

# Transplantation of hematopoietic stem cells: historical aspects



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## ABSTRACT

*The historical review covers more than 60 years of the development of hematopoietic stem cells transplantation (HSCT) in the world: from animal experiments and first bone marrow transplantations to incurable patients to the widespread use of HSCT as an effective treatment for a number of hematological, oncological and other diseases. During this period on the way of its development, a number of scientific, technical and applied problems have been overcome. The author focuses on the achievements in many related fields of medicine and biology (hematology, oncology, immunogenetics, pharmacology, radiotherapy, transfusiology, cryobiology, etc.), which have changed the role of HSCT from the «therapy of despair» at the terminal stages of the disease to the priority therapeutic strategy for the treatment of a number of cancer and non-malignant diseases in the early stages of the disease. The study of historical experience will be useful for Ukraine, which relatively recently has begun to introduce the method of HSCT into clinical practice.*

**KEY WORDS:** hematopoietic stem cells transplantation (HSCT); bone marrow; umbilical cord blood

Today, the system of transplantation has been established and successfully operates in the world. Worldwide experience in the implementation and application of hematopoietic stem cell transplantation (HSCT) is more than 60 years old. Currently, the number of transplantation teams that use autologous and allogeneic HSCT, related and unrelated donors, myeloablative and non-myeloablative conditioning regimens, as well as various sources of hematopoietic stem cells (from bone marrow, peripheral blood and umbilical cord blood) are rapidly increasing in the world. Growth in the number of registries of voluntary HLA-typed donors and umbilical cord blood banks in many countries of the world stimulated international cooperation in the search and exchange of histocompatible donor material for allogeneic HSCT from unrelated donors. Today this innovative, multi-disciplinary and high-tech treatment method is successfully used to treat a number of malignant and non-malignant diseases. However, the path to the success of HSCT was not easy. To make HSCT a priority therapeutic strategy in the treatment of the aforementioned diseases, a number of scientific, technical and applied problems have been solved.

Each stage of HSCT development in the world in the systemic-historical aspect has scientific discoveries that can be considered innovative for their time. The medical consequences of the use of nuclear weapons in Japan during World War II prompted researchers to study the properties of hematopoietic stem cells (HSCs). Scientists have begun searching for ways to protect people from radiation. The results of the first experiments published in 1949 by Jacobson with co-authors showed that mice irradiated with a lethal dose of ionizing radiation could survive if their spleen was protected by lead foil screens [1]. In 1951, Lorenz et al. reported that the protective effect from lethal doses of ionizing radiation could be achieved by infusion of bone marrow or spleen cells from healthy to lethally irradiated animals [2].

In 1956, the idea appeared that bone marrow transplantation (BMT) could have an additional therapeutic effect on malignant tumors. Barnes et al. described the anti-leukemia effect in mice that received lethal doses of ionizing radiation followed by the introduction of non-syngeneic bone marrow. Subsequently, the animals died due to «exhausting disease», which is now called graft-versus-host disease (GVHD) [3].

The modern stage of the development of HSCT in humans began in the 1950's. Information that the function of bone marrow destroyed by lethal doses of ionizing radiation can be restored in animals by infusion of the syngeneic bone marrow prompted the researchers to use this approach in the treatment of leukemia in humans.

In 1957, Thomas and his colleagues published the first article in which they described a radically new approach to cancer treatment: radiotherapy and chemotherapy followed by intravenous bone marrow administration from a healthy donor. At the end of the 1950s, Thomas and his colleagues provided proof of this concept. It has been shown that BMT from the histologically identical twins can provide restoration of hematopoiesis in patients with acute leukemia, after irradiation of the whole body with the lethal dose of ionizing radiation. Although patients' hematopoiesis restored, they all died within a few months due to the relapse of the disease [4, 5].

In 1959 in Europe, Mathé et al. reported an attempt to treat several patients who suffered from accidental damage by ionizing radiation. Allogeneic bone marrow was injected to patients to restore hematopoiesis. Temporary transplant grafting was observed in some patients. However, those who survived had an autologous reconstitution of hematopoiesis [6].

In 1958, Kurnick et al. reported the first attempts of autologous BMT at malignant diseases. They conducted collecting and cryopreservation of bone marrow cells in two patients with metastatic lesions. After a high dose radiotherapy, thawed autologous bone marrow cells were injected

intravenously. Although the authors could not be absolutely sure, they considered it quite probable that the recovery of hematopoiesis was due to autologous BMT [7].

