STUDIA UBB BIOETHICA, LXI, 1-2, 2016 (p.33-42)
(RECOMMENDED CITATION)

BIOETHICAL CONCEPTS RELATED TO HEMATOPOIETIC STEM CELL TRANSPLANTATION IN THE RELIGIOUS AND SOCIO-CULTURAL CONTEXT

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REZUMAT. Concepte bioetice relative la transplantul cu celule stem în contextul religios şi socio-cultural. Medicina translaţională este o disciplină modernă care îşi propune să creeze o punte de legătură între cercetarea experimentală, cercetarea clinică şi implementarea tuturor acestor date ştiinţifice în practica clinică. Medicina translaţională presupune, de asemenea, aspecte juridice şi socio-culturale care pot avea rol decisiv în rezultatul acestui proces. În transplantul de celule stem hematopoietice (HSCT), cercetarea evidenţiază conceptul de celule stem, actualizat continuu, necesare în ameliorarea clinică a alo- şi autografelor de celule stem hematopoietice.

Între datele experimentale şi practica clinică în sine, pot exista lacune, uneori legate de capacitatea de a obţine rezultate viabile şi utile prin cercetare sau privind abordarea unei medicini care nu este suficient centrată pe pacient. Acest ultim obstacol a fost studiat de autori. Obiectivul principal al lucrării a fost de a stabili dacă convingerile religioase ale pacientului poate influenţa alegerea pentru terapia cu celule stem. Lucrarea a prezentat patru cazuri de pacienţi de la Clinica de Hematologie, Spitalul Clinic Judeţean de Urgenţă Arad. Rezultatele au arătat ca pacienţii au avut un rol crucial în selectarea terapiei HSCT. Doi pacienţi au urmat HSCT; unul dintre ei a refuzat alografa din considerente religioase. Una dintre cele mai frecvente motive invocate de către pacienţi este refuzul sângelui şi a produselor sanguine bazat pe motive sociale, culturale şi religioase.

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Cuvinte-cheie: *bioetică, transplant de celule stem hematopoietice (HSCT), transfuzii de sânge, alo-grefare, auto-grefare.*

ABSTRACT. Translational medicine is a modern discipline which aims to create a bridge between experimental research, clinical research and implementation of all these scientific data into clinical practice. Translational medicine also entails legal and socio-cultural aspects that can decide the outcome of this process. In hematopoietic stem cell transplantation (HSCT), research emphasizes the concept of stem cell, continuously updated, necessary for the clinical improvement of allo- and autografting of hematopoietic stem cells.

Between the experimental data and the clinical practice itself, there can be gaps, sometimes related to the capacity of obtaining viable and useful results through research, or the approach to a medicine which is not sufficiently centered on the patient. This last obstacle has been studied by the authors. The main objective of the paper was to establish whether the patient's religious beliefs can influence the choice for stem cell therapy. The paper presented four cases of patients from the Hematology Clinic, Emergency Clinical County Hospital of Arad. The results showed that the patients had a crucial role in selecting the HSCT therapy. Two patients underwent HSCT; one of them refused the allo-grafting for religious considerations. One of the most frequent reasons invoked by the patients is the refusal of blood and blood product transfusions based on social, cultural and religious grounds.

Keywords*: bioethics, hematopoietic stem cell transplantation (HSCT), blood transfusion, allo-grafting, auto-grafting.*

Introduction

Hematopoietic stem cell transplantation (HSCT) is the therapeutic method by which a patient is infused autologous or allogeneic stem cells in order to re-establish hematopoietic function, in the case of pathologies in which the patient's hematogenous marrow or immune system are non-functional or damaged. At present in onco-hematology, modern medicine offers new therapies that can induce complete remission without the need for HSCT, but the indication of HSCT remains absolutely necessary in certain onco-hematological pathologies.

The concept of hematopoietic stem cell is part of the hematological research of recent years. Multipotent stem cells have a research history of over 40 years and have been successfully used until now in treating such illnesses as leukemia. The use of this type of stem cells is to a lesser extent marred by ethical and religious dilemmas, since these cells are naturally found in the body.

