COMPARATIVE LAW AND REGULATION OF THERAPEUTIC USE OF CORD STEM CELLS: A CONVERSION OF BIOLOGICAL WASTE TO A GIFT FOR LIFE

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ABSTRACT

Currently cord blood is considered an innovative and particularly useful source of stem cells. They can be readily stored in biobanks. The success of the early cord blood transplantations stimulated the establishment of cord blood banks and of legislation to regulate collection, processing, and storage of donated cord blood. In Europe the specific technical quality and safety requirements for samples of cord blood are regulated by three directives (2004/23/EC, 2006/17/EC, 2006/86/EC), transposed by members of European Union into national legislation and integrated with specific national laws. Two main cord blood banking options are available: non-profit public and commercial private banks. The latter are disallowed in most European Community member because of their speculative and marketplace dealings.

KEYWORDS

Cord blood, stem cell, Biobanks, Health Laws, Bioethics.

RESUMEN

Actualmente, la sangre del cordón umbilical se considera una fuente interesante de células madre a conservar en biobancos. El éxito del primer trasplante de sangre de cordón umbilical ha propiciado el establecimiento de bancos de sangre de cordón umbilical, así como la redacción de normas para regular la recolección, el procesamiento y la conservación de las unidades de sangre de cordón umbilical. En Europa, los requisitos técnicos específicos de calidad y seguridad de las muestras se rigen por tres directivas (2004/23/CE, 2006/17/CE, 2006/86/CE), transpuestas por los Estados miembros de la UE en su legislación nacional, junto con otras normas nacionales específicas. Hay dos tipos principales de bancos de sangre de cordón umbilical: bancos públicos sin fines de lucro y bancos comerciales privados. Estos últimos están prohibidos en la mayoría de los Estados miembros de la Unión Europea, por sus propósitos especulativos y comerciales.

PALABRAS CLAVE

Células madre. Cordón umbilical. Biobancos. Derecho Sanitario. Bioética

INTRODUCTION

The scientific advances in regenerative medicine have made it possible to obtain repair of traumatized organs and treatment of certain degenerative disease conditions with the use of stem cells. In an increasing number of genetic and degenerative pathologies, such as leukemia, multiple sclerosis, myocardial infarction, stem cell transplantation has demonstrated to be a valid, effective therapy. Many different types of stem cells are obtained from various loci: umbilical cord stem cells, embryonic stem cells and adult stem cells. In the past the umbilical cord was viewed as waste material and was discarded after parturition, while currently it is considered a specific, valuable source of certain functional stem cells. They can be stored in biobanks and subsequently used for two types of transplants: autologous and allogeneic transplantation. In autologous stem cell transplant, the blood stem cells come from the same patient who will get the transplant, while in allogeneic stem cell transplant, the stem cells come from a matched related or unrelated donor.

Cord blood stem cells were used for the first time in 1989 to treat a severe form of Fanconi's anemia, as an alternative to bone marrow transplantation (Gluckman *et al.,* 1989). A unit cord blood, i.e. the pool of blood derived from one umbilical cord and placenta, is typically more readily available than bone marrow and the cells are collected, stored and frozen, without risk to the donor. The harvesting of stem cells from the peripheral blood is also an invasive procedure with its associated disadvantages. Researchers report that the rejection rate for cord blood stem cell transplantations is lower than the rejection rate for bone marrow stem cell grafts. In fact the cord blood stem cells activate fewer immune cells of the recipient than a sample of an adult's bone marrow cells might stimulate because cord blood lymphocytes are less immunologically reactive than lymphocytes from bone marrow. Cord blood transplants can accommodate a mismatched transplantation where one human leukocyte antigen locus (HLA) is involved while bone marrow transplantations require 100% HLA matches (Ballen *et al.,* 2001).

However, the number of cells in one unit of cord blood is generally insufficient for adult's transplantation. Multiple units are necessary. One cord blood unit is suitable for a child of 20-30 kg of body weight (Moise, 2005). The success of early cord blood transplantations stimulated the establishment of cord blood banks and of legislation to regulate collection, processing, and storage of donated cord blood units.

STORAGE OF CORD BLOOD: THE BIOBANK

In 1991 the first public cord blood bank was established at the New York Blood Center, USA. Subsequently, the recognition of the therapeutic utility of umbilical cord stem cells has stimulated the worldwide institution of banks for their cryopreservation. About 100 banks have been established throughout the world: approximately 40 in Europe, 30 in the United States, 20 in Asia, and 10 in Australia.