In the 1960s, experimental and clinical studies are ongoing to improve BMT technology. In the early 1960s, Thomas et al. performed BMT in high-dose irradiated dogs. The studies allowed to determine the dose of radiation necessary to achieve transplant engraftment. The requirements for the histocompatibility of the donor and the recipient have been clarified in order to prevent the fatal outcome of the GVHD or rejection of the graft. The ability of methotrexate to adequately suppress acute GVHD was shown [8-11].

Dog studies have shown that DLA (dog leukocyte antigens) compatibility of the donor and the recipient is important for the success of the allogeneic BMT [9, 11]. Understanding the role of histocompatibility for long-term survival of patients with allogeneic BMT and the discovery of human leukocyte antigens (HLAs) by Dausset and van Rood et al. allowed significant progress in BMT [12-14]. The ability to select HLA-compatible siblings as donors for BMT was one of the major achievements that made it possible to reduce the risk of transplant rejection and GVHD development. This ultimately led to the success of allogeneic BMT in humans.

During the 1950-1960s, BMT technology was upgraded, supportive therapy improved, which created the prerequisites for the first successful BMT in humans. In 1963 in Paris, Mathe et al. reported the successful engraftment of allogeneic bone marrow [15]. The patient had been living for 2 years with the manifestations of chronic GVHD, before he committed suicide [16].

In 1965, Mathé et al. described long-term bone marrow engraftment from patient's brother, demonstrating chimerism, tolerance, and anti-leukemic effect of the transplant. Although the transplantation was successful, the patient suffered from GVHD and died within 20 months of encephalitis caused by herpes virus [17].

In 1968 in Minneapolis, Gatti and Good et al. reported a successful BMT in a child with a severe combined immunodeficiency syndrome from a sibling [18]. It was believed that the donor and the recipient were identical in the HLA system. However, the following HLA typing showed that the patient and donor differed in one locus. A bit later, Bach et al., as well as de Koning and van Bekkum, inform colleagues about two similar successful transplantations [19, 20]. The information that all three patients were alive was published 25 years later [21].

In 1970, Bortin summarized the results of 203 transplantations that were performed between 1958 and 1968. Only 3 patients remained alive at the time of publication of the article [22]. The main causes of death were transplant rejection, GVHD and a relapse of the disease. After these disappointing results, the number of BMT in the world have significantly decreased. In spite of this, Thomas et al. continued BMT series using HLA-compliant siblings as donors for patients with a terminal stage of leukemia and aplastic anemia. All transplantations were performed after the usual therapy was not successful [23, 24].

In 1975, Thomas et al. published BMT results in 37 patients with aplastic anemia and 73 with leukemia. Transplant engraftment was successful in some patients with aplastic anemia. There was also observed engraftment with the achievement of remission in several patients with leukemia [25].

In 1977, Thomas et al. reported the results of 100 BMT from HLA-compatible siblings in patients with acute leukemia, who received chemotherapy and total body irradiation before transplantation. At the time of the report, 17 out of 100 patients had lived from 1 to 3 years after transplantation [26, 27]. It is known that 8 out of these 17 patients were still alive 23 years later [28].

Survival without signs of the disease has shown that some patients with acute leukemia can be cured by BMT. Nevertheless, in the 1970s, evaluating the role of BMT in the treatment of leukemia was difficult. After all, almost all patients received BMT at the terminal stages of the disease after the failure of conventional therapy. The success of BMT in some patients at later stages of the disease has allowed to consider the possi-

bility of its application before the terminal stage. At the end of the 1970s, transplantation at leukemia in the first remission or with the first signs of relapse significantly improved overall survival [29, 30]. Among the first 19 patients with acute myeloid leukemia who received BMT in the first remission, 8 were alive and healthy in 2000. By that time, they had lived from 19 to 21 years after BMT [28].

In the 1980s and 1990s, many of such observations quickly led to the use of HSCT in the early stages of malignant diseases, which have a high probability of relapse after conventional therapy. BMT in the early stages of non-malignant diseases also had a positive effect on the results of treatment. Transplantation at these diseases, except for severe diseases of the immune system, began with patients who suffered from aplastic anemia [24, 31]. In the first patients, survival was very low. Negative role was played by numerous transfusions of blood components and other methods of treatment that were applied to BMT. The results have improved significantly when transplantations began to be carried out in the early stages of the disease [32]. Subsequently, BMTs were successfully used for thalassemia and sickle cell anemia [33-35].

