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Advancement in cellular therapies: selected reports from the 37th International Congress organized by the International Society of Blood Transfusion (ISBT) in Kuala Lumpur, June 4–8, 2022

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Summary

Hematopoietic stem cells (HSCs) are used in the management of numerous diseases, mainly for renewal of the hematopoietic system following myeloablative therapy. The cryopreservation techniques that are currently available allow for safe stem cell storage until transplantation. The first reports of autologous transplants date back to the 1980s. Since then, significant advancement in stem cell therapies has been recorded. The subject of this paper are selected scientific reports related to the collection, preparation and storage of HSCs presented at the 37th International Society of Blood Transfusion (ISBT) Congress, held in 2022 in Kuala Lumpur.

Keywords: cell therapies; hematopoietic stem cells; transplantation; hematopoietic diseases

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Introduction

Founded in 1935, the International Society of Blood Transfusion (ISBT) is the leading organization dealing with issues related to clinical and laboratory transfusion medicine as well as the safety of blood and blood components. Over the years, ISBT organized 37 international and 33 regional congresses. The Congress in Kuala Lumpur, Malaysia (June 4–8, 2022) was held as an online meeting due to the restrictions imposed by the COVID-19 pandemic. ISBT transmitted more than 60 sessions, including topic presentations, expert interviews and panel discussions. The topics covered red blood cell immunohematology, transfusion-transmitted pathogens, methods for supporting safe transfusion, platelet and granulocyte immunobiology, clinical transfusion medicine and issues related to blood components and blood-derived products. The presented papers also included reports on the SARS-CoV-2 pandemic, its impact on blood and blood component-based therapies, as well as difficulties in performing procedures of stem cell collection and transplantation.

International experience and cooperation

The 11th congress-session was mostly devoted to modern aspects of cell therapies. Attention was

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focused on problems related to donor shortage and the need for steady supply of blood which could be provided with the use of cultured erythrocytes. The impact of immature cultured RBCs with the expression of $CD45^+$ and $CD71^+$ on host immune response is not known. The work of A. Alshalani et al. [2] from the University of Amsterdam, the Netherlands, and the King Saud University, Saudi Arabia, presented a study which contributes to the characterization of CD45+ and CD71+ cell surface differentiation markers in cultured mononuclear cells from the erythroid lineage. The study also aimed at determining the impact of RBCs from peripheral blood mononuclear cells (PBMCs) on T-cell proliferation and host response following whole blood (WB) stimulation. WB samples were collected from healthy volunteers. PBMCs were seeded in an erythroid expansion medium. $CD71^+$ cells were isolated after 21 days of culture and incubated with either purified T cells or with medium--stimulated WB. Controls were incubated with medium. CD45+, CD71+ and CD235 expression was measured. CD71+ cells were then isolated and incubated with T-cells or WB from the same donor (control sample incubated with medium only). Cultured erythroid cells can modulate the immune response by promoting T-cells proliferation and inhibiting IL-6 secretion following WB stimulation. The study also suggests that the erythroid culturing process should be continued until full cell maturity and loss of the remaining intracellular cell membrane receptors will be achieved.

An international team led by L. Delila (Taipei, Taiwan) presented a study focused on the preparation of nanofiltered human platelet cell lysate and its neuroprotective effects on brain damage, both traumatic and resulting from Parkinson's disease. Heat-treated human platelet cell lysate (HPPL), rich in neurotrophins, antioxidants and anti-inflammatory proteins when administered to damaged areas of the brain may be a potential new biological therapy in neurodegenerative diseases and injuries of the central nervous system. In order to achieve batch-to-batch consistency, HPPL should be prepared from pooled platelet concentrates (PCs), which requires implementation of dedicated methods for reduction of the viral content that may be present in the lysates (eg. nanofiltration). Cellular and in vitro models were developed to evaluate the neuroprotective and anti-inflammatory properties of nanofiltered human platelet pellet lysate (NHPPL). Differentiated human midbrain dopaminergic neurons (Lund cells) were used as model of Parkinson's disease. They were pre-exposed to NHPPL and then subjected to a 24-hour exposure to erastin (a neurotoxin). Cell viability was quantified using the CCK-8 assay (Cell Counting Kit 8, Sigma). An *in vivo* assay was also performed on a mouse model of mild traumatic brain injury to evaluate intranasal administration of NHPPL for reduction of expression of pro-inflammatory mRNA markers (use of RT-PCR). NHPPLs exhibited detectable neurotrophicity and lower expression of prothrombotic compounds, as well as a lower procoagulant activity [3].

Another study from Taipei (N. Le et al. [4]) devoted to human platelet lysates (HPL) was focused on the proteolytic properties of lysates, which may enhance the effects of cell therapies and regenerative biotherapies. The study goal was to identify the biological functions of different HPLs with the aim of upgrading their quality, safety and clinical use. Outdated allogeneic PCs were used at the Taipei Blood Donor Center for preparation of different types of platelet lysates. Label-free proteomics was performed to obtain a global understanding of the HPL proteomes by precipitating proteins with acetone. HPLs were also deprived of 14 large plasma proteins. Peptides obtained through trypsin digestion were then subjected to reverse-phase fractionation at high pH and analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Elimination of interference proteins contributed to higher resolution of proteomic analysis, and protein-level tandem mass tag (TMT) chemical labeling enabled more precise protein quantification. A total of 1441 proteins were isolated and quantified by label-free LC-MS/MS. The isolated and quantified proteins were characterized and the signal was amplified with bioinformatics platforms. HPLs differed in the content of platelet-derived proteins. The differences were brought about by the dissimilarities in procedures for blood component preparation (including plasma preparation or filtration) which may affect the composition of HPLs and their functions in the clinical setting.