The purpose of biobanks is to promote the progress of biomedical research and health care for diagnostic and therapeutic purposes. The Regulation of the European Parliament 2016/679 regulates the processing of personal data in the health care and in bio-scientific research. Sample collection, storage, and subsequent use always require appropriate written consent from patient: the sample donated to the biobanks is property of the subject and is associated to sensitive personal data, to protect them (Bombillar-Sáenz, 2017).

Two main cord blood banking options are available: public and private. The 75% of biobanks in the word are public and non-profit, and obtain cord blood via donation following informed consent of the donor. The blood cells of each donation are immunologically typed to establish compatibility for allogeneic transplantation and then cryopreserved. The cord blood bags become property of the public bank and are available for the community and included in international registries. Samples that are considered unsuitable for therapeutic purposes, e.g., those with a low number of stem cells, may be used for research.

The private commercial banks (25% of banks in the world) conserve cord blood cells for the benefit of their own exclusive clients, for autologous or allogeneic use for a family member. In this case the sample remains property of the client (Petrini, 2013; Casado-Blanco *et al.,* 2015).

EUROPEAN LEGISLATION ON CORD BLOOD BIOBANKING

The European directives 2004/23/EC, 2006/17/EC, 2006/86/EC established the specific technical

requirements of quality and safety of samples for the donation and storage. All the member states of European Union transposed the three directives into national legislation and have integrated them with specific national laws. In some states the commercial banks are allowed to function although article 12 of 2004/23/EC declares that "the procurement of tissues and cells as such is carried out on a non-profit basis."

Spain

From a technical point of view, the National Transplant Organization establishes that cord blood extraction takes place after birth and when the placenta is still in the uterus, to obtain a quantitatively and qualitatively appropriate stem cell fraction. The first Spanish laws regulating the donation and transplantation of human tissues (Law 30/1979 and Royal Decree 2070/1999) focused that the biological material manipulation centered on the principles that biological material manipulation has to be voluntary, express solidarity with the best of medical ethics, and be conducted without profit. The successive Royal Decree 65/2006 established requirements to import and export human biological samples for diagnostic purposes, excluding the cord blood units and human tissue for transplantations. The exportation of cord blood samples was permitted by the Royal Decree 1301/2006. According to the article 7.1 of above decree, the donation cannot be made by minors, mentally ill, i.e. those who are unable to give their consent. In these cases, the informed consent can be provided by a legal representative. The above royal decree allows the storage of samples for autologous use in public banks. All samples are recorded in the Spanish Registry of Bone Marrow Donors (Registro Espanol de Donantes de Medula Osea, REDMO) and the patient is informed of the current knowledge concerning the therapeutic use of autologous stem cells.

When a given sample is collected for autologous use and it found to be compatible for a patient in need of a transplant, it will be so used. This has induced Spanish families to export and store their samples in private banks abroad. The Royal Decree 65/2006 forbade the exportation of biological samples. However a subsequent Decree 1301/2006 consents to the storage of biological in private banks abroad. Therefore, while the decree does not permit the establishment of national private banks it does allow sample collection in international private banks (Larios Risco, 2001). Crown Prince Felipe stored the cord blood stem cells of his child in abroad private bank.

The law 14/2007, the Umbilical cord blood national plan of 2008 and the Royal Decree 1716/2011 are concerned with the therapeutic use of cell and tissue transplantation and the guidelines for quality and safety, by respecting the human dignity. Not all pregnant women can donate the cord blood cells. Requirements have been established. The women must be healthy, without the risk to transmit any infectious or genetic disease, knowledgeable about the extraction protocol and its risks, and have signed the informed consent authorization. The information is provided by the physician who performs the extraction procedure.

The Royal Decree 1301/2006 was annulled by the Supreme Court judgment of May, 30 2014 and replaced with the royal legislative decree 9/2014, which declares that the cells can be stored in institutes authorized by the competent health authority, based on the requirements established in the royal decree 1277/2003, and the sample exportation has to be justified.

Italy

The Italian legislation on umbilical cord stem cell storage allows the free and supportive donation of samples only to public banks, coordinated by the National Transplant Center, a structure of the Ministry of Health (December 30, 2002). Commercial private banks are forbidden but the export and storage of samples is allowed in abroad private banks. The sample can be stored for "autologous directed use" when the patient has a specific pathology which could be treated with stem transplantation (Ordinance on April, 13 2006; Law Decree on November 18, 2009). The Law Decree on November 2, 2015 defines the legislative and technical aspects of cord blood donation. Accurate controls are carried out on the parents of the newborn to verify the absence of infectious and genetic diseases. All procedures are documented to ensure the traceability of a sample and its immediate availability for a compatible patient through the national and international Cord Blood Network. If the sample contains an insufficient number of stem cells for transplantation, it will be donated for research, after an adequate informed consent of the family (European Group on Ethics in Science and New Technologies, 2004).