However, from a medical point of view, their limited differentiation potential restricts their practical use [8]. Translational research is a recent concept, whose main aim is to categorize practical, outcome-oriented research. In medicine, there are still different definitions, according to the number of phases and other elements of the process [4]. Most current definitions considered it as a process that begins with fundamental research (genetics, molecular biology, proteomics, and so on), and ends at a worldwide level (social healthcare, access to healthcare or education, etc.) [7].

One definition states that translational medicine seeks to create new continuity between research and medical practice, through three phases: fundamental research, clinical knowledge and clinical practice, as well as the therapeutic decision made for each separate patient. In this case, two gaps appear between these phases, one between the laboratory and the patient's bedside, and the other within the attempt to translate medical knowledge to the patient's bedside [3].

Religious issues can be raised in donating tissues or cells [1] and in their acceptance by the donor [5], [6].

Some Legal Aspects Concerning Human Organs, Tissues and Cells Transplantation, in Romania

The issue of human organ and tissue transplantation was officially raised after 1990, the first law to regulate this area being passed in 1998. This referred especially to harvesting and transplanting human tissues and organs for therapeutic purposes. There have been several subsequent normative acts, among which the Law no. 104/2003 on Handling Human Corpses and Harvesting of Organs and Tissues from Corpses for Transplantation Purposes [11], republished in 2014 and amended and supplemented by Law no. 47 of 14 March 2013 [14]. Some of the changes refer to services for using corpses in anatomy subjects at university.

Another legal document is Law no. 95/2006 on Health Reform [12], republished in 2015.

Title VI of this law – Harvesting and Transplantation of Organs, Tissues and Cells of Human Origin for Therapeutic Purposes, establishes in Chapter II the rules on donation and donors of organs, tissues and cells of human origin. Chapter III is entirely dedicated to the Transplantation of organs, tissues and cells of human origin. This chapter mentions that "the transplantation of organs, tissues and cells of human origin is performed with the written consent of the recipient, after having been informed on the risks and benefits of the procedure,

according to the form template approved by order of the minister of health". It also indicates the procedures for the case in which the recipient is unable to express consent.

The Order no.1527 issued by Ministry of Health in 2014 [15], established the methodological norms to apply title VI "Harvesting and Transplanting Organs, Tissues and Cells of Human Origin for Therapeutic Purposes" within this law.

An important piece of legislation is the Order of the Minister of Health no. 477/2009 on the establishment of the National Registry of Transplant within sanitary units, designating persons responsible for the management of data from the National Registry of Transplant within health units accredited to perform organ transplantations and establishing the data required for registration of a person for the assignment of the unique registration code from National Transplant Agency, as subsequently supplemented [13].

The latest legislative document is Law no. 9/2016 of 18 January 2016 for ratifying the Additional Protocol to the European Convention for the protection of human rights and human dignity regarding the applications of biology and medicine, with reference to the Transplantation of Organs and Tissues of Human Origin, signed in Strasbourg on 20 February, 2015 [16].

Starting from the aim of the Council of Europe to achieve a greater unity between its members and that one means of achieving that aim is the protection and realization of human rights and fundamental freedoms, the aim of the Convention on Human Rights and Biomedicine, as it is defined, is "to protect the dignity and identity of human beings and to guarantee for everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to its application of biology and medicine" [9].

In conducting transplants one must take into account several aspects such as the ethical, psychological, social and cultural issues related to the transplantation of tissues and organs, the proper use of tissues or organs, so that as not to affect human life or dignity, the conditions under which the transplantation is performed, monitoring compliance with individual rights and freedoms and the prevention of illegal trafficking of organs. All these are aimed at achieving progress in medical sciences, saving lives and increasing the quality of human life. This law regulates, in addition to object and scope, some major issues such as: the transplantation system, harvesting of organs and tissue from live and deceased persons, financial gain, confidentiality etc.

Regarding international agreements on the exchange of organs, the procedures must have a justified distribution among participating countries, taking into account the principle of solidarity within each country.

Likewise, it is very important to provide correct information to the donor about the purpose and nature of harvesting, and about its consequences and risks. The donor must also be informed on the rights and guarantees provided by law for their protection. Also, it should be noted that obtaining any financial gain or comparable advantages is prohibited. In some EU member states there is a donation card by which a person can express donation consent during their lifetime.

