Multidisciplinary Development Issues of Hematopoietic Stem Cell Transplantation Program in Ukraine: Role of Auxiliary Cryopreservation Technologies

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Abstract: Hematopoietic stem cell transplantation (HSCT) is a life-saving medical technology for many serious diseases. Active international exchange of transplant material is ensured through productive cooperation of world international donation, transplantation, cell therapy organizations, along with their associations. Analysis of the experience of many countries has allowed the development of key recommendations from the Worldwide Network for Blood and Marrow Transplantation for establishing HSCT programs. According to them, to make the most effective use of the capabilities of this medical technology, the creation of new transplant programs requires both sufficient investment and the presence of specialized professional teams for multidisciplinary support of the entire process.

This article discusses prospects for the development of the national transplant program in Ukraine. In particular, the role of Ukrainian national scientific and practical traditions detailed in the creation of cellular processing technologies and cryopreservation as part of the team support providing components of transplantation medical technology. It is looked forward that the development of the HCST program in Ukraine will take place through continuous improvement in order to meet the criteria of the highest quality and safety. Its serious basis is the solid scientific traditions, historical and modern experience of many directions that provide the field.

Keywords: Hematopoietic stem cell transplantation, Transplant program requirements, Cryopreservation.

INTRODUCTION

The growth of activity in the field of hematopoietic stem cell (HSC) transplantation (HSCT) has recently reached significant rates [1]. It is facilitated by the globalization of the direction and the regular system optimization, that occurs due to the scientific and practical cooperation of several international organizations and professional institutions. The reliability of approaches to quality ensuring of allogeneic transplant material is the key to effective international exchange [2].

Recently the Worldwide Network of Blood and Marrow Transplantation has provided level requirement recommendations for new HSCT programs according to country-specific capabilities [3]. It is essential to consider the nature of the development of the transplantation system in Ukraine, a large Eastern European country with a population of over 44 million people. There is a clear need in the country to ensure maximum HSCT quality and safety. Solid scientific traditions, historical and modern experience of the functioning of many branches providing this sphere are a significant basis for effective maintenance of our national transplantation program. Such skills of Ukrainian specialists are the creation of technologies for low-temperature storage of hematopoietic cells, clinical use of fresh and cryopreserved grafts, including those carried out in the most severe anthropogenic disaster, namely the accident at the Chernobyl nuclear power plant.

1. Prospects for the Creation of a National Hematopoietic Stem Cell Transplantation (HCT) Program in Ukraine in an Aspect of International Requirements for Priority Access to Specialized Professional Care

Today there is a well-considered global procedure for harmonization of regulations on quality assurance systems, standardization and implementation of special accreditation programs at each stage of the transplantation process [4]. Thus, the activity of HSC registries largely depends on the ability to uniquely identify individuals and their products while maintaining confidentiality [5]. The identifier system has signs of comprehensiveness and general acceptability to enable electronic data exchange while searching for unrelated voluntary donors and HSC products, both nationally and internationally. Due to this, the trade between the countries provides almost half of the transplants.

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E-ISSN: 2312-5411/21

Regular optimization of the global HSCT system is taking place thanks to scientific and practical cooperation and the efforts of many international organizations. National donor registries with public umbilical cord blood (UCB) banks are the infrastructural foundation for the development of the system, along with functional centers for the facilities involved in the process. The World Marrow Donor Association (WMDA) oversees the standardization of these authorities to benefit stem cell donors and patients by promoting global collaboration and the exchange of best practices among its members [6]. Registries that are certified, qualified and accredited by WMDA have all the capabilities and mechanisms to effectively provide the high quality of both HSC products and donor safety. WMDA standards focus on transactions for the registration of prospective donors and UCB units, as well as other guidelines for registries. Aspects of non-family donor transplantation outside this list are included in the standards of other organizations [6, 7]. Since 2017, WMDA has taken the function of The World Bone Marrow Donor Registry (Bone Marrow Donors Worldwide (BMDW)) and the NetCord Foundation.

Since 2007, The Worldwide Network for Blood and Marrow Transplantation (WBMT), founded by the WMDA, The European Society for Blood and Marrow Transplantation (EBMT), Center for International Blood and Marrow Transplant Research (CIBMTR), Asia Pacific Blood and Marrow Transplantation (APBMT), as well as leaders of large HSCT groups with donor registries from around the world, is on a mission to promote best practices in transplantation, hemopoietic cell donation, and cell therapy. WBMT is in official relations with The World Health Organization [8]. WBMT includes 22 member societies and seven standing committees with international influence [9].