France

The umbilical cord blood collection is regulated by the French Public Health Code (articles 1242 to 1245).

The cells from cord and placental blood can be extracted only for therapeutic or scientific purposes and when the mother, while pregnant, gives written consent, after receiving information concerning the stem cell use. Only public allogeneic banks are allowed to operate and their functions are underwritten by voluntary anonymous donations. In some cases storage of autologous or familial transplant is permitted in accordance with clinical indications listed by the Agence de la Biomédecine Indications (e.g., when a brother has haematological disorders that require a stem cell transplantation). In 2009, the commercial bank authorization, to store the samples for private autologous use, was proposed in parliament but immediately rejected. The Comité Consultatif National d'Éthique pour les Sciences de la Vie et de la Santé (2012) reaffirmed the opinion that the establishment of commercial banks would be against the principle of solidarity and could encourage the development of business relationships regarding births and cord blood collection, especially in the underdeveloped countries (Katz, 2010).

Germany

The German Federal Medical Association (Bundesärztekammer) has established "Guidelines for the transplantation of cord blood stem cells" (1999). Germany has six nonprofit banks for allogeneic preservation and one for autologous cells. The latter is utilized only in case of specific request by the physician and the family. Private banks are also permitted to operate. The same legislation is applied both for private and public banks. Distribution of cord blood bags is regulated by the German National Registry of Blood Stem Cell Donors (Zentrales Knochenmarkspender Register Deutschland) (Petrini, 2012).

United Kingdom

The cord blood unit collection is regulated by Human Tissue Authority (The Human Tissue Quality and Safety for Human Application Regulations, 2007) and the samples are registered in the British Bone Marrow Registry and in the Bone Marrow Donors Worldwide Registry for international searches. There are three public banks and one mixed bank in the United Kingdom. The mixed bank is Richard Branson's Virgin Health Bank. In this facility, one aggregation of samples is conserved for autologous use (80%) and the another (20%) is devoted to allogeneic donation. The allocation is determined according to the number of cells in a given unit. A donated fraction can be recovered for private use if needed (Fisk, 2008). This type of preservation requires a higher number of stem cells that is not always obtained in given blood samples. A greater number of stem cells has been observed in samples of blood obtained from pre-term pregnancies (Basford et al., 2009).

Netherlands

The Act relating to human tissues and cells (Wet veiligheid en kwaliteit lichaamsmateriaal, 2006) implemented the Directive 2004/23/EC and regulates human biological material storage. The cord blood cryopreservation is supervised by Sanquin, a nonprofit organization controlled by the Health Ministry. In Netherlands there are only public biobanks, where the samples are stored for allogeneic and autologous transplantation, permitted following hospital authorization (Code for proper secondary use of human tissue in the Netherlands, 2002).

Austria, Belgium and Denmark

In Austria, according to the "Gewebesicherheitsgesetz" (Tissue Safety Act, 2008/49), the biobanks can store the samples only after receiving donor authorization and informed consent. It is forbidden to award any financial payment or other form of recompense to donors. Some commercial private biobanks operate for autologous cell storage, but aggressive advertising by private biobanks is prohibited (Austrian Bioethics Commission, 2008).

In Belgium, the law allows the storage of biological materials for autologous or allogeneic use for a specific recipient suffering from a pathology for which the usefulness of the transplantation is scientifically proven. The law prohibits all uses of human biological materials that are not performed for precise therapeutic or scientific research approved by Ethics Committee (Agence Fédérale des Médicaments et des Produits de Sante, 2008).

In Denmark, the preservation of cord blood is currently carried out exclusively in private biobanks for autologous storage, but the health authorities promote collaboration between hospitals and the Finnish public bank, which serves all the Scandinavian countries (Petrini, 2012).

Other Countries

The European Directive 2004/23/EC was applied in Cyprus in 2007, and in Croatia and in the Czech Republic in 2008. Public as well private Biobanks are maintained in these countries while cryopreservation of cord blood cells for autologous use is forbidden in Luxembourg (Grand-Duché de Luxembourg, 2007, Petrini 2012).

BIOETHICAL CONSIDERATIONS

Autologous stem cell usage in transplantation has obvious life-saving benefits. But, from an overall perspective this endeavor currently fails to attain its scientific and ethical potential.

