Life flows because of you...

The report on the transfusion activity in Slovenia 2015 - 2016

A special publication on the 25th jubilee of the Slovenia Donor – the registry of the unrelated HSC donors

SLOVENIJA DONOR

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SLOVENIAN BLOOD DONATION AND TRANSFUSION SERVICE ID CARD

2 million inhabitants ***62,000 blood donors per year*** **3 % of the population donate blood**

31 blood donors per 1,000 inhabitants *100 % voluntary, non-remunerated and anonymous blood donors*

370 mobile blood donor sessions **10 % of new blood donors per year**

1150 blood donor sessions *13 % of rejected blood donors per year*

Blood donors per gender

60 %
male

40 %
female

Frequency of blood donation per year

60 % - - - → blood donors donate blood **1x** year

28 % - - - → blood donors donate blood **2x** year

10 % - - - → blood donors donate blood **3x** year

2 % - - - → blood donors donate blood **4x** year

THE TRANSFUSION SERVICE COLLECTS APPROXIMATELY 90,000 BLOOD UNITS ANNUALLY:

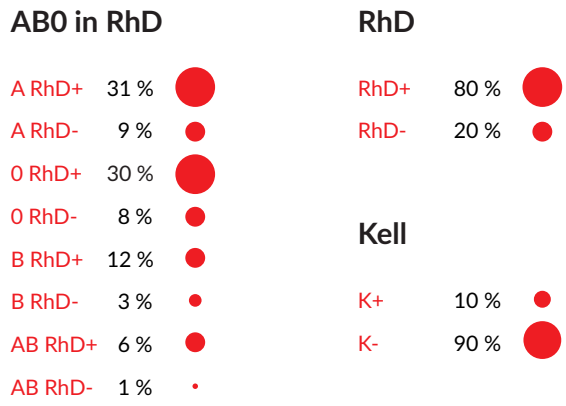
95 % of whole blood:

43 whole blood units per 1,000 inhabitants
66 % are performed by BTC Ljubljana with associated centers
24 % is performed by TMC Maribor with its units
10 % is done by TC Celje
45 % of the whole blood is collected on the mobile blood donor sessions
55 % of the whole blood is collected in transfusion facilities (fixed sites)

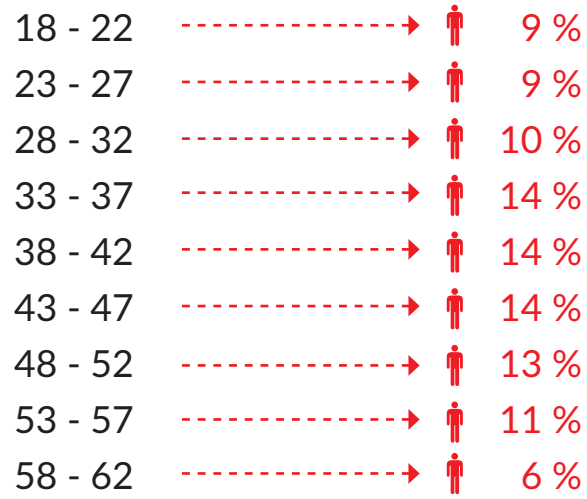
5 % apheresis blood collecting:

2.2 apheresis collections per 1,000 inhabitants
98 % of apheresis collections is carried out by BTC Ljubljana

Distribution of blood donors by blood type



Age distribution of blood donors



We prepare

200.000
blood components

We provide

More than 1.5 million
diagnostic services

4.000
therapeutic services

(autotransfusion, therapeutic whole blood, collection and storage of HSC and other procedures)

01 AB

INTRODUCTION

THE TRANSFUSION SERVICE IN SLOVENIA CONSISTS OF ORGANIZATIONAL AND FINANCIALLY SEPARATE INSTITUTIONS:

The Blood Transfusion Centre of Slovenia in Ljubljana and associated Blood Transfusion Units in Novo mesto, Trbovlje, Slovenj Gradec, Izola, Nova Gorica and Jesenice

Transfusion Medicine Centre at the Maribor University Clinical Centre with Blood Transfusion Units in Ptuj and Murska Sobota

Transfusion Centre at Celje General Hospital

All institutions with associated centres and units have established **a quality management system** and obtained the ISO 9001 certificate, and their main task is to provide patients with adequate, high quality and safe blood as well as blood products.

The basic guideline of transfusion medicine **is safe, adequate and quality blood.** As part of the medical profession, the transfusion service deals with three very different, but closely linked and intertwined assemblies: blood supply, laboratory testing, and treatment with blood products and cells. All blood transfusion centres/units carry out blood collection activities in transfusion facilities and on mobile sessions. The testing of blood and processing into components is performed at the Blood Transfusion Center in Ljubljana (BTC), Transfusion Medicine Centre at the Maribor University Clinical Centre (TMC) and the Blood Transfusion Centre at Celje General Hospital (TC). A specific part of blood testing (NAT) is performed only at BTC. The processed blood is returned to the centers/units according to the needs and plans for the supply of hospitals in their area.
Within the BTC there is a national register of unrelated donors of the hematopoietic stem cells, Slovenia Donor (SD). All blood transfusion centres/units sign up donors and participate in the SD enlargement. The SD register celebrates its 25th anniversary this year, and this year's report focuses on this jubilee.

The Slovenia Donor register celebrates its 25th anniversary this year, which is why this year's report focuses on this jubilee.

MANAGING IN 25 YEARS OF SLOVENIA DONOR

We are proud that within the framework of the Blood Transfusion Centre of Slovenia, the register of unrelated donors of HSCs - Slovenia Donor has been operating for 25 years. For this we must first thank our predecessors who had the vision and the power to keep up the pace with the big and developed countries and set up the register and enable it to operate.

Their perseverance and energy are inherited by the next generation, which upgrades the registry. With 20,000 potential donors this year, Slovenia Donor equals to a group of medium-sized European registers, which increases its reputation and influence in the international arena. The increase in the registry for 3,000 donors in the last year is the result of a successful "Put yourself on the list" campaign. We would like to thank the Slovene Association of Patients with Lymphoma and Leukemia who initiated the campaign for their excellent cooperation.

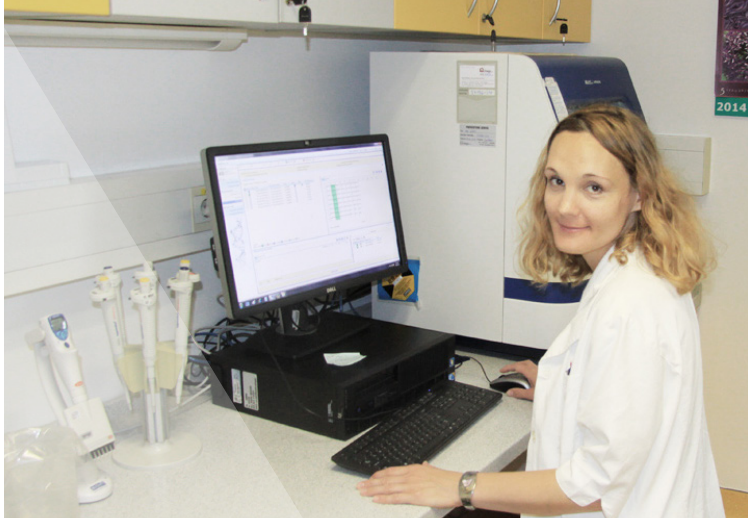
This is great news especially for patients who require hematopoietic stem cell transplantation, as a more extensive registry increases the chance of finding the right donor for the patient.

At this 25th jubilee and an enviable success, we congratulate all those who contributed to the establishment of the register and to those who continue their work. We would also like to thank the participants in the national program for the treatment with HSCs. On behalf of patients, we would like to thank the donors who have already donated hematopietic stem cells and to everyone signed up in the register.

Head of the Slovenia Donor Registry
Blanka Vidan - Jeras, PhD, MPharm., spec.

Medical Director of the
Blood Transfusion Centre of Slovenia
Polonca Mali, M.D., spec.

Managing Director of the Blood Transfusion Centre
Danijel Starman, PhD, BA in Econ.




PREDSTAVLJAJ SI, DA NE
BI BILO NIKOGAR, KO BI
TREBOVAL POMOČ.

02

"If you were to have a look at the receiving procedure, you might say: it's quite simple, you are lying there and a red liquid is slowly running into your vein. It's as if you have been given blood. But actually, you have been given a life."

MILENA

HSCs RECIPIENT

HOW AND WHY IT STARTED

Jože Pretnar,M.D., Specialist of internal medicine and specialist of hematology, Department of Hematology, University Medical Centre Ljubljana

Professor Thomas started with the first bone marrow transplant (BMT) in patients with advanced leukemia in Seattle in the 1950s. In 1960, professor Mathe in Paris carried out BMT in several patients who were radiated in the wake of the nuclear reactor accident in Vinča near Belgrade. The wave of enthusiasm over the new method of treatment quickly reached Slovenia. Thus, the first BMT were carried out in Maribor, Slovenj Gradec, Brežice and Jesenice. Some of these transplants were also described in the Medical Journal. Due to the immunological reasons, most patients experienced complications because of the lack of knowledge of the tissue antigens, namely human leukocytic antigens (HLA), and this method of treatment died out. Its re-launch was possible after the discovery of the HLA system in the 1950s.

In the former common state, the modern method of HSCT was initiated in 1983 in Zagreb. The establishment of a transplant unit was associated with the launch of the nuclear power plant in Krško. The efforts of the then head of the hematology department, professor Bohinjec, were unsuccessful at establishing the program in Ljubljana. The doctrine of transplantation at the time required treatment in "sterile tents", which was associated with extraordinary costs. In 1983, I was introduced to professor Prentice, who successfully performed transplants in regular single-bed rooms with a reverse insulation system similar to that in operating rooms. Due to the proliferation of indications, it has been clear after several years that having only the Zagreb Centre for the whole country will not suffice, so we started reviving the idea of establishing a unit for HSCT at the hematology department in Ljubljana. We started the preparations in 1985. To establish the unit and implement the program, it was necessary to overcome numerous administrative, personnel, spatial and financial obstacles.
Thanks to the sacrifice of all employees in the program from the hematology department of Internal (Pretnar and Černelč with colleagues) and Pediatric Clinic (Anžič and Benedik with colleagues), the Blood Transfusion Centre (BTC), the Institute of Oncology (Habič and Zwitter and co-workers) and the institutes of the Faculty of Medicine and with the help of colleagues from the Rebro Clinical Centre in Zagreb and the Royal Free Hospital in London, we collected and froze the first bone marrow in December 1988 and then carried out the first autologous HSCT in January 1989. At the same time, preparations for the HSCT were necessary to develop a number of other activities, such as whole - body radiation, radiation of blood products and typing of patients and bone marrow donors. This part of the program was carried out by professor Bohinjec and colleagues at the Tissue Typing Centre at BTC.