A recent careful analysis of the set of elements that make up the design and operation of national transplant programs in specific settings carried out under the auspices of the Transplant Center and Recipient Issues Standing Committee for the WBMT has shown a gradation of priority requirements (from absolute requirements to preferred requirements) [9]. First of all, the requirements for national HSCT programs depend on the availability of the following points: resources for their implementation in a given country, access to the specialized professional care of high complexity in various fields of medicine. Secondly, the definition of priorities for the necessary and sufficient elements is associated with the prevalence and diseases spectrum, the need for certain types of transplants in a particular region [3, 9]. Thus, the analysis and generalization of the world's existing approaches to the organization of the HSCT system indicate the priority of this area for national health systems. However, not the least role in the functioning of national transplantation systems is assigned to the norms applied in local legal and regulatory environments and constitute practical support for effective operation and cooperation of the main elements of this system (transplantation centers, HSC collection, UCB banks, and donor registries) [6].

Ukraine, located on the European continent, is a promising country for the widespread introduction of transplants with varying levels of complexity. Therefore, in addition to the standards of the above-mentioned global organizations, the legal and regulatory rules of the EU member states are always relevant for our country, which guarantees the promotion of free donation, fair distribution, and proper use of human cells and tissues. They are established by the relevant directives of the European Parliament and the Council of Europe (2004/23/EC, 2006/17/EC, 2006/86/EC, Commission Directive (EU) 2015/565 of 8 April 2015 amending Directive 2006/86/EC) [10-13]. In this case, recommendations on the quality and safety of tissues and cells intended for human use, specially developed by the European Directorate for the Quality of Medicines and HealthCare (EDQM, Council of Europe), come in handy as guidelines [7].

Unfortunately, the lack of resources to create such essential institutions as the national register of HSC donors and the public UCB bank still exists in Ukraine. It causes an acute problem of providing patients with transplant material of unrelated origin. Although guaranteeing and creating appropriate conditions for the donation, storage, use of human tissues and cells, as well as responsibility for the proper performance of control functions in this area is the prerogative of the state, research in the transplantation field, including biotechnology development, is also a significant component of success. In this context, the presence of s scientific traditions, historical and modern experience of successful transplants, development in quality management, the existence of professional teams of specialists, including interdisciplinary support of the whole process should be considered a significant potential for launching the national HSCT program [14-18]. Accordingly, the nationwide transplant program in Ukraine has the prospect of getting the highest quality, which can ensure high performance of life-saving

technologies with minimizing risks for individual patients, while adhering to the concept of balance [19] between the proper quality of procedural technologies and cost savings.

2. Cell Processing and Cryopreservation as Requirements for the Development of the HSCT Program

The best international practice has shown that one of the minimum requirements for developing the HSCT program is the presence of cell processing laboratories, which are supposed to carry out cryopreservation procedures and the possibility of storing cryopreserved material [9]. For more advanced programs designed for allogeneic transplantation, access to the possibility of minimal manipulation of the graft (reduction of red blood cells, $CD34^+$ cell enumeration), as well as the availability of cryopreservation and storage of cryopreserved material) with highly qualified personnel in this field are among the "preferred requirements" [8]. Such the domain within the multidisciplinary team is defined as a link that helps to optimize HSCT safety.

Moreover, in current conditions, the role of the latter requirement is growing significantly. It has become clear that SARS-Cov-2 highly increases the risk of mortality from transplantation [20, 21]. It increases the value of the cryopreservation option and the availability of the HSC bank to create transplant programs of appropriate quality, designed for both autologous and allogeneic transplants.

Thus, in early 2020, the first versions of the HSCT guidelines were published by institutions such as the British Society of Blood and Marrow Transplantation and Cellular Therapy, EBMT, the National Institute for Health and Care Excellence (NICE) [NG164] [21-23]. It is emphasized that the developers of the transplant program should take into account both the creation of conditions for the safety of HSC recipients from COVID-19 and the implementation of measures to reduce the risk of potential disruption of the planned transplantation. Thus, one of the main innovations in the allogeneic transplant procedure is to consider in addition to such sources of HSCs, such as HLA mismatched (haploidentical) family members and UCB units but also pre-cryopreserved donor hematopoietic stem cells as an alternative to fresh HSC products. The availability of such products prevents the delay of transplantation. Donor examination, carried out in advance, with the provision of cryopreserved material avoids problems that may arise in conditions of restricted movement, as well as quarantine circumstances and measures for the donor (direct collection of cells, timing of their transportation, etc.) [24].