In the early 1970s, the importance of HLA compatibility for a successful BMT was recognized. By this time, only siblings were used as donors, which limited the use of BMT in cases where there was no histocompatible related donor. The use of transplants from unrelated HLA-compatible donors began to be discussed in the early 1970s in the Netherlands when a group of physicians suggested creating a registry of potential volunteer donors in order to facilitate the search for histocompatible unrelated donors for BMT.

In 1974, in the UK, a mother of a young patient who needed BMT established the world's first bone marrow donor registry, the Anthony Nolan Bone Marrow Registry (ANBMR). The registry dealt with the involvement of volunteer donors for unrelated BMTs and creation of a database to quickly search for an HLA compatible donor-recipient pair. The first successful transplantations from unrelated donors were performed in the 1970s [36-38]. In 1986, the ANBMR reported that, with its assistance, 14 BMTs were performed from unrelated donors [36].

In 1987, in the USA, following the example of Europe, the American Red Cross, the Council of Community Blood Centers and the United States Navy founded the National Bone Marrow Donor Registry to promote unrelated donation [36].

Thanks to the initiative of specialists from the United States, the United Kingdom and the Netherlands in 1986, the Bone Marrow Donors Worldwide (BMDW), international bone marrow donor search system was founded in Leiden, the Netherlands. In 1988, experts from these countries organized the Cooperative Marrow Donor Program to develop guidelines and promote unrelated donation around the world. This led to the creation of the World Marrow Donor Association (WMDA) in 1994 [36]. Today, registries of unrelated donors from around the world are collaborating with the WMDA to expand the international exchange of HSCs for transplantations. In 2016, BMDW Database included 76 HSCs donor registries from 53 countries of the world and 53 umbilical cord blood banks from 36 countries. As of May 2018, nearly 31.9 million potential donors and more than 750 samples of cord blood were amounted in the world registries [39].

Historically, the primary and only source of hematopoietic stem cells for transplantation was bone marrow, although it was known about the presence of HSCs in peripheral blood of adult animals and humans [40-43]. Further studies of the properties of hematopoietic cells and achievements in the field of cryobiology, pharmacology (development of colony-stimulating factors), as well as the development of medical technologies in the field of gravitational blood surgery gave the possibility to use peripheral and cord blood as sources of HSCs equally with bone marrow.

The first reports of successful recovery of hemopoiesis after the transplantation of autologous HSCs of peripheral blood were published in the 1980s in the United Kingdom, the United States, Germany, France and Australia. HSCs for these transplantations were collected from peripheral blood by apheresis (without mobilization by colony-stimulating

factors) and used after myeloablative conditioning regimens [44–49]. The development of colony-stimulating factors has created the prerequisites for mobilizing and collecting HSCs from peripheral blood in healthy donors. In the 1990s, successful clinical studies were conducted on the use of allogeneic HSCs of peripheral blood for transplantation [50–54].

Studies conducted in the 1980s by Broxmeyer and Gluckman with co-authors allowed the umbilical cord blood to be considered as a potential source of HSCs for human transplantation. The first transplantation of cord blood HSCs was performed in 1988. A baby with Fanconi anemia had a transplantation of cord blood from her sister, which successfully restored hemopoiesis. The patient was alive and healthy with complete restoration of donor hemopoiesis 15 years later [55–58]. The success of this transplantation contributed to the creation of the first donor bank of the umbilical cord blood in 1991. After that, public banks of the umbilical cord blood were established in many countries of the world [36, 58–61]. The first reports of successful transplantations of cord blood from unrelated donors were published in the second half of the 1990s by Kurtzberg, Wagner, Rubinstein et al. [36, 62–66].

International non-governmental organizations EUROCORD (1996) and NetCord (1998), which interact with BMDA and BMDW [58, 61, 67], were created in order to promote international cooperation in the field of donation, banking, exchange and clinical application of cord blood. Today in the world of donor banks or registries of umbilical cord blood, there are more than 750 thousand samples [39].

The use of HSCs from various sources has led to changes in terminology. Among the hematopoietic stem cell transplantation (HSCT) depending on the source of HSCs, there are bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSCT), and cord blood transplantation (CBT). Currently, in the world, the main source of HSCs for transplantation is peripheral blood (66 %). The following positions are taken by bone marrow (24 %) and cord blood (10 %) [68].

In the course of the development of HSCT, the conditioning regimes were improved to prepare the patient for transplantation. Modern chemotherapeutic regimens made it possible to refuse additional application of total irradiation of the patient's body at a number of diseases [69–72]. The introduction of non-myeloablative conditioning regimen at HSCT allowed to reduce the mortality associated with the high toxicity of high-dose myeloablative regimens, which created the prerequisites for the use of this method of treatment in exhausted and elderly patients [73–75].