We collected and froze the first bone marrow in December 1988 and then carried out the first autologous HSCT in January 1989.

Similar to other European countries, due to the small size of families, it was often impossible to find an appropriate related donor in Slovenia. In 1974, the UK's register of unrelated donors - Anthony Nolan, was established. Later on, similar registries were established in a number of other countries, thus enabling the treatment of BMT with many patients who otherwise would not have these options. Patients who did not have the appropriate related donor were sent to unrelated BMTs abroad, especially to the United Kingdom.

Only about 25% of patients requiring transplantation could be treated with related HSCT. In addition, the unrelated HSCT procedure abroad was very time-consuming and expensive, so we decided that such a program should be implemented in Slovenia as well. In order to implement the unrelated HSCT program, it was necessary to establish a register of Slovenian donors and to obtain the permission of the European Society for Blood and Marrow Transplantation (EBMT). The Slovenian register of voluntary unrelated bone marrow donors Slovenia Donor (SD) was founded by professor Bohinjec in 1991 within the framework of the Tissue Typing Centre. In the register, only a few hundred patients were initially involved, and their numbers increased substantially after the action of the renowned artist Irena Grafenauer, who required a donor. The first bone marrow removal for an unrelated recipient abroad was carried out in 1995 and the first unrelated HSCT for the Slovene patient with the donor from abroad was carried out in 2002, when we obtained the EBMT license.

Today more than 19,000 donors are registered in the SD Register, all of which are included in more than 30,000,000 unrelated donors in the Bone Marrow Donors Worldwide (BMDW) registry. From the beginning of the implementation of the unrelated HSCT program, 227 patients were treated by the end of 2016. For some patients, the hematopoietic stem cells (HSC) are obtained from our registry, while others are derived from foreign, most often German and American registry. Also, 6 Slovenian donors yearly donate HSCs for patients living abroad.

From the beginning of the implementation of the unrelated HSCT program, 227 patients were treated by the end of 2016.


03
"Upon signing up at the register I was determined to also be a donor should the need arise. Namely, the whole point of signing up is to help someone in need. If we are healthy it is our duty to help."
VESNA
HSCs DONOR

SLOVENIA DONOR BACK THEN, TODAY AND TOMORROW

Dr. Blanka Vidan - Jeras, PhD, MPharm. spec.,
Head of the Tissue Typing Center, Head of the Slovenia Donor Register, Blood Transfusion Center of Slovenia.

Incompatibility in tissue antigens - barrier to the transplantation of hematopoietic stem cells

In the 1970s, hematopoietic stem cells (HSC) transplantation became an increasingly successful way of treating leukemia and related malignant blood diseases. The desire to help an individual with the donation of HSC is unfortunately not always sufficient for successful transplantation. A precondition for this is that there is no incompatibility between the recipient and the donor in tissue antigens, namely human leukocyte antigens (HLA). Today we know that each individual carries the latter on most of cells, but for historical reasons, the term "leukocyte antigens" is preserved, since they were first discovered on leukocytes. A collection of tissue antigens or HLA genetic variants of each person is called the HLA type. Two random individuals who are not related are very rarely of the same HLA type, therefore they are not likely to be histocompatible. However, we can expect that persons of the same race and (even more) ethnic groups will be more similar to each other than persons of different races or ethnic groups.

With the help of the "Put yourself on the list" campaign, the number of registered donors at SD has risen to over 19,000.

The first successful transplant of HSCs from an unrelated donor in the world

Despite the low likelihood of success, it is not surprising that in 1973, as the solution for saving the life of the four-year-old Simon Bostic, whose only chance of survival was the HSC transplant, they came up with an idea that the donor would also be looked for among non-relatives. Doctors told the Londoner parents that none of the family members were suitable HSC donor and that their son could only survive through the transplantation of HSC. Simon's mother in desperation sought help from the media to encourage potential donors to sign up. Over the course of two months, thousands of people have applied to get tested and determine whether they are compatible with Simon. An unbelievable thing happened - one of them was indeed compatible, and in 1973, in England, Simon had the first successful HSC transplant from an unrelated donor in the world. In 2013, he celebrated the 40th anniversary of this event.

Searching for a histocompatible donor – the reason for the creation of lists (registers) of donors

As a result of Simon's experience, the following year in England the first register of unrelated donors of HSCs, The Anthony Nolan Bone Marrow Donors was established by the mother of the second patient, Anthony. Today, this register counts 620,885 donors and annually helps find a histocompatible donor for 2,000 British patients. Gradually, similar registers began to emerge elsewhere in the world. Thus, 25 years ago, the world's largest register, the American Be the Match, was established. In order to enable the search for a donor for each patient in all registers, thereby increasing the possibility of finding him/her at the initiative of Professor Jon van Rood from Leiden, the Netherlands, in 1988, the individual registers were joined into the world register, The Bone Marrow Donors Worldwide (BMDW). The latter still has its headquarters in Leiden, bringing together more than 30 million adult donors from around the world and 700,000 umbilical cord blood units, which eventually proved to be a suitable HSC source for transplantation.

Slovenia Donor

Professor Mateja Bohinjec, together with her colleagues at the Tissue Typing Center (TTC), created conditions for the set up of the Slovenian register of unrelated HSC donors, Slovenia Donor (SD) for several years. For the establishment and development of such a national register, a lot of interdisciplinary cooperation was needed, involving both experts from all departments of the Blood Transfusion Center of Slovenia (BTC) as well as external collaborators, notably from the Clinical Department of Hematology of the University Clinical Center (UCC). Later on, experts from the Hematology Department of the Pediatric Clinic in Ljubljana, the Slovenia Transplant, the transfusion institutions in Maribor and Celje and the blood transfusion centers all over Slovenia have joined. On November 1991, upon request by Dr. Jože Pretnar, the Republic Medical Expert Committee on Ethics approved the establishment and operation of the SD registry. Under the watchful eye of the first medical doctor of the registry, Dr. Urška Lunder, donors began to collect in the registry, with serologically determined HLA antigens in the laboratories of Tissue Typing Center (TTC).

Old yellowish papers testify that the data on HLA types of the first 100 registry donors travelled on a floppy disk to the BMDW on January 31st 1992, making SD visible and recognizable in the world, and our donors were offered not only to Slovenian but also to all other patients.

The SD registry appeared in Slovenian legislation for the first time in 2003 with the Ordinance on the method of operation and conditions for the development of the national program for the transplantation of HSC and the manner in which the registry of unrelated donors of HSC operates. The creation of this as well as of many other invaluable documents prepared for the registry were made possible through the creative assistance of Mrs. Lea Lampret, the long-standing secretary of the TTC. The registry experienced its boom after December 2003, when it was announced to the public that the acknowledged flutist, Irena Grafenauer has leukemia and needs a HSC transplant, where she would, with the genetic characteristics of the population, have the largest chance of finding a histocompatible donor right in the Slovenian register, which at that time had 400 donors. At this turning point, the register's long-time head, professor Matjaž Jeras, played the crucial role, supported by all employees in the TTC and numerous others at the BTC, their number is too large to list here. A special acknowledgement for unconditional support to the SD registry also goes to Dr. Božidar Voljč,MD, the then director of BTC and prim. Irena Bricl, MD,, the than medical director of BTC. By regulation of the financing of the SD by the Ministry of Health, which is still underway through Slovenia Transplant, the conditions for expanding the register were met. The resonance in the media, which, as an avalanche, was triggered by Irena Grafenauer's announcement, resulted in numerous actions (104), through which the register recruited new donors across Slovenia. They were led by a long-term medical supervisor of SD, Mihael Tonejc, MD, MSc.

The operation of the registry would not be possible without computer programs that allow both the maintenance of the registry database and the transfer of HLA types from the TTC database to the SD and to the BMDW.

The first SD computer programs were prepared by Bojan Jurca, MSc and some of them are still in use in an advanced format. Mrs. Cvetka Flajs Cotič, an economist and the organizational coordinator, has given a special note to the SD registry since 2005.

In 2014, the Association of Patients with Blood Diseases awarded her for the outstanding work within the Transplantation of HSC of Unrelated Donors Program. She was also given the praise by the Association of Hematologists of Slovenia for her devoted and selfless work. Along with her, the SD registry is supported through work of Primož Poženel, M.D. (medical supervisor of the register), Dr. Sendi Montanič (immunogeneticist and coordinator for searching of the unrelated donors), Sabina Kunilo Jamnik, MA lab. biomed. (immunogenetics and bioinformatics), Marjeta Voje Planinšek (commercialist), Dr. Blanka Vidan-Jeras (head of the registry), all employees at TTC and many at BTC and external associates who respond whenever the registry needs them.

Since the establishment of the registry in 1991 to 2012, the number of donors in the SD has grown to reach 16,000 to 17,000 members. This number was maintained until the end of 2016, when the initiative of the Slovene Association of Patients with Lymphoma and Leukemia came just in time. At that time, we initiated together the campaign Put yourself on the list, which requires a lot of enthusiasm and energy from the organizers. We draw it from the desire to provide an optimal donor to as many patients as possible. Also, the sources of inspiration are certainly the numerous Slovenian students and people with good intentions who registered in the Slovenia Donor at the time of its 25th anniversary. Like every year, also this year, on behalf of all patients, I would like to thank those who are willing to donate, and especially those who have donated a part of themselves to help others regain life, and I take this opportunity to express my personal respect to them.