Therefore, to reduce the risks to patients and donors on the HSCT steps during the pandemic, the importance of timely incorporation of modern cellular cryotechnologies into transplantation programs should be considered in the design and development of a national system for providing such transplantations. Ukraine has many advantages in this sense, which are closely related to the availability of scientific and practical experience and traditions in the field of hematopoietic tissue and blood cell cryopreservation.

Hematopoietic Cell Cryopreservation: Historical Aspect and Traditions of Specialized Care in Ukraine. A significant amount of research on the effect of the bone marrow (BM) transplants on the course and outcome of acute radiation syndrome in various species of experimental animals has accumulated by the middle of the last century. Positive results stimulated the interest of clinician hematologists in the development of these studies. Prospects for the practical application required the development of procurement methods, preservation, and long-term storage of BM transplants.

At that time, research in the low-temperature storage field of various cells was a real scientific basis for global trends to solve this problem. The results clearly showed that the cells, that are in conditions of deep cold, can fall into an anabiosis state with almost complete suppression of vital processes and their subsequent recovery after thawing. In the early twentieth century, such leading scientists as Bakhmetyev, Rahm, Kadisch, Lipman, Luyet, Kalabukhov, Milovanov, Lozina-Lozynsky, Schmidt, and others made a significant contribution to the study of the use of cold to preserve biological objects [25-27]. In the 50's it was possible to reveal the basic mechanism, to outline the physicochemical problems of the damaging effects of freezing on cells (Rey, 1959), and to find ways to protect cells with protective substances against freezing destruction (Polge, Smith, Parks, 1949; Lovelock, Bishop, 1959; Doebler, Rinfret, 1959, etc.). Several theories developed at that time, namely: "intracellular ice formation", "damage development due to the effects of the solution, and freezing factors" became useful [28-31]. Theoretical and practical achievements in the 60-70 years period of the twentieth century were further reflected in some monographs: Smith AU. "Biological effect of freezing

over supercooling"[32], Re L. "Conservation of life by cold" [28], Meryman HT, *et al*. “Cryobiology” (1966), Lozina-Lozinski LK. "Essays on cryobiology / Adaptation and resistance of organisms and cells to low and ultra-low temperatures" (1972) and others [26]. Even then, it was found that the survival of frozen cells during cryopreservation usually requires the use of cryoprotective substances, which were classified as a special class of compounds necessary for the preservation of viability [33, 34]. The protective properties of penetrating cryoprotectants were first discovered using glycerol in 1949 [35]. Polyols such as dimethyl sulfoxide (DMSO) [29], as well as 1,2-propanediol (PROH), 1,2-ethanediol or ethylene glycol [30, 36] were used later.

Several notable achievements were made during the first studies on the freezing and use of HSCs in the 1950s, which were conducted on animal models under lethal exposure [37]. Since the early groundbreaking reports of BM transplantations by Nobel laureates Thomas, *et al*. [38], many experiments were conducted to improve the overall recovery and functional capacity to restore the recipient's hemopoiesis. For this purpose, the HCS cryopreservation protocol has also improved.

At that time, the problem of BM preservation using protective media at low and ultra-low temperatures was considered extremely important. In Ukraine, the beginning of the activities of scientific schools in this area can be considered the organization of scientific and practical developments in the 60-70 years of the twentieth century. This took place in laboratories and research departments of such research institutes as the Kyiv Institute of Hematology and Blood Transfusion of the Ministry of Health of the USSR (State Institution "Institute of Hematology and Transfusiology of the National Academy of Medical Sciences of Ukraine) and the Institute for Low Temperature Physics and Engineering of Academy of Sciences of USSR (B.Verkin Institute for Low Temperature Physics and Engineering of the National Academy of Sciences of Ukraine) [17,39]. Many significant patterns and critical data on the optimal regimes and rates of BM freezing have been identified as a result of many years of research. Further progress in the cryobiology and cryomedicine fields received a proper impetus in the development of basic research using biophysical, biochemical, morphological, immunological methods. In 1972, with the establishment of the Institute of Problems of Cryobiology and Cryomedicine of the National Academy of Sciences of Ukraine in Kharkiv, domestic cryobiology, as a relatively young branch of science at the time, was significantly developed by deepening research with the integrated assessment of a wide range of natural sciences.