Moral, Ethical and Religious Issues Related to Communication with Patients

The idea behind this work came from interdisciplinary collaboration offered in hematologic patient care, by addressing both the moral conscience and ethical norms and relations from a particularly introspective perspective.

Thus, the main problem that arises in the discussion with these patients appeared since communicating the diagnosis, and some of the main dilemmas that we found were those related to the questions "why did I get the disease?" and "what is the healing promise we can get?" This context reminds us how important is the role of confessor (spiritual leader) in human life, which is connected to religion as a guide, helping him discern the path of good or evil.

The study of the history of world culture highlights the fact that the issue of good and evil is present in any ancient culture, being widely debated in the mythology and religion of ancient peoples, long before the emergence of philosophy as a manifestation of human spirituality (a concept proposed by the great Greek philosopher Plato, who situated the idea of "good" at the center of his entire philosophy, and criticized by Aristotle, who believed that there is an asymmetry in the good-evil polarity, with evil being definitive, and good only purporting to be).

A confessor is one who can provide, first of all, support in the patient's struggle, a struggle which, in a perhaps abstract, and yet so real manner, refers to the very battle between good and evil. Besides support, he can also provide constant objective advice, which does not take into account the fact that, before disease or other individual issues, there are no social classes advice, regardless of the phases through which the individual is going, regardless of context and the time. A confessor is required to be a parent who guides the individual on a good course.

One of the important issues that they have raised is whether the illness occurred due to lack of love in the patient's life, and another question is how can those who want to remain faithful to the Christian belief respond and

accept the challenges and opportunities offered by medical progress (Statt's double listening concept). The patient considers the onset of the disease to be a genetic alteration influenced by environmental factors. Is our body a survival and gene multiplication machine (Dawkins' concept), do we function according to a predetermined genetic program that we cannot influence, or is it just the role of divinity in both the occurrence of disease and the outcomes of the treatment?

They also considered it necessary to communicate the truth. From a moral perspective, human relationships based on lies are degrading, having a strong diminishing effect on the human condition. Living a lie influences human relationships to such an extent that it completely cancels the values that underlie and give meaning to authentic human life. Many of those who lie punish themselves and their punishment is, among other things, that a lie always needs another lie to support it, that one has to exert one's memory a lot to remember what they said and worse, the fact that not only are they not believed, but they can no longer believe in anyone. A. Gide said that most detestable lies are those closest to the truth. Therefore we agree with Lucian Blaga, who said it would be terribly unfortunate if the truth were to always be found "in the middle". There are cases where we can talk about a limit to speaking the truth, but mainly the communication of truth has been extremely important for patients.

Regarding the acceptance of the transplant procedure, patients were informed on the therapeutic method involved by the transplantation, be it or allogeneic or autologous.

Ethical and Religious Issues in HSCT Therapy Cases

Allogeneic HSCT has broader indications, because it can provide complete curability in multiple pathologies such as acute leukemia, multiple myeloma, non-Hodgkin's malignant lymphoma, Hodgkin's disease. Autologous HSCT can also be used, but it uses the patient's stem cells, in this case the technique depending on getting a remission of the disease in advance. Rates of mortality and morbidity related to HSCT decreased considerably due to improved conditioning regimes, more efficient HLA typing, supportive therapy and prevention and treatment of serious infections. The types of stem cells that can be used for HSCT are bone marrow, peripheral blood after stimulation with granulocyte colony-stimulating factors, cord blood from related or unrelated donors.

One of the nonmedical issues raised by HSCT is blood infusion by the transplantation itself and the need for supportive therapy with blood preparations in transplant patients. This restriction occurs in patients who, for religious reasons, do not accept blood transfusions or blood preparations.

Modern medicine offers these types of patients, as well as others, a type of HSCT called bloodless transplant [6]. This type of transplant takes particular care that blood components are as much as possible removed by washing and subsequently replaced with albumin in the donor's apheresis product and the use of pretransplant and posttransplant methods to reduce the need for transfusions. Of course, the cytometrical selection of stem cells is done using modern technology, with maximum accuracy.