THE NUMBER OF HSCS DONORS FROM ABROAD FOR SLOVENIAN PATIENTS

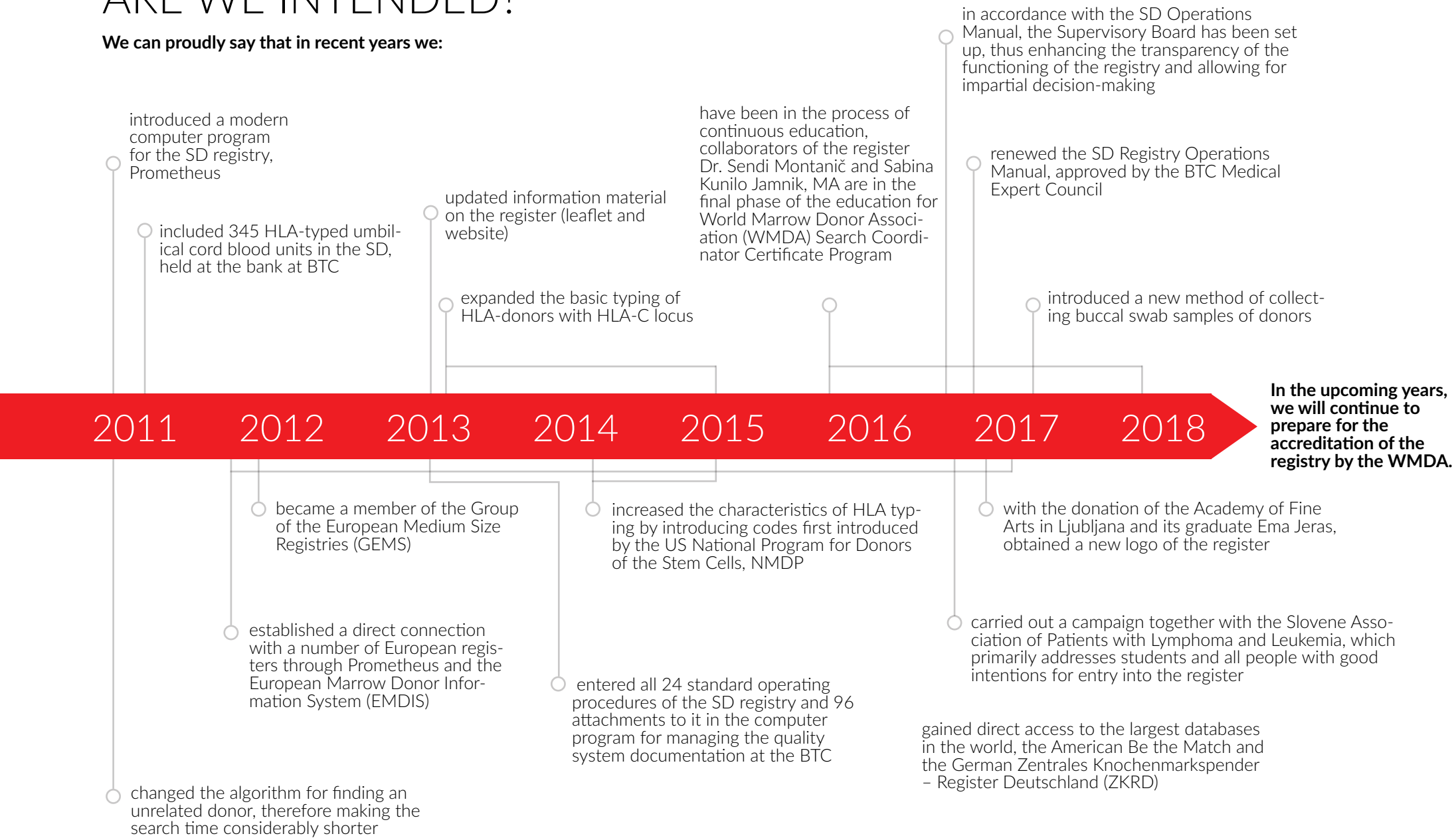
2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
3	4	8	5	7	10	11	14	15	19	23	27	22	23	27

THE NUMBER OF FOREIGN DONORS OF UMBILICAL CORD BLOOD UNITS FOR SLOVENIAN PATIENTS

2011	2012	2013
3	2	2

WHERE ARE WE TODAY AND WHERE ARE WE INTENDED?

We can proudly say that in recent years we:




04

HISTOCOMPATIBILITY TESTING IN HEMATO-POIETIC STEM CELL TRANSPLANTATION

Blanka Vidan - Jeras, PhD, MPharm. spec,
Head of the Tissue Typing Center, Blood Transfusion Centre of Slovenia, Ljubljana

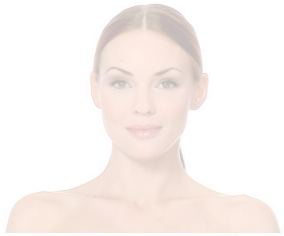
In 2003, the Minister of Health authorized Tissue Typing Center (TTC) at the Blood Transfusion Centre in Ljubljana (BTC) for histocompatibility testing in organ and tissue transplantation in the Republic of Slovenia. The years of TTC experience go back to 1969 when professor Mateja Bohinjec founded its first laboratory. The methods used then were exclusively serologic, which meant that they allowed determination of antigens expressed on the surfaces of the lymphocytes.

Each person carries **a particular human leukocyte antigen (HLA)** type on cellular surfaces, consisting of a variety of HLA antigens such as HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ and HLA-DP. Genetic records for them are located on loci, separate places on the chromosome. When we observe HLA types of larger groups of people, e.g. thousands of donors from the Slovenia Donor registry (SD), we can find many genetic variants (alleles) on each of the HLA loci. On the HLA-B locus, for example, to date, 4,859 alleles have been confirmed, and all of the genetic variants of the HLA together are now at more than 17,000 which makes the HLA region one of the most diverse parts of the human genome.

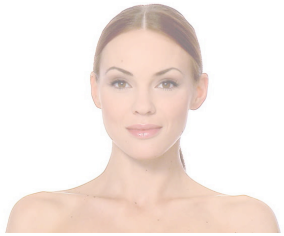
The first donors of the SD, registered in 1992, were **serologically typed.** With the same method we acquired the HLA types of patients and their donors, which made it possible to determine histocompatibility between them before the transplantation of hematopoietic stem cells (HSC). Serological typing of HLA gave **a low-resolution level** result, so the HLA types could be roughly defined. In this case, many details remained unknown which was of decisive importance in the transplantation of the HSC. To overcome this deficiency, functional tests were performed at the laboratory under the supervision of professor Matjaž Jeras. It included mixed lymphocyte cultures and the determination of precursors of cytotoxic lymphocytes T. The key development-research milestone was the onset of **HLA typing at the level of deoxyribonucleic acid (DNA) in 1992,** which was introduced in collaboration with professor Katja Breskvar and professor Vita Dolžan. In a laboratory led by Dr. Vidan – Jeras (with co-workers Irena Kemperle and Natalia Ambrož), we initially carried out HLA typing at a low-resolution level, which gave similar results to serological typing, but it allowed also the determination of genetic records for antigens that are poorly (or not at all) expressed on cell surfaces. Such are, for example, many HLA-C and HLA-DQ loci antigens.

However, with the advancement of the typing methods, the HLA type could be determined at the **medium** and afterwards at **high resolution levels.** The latter was mainly facilitated by the sequencing of the DNA using the Sanger method, thus obtaining sufficiently accurate information on HLA-type of patients and possible donors before HSC transplantation. Therefore functional tests were no longer necessary. A few years ago, at TTC laboratories, we (S. Montanič, I. Kemperle and S. Kunilo Jamnik) started a very demanding internal development and research project of HLA typing with a new generation sequencing. We expect that the method will be introduced into routine work in 2018, and thus we will catch up with modern laboratories in determining histocompatibility.

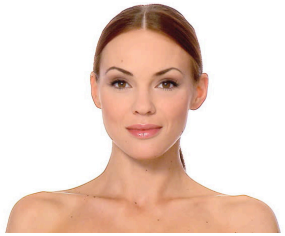
A great step towards improving the quality of work was done by TTC in 2000 when it successfully passed the assessment of the European Federation for Immunogenetics (EFI) and obtained a certificate to perform its work in accordance with the standards of the organization. The EFI accreditation, which is also required by the World Marrow Donor Association for laboratories participating in HSC donor registries, is still maintained today.
From the early years to the present in immunogenetics, which combines immunology and genetic, studies focusing on the diversity of HLA antigens and alleles among individuals, ethnic groups, nationalities and races are the red thread of the profession. The Tissue Typing Center in Ljubljana is no exception. One of the key reasons for this kind of research is the desire and the need for new knowledge about the influence of histocompatibility between the donor and the recipient of an organ, tissue or cells on the outcome of the transplantation.



Low resolution level



Medium resolution level



High resolution level

Professor, dr. Samo Zver, who persistently helps life to keep flowing

TREATMENT WITH HSCT IN SLOVENIA WITH THE EMPHASIS ON THE UNRELATED DONORS

Professor, dr. Samo Zver, M.D., specialist of internal medicine / specialist of hematology, Clinical Department of Hematology, Head of Hematopoietic Stem Cells Transplantation Unit, University Clinical Center Ljubljana

Hematopoietic stem cells (HSC) suitable for hematopoietic stem cells transplantation (HSCT) are found in the bone marrow, peripheral blood, and cordial blood in the newborn child. Consequentially the term - "bone marrow transplantation" – has become unfit and too narrow. Therefore, today we are talking about transplantation of the hematopoietic stem cells (HSCT), thus capturing all HSC sources: peripheral blood, bone marrow and cord blood.

With HSCT we may cure or at least for a number of years in a way "heal" many malignant and non-malignant diseases. The typical features of HSC which allow treatment with HSCT are:

- regenerative ability,
- the ability to differentiate into highly specific blood cells,
- the ability to find a path to the recipient's bone marrow through the blood circulation, where it retains, survives, and subsequently divides or regenerates,
- ability to maintain vitality even after a long period of storage at very low temperatures (cryopreservation).

In 2015 more than 42,000 patients were treated with HSCT in Europe, of which more than 17,000 were allogeneic (related and unrelated) and 25,000 with autologous HSCT. Their number grows steeply. First among the indications for allogeneic HSCT are acute leukemias, and for autologous, the lymphoproliferative, included clonal plasma cell dyscrasias. In adult patients around 130 - 140 treatments with autologous (approximately 85) and allogeneic (approximately 45) HSCTs are performed annually in Slovenia. Here we also include the treatment of children with HSCT, which is about 10 cases per year. If we take into account Slovenian needs, we are self-sufficient in treatment. In 2016, 134 patients - 126 adults and 8 children were treated with HSCT. In total, 89 autologous and 45 allogeneic HSCTs were performed, of which 27 with unrelated donors.