Developments of Ukrainian scientists (Prof. SS Lavryk, *et al*., 1966, 1971; Dr. GI Kogut, *et al*., 1988; Prof. MS Pushkar, *et al*., 1968; Prof. AO Tsutsaeva, *et al*., 1979; Prof. AM Goltsev, LV Ostankova, *et al*., 1979 [40]) were introduced in the institutions of the blood service of Ukraine. Blood and BM banks for long-term storage were also created. The material was used for transplantations in hematological and oncological clinics in Kyiv (Prof. SS Lavryk, Prof. AF Romanova, Dr. GI Kogut, Prof. VG Bebeshko, Prof. VI Klymenko, *et al*.). New cryogenic equipment was created (Institute for Low Temperature Physics and Engineering of Academy of Sciences of USSR (B. Verkin Institute for Low Temperature Physics and Engineering of the NAS of Ukraine), as well as in other institutions of the country). Equipment for microscopic examination for biological objects in the temperature range 4.2 - 300 K was developed by physicists of the Ukrainian Institute of Physics and Technology of the Academy of Sciences of USSR (National Science Center “Kharkiv Institute of Physics and Technology” of the NAS of Ukraine). It allowed conducting the necessary research on human BM. During the liquidation of the accident at the Chernobyl nuclear power plant (1986), cryopreserved BM with storage at liquid nitrogen temperatures from 10 days to 8 years was used to treat patients with acute radiation sickness. The positive effect of BM grafts in these patients was associated with: early diagnosis of the degree of myelosuppression, the degree of the HLA system compatibility in a donor-recipient pair, and sufficient preservation of thawed hematopoietic cells (Prof. LP Kindzelsky, *et al*.) [16].

Reduction of the influence of the stress-induced triggering factors for cell apoptosis using new substances in the composition of cryopreserved solutions is considered promising in improving cell technologies at the present stage of scientific research. In addition, the study of the potential properties of cryopreserved hematopoietic cells, as well as the possibilities of graft enrichment is a recent research trend carried out in research institutions of the National Academy of Medical Sciences of Ukraine and the National Academy of Sciences of Ukraine.

Mechanisms of Cryopreservation and Cryoprotection of Cells. The most reliably frozen

biomaterials can be stored at a temperature close to minus 196 ºC when the cells have suppressed all metabolic and biophysical processes [25].

Cryoprotective agents that restore cells to high levels of functionality after thawing play a key role in storage at deep cryogenic temperatures. These substances have a wide range of metabolic and biophysical effects, according to their mechanisms of action. Early advances in cryopreservation have been achieved with an empirical methodology for the selection and application of the cryoprotectant agents. Later, the mechanisms of their action became known, which allowed optimizing the use of these components for freezing living objects. There is a problem of inconsistency between the toxicity of these solutions and the need to use them in molar concentrations that significantly exceed the levels found in normal metabolism, with a potential complication of cell function. Continuous improvement of technologies is mainly through the use of effective cryoprotectants in safe concentrations [25, 40, 41].

Technologies used in HSC long-term storage laboratories involve harvesting, fractionation, preparation of cell suspension for low temperatures, freezing at controlled rates, and restoration of morpho-functional qualities of cells after thawing.

Preparation for freezing involves the selection of the fraction of nuclear cells in the most viable state, as well as their equilibration in protective solutions. The choice of equilibration parameters varies depending on the nature of the cryoprotective substance and the components of the cell suspension.

Further freezing is carried out according to a special program, the choice of which depends on the structural and functional qualities of the cells, as well as on the nature of cryoprotective substances, their molarity, and concentration in the protective solution. The cooling rate varies in different temperature zones with the implementation of temperature stops [41, 42].

The selection of cooling parameters for each cell type requires experimental determination [42]. The degree of supercooling of the cell samples should not exceed certain values ($\Delta t \approx 2$ o C) to prevent the formation of intracellular ice crystals, as well as to limit the osmotic gradients, which is the driving force for the exit and entry of water into the cells. Changes in the phase of ice formation in cells are a two-stage process for the formation of ice nuclei and their subsequent growth [41-43]. Ice nucleation and the possibility of its limitation have been the subject of experimental modeling recently [44]. The optimal rate of the cell suspension cooling is determined by the permeability coefficient of the cell membranes for water and cryoprotectants, the osmotic volume of water in the cells, as well as the surface area of the cells.

The addition of cryoprotective agents to the biomaterial inhibits the formation and growth of ice crystals during cryopreservation [45]. The dehydration degree of a biological object in the first stage of low-temperature preservation significantly depends on both the freezing rate and the cryoprotectant agent presence in the cryopreservation medium.