There are other mindsets of patients, according to the author's experience, which in part are related to the Romanian cultural and social context, according to which the introduction of foreign cells in one's body is seen as a deterioration of the human being. This type of mindset has been noted in patients described in the casuistry of Arad Hematology Clinic.

All patients are informed in advance about the specific HSCT procedure, its benefits and risks, and they sign an informed consent form. According to Law no. 46/2003, correct and complete information of each patient, regardless of religious belief, is part of patient rights and is essential in the therapeutic management of the patient [10].

Regarding the ethical issues that may be raised by HSCT, the patient's decision between a therapy that may be their only salvation or which might even turn out to be fatal is most acute [2]. Questions were also raised about preserving the dignity of the transplanted person. The moral obligation to use live-saving technologies if they are available is another question that HSCT raises. The conclusion of meta-analysis is that, morally speaking, the patient's safety is paramount.

Clinical hematology patients studied in Arad were aged between 23 and 56 years, of the Christian religion. The first case was a 54-year-old woman with acute myeloid leukemia who had two allogeneic HSCTs. The patient hails from an urban background, is highly educated, and had her family by her side at all times (husband). Doctor-patient communication was appropriate, with information from the clinician and answers to all questions asked by the patient and her family. The patient accepted two allogeneic HSCT as the only curative therapy in onco-hematologic disease at the time. Survival was 2 years since the last HSCT.

The second case was a 56 year-old woman with multiple myeloma. The patient came from a rural areas, had completed secondary studies, and family presence during hospitalisation was reduced. This patient's relationship with her carers was not constant. The patient refused allo-transplantation due to the risks involved, the difficulty of finding a compatible donor of hematopoietic stem cells, and religious reasons regarding the acceptance of regenerative tissue from an unrelated donor. Therefore the patient was administered an autologous transplant, with unfavorable outcomes.

The third case is a 23 year-old woman with Hodgkin's disease. The patient comes from the urban area, having completed high school at the time of diagnosis. The patient was accompanied by friends, not family. The patient refused allo-HSCT, citing the following reasons: fear of having foreign cells infused into her body, which could change her identity, indirectly refusing transfusion of blood preparations. This refusal also made self-HSCT impossible, as the conditioning phase and the post-transplant aplastic anemia phases often require the transfusion of blood preparations. The patient had strong religious beliefs, which influenced her conduct and therapy decisions. In addition, the patient refused radiotherapy which is standard protocol in Hodgkin's disease.

The fourth case is a 51 year-old man with acute leukemia. His origin was rural, secondary education, permanently accompanied by his wife. The patient was directed to preparations prior to allogeneic HSCT, but refused it citing uncertainties offered by this therapy, being largely influenced by the outlook of his family and entourage on this therapy.

Conclusions

The patient is a person who does not live in isolation, but is a social being, directly influenced by entourage, family, faith and their own conceptions about life. In conclusion, the patient should always be approached in a complex manner, not just from a biological perspective, but also from a psychological, spiritual, cultural standpoint, in order to be able to offer them health care to the highest standard, but while respecting the dignity and autonomy of the human being.

The HSCT therapy is a complex one and implies a lot of decisions for both physician and the patient. Therefore, in addition to legal and medical aspects that should be considered, often a more important role is played by ethical, moral and religious aspects that can decisively influence the medical act.

The results showed that the patients had a crucial role in selecting the HSCT therapy. Two patients underwent HSCT; one of them refused the allo-grafting for religious considerations. One of the most frequent reasons invoked by the patients is the refusal of blood and blood product transfusions based on social, cultural and religious grounds. The conclusion was that the patient is a person who must be addressed in all his complexity, his decisions being made in accordance with the principle of autonomy and patient's rights, and defining the trajectory towards healing or disease rebound.

Acknowledgement

The study was conducted with the support of 16_PA07-C1 Start Danube Region Project - BioEthics Standards in Transnational Research: an Integrated Approach to Bioethics Education in Biomedical Sciences and its Role in Development of the Knowledge Society in Danube Region Countries (BEST-NetWORK).

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