Distribution of HSCT and the basic principles of treatment

If we take into account the relationship between the donor and the recipient, the HSCT may be syngeneic, autologous or allogenic. In the event that the donor is an identical twin, we are talking about a **syngeneic HSCT.** Its characteristic is that due to complete histocompatibility there is no graft-versus-host disease (GvHD), since it is a kind of **autologous HSCT.** In autologous HSCT, the HSC source is the patient himself, and the main problem is the relapse of the underlying blood disease. The main reason for this is the absence of tumor / leukemia (GVT / GVL) graft reactions and, to a lesser extent, the fact that within the autologous transplant there are often residual tumor / leukemia cells. For an **allogeneic HSCT**, the patient must have suitable donor, which we are looking for on the basis of histocompatibility or in another word similarity in genes for human leukocyte antigens (HLA).

Due to the extremely high polymorphism of the HLA genetic region - more than 17,000 alleles are known - we are able to find a suitable donor for approximately 80% of patients which we want to treat in with transplantation. Thus, we classify HLA Class I alleles (HLA-A, -B and -C) and Class II (HLA-DQ and -DR). We mostly tolerate incompatibility in one HLA allele (9/10), but also in two (8/10) if the graft source is the cord blood. The latter contains immunologically unexplained, naive lymphatic cells with immune tolerance greater than the one of an adult person. The most immunogenic are the HLA-A, -B and -DR antigens, slightly less HLA-C, -DQ and -DPw. A completely HLA compatible, related or unrelated donor is found in about 50% of cases. With increasing discrepancy in HLA alleles, there is a greater likelihood of the occurrence of acute and chronic GvHD, which affects the survival of treated patients.

In addition to the HLA system, there are many other antigenic systems that we do not yet know the true meaning of, for example, minor antigens, therefore we do not carry out typing at this level. If the HSC donor is unrelated, in comparison with the related donor the occurrence of the acute and chronic GvHD in the recipient is higher, and consequently the mortality after treatment with HSCT is also higher. With years and increasingly effective immunosuppressive drugs, the difference is becoming less important. There is also a greater likelihood that the graft that is not fully HLA compatible, will not work in the recipient's bone marrow (graft failure). This is seen in up to 10% of cases, and the probability increases in proportion to the disparity of HLA antigens. To date, around 30 million of unrelated donors of HSC have been typed in many national registries, of which over 19,000 in Slovenia. The solid probability that the appropriate HSC donor will be found in the registry exists in the case when about 1% of the population is typed in the HLA register, which in case of Slovenia means at least 20,000 people.

In recent years, the increasingly commonly used method of treatment with allogeneic HSC is **haploidentical HSCT.** The donors in this treatment modality are most often parents, but also other relatives, who match with the patient in half or in one HLA haplotype. This type of HSCT is a good choice especially due to the fact that the donor is, as a rule, very quickly found and the typing procedures are quick. The latter is important if the patient is in a hurry. Because of the significant level of the HLA mismatch, in this way are treated, younger patients who do not have a more convenient HSC donor and have a poor prognosis of blood disease without HSCT. Nowadays, treatment is safer due to new approaches to preparing the patient for the HSCT and more effective ways of immunosuppressive treatment.

In 2016, 134 patients - 126 adults and 8 children were treated with HSCT. In total, 89 autologous and 45 allogeneic HSCTs were performed, of which 27 with unrelated donors.

06

Boštjan Kljun demonstrates the method of collecting buccal swab sample

SEARCH AND DONOR SELECTION PROCESS FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Dr. Sendi Montanič, PhD., BA Univ. biochem., Head of the Histocompatibility Testing Unit at the Tissue Typing Center, Search coordinator at the Slovenia Donor registry, Blood Transfusion Centre of Slovenia, Ljubljana

Incompatibility in human leukocyte antigens (HLA) is one of the main reasons why many patients do not have a suitable related or unrelated donor of the hematopoietic stem cells (HSCs) and has a decisive influence on the occurrence of graft-versus-host disease (GvHD) and the survival of the patient after transplantation. In the Slovenian transplantation program and elsewhere in the world, the search for a suitable donor starts within a patient's family. The ideal donor (with regard to HLA) is identical monozygotic twin, followed by the patient's **HLA identical sibling,** and the HLA compatible unrelated donor. When HLA types of parents and descendants are known, we can define family inheritance pattern by identifying the HLA genes inherited by the patient from both mother and father. According to Mendel's inheritance laws, we can theoretically expect the identical siblings in 25% of families with two children. When a sufficient number of family members are available to clearly understand the pattern of inheritance of HLA alleles from parents to descendants, the family members can be typed at low-resolution level. If the pattern of inheritance cannot be determined, the patient and the donor are typed as unrelated.

With a study we carried out in 2012, we ought to determine the percentage of patients who found a histocompatible related donor in practice. We analyzed 744 families that were treated in the Tissue Typing Center between 1996 and 2011. We found the highest percentage of related donors for our patients in the year 1998 (43.6%). The decline in the average number of children within Slovenian families has a significant impact on the possibility of finding a related donor. As a reflection of the events in Western Europe a further decline in the number of children in Slovenian families can be expected and it is likely that the transplantation of HSC of unrelated donors will be increasingly important. When there is no suitable donor among family members, we expand the search for the donor in registries of unrelated HSC donors.

With the unrelated HSC donor transplant the histocompatibility testing between the patient and the donor is wider and deeper than that of related couples, as it considers 5 HLA loci at high level of typing resolution. Since each individual has 2 alleles of each locus, 10 alleles are taken into account (two A + two B + two C + two DR + two DQ). Recent studies suggest that T-cell epitopes of HLA-DP antigens are also important, as mismatches in DP epitopes increase the risk of GvHD after HSC transplantation. In recent years, we provide our patients with HLA-DP epitopes matched donors.

In Slovenia Donor (SD) registry, we search for an **unrelated donor** for Slovene patients, always starting with Slovenian donors using the Prometheus computer program, and we continue the search in Bone Marrow Donors Worldwide (BMDW) registry. Finding the right donor among more than 30 million donors registered in BMDW can be fast or very complicated and time-consuming, but it is always supported by a computer program provided by BMDW and later by individual national registries where potential donors are found. For Slovene patients with HLA types, which often occur in populations of European origin, the search for the donor is usually very fast. Complications occur for patients with rare HLA types. Most Slovene donors (approximately 40%) have donated for Slovenian patients also due to the characteristic HLA types that are observed in the Slovenian population, so our national registry has a special significance.

The speed at which a donor can be found for a particular patient also depends on the level of resolution of the donor typing in the registry. BMDW donors from different national registries have HLA types defined at different levels of typing resolution, some have high, some low, and some intermediate level. The lower the level of typing resolution is, the more time we spend on additional HLA typings that we order at the registry which the donor is from. For incompletely typed donors, the knowledge of the population genetics of the HLA system is of great help. We must predict which of the potential donors has greater possibility to match patient's HLA type. Computer programs based on population genetic studies are of major assistance here, in particular the computer programs from the American registry "Be the match" which is free of charge for all other registries. When several donors are all fully compatible in HLA alleles with a patient, the final selection also takes into account the infection of the patient and the donor with the cytomegalovirus (CMV), the match in ABO blood groups, the age, gender, weight of the donor, and the number of pregnancies if the donor is female.

Interconnection and close co-operations between registries are of major importance for fast and efficient identification of well-matched stem cell donors, which is in most cases crucial for patient's survival.

07

VANJA

HSCs RECIPIENT

"The feeling that there is a person in this world who can save your life is inexplicably good. I myself have had the immense fortune that the right person decided to become a donor."

THE DONOR AND THE HARVESTING OF HSCS

Primož Poženel, M.D., specialist of transfusion medicine, Medical Head of the Slovenia Donor, Blood Transfusion Center of Slovenia, Ljubljana

The collection of human stem cells (HSCs) in Slovenia was well under way for decades, in a manner that the hematologists collected the bone marrow from the pelvic bone into the collecting bag by using multiple aspirations. The change was made in 1994, when the first collection of HSC with a cell separator was carried out at the Blood Transfusion Center (BTC) in the context of a related HSC transplantation.

In the case of an unrelated donor, HSC were first collected by apheresis in 2004.

It is a safe and proven procedure in which stem cells are collected from the peripheral blood of a healthy stimulated donor. The donor receives growth factor filgrastim (G-CSF) for 5 days, which causes intense release of both immune and bone marrow stem cells. The cellular separator, which has a built-in centrifuge, excludes mononuclear cells according to the principle of elutriation, including HSC. Upon the completion of collection these cells are then accumulated in the collection bag, which is transported in a cooled bag to the recipient – patient.
The cell separation is by far the most common way of collecting HSC. The side effects that may occur with such a method of donation are mainly related to the side effects of growth factor stimulation - there may be joint or muscle pain, headache, fever, diarrhea, etc. In very cases, the problem is so severe that the condition requires doctor's attention. It is mostly a mild or moderate problem that disappears after completing the growth factor stimulation.

So far, there is no evidence (although G-CSF has been in use for more than 20 years) that stimulation with growth factor causes blood cancers or increases the risk of other types of cancers, which means that the established practice of donor preparation is safe.
Safety is a key issue in unrelated donation. The donor and the recipient are in a special relationship: the recipient urgently needs a HSC transplant, and the donor does not need to necessarily donate. Even more, the immediate benefit for health - if we do not count the personal satisfaction with helping a human being – is not there. It is therefore extremely important that the donor, already at the time of enrolment in the register and, of course, at later stages of the selection process, is fully aware of what the HSC donation is, what risks it involves and why the patient needs the HSC transplantation. Only on the basis of the complete information can he sign a solid consent for donation. Namely, the patient's fate becomes very uncertain, if the (poorly informed) donor in the late stage of preparation for donation (e.g., after the examining at the hematologist's, or even worse, during the G-CSF stimulation), cancels cooperation.

When inscribing in the register we check the presence of all possible medical conditions of the donor, which could pose a risk to him during the stimulation and donation process. We must not overlook the possible autoimmune diseases, past cancer related diseases, circulatory diseases, chronic pain, neurological diseases and hereditary diseases, or also the transmission of these, in case of an increased risk for other disease occurrences. Much about the course of potential donation of HSC is shown through a tendency to vasovagal syncope or weakness or fainting with previous blood donations or withdrawals. Family history plays its role, especially in the case of frequent occurrence of blood cancers within the immediate family. Although the majority of blood cancers are due to somatic mutations, in these cases, we must be very careful.