Increasing the concentration of cryoprotectant can reduce the likelihood of ice formation and promotes vitrification [46]. However, this raises another problem: the toxicity potential of the cryoprotective substance increases with increasing concentration [47]. Given the known biological and physicochemical effects of cryoprotectants, their toxicity is considered the key factor limiting experts in developing successful protocols for cryopreservation of the cells and the tissues [48]. The difficulty of maintaining the balance between inhibiting crystallization processes, reducing toxicity, and maintaining structural integrity is one of the main problems in the application of cryopreservation technologies [49-51].

It is known that cryoprotective substances of the exocellular action mechanism enhance the growth of the hypertonic gradient on cell membranes due to the increase in the concentration of solutions during freezing [40, 52, 53]. However, the protective effect of endocellular substances is associated with inhibition of the formation of hyper-concentrated solutions and reducing the cell dehydration effect during freezing [53].

Combined cryopreservation solutions, which contain several cryophylactics with different mechanisms of action, are increasingly used for blood cell suspensions and HSCs. It reduces the cell dehydration effect, relieves hypertensive stress from the enveloping cryoprotectant action, and weakens the organ toxicity effect by reducing the effective concentration of the "main" endocellular cryoprotectant [54, 55].

The choice of cooling program in the presence of any cryoprotectant agents is based on the desire to achieve cell dehydration optimum. On the contrary, there is a need to choose slow cooling rates, when using a penetrating cryoprotectant agent in a freezing

medium (dimethyl sulfoxide, glycerin) since inhibition of cell dehydration increases the likelihood of formation of intracellular ice crystals in this case [25, 56]. Ensuring the high safety of frozen cells under the action of combined protective solutions avoids significant hypothermia at the point of initial crystallization [56, 57].

Taking into account modern views on the pathophysiological mechanisms of cryopreservation (mitochondrial dysfunction, DNA fragmentation, oxidative stress, osmotic stress, and induction of apoptosis) helps to achieve better results through improved technology. Both the direct destruction of some membrane phospholipids during freezing-heating, and their indirect damage due to oxidative stress caused by physicochemical factors, are among the mechanisms that ultimately cause cold-induced cell lysis [58, 59]. Intensification of free radical oxidation processes leads to increased formation of highly toxic substances, in particular, products of lipid peroxidation [60, 61]. Intense damage to cell biomolecules, uncontrolled release of calcium ions into the cytoplasm, disruption of intracellular signaling, as well as the work of enzyme systems, etc. occurs under these conditions. The accumulation of degradation products promotes the further development of low-temperature photochemical processes in cell membranes. Such molecular processes deserve special attention, given that their development may later become irreversible for the viability of cells in the process of cryopreservation [62].

Today, there are many reports on the possibility of preventing these effects by varying the composition of the environment for cryopreservation by adding various biologically active substances (trehalose, taurine, α-tocopherol, ascorbic acid, catalase, etc.) [63-65].

CONCLUSION

Advance careful planning is crucial when designing the HSC transplant program to meet the expected challenges [66]. Therefore, when creating the national HSCT program, we should consider the role of national traditions and opportunities in such interdisciplinary areas of the process providing as cryobiology and cryomedicine.

The COVID-19 pandemic has impacted all aspects of HSCT [67]. Cryopreservation of fresh HSC products and the operation of the public banks for blood and the HSCs from various sources create opportunities to avoid the catastrophic consequences of interrupting the planned transplant procedure in case of COVID-19 infectious threat. In this regard, the new recommendation of donor registries, proposed by the consensus of expert groups during the pandemic, on cryopreservation of HSCs before the start of the recipient's conditioning procedure deserves special attention.

Options such as accumulated experience in theory and practice in the cryopreservation field (understanding the mechanisms of cryopreservation, cryoprotection, and cell repair capabilities), the availability of technology, as well as highly specialized specialists with the multidisciplinary approach to the creation and operation of cell processing laboratories and low-temperature banks are a fundamental resource available in creating a national HSCT program in Ukraine.

Therefore, there are reasonable hopes that the development of the HSCT program in Ukraine will be achieved by obtaining the highest quality and efficiency of technology in balance with a wise investment. It will provide opportunities to meet the needs not only locally but also internationally.

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Received on 20-09-21 Accepted on 13-10-21 Published on 14-10-2021

DOI: http://dx.doi.org/10.12974/2312-5411.2021.08.4