenchymal stem cells, diseases of the central nervous system and regulatory T cells.

There is a general consensus and a collaborative effort to establish international guidelines for better use of UCB and cell products for cell therapies. The NetCord-Fact international standard [46,47] is now the reference for inspection and accreditation programs for standards cord blood collection, banking and release for administration.

The European Group on Ethics in Science and New Technologies has adopted a position on the ethical aspects of the private cord blood banking. Even autologous or family sibling banking is unlawful in some countries, some of them (Italy and Spain) regulate transport and storage in foreign accredited private banks in Switzerland and England where public banks coexist with the private ones.

In contrast to Europe where there is a strong bias in favor to public banks [41,42], United States are less critical of private banking despite of the negative position of some professional organizations such as the American Academy of Pediatrics (AAP) [48]. In Australia, UCB transplantation is restricted to recognized applications and specific ethical issues are associated with collection, storage and access [49]. The Canadian Blood Services provide UCB units for banking and research in parallel to existing private banks [50]

In some countries of Asia, UCB stem cell banking is permissible and all UCB banks are regulated strictly as the blood banks such as in India. In China, there is only one public bank whereas in Japan and Korea private banks are dominants [51]. In the absence of a clear regulation to govern the status of stem cell banks, some Eastern Arab countries banks are created as agents to well-known banks outside (as Future Health, Cells4Life, Cytocare,...). In Iran, public bank provides UCB banking since 2012 with more than 3000 units. In some other countries such as Oman and Lebanon, public and private banks cohabit and provide tissue banking [52]. Saudia Arabia, United Arab Emirates (UAE), and Qatar have recently establish importants programs for promoting medical innovations and create public funding to support bank creation and processing [53]. Jordan, Saudia Arabia and Qatar have currently private banks and undergo general regulations for the first and religious decrees for the lateres while Banks in UAE are under specific laws [53].

In north Africa, ministry of public health of Algeria gave permission to UCB bank in 2010 where prelevment and processing of UCB units were performed since 2000 [54]. Ethical committee remains the official authority regulating all the process since prelevment to transplantation. Egypt has two private banks licensed to keep cord blood cells, and three other banks are waiting for license, but the practice of stem cell therapy is limited by the Ministry of health and population to only two publics centers of excellence [55]. The Tunisian UCB bank follows the guidelines by well established national laws dealing deontological practices and ethics and is established in the Centre National de Transfusion Sanguine [56].

MOROCCO: The first CB bank

In Morocco, the first hematology department was created in Casablanca in 1980 and it is still the only public facility where adult patients can be treated for hematological diseases. Pediatric hematological disorders and cancer are treated in two other units. Some patients are treated in private clinics located in Casablanca and Rabat. The public hospitals still have limited resources and rely heavily on nongovernmental organizations to care of these patients [57]. The number of equipped bed ward set up remain insufficient while therapeutic needs of stem cell transplantations are well identified in children and adult patients and matched related family donors are not usually found. Unfortunately, only two allogeneic bone marrow transplantations have been realized till now. In addition, the cost of the transplantation procedure, in case of presence of matched donors, couldn't be supported by all population in the society.

But, the biggest obstacle to implementation of a UCB bank remains the revision of the law of organ donation and clinical trial authorization. While the world highlights the scientific and therapeutic advancement of embryonic and adult stem cells, efforts of Moroccan health system promote most often allopathic treatments. This, is due in general to the non commitment of Moroccan laws to the international advancements in stem cell therapy and to many other medical devises. While infrastructures are evolving with regard to national and international standards quality, and high technologic equipments are available, laws regulating clinical applications in new fields are still lagging behind.

Legislation

The law No. 16-98 relating to organ donation does not allow the altruistic donation, even free. However, the prelevment of organs from dead brain person is finally allowed for the future organ bank. It remains that the anonymous collection of UCB, considered as "surgical waste" and it's ex-vivo manipulation and unrelated administration are simply prohibited, even if the therapeutic need is justified (in sibled family in the case of hematological malignancies).

Ethic between the social benefit and the financial profit

The issues related to the creation of a stem cell bank, revealed by the feasibility study carried out by our laboratory since 2008 using a questionnaire distributed in the maternity of the Centre Hospitalier Universitaire (CHU) Ibn Rochd in Casablanca (In press) are multiples and importants.

Clinicians interested in these new therapies could more easily find stem cells or other cell products for some transplants in the absence of organ donors and an established organ bank (example type I diabetes). Areas of medical applications are

multiples and concern oncology, endocrinology, kidney disease, severe burns, immunotherapy, toxicological studies, muscular dystrophy and neurodegenerative diseases. These applications can generate significant financial returns provided that adequate legislation is in place and a good financial model is identified.

The existing national ethic committee created by ministerial decree have just an advisory role and couldn't have an executive action especially with no specific drawn rules. However, it's main and first goal is to make cell therapies accessible for all the population.

RECOMMANDATIONS

Morocco should follow some guidelines and recommendations for its attractiveness and competitiveness in the field of UCB cell therapy. These recommendations focus on the legal and technical aspects of the use of stem cells or their derivatives in therapy and should be proposed in official texts.

To facilitate integration of cell therapy, several critical points should be considered:

- Allow altruistic donations of UCB cells and regulating their prelevment and transport to the processing laboratory;
- Allow expansion of ex-vivo stem cells and the production of manipulated stem cells for cell therapy;
- Create the institution involved in the manipulation and conservation of the stem cells derived UCB units and derivatives, and authorize their marketing through the creation of a national UCB bank;
- Promote a public bank but allowing private transplant centers in the same way as the public one's to practice stem cell therapies;
- Allow biomedical research with cell therapy products derived from UCB and cord matrix by conducting trials for clinical validation of new treatment protocols and authorize the use of these products in public and private institutions approved in advance by the Ministry of Health;
- Authorize the export of these UCB units to international transplant centers to be used as unrelated donor transplant to our residents abroad (MRE);
- Adopt a policy of pricing and reimbursement of these UCB units and derivatives to encourage public institutions to carry out treatments and projects in clinical phase.

There is also evidence for the creation of a group of experts which can play a role of a regulatory agency rule on requests, for authorizations of advanced UCB stem cell therapy for biomedical research implementation. This group may also give

an opinion on the changes in biomedical research using stem cell products, or in case of serious side effects observed after administration of the therapeutic. Steering committees can also be created with various objectives and timelines. This committee will define and approve new clinical investigations related to national priorities in terms of public health, cost and ethics.

CONCLUSION

Our principal goal is to consider the therapeutic benefit of the stem cell products and derivatives and to make stem cell therapy accessible to Moroccan people. On the other hand, many misconceptions about donation of organs or blood are conducted by illiterate and ignorant people and getting doubt about what is going to be done with them. In Arabic and Muslim cultures, people are educated to make offerings of their property, money and time, but never from himself, even if the religion does not prohibit this type of donation. So, considerable efforts have to be done on educating large numbers of people and especially parents regarding UCB use and laws by developing communications and networking between authorities, professional associations, physicians, non-governmental organizations and opinion leaders.

DISCLOSURE

The second and third author have participated equally to this work.

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