Whenever there is doubt as to whether a potential donor could undergo G-CSF stimulation and apheresis (sometimes also classical deprivation with aspiration of the bone marrow), it is necessary to decide against the entry in the register or against donation to protect his health. The same should be decided when transplantation of a donor's HSCs could pose a risk of disease transmission to the patient. Since the donor is thoroughly tested (viral markers, biochemistry, hemogram) and examined (specialist in transfusion medicine, hematologist) before the start of stimulation, the risk of transmission of the disease is low. In the case of unrelated donation, the balance of safety assurance is shifted towards the donor - "primum nil nocere" ("first, do no harm").
It is precisely for this reason that the unrelated donation is such a delicate area. For a person who has decided to donate his cells to an unknown patient out of altruism an altruism, we must ensure the greatest possible safety of the donation, although we are faced with a number of unknowns: we do not know how the donor will tolerate G-CSF stimulation, how much collection will be needed to ensure the therapeutic dosage of cells, how he will tolerate withdrawal, etc. There is no complete predictability - as in anywhere in medicine or elsewhere - so it is difficult to promise complete safety to the donor despite all previous investigations and extensive history. The issue of donor safety becomes important when we begin to promote HSC donation and promote the entry into the register.

The question arises as to how much information about the risks of HSC donation is enough? A quick and humorous answer would be that just the right amount of information is enough.

However, we are constantly searching for and re-checking how much that means in practice. We must not fall into the idealization of HSC donation in order to increase the inclusion of potential donors in the register and, on the other hand, we also should not catalogue the all-time reported undesirable effects of donation.

First HSCs transplant of a Slovene donor to a Slovene recipient has been performed in 2007.

Clear awareness is needed that the HSC donation is still in the domain of medicine, but it has its own risks that cannot be completely eliminated, and that fundamentally it is still a great humanitarian act that can save the patient's life.

In the last decade, the debate about the age limit for enrolment in the register of unrelated donors is becoming increasingly important. The age criterion in fact determines which grafts will be received by patients. Not in terms of quantity (the dose of CD34 + cells), because in most cases, ensuring a minimum dose of CD34 + cells is not a problem, but in terms of quality - it is known that with age, the lymphoid potential of HSC decreases while the proportion of myeloid-type cells increases. These changes affect the survival of patients who receive an "old" or "young" graft, which has been clearly demonstrated by several clinical studies. We are less aware of the concrete mechanisms by which these changes have impact on the events after the HSC transplantation. They are most likely to be involved in the mechanism of immune control of cancers (GVL - "graft versus leukemia") and / or pathogenesis of graft-versus -host disease (GvHD). The importance of choosing a donor according to age is clearly shown in the average age of HSC donors for Slovene patients – 27 years old in 2017.

The question of the age limit is not only of professional importance, but it also has economic consequences. It influences allocation of funds reserved for future HSC donors testing. Concrete questions are, what is the point of testing a donor who, with his age, is already heavily above the average selected when entering the register, and where the line should be drawn. In any case, the answer is worthy of a thorough debate. Slovenian register Slovenia Donor, with an upper entry age of 45 years is among the more friendly/inclusive registers in the world, and the maximum donation limit is 60 years.

In the future, when the drugs that completely eliminate cancerous blood diseases appear and prevent recurrence, or when it is possible to prepare artificial blood stem cells compatible regarding the system of human leukocyte antigens (HLA), there may be no longer a need for donors of HSC. But until then, they remain an indispensable part of the treatment of the worst forms of blood disorders, and the need for them is constantly increasing.

THE NUMBER OF SD DONORS FOR THE PATIENTS ABROAD

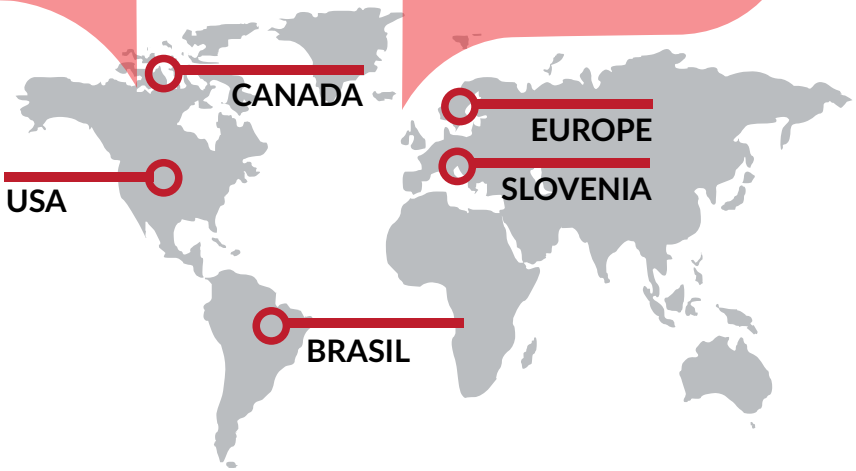
2004	2005	2006	2007	2008	2009	2010	2011	2012	2015	2016
1	2	2	5	3	3	6	2	3	2	5

THE NUMBER OF SD DONORS FOR THE PATIENTS IN SLOVENIA

2007	2008	2009	2010	2011	2013	2014	2015
1	3	4	3	1	2	4	5

The patients were from fifteen European countries, Canada, USA and Brazil. The largest amount of 40% (23) of HSCs of our donors have not traveled as far, as they were received by Slovene patients.

Since 2004 until the end of 2016 the HSCs have been donated by 57 members of the SD registry.



Jani, darovalec KMC:
"Ne vem, zakaj bi nekdo o vpisu v register sploh moral razmišljati. Še posebej, ker je darovanje KMC tako enostavno: usedeš se na stol, kot tolikokrat vsak dan, in daš kri. In s tem rešiš življenje."

Več na **www.dajsenaseznam.si** **#DajSeNaSeznam** **dajsenaseznam**

Vesna, darovalka KMC:
"Ob vpisu v register sem bila trdno odločena, da bom tudi darovalka. Če do tega pride. Smisel vpisa je namreč pomoč nekomu, ki je v stiski. Če smo zdravi, je to naša dolžnost."

Več na **www.dajsenaseznam.si** **#DajSeNaSeznam** **dajsenaseznam**

TOMAŽ

HSCs RECIPIENT

08

"All the people who register are my fathers, my mothers because without all of those registered there would not be a suitable donor for me. And I would not be here today."

THE MEANING OF IMMUNOHEMATOLOGICAL AND MICROBIOLOGICAL TESTS OF THE DONOR AND THE RECIPIENT OF HSCS

Klara Železnik, M.D., specialist of transfusion medicine,
Blood Transfusion Center of Slovenia, Ljubljana

The appropriate choice of a donor of hematopoietic stem cells (HSCs) is crucial for the successful treatment of the patient. Before the HSC transplantation, besides to matching the donor and patient in human leukocyte antigens (HLA), additional laboratory tests are needed. In the immunohematological laboratory, AB0, RhD and Kell blood types (BT) of the patient and the donor are determined. In order to avoid administrative errors, blood group is optimally determined from two separately collected blood samples. To prevent the transmission of infectious agents with HSC product, we also test the donor for the presence of certain blood borne infections. In order to select the appropriate donor and to optimally manage the immunocompromised patient during the peritransplant period, the patient is also tested for the presence of selected infectious markers.

Incompatibilities in AB0 blood group antigens are not a barrier to successful HSC transplantation. In solid organ transplantation, AB0 compatibility may be essential. However, pluripotent and early committed progenitor cells lack AB0 antigens, thus engraftment of HPCs is uninhibited even in the presence of circulating AB0 antibodies. AB0 antigens are expressed on erythrocytes (red blood cells) and platelets (important for blood clotting), which are differentiated from transplanted donor HSCs.
In allogenic transplantation, the relationships between the AB0 types of the donor and recipient fall into four categories: compatible (donor's and recipient's blood is of the same type), incompatible in the major crossmatch (e.g., the patient has BT 0 and the donor is BT A), incompatible in the minor crossmatch (e.g., the patient has BT A, the donor is BT 0) and bidirectionally incompatible (e.g., the patient has BT A, and the donor is BT B). In the case of a major incompatibility, the recipient already has naturally occurring antibodies against donor erythrocyte antigens in his blood, and because of a possible ongoing production of AB0 antibodies by host immune cells extended period of anemia and transfusion dependence can be expected, as these antibodies can prolong red cell engraftment. In a minor incompatibility, the donor lymphocytes form antibodies against the patient's erythrocyte antigens, which can lead to a reduced survival of the remaining patient erythrocytes. In the bidirectional AB0 incompatibility, complications arising from both major and minor AB0-incompatible HSC transplantation can occur in the recipient.

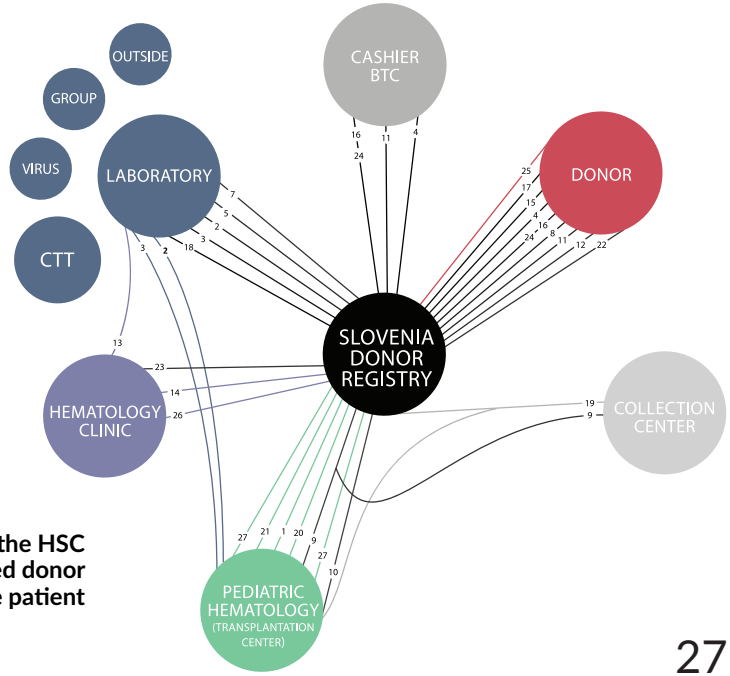
Because of the intensive chemotherapy, patients are anemic and have low platelet counts, and often frequent transfusions of concentrated erythrocytes and platelets are necessary. Some patients have transient need for treatment with transfusions of concentrated granulocytes due to severe infections refractory to standard treatment during a period of severe neutropenia (a low number of neutrophils important for the defense against microorganisms).