The principle scientific deficiency resides in the limited use of autologous cells. An autologous transplantation should be conducted (in the absence of major serious contraindications) if the patient (from whom the stem cells are derived) develops a degenerative disease. The maximum cryopreservation period of these cells, according to current knowledge, is about 15-20 years and the probability of needing an hematopoietic autologous transplantation before of 20 years of age is very low.

Moreover the use of one's own umbilical cord blood stem cell is contraindicated in cases of genetic disease, because the alteration already exists in the genetic material of the cord blood cells (Percer, 2009). The family should be informed about the hypothetical therapeutic applications of employing one's own cord blood cells as understood in contemporary scientific knowledge (Contu, 2011).

Article 21 of the Oviedo Convention states that all parts of human body must not serve as a source of profit. The Additional Protocol (January 24, 2002) of the Convention declares that the latter article has to be also applied to hematopoietic tissues and stem cells. According to the Helsinki Declaration (article 32) physicians have to obtain informed consent for collection, storage and biomedical research use of biological samples of human origin. When it is impossible or impractical to obtain an informed consent the samples can be used and stored after the Ethics Committee approval.

The employment of stem cells should have a high regard for the principles of bioethics as espoused by Beauchamp *et al.,* (2002) and implemented by the European Group on Ethics in Science and New Technologies to the European Commission (2004). The banking of cord blood has to respect human dignity, the non-commercialization of human body and the autonomy of patients, on the basis of complete and correct information and the written consent requirement, without any form of coercion. Cord blood donation represents an act of justice, solidarity, and beneficence and it incompatible with business (Leanza *et al*., 2012). The observance of these principles should allow all people to access health services, thus excluding the advancement of private banks. The principles of beneficence are not undertaken by private banks, that might offer a service, for example, based on false promises, such as a biological insurance of stem cell use for which scientific evidence is non-existent (Serrano-Delgado *et al.,* 2009). Conversely, the European Commission has declared that the activities of private banks should be discouraged but not completely banned, because it would represent a restriction on the freedom of choice of individuals and couples.

The Italian National Bioethics Committee recognizes that cord blood is an important source of stem cells and points out that the use of cord stem cells must respect the principle of non-commercialization of parts of the human body. It further states that suitable measures will be taken to inform the non-specialist public concerning the realistic therapeutic applications of cord blood-derived stem cells (2000, 2007).

The Bioethics Committee of Spain and the National Council of Ethics for the Life Sciences of Portugal (2012) promote the free and altruistic donation of cord blood for use in allogeneic transplantations, implementing the public obstetrics services with the equipment needed for that collection. The public bank storage is based on the principles of altruism, gratuity, confidentiality and the fact that the usefulness of allogeneic transplantation has been proven. Everyone can thus take advantage of altruistic donations of allogeneic stem cells collected throughout the world through the international network.

The storage of stem cells in private banks for their own use is based on a business model. It has the potential problem of promoting unreasonable expectations such as treatment of adulthood diseases when the current limit of cell preservation is 20-25 years. In addition, their stored autologous cells are not useful in a donor's hereditary disease because their cells carry the mutation causing the disease. Moreover,

autologous transplant can't produce the "graft-versus-cancer" effect.

The Ethics Committee of Cataluña (2011) has also expressed disfavor of private banks and encouraged the institution of public banks that certify the quality of preserved and available samples for all people (Amo Usanos, 2009).

CONCLUSIONS

Umbilical cord blood is a documented, bona fide alternative source of hematopoietic stem cells. To be effective for transplantation, samples of cord blood have to contain an adequate number of stem cells. Blood banks pay attention to this aspect at the time of collection and process deficient samples differently for other appropriate purposes.

Every pregnant mother has not only a new life in her womb, but the cord blood donation really could save another life and, in case of necessity, she can rely on the same "gift" from another family.

Cord blood donated for transplantation and collected in a public biobank represents an altruistic gift in contrast to autologous stem cell storage in a private bank. In the latter instance such sequestration is scientifically based, rational, and perhaps limited to the affluent population. However it is considered by many a less than ideal choice because the infant donor or its family members are unlikely to need to access the cells for therapeutic reasons. These cells it is argued would best serve an unrelated individual who needs for a transplantation.

The population should be encouraged to donate cord blood to public banks and measures should undertaken to provide relevant information regarding the nature and functions of biobanks.

Currently, the priority is the improvement of the hospitals, which should be equipped with a specialist biologist, able to take cord blood at the time of delivery.

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