Thanks to achievements in immunogenetics, molecular genetic methods of high-resolution HLA typing were introduced into clinical practice. Selection of donor–recipient pairs began to be performed at a higher quality level compared with serum HLA-typing methods, which significantly improved the results of HSCT from unrelated donors [76–82].

Achievements in the field of immunology have contributed to the development of new approaches to the prevention and control of GVHD. In addition to immunosuppressants, T-lymphocyte depletion began to be used to prevent GVHD. The study of the «graft versus leukemia» or «graft

versus tumor» phenomenon allowed the use of intravenous infusion of donor lymphocytes to fight relapse of leukemia or lymphoproliferative diseases after allogeneic HSCT [83–96]. The development of means to overcome the HLA barrier allowed the use of partially compatible donors and started triggering allogeneic HSCT from haploidentical related donors [97–104].

Many years of hard work of many researchers, first of all Thomas et al., has led to the fact that the method of HSCT was recognized throughout the world, and the researcher received the Nobel Prize for his achievements in 1990. In the Nobel lecture, Thomas noted that the timely use of HSCT could significantly improve the results of treatment in patients with malignant and non-malignant diseases of the hematopoietic and immune system, which were previously considered incurable. The maximum effect of transplantation can be obtained when the method is used promptly in the early stages rather than in the later stages of the disease. In particular, 5-year relapse-free survival after HSCT in the first or second remission of acute lymphocytic leukemia (30–60 %), the first remission of acute myeloid leukemia (45–70 %), and the early phase of chronic myeloid leukemia (60–90 %) was significantly higher than at relapse of acute leukemias (10–30 %) and the acceleration or blast crisis of chronic myeloid leukemia (10–30 %). Similar results were obtained in lymphoproliferative diseases (40–60 % vs. 10–30 %), aplastic anemia (80–90 % vs. 50–70 %), thalassemia (85–95 % vs. 60–85 %), immunodeficiencies (90–50 %) and other diseases [105].

A brief historical excursion gives us an idea that HSCT is an innovative, high-tech and multidisciplinary treatment that incorporates many of the latest advances in various fields of medicine, biology, pharmacology, immunogenetics, and medical and laboratory technology. The efforts of several generations of researchers from many countries have changed the role of HSCT from the therapy of despair at the terminal stages of the disease to the priority therapeutic strategy for the treatment of a number of hematological, cancer and non-malignant diseases in the early stages of the disease. From the first BMT in 1957, the total number of transplants in the world is gradually increasing: almost 10,000 in 1985, to 100,000 in 1995 and projected to reach 1 million in 2012 [106].

The infrastructure associated with HSCT is being developed. In 2012, 1,566 transplantation teams operated in 77 countries of the world that performed over 68,000 HSCTs during the year. Autologous HSCT made up 53 %, allogeneic – 47 % (24 % – from unrelated and 23 % – from related donors). The growth of the number of HLA-typed donors in world registries and umbilical cord blood samples led to an increase in the number of allogeneic HSCT from unrelated donors. International transplant exchange was facilitated by professional non-governmental organizations such as WMDA, BMDW and NetCord. Since 2017, WMDA has taken over the functions previously performed by BMDW and NetCord. The use of haploidentical donors is increasing. In recent years, in the world, the number of HSCT from haploidentical donors exceeds the number of transplantations of the umbilical cord blood [68, 106, 107].

## CONCLUSION

***An analysis of scientific papers suggests that over a relatively short historical period, HSCT has gone from experimental animal studies to clinical application in humans. The success of clinical use depended on achievements in many related fields of science and technology. Studies in immunogenetics allowed formulating the requirements for the histocompatibility of the donor and the recipient. Discoveries in pharmacology have made it possible to create effective anticancer chemotherapeutic and immunosuppressive drugs, develop colony-stimulating factors and new broad-spectrum antibiotics, antiviral, antifungal and other therapeutic agents. The development of transfusiology and methods of gravitational surgery of the blood allowed to obtain HSCs from peripheral blood by a non-invasive apheresis method and provide adequate replacement therapy with blood components (especially platelet concentrate). Studies in cryobiology have allowed cryopreservation of HSCs to be maintained and their long-term storage at low temperatures prior to transplantation. The introduction of clean room technology enabled the creation of aseptic blocks to effectively prevent infections. Creation of registries of voluntary HLA-typed donors of HSCs and donor cord blood banks and registries in many countries of the world stimulates to further development of international cooperation on the search and exchange of histocompatible donor materials for allogeneic HSCT from unrelated donors.***

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