Knowing the AB0 blood group of the HSC donor and the patient is important for optimal transfusion support with blood components in the post-transplant period. For each patient after allogenic HSC transplantation, in cooperation with the patient's hematologist, we prepare guidelines for transfusion therapy, which are strictly taken into account in the post-transplant period. By selecting the blood components of the appropriate blood group, we ensure an unaffected maturation of blood cells and prevent hemolysis as much as it is possible.

Various infections can be transmitted to the patient with the HSC product, so the HSC donor and the patient are tested for the presence of viral (HIV, hepatitis B and C, cytomegalovirus), bacterial (Treponema pallidum, which causes syphilis) and parasitic (Toxoplasma gondii, causing toxoplasmosis) infections. In addition to the possibility of transferring infection from the donor to the patient, the infection with cytomegalovirus and Toxoplasma gondii has also been considered important in the patient, because due to severe immunosuppression in the post-transplant period, reactivation of the infection with life threatening complications can occur.

Despite numerous complications that can accompany allogenic HSC transplantation, for many patients transplantation is the only path to recovery.

Treatment of such patient is complex and multidisciplinary, and numerous diagnostic laboratory tests, which are necessary for optimal management, are carried out at the Blood Transfusion Center (BTC).



The coordinating role of the registry with the HSC transplantation of the SD registered donor for the Slovene patient

09

PUT YOURSELF ON THE LIST FOR PATIENTS WITH BLOOD CANCERS

Kristina Modic, the Executive Director of the Slovenian Association of Patients with Lymphoma and Leukemia, L & L

"The feeling that there is a person in the world who can save your life is indescribably good. And I had the immense fortune myself that the right person decided for donation. "

Vanja Žulič, recipient of the hematopoietic stem cells

Slovenia's register of potential donors of the hematopoietic stem cells (HSCs), Slovenia Donor (SD), through all the years of its existence, for many cancer patients - both adults and children – represents the only hope for survival. It links donors of HSC, their recipients, experts in various medical and non-medical professions, committed registry staff, and patient societies that have common goals – the survival of patients with blood diseases and the treatment of severe illnesses. Delivering these goals brings happiness to many patients and their families from all over the world as well as gratitude and the opportunity for a new life, and to healthcare professionals it is an important tool for successful work. Without the SD registry and its membership in Group of European Medium Size Registries (GEMS) and the world registry Bone Marrow Donors Worldwide (BMDW), many lives would be extinguished.

For a number of years, the SD has been responsibly and diligently concerned with keeping the register expanding and to include more and more young and healthy people from Slovenia. The suitability of the donor's HSC for a particular patient is also geographically conditional - a larger domestic register gives more opportunities to find the right donor for patients.
At the initiative of patients, their relatives and patients' organizations at the institutes for transfusion medicine, blood transfusion centers and, in particular, organized group entries in the patient's local environment, numerous large actions took place that significantly contributed to the expansion of the Slovenian register and the awareness of the Slovenian public about blood cancers and the meaning of the SD registry.
The Slovene Association of Patients with Lymphoma and Leukemia, L & L, has in the past organized (or joined the organization) of quite a few group entries in the register. This spring, together with the Blood Transfusion Center in Ljubljana (BTC), we launched a national campaign PUT YOURSELF ON THE LIST. It is a loud call that directs the Slovenian public towards signing up among potential unrelated HSC donors. The project has several important goals, namely: expanding the register of potential donors SD; breaking taboos and beliefs that the donation of the hematopoietic stem cells is terrible and very painful; to make people aware of the simplicity and security of the HSC donation process, which has progressed in accordance with the times; to inform the public about diseases treated with HSC transplantation; to ensure the long-term growth of the register and to encourage altruism among younger generations.
Since mid-April to the end of November 2017, the L & L and BTC have carried out group entries at the Slovenian faculties. Through calls, social networks, student institutions, various companies and media contributions we achieved an extremely ambitious goal - approximately 3,000 new donors for the SD register. This goal has been achieved smoothly thanks to the members of the L & L Association and SD employees who, with the help of student volunteers and with the strong support of the Student Organization of the University of Ljubljana, quickly and accordingly adjusted to the situation in the field and successfully pursued the campaign all the way towards the finish line.
In Styria, for several years – and even more so during the campaign Put yourself on the list – there operates a project called "Epruvetka" (test tube), which fulfills its mission also with the entries of students of the Maribor faculties into the SD register. The efforts, courage and the enthusiasm of all those involved have contributed to successful campaigns and to the recognizability of the topic in public.
On the occasion of the high jubilee of the SD registry, on behalf of the patients with blood cancer, we would like to give our heartfelt thanks to all the employees of the registry and BTC, who for many years have been responsible for the smooth functioning of the registry and its growth, thus significantly contributing to the survival of patients. Also, a huge thank you to all HSC donors who have already had the chance to donate cells and have decided for this humane step without thinking. A special thanks to the large family of nearly 20,000 registered potential donors in the register, who are still waiting for the opportunity for donation. Thank you very much to all the expert hematologists who have been in charge of the development of the profession in the field of healing with HSC transplant for many years and, in cooperation with the SD registry experts, saved the lives of children and adult patients with blood cancer.

We believe in the long-term growth of the registry, the constant development of the profession and the great heart of all potential donors in the SD registry, therefore we are not afraid for the future of patients with blood cancer.

www.dajsenaseznam.si

www.limfom-levkemija.org


10

TRANSFUSION MEDICINE IN SLOVENIA

The origins of transfusion medicine and blood donation in Slovenia date back to the period before World War II, when several cases of direct blood transfusion were recorded (from the donor's vein to the recipient's vein). During the World War II, no special blood transfusion service was organized in Slovenia - if they needed blood, it was donated by the medical staff accompanying the surgeon. Due to an increase in the need for blood, a blood transfusion department was established at the Central Military Hospital in Ljubljana after the end of the World War II, followed by the establishment of blood transfusion stations in other hospitals across Slovenia.

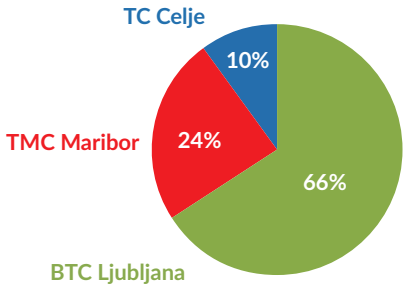
The date marking the beginning of the transfusion activity in Slovenia is June 4th 1945, when the first 19 blood bottles were taken and conserved at the blood department in Ljubljana, so on this day we celebrate Blood Donor Day. Already since 1953, when the organization of blood donation was taken over by the Red Cross of Slovenia, blood donors have been donating blood voluntarily, non-remunerated and anonymously. Under a public authorization the Red Cross of Slovenia with 56 Regional Red Cross Associations, volunteers and supporters successfully carries out campaigns for recruiting blood donors and organizes blood drives for years.

During all years of enviable development in medicine, continuous improvements innovations and expansion of the activity, blood donors / donors remain the first and irreplaceable link in providing the sufficient blood supply of blood and blood products for treatment of patients.

The basic guideline of transfusion medicine is **safe, adequate and quality blood.** The transfusion medicine covers three very different but closely connected and intertwined activities: blood supply, diagnostic/laboratory tests and treatment with blood products and cells. The register of unrelated donors of blood stem-cells Slovenia Donor is integrated in all three.

The blood supply starts with a sufficient number of responsible and safe blood donors who are ready to respond and donate blood and are national treasures for each country. In Slovenia, we can be proud of the successful long-standing tradition of blood donation and blood donors, which have been providing the blood supply for years. Blood can be donated at blood transfusion establishments and in mobile sessions, within the organized sessions or on their own decision based on published blood stocks on the BTC website ***(www.ztm.si).***

The share of collected blood by transfusion service



The number of registered blood donors

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
BTC Ljubljana	45.770	46.487	49.788	53.142	52.400	55.036	52.320	49.567	45.144	46.225	49.696
TU Izola	5.409	5.496	5.377	5.785	6.383	6.843	5.952	5.994	5.861	5.573	5.758
TU Jesenice	2.372	2.598	3.419	3.472	2.254	2.178	1.969	1.982	2.003	1.905	1.789
TU Nova Gorica	3.815	3.366	3.752	3.661	3.663	3.886	3.757	3.690	3.613	3.136	3.270
TU Novo mesto	4.285	4.440	4.746	5.662	6.041	6.846	6.602	6.616	6.586	6.601	6.746
TU Slovenj Gradec	3.018	2.907	2.840	3.290	3.379	3.328	3.010	2.861	2.873	2.879	2.917
TU Trbovlje	1.458	1.350	1.477	1.322	1.360	1.318	1.154	993	998	864	861
Altogether BTC	66.127	66.644	71.399	76.334	75.480	79.435	74.764	71.703	67.078	67.183	71.037
TMC Maribor	12.578	12.457	13.600	14.726	15.121	15.739	14.823	15.195	15.377	14.948	15.236
TU Murska Sobota	4.741	4.680	4.929	4.765	4.642	4.687	4.686	4.538	4.366	4.357	4.150
TU Ptuj	3.296	3.374	3.535	3.638	4.203	4.167	4.276	3.938	3.883	3.911	3.951
Altogether TMC Maribor	20.615	20.511	22.064	23.129	23.966	24.593	23.785	23.671	23.626	23.216	23.337
TC Celje	9.625	9.900	10.711	11.345	11.051	11.061	10.953	9.863	9.704	9.573	9.263
Slovenia	96.367	97.055	104.174	110.808	110.497	115.089	109.502	105.237	100.408	99.972	103.637

The number of whole blood units collected

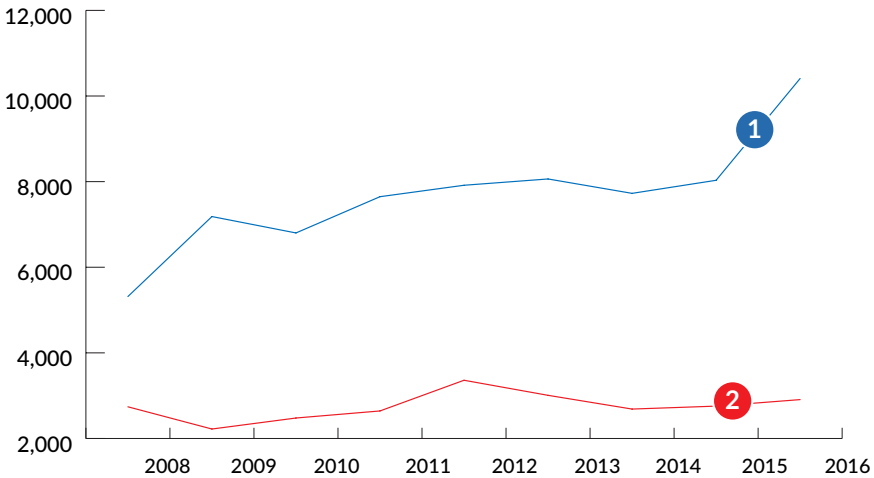
Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
BTC Ljubljana	56.200	56.529	61.538	64.040	63.872	66.259	62.267	58.916	56.563	55.379	57.538
TMC Maribor	18.419	18.234	19.686	20.819	21.489	21.912	20.942	23.109	21.112	21.030	20.796
TC Celje	9.141	9.340	10.055	10.531	10.240	10.136	9.890	8.611	8.934	8.986	8.662
Slovenia	83.760	84.103	91.279	95.390	95.601	98.307	93.099	90.636	86.609	85.395	86.996

In the blood transfusion service, **"blood components"** are prepared from the donated blood. Treatment with components is more effective and safer, as the patient receives only those components needed. By collecting blood into a closed system of plastic bags and physical methods such as centrifuging and filtering, full blood is separated into concentrated erythrocytes, concentrated platelets and fresh frozen plasma.

To reduce the possibility of adverse effects of concentrated erythrocyte transfusion, a blood filtration procedure (removal of leukocytes) is carried out immediately after removal. Platelets are prepared in the additive solution within a closed system, most of the leukocytes are removed from the blood, amount of plasma is decreased, which significantly reduces the frequency of adverse reactions after transfusion.

An important advantage of the new platelet preparation is possibility to perform the procedure of pathogens inactivation, thereby further reducing the likelihood of transmission of infectious diseases and septic reactions that could occur due to the multiplication of bacteria during the storage of platelet preparations.

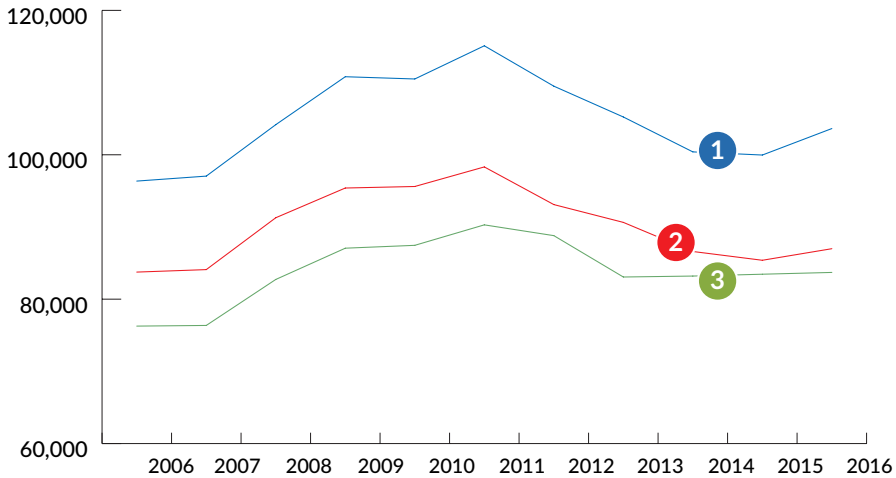
Number of polled platelets units and apheresis unit issued



1 Number of polled platelets units issued

2 Number of apheresis – platelets units issued

Presentation of registered blood donors, the number of collected blood units and number of concentrated erythrocytes units issued



1 Registered blood donors

2 The number of whole blood units collected

3 The number of issued concentrated erythrocytes units

The number of issued units of concentrated red blood cells

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
BTC Ljubljana	51.280	51.808	55.642	58.584	59.570	60.479	59.909	55.312	53.470	53.727	55.199
TMC Maribor	17.205	16.978	19.534	20.443	20.708	22.293	20.827	20.695	21.332	21.403	20.660
TC Celje	7.792	7.583	7.554	8.028	7.173	7.510	8.055	7.062	8.398	8.325	7.843
Slovenia	**76.277**	**76.369**	**82.730**	**87.055**	**87.451**	**90.282**	**88.791**	**83.069**	**83.200**	**83.455**	**83.702**

The number of issued pooled platelet units

Year	2006	2007	2008*	2009	2010	2011	2012	2013	2014	2015	2016
BTC Ljubljana	18.999	18.073	3.225	4.689	4.569	5.006	5.340	5.551	5.238	5.502	7.561
TMC Maribor	4.813	6.581	1.785	2.166	1.816	2.092	2.090	1.997	1.864	1.796	2.135
TC Celje	2.175	2.710	306	329	416	550	485	514	624	733	713
Slovenia	**25.987**	**27.364**	**5.316**	**7.184**	**6.801**	**7.648**	**7.915**	**8.062**	**7.726**	**8.031**	**10.409**

* *Fusion*

The number of performed platelets apheresis

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
BTC Ljubljana	995	1.034	1.345	1.248	1.611	1.724	2.104	1.999	1.915	2.274	2.421
TMC Maribor	249	173	129	127	135	192	239	115	76	49	59
Slovenia	**1.244**	**1.207**	**1.474**	**1.375**	**1.746**	**1.916**	**2.343**	**2.114**	**1.991**	**2.323**	**2.480**

The number of issued apheresis platelet units

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
BTC Ljubljana	1.868	1.990	2.496	2.098	2.355	2.484	3.120	2.891	2.611	2.714	2.832
TMC Maribor	259	177	243	122	122	158	236	117	76	42	76
TC Celje	3	6	1	1	1	1	4	0	0	0	0
Slovenia	**2.130**	**2.173**	**2.740**	**2.221**	**2.478**	**2.643**	**3.360**	**3.008**	**2.687**	**2.756**	**2.908**

The units of fresh frozen plasma not used for the clinical treatment of patients, the units collected with the plasmapheresis procedure are derivate source for blood-derived medicines. Plasma is processed according to prescribed procedures with the selected contractor abroad. All medicines produced from plasma collected in Slovenia are always fully delivered back for the treatment of patients in Slovenia.

Blood derived medicines are registered and manufactured in accordance with the Good Manufacturing Practice (GMP) and European Pharmacopoeia (Ph. Eur.) principles. Needs for the treatment of hemophilia patients with human blood clotting factors from plasma collected in the Republic of Slovenia are fully covered, while only approximately 60% of human albumin and human polyspecific immunoglobulins needs are sufficient in Slovenia.

The number of plasmapheresis performed

Leto	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
BTC Ljubljana	1.099	593	430	717	512	711	623	902	100	565	1.919
TMC Maribor	5	17	7	25	65	10	0	0	0	0	0
Slovenia	**1.104**	**610**	**437**	**742**	**577**	**721**	**623**	**902**	**100**	**565**	**1.919**

The number of issued units of fresh frozen plasma

Leto	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
BTC Ljubljana	17.588	18.810	17.042	19.775	18.595	19.147	19.143	17.029	13.356	13.461	15.654
TMC Maribor	9.881	9.293	9.576	9.124	9.187	9.398	9.354	9.089	8.431	7.127	7.400
TC Celje	2.795	2.850	2.892	2.394	2.097	1.762	2.074	1.767	1.145	1.027	913
Slovenia	**30.264**	**30.953**	**29.510**	**31.293**	**29.879**	**30.307**	**30.571**	**27.885**	**22.932**	**21.615**	**23.967**

In order to ensure the safety and quality of blood, donors are carefully selected, blood units properly processed and tested. In the meantime the blood units are processed, **laboratory screening tests** for transfusion transmitted infectious agents as well as blood-grouping procedures are performed.

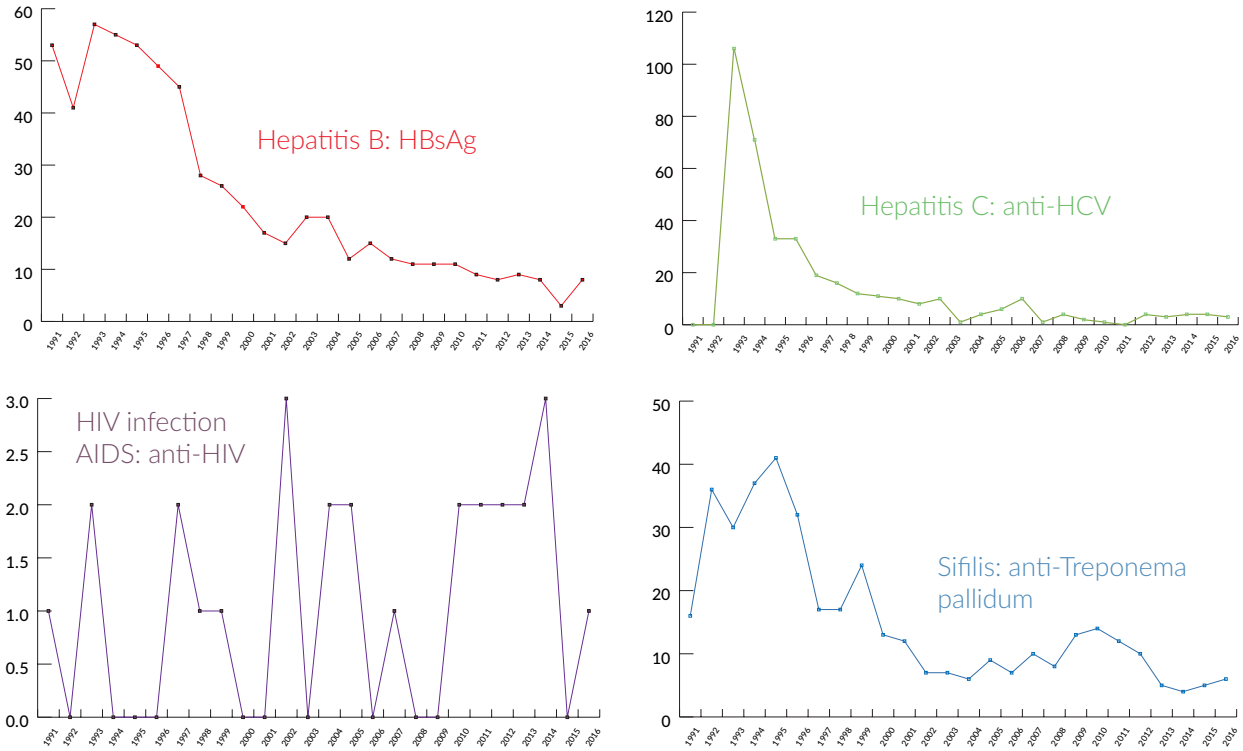
Each collected blood unit is tested for markers of AIDS, hepatitis B and C and syphilis with the latest testing methods that are licensed in accordance with the strictest international criteria, and are completely automated. An obstacle in ensuring the perfect safety is represented by the so called diagnostic window, a period from the moment of infection to the appearance of infection markers, which we are looking for with a specific test.

In 2007, at the Blood Transfusion Center in Ljubljana - centralized for the whole of Slovenia – the screening of individual blood units for blood born pathogens with Nucleic Acid Techniques (NAT) were additionally introduced. The application of these methods strongly shortens the diagnostic window, as they help us detect an infection much earlier than any of the direct serologic infection markers appear. Blood tested with the NAT method is much safer also because this method is extremely sensitive, since it enables detecting also infections with a low viral burden.

In order to ensure a safe and effective treatment with erythrocytes, it is vital to choose blood which is identical/compatible in terms of all immunologically important antigens. Antigens of the blood group AB0, RhD and Kell, and the antigens of Rh system (C, c, E, e) are thus determined for each collected blood unit. In order to prevent the transmission and harmful effects of unexpected **erythrocyte antibodies** from a plasma donor to its recipient, we perform antibody screening test (Coombs test). The units in which such antibodies are detected are not used for transfusion.

After processing and performed tests, blood products are stored and ready for transfusion.

Frequency of viral markers detection in blood donors in the period from 1991 to 2016



	Number of detected donors	Annual average	Occurance at 100.000 collected units	Prevalent occurrence among the collected units
Hepatitis B	HBsAg	78	10	10,5/105 1:9.523
	HBV DNA	38	5	5,1/105 1:19.547
Hepatitis C	Anti-HCV	25	3	2,5/105 1:29.711
	Samo HCV RNA	1	0	0,1/105 1:742.770
HIV	Anti-HIV 1/2/0 in p24	12	2	1,6/105 1:61.898
Sifilis	Anti Treponema pallidum	76	10	10,2/105 1:9.773

Frequency of detecting unsuitable units of blood due to the content of infectious markers between 2008 and 2016

The number of tested units: 742.770

Treatment of patients with blood transfusion

Most of the blood supply is intended for patients with various haematological or oncological diseases; however, it is also used for patients undergoing surgeryes and organ transplantation and for others with serious injuries who require large amounts of blood.
Blood compatibility is ensured by performing **immunohaematologic tests** which allow safe blood transfusion, organ and tissue transplants and prevent some adverse immune reactions after transfusion, transplantation and during pregnancy.

In ideal circumstances, patients receive blood identical to their own in all clinical important erythrocyte antigens. Due to the large number of antigens and their possible combinations, we strive to transfuse blood units that match as closely as possible.

Compatibility is examined with compatibility test **"cross-match"** for each unit.

In order to prevent adverse effects of transfusion due to unexpected erythrocyte antibodies from a plasma recipient, we perform indirect Coombs test to each patient.

In order to ensure safe and effective treatment with erythrocytes in certain patients, it is necessary to select identical / compatible blood unit in immuno-relevant antigens.

Serological tests for the determination of erythrocyte, thrombocyte and granulocyte antigens, and the determination of thrombocyte and granulocyte antibodies and their specificity are performed only at BTC, where in recent years more and more **molecular biological techniques** are used for DNA-typing.

The transfusion service also participates in the **pregnancy management program**, through immune-hematological investigations and counseling in the case of the protection of RhD-negative pregnant women, in case of detection of unexpected erythrocyte antibodies. These tests and the prevention with specific antibodies have significantly reduced the mortality of the fetuses during pregnancy and as well as newborns.

Within the immuno-hematological tests for patients, we performed:

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Cross-match tests	118.831	117.364	127.974	133.317	135.766	143.288	136.792	132.575	131.464	130.074	140.616
Determination of blood group AB0, RhD and Kell	77.607	79.383	89.955	83.655	74.898	76.789	71.398	66.650	71.892	64.163	64.710
Coombs tests	42.232	61.604	62.145	67.842	70.293	90.836	94.270	96.183	94.560	93.392	94.456
Erythrocyte antibodies specifications	2.204	2.846	2.599	2.217	1.925	2.553	2.512	2.729	2.607	2.647	2.838
Tests before Ig anti-D injection	4.370	5.023	5.949	6.191	6.624	6.851	8.387	8.553	8.354	8.475	8.984
***Platelet tests**	833	1.067	1.134	1.175	1.152	1.247	1.063	914	962	929	1.061
***Granulocytic tests**	66	46	65	72	59	459	84	184	181	189	46
***Molecular-biological tests**	95	99	176	124	229	351	189	328	439	329	211

**Performed by BTC Ljubljana*

In the **national organ and tissue transplantation programs,** we cooperate with the histocompatibility testing. On the one hand, this involves complex investigations (typing of human leukocyte antigens (HLA), screenings for anti-HLA antibodies, cross-mach tests between recipients and organ donors), which allow organ transplantation in patients on the waiting list of the Eurotransplant, the non-profit organization for the exchange of organs of which Slovenia is also a member. We also follow the immune status of patients after organ transplantation, in order to prevent rejection episodes that can lead to organ loss. On the other hand, the most demanding HLA typing at a high level of resolution, performed by DNA sequencing, provides basis on which we can begin searching for histocompatible donors of hematopoietic stem cells (HSC) for patients with many malignant and non-malignant diseases.

By identifying the presence of certain genetic variants of HLA, which represent the risk factors for the development of certain autoimmune and other diseases, we also offer support for their diagnostics.

Strongly related to the histocompatibility testing is the work done in the Slovenia Donor register, because only the histocompatible patient and his donor are the appropriate pair on the path to the successful transplantation of HSC. In the vast majority of cases, the latter is carried out in BTC's Department for Therapeutic Services.

Transfusion medicine is now expanding to the field of **therapeutic services** in patients, where it is becoming a part of an interdisciplinary approach in the treatment with cells and the transplantation of tissues and organs. In line with global trends, the Department for Therapeutic Services was established at the BTC in 2014 with the aim of providing quality cellular products for advanced treatments such as HSC abnormalities and transplantation, extracorporeal phototherapy, treatment of cardiac failure, treatment of certain cancers (tumor vaccines), withdrawal of granulocytes for the treatment of immunocompromised patients, therapeutic leukopheresis in leukemia, and therapeutic withdrawal of whole blood in diseases caused by accumulation of iron and certain other diseases.

The key to successful and effective work in the field of transplantation medicine is the harmonious work of professionals from different disciplines.

The vast majority of transfusions take place without complications, but in some cases they do occur. In order to recognize and prevent unwanted reactions and events in blood transfusion, we collect information about complications from the donor to the recipient of the blood by using the **hemovigilance system.**

Transfusion service professionals within various professional bodies and associations, both at home and abroad, are involved in the development of professional guidelines in the field of blood treatment and the manufacture of products for advanced treatment medicine and organ transplantation. Research is an important part of the activity by which we develop new technologies, products and services that enable the implementation of safer blood transfusions and transplantations, new cell and tissue therapies, and improved diagnostics. We work in the field of education, where we spread our knowledge and experience and pass it on to colleagues and future co-workers.

In Slovenia, transfusion medicine meets European standards and criteria for patient care by providing blood and blood products and diagnostic and therapeutic services comparable to the most developed countries in the world. In the future, we will endeavor to maintain a high level of services and will, in the interests of patients, follow the novelties, improvements and scientific research and development in the field of transfusion and transplantation medicine.

Performed tests and services in relation to the histocompatibility testing

Year	2008	2009	2010	2011	2012	2013	2014	2015	2016
Services which support organ transplantation	8.714	9.103	10.565	9.681	8.591	11.035	10.430	12.770	11.117
Services which support HSC transplantation	3.214	3.299	3.187	1.735	1.905	1.858	3.005	1.944	1.736
HLA typing for the Slovenia Donor registry	1.219	1.348	1.602	2.117	1.499	1.000	3.071	2.306	1.386
Diagnostic services (autoimmune disease)	322	395	828	717	408	132	155	74	89
Services of the Slovenia Donor registry	739	656	635	559	264	257	304	227	209

Services at BTC in Ljubljana, performed within the special therapeutic services

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Autologous collection of the HSC	125	107	106	154	147	162	181	177	121	188	153
Allogeneic collection of the HSC	17	23	26	21	25	18	16	14	16	21	28
Granulopheresis			26	27	31	37	84	86	67	95	79
Transfusion of HSC	85	87	86	83	90	79	75	79	69	86	109
Freezing of cells	129	101	107	145	141	148	157	157	130	162	140
Isolation of CD34+ cells	3	14	8	16	17	27	39	32	33	37	27
Photopheresis							1	214	446	632	614

Number and type of reported adversereactions to blood transfusion in Slovenia /Heamovigilance between 2011 and 2016

Reaction	2011	2012	2013	2014	2015	2016
Haemolysis	3	7	1	1	2	
GVHD						
TRALI	1	1	2	1		
TAC	10	13	9	8	5	11
PTP						
Allergy	57	66	49	58	53	51
Anaphylaxis	7	5	3	3		4
Non-hemolytic transfusion reaction	52	60	34	38	53	60
Bacterial infection				1		
Viral infection	1		3	2	1	2
Hypotension		2	1	1	3	
Dyspnea	4	3		1	1	1
Other	7	5	11	5	1	
Altogether	**142**	**162**	**113**	**118**	**119**	**129**

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