During the 18^{th} parallel congress-session, the participants discussed the topic of new blood--derived products. Strong et al. [5] (USA) presented a study on platelets genetically modified with lipid mRNA nanoparticles, which may function as transfused platelets. Mature platelets are capable of *de novo* protein synthesis which makes them amenable to mRNA gene therapy. Platelet transfusions are indispensible for bleeding prevention but insufficient when hemorrhage is severe.

Gessoni et al. [6] made use of mononuclear cells (MNC) to develop an innovative treatment for triple-negative breast cancer (TNBC). In the clinical phase, they used donor lymphocytes infusion (DLI). They optimized and standardized the methods used for characterization and isolation of MNCs as well as developed methods for expansion of MNC using both bioreactor and "open" methods. However, prior to the clinical phase of the study, a pre-clinical study will have to be performed to evaluate the results obtained from culturing Activated Protein C (APC) derived from the expansion of MNC isolated from clinical specimens in the presence of tumor cells. The research is promising for the efficiency of international healthcare systems through lower treatment costs, support of the patients' health, but most of all because it promotes better quality of life and increases life expectancy.

Z. Yusoff [7] from the National Blood Center (NBC) in Malaysia (Kuala Lumpur) focused on cord blood unit as the most abundant reservoir of hematopoietic stem cells with regenerative potential, finding applications in many genetic disorders, blood cancers and immunomodulation processes. Umbilical cord blood banking is a process that begins immediately after the baby is born. Cord blood is collected from the severed umbilical cord and stored frozen. The first Public Cord Blood Bank in Malaysia was established by the Ministry of Health in July 2002 at the NBC. All stages of the process (collection, preparation and banking) are performed according to standard operating procedures to maintain a sufficiently high level of stem cell viability in the clinical material. Various techniques for cord blood preparation and cryopreservation have been developed and implemented focusing on cell quantity and quality. Methods need to be validated to demonstrate that both quality and quantity of progenitor/stem cells are preserved.

Useini et al. [8] concentrated on the safety and efficacy of hematopoietic stem cells apheresis collection from peripheral blood of healthy donors. The retrospective study and conducted at the Institute of Transfusion Medicine in North Macedonia and the University Department of Hematology (UCH) in the period 2000–2022. HLA matching between all donors and recipients was performed. The donors were notified about the procedure and requested to sign an informed consent form for cell harvesting. The minimum dose required to optimize engraftment after successful transplantation was 2×10^6/kg CD34+ cells and/or 2×10^8/kg MNC. PBSC harvesting was performed using Baxter CS3000, COBE Spectra and Terumo BCT Spectra Optia continuous flow cell separators. Recombinant human granulocyte colony stimulating factor (G-CSF) was used for mobilization. The mere adverse reactions observed were bone pain in reaction to G-CSF and limb numbness as a reaction to ACD-A (hypocalcemia). These occured rarely and were rather moderate.

In one of his studies, Chen et al. [9] (Taipei, Taiwan) described the mobilization and collection of peripheral blood stem cells from healthy pediatric low-body-weight donors. The study, based on the 30-year experience of the Taipei Transplant Center (Taipei Veterans General Hospital) demonstrate a significant increase of interest in hematopoietic stem cells used for allogeneic transplantations in children with malignant and non-malignant blood diseases over the past few decades. The study considered the demographic and clinical donor characteristics as well as various apheresis-related mobilization strategies. After 1990, cytokine mobilized (G-CSF) peripheral blood stem cells have become the preferred source of stem cells for autologous transplantation. However, peripheral blood stem cells collection from children remains a challenge. Lower body weight, low peripheral blood volume and susceptibility to diseases present much more difficult obstacles to overcome in children than in adult donors. Despite the greater complexity of the procedure in pediatric patients, all recipients included in the study succeeded in achieving the required minimum PBSC content during one- or two-day apheresis collections.

Daane and Robertson [10] (bioMérieux, Chicago, USA) undertook testing on transplant specimen-samples for the presence of *Mycoplasma*, using a quick and easy method in the BIOFIRE®Mycoplasma System that provides results within approximately one hour. Results from two GMP cell therapy manufacturers were presented. The disposable BIOFIRE®Mycoplasma kit is a closed disposable cartridge that contains all the necessary reagents for automated cell lysis, nucleic acid purification, reverse transcription, first and second step polymerase chain reactions (PCR), and analyte detection to isolate, amplify, and detect more than 130 *Mycoplasma* species from a single sample. All tested matrices used in the cell therapy (up to 10^6 CAR-T cells/mL), culture media, sera and cryoprotectants were found valid and no false positive results were reported. The BIOFIRE® FILMARRAY® 2.0 Industry system is well suited both for a release-to-use test and for a process control test for samples used in cell therapy. The results showed no product interference and high

sensitivity resulting in reliable *Mycoplasma* detection in less than 1 hour.

In another study, H. Low et al. [11] (Malaysia) compared the results of HLA typing from blood samples and buccal swabs of patients with blood transfusion history who were getting ready for stem cell transplantation. The research team determined the differences between HLA typing from the DNA extracted from blood sample and buccal swab sample. Samples were collected from 66 patients with various hematological malignancies who were scheduled for hematopoietic stem cell transplantation. The patients were administered at least one unit of RBC or PLT 1–14 days prior to blood sampling. DNA was extracted from all 66 blood samples and 66 buccal swab samples. All samples were typed for six loci (HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1 and HLA-DPB1) using next-generation sequencing (NGS). No differences were reported between the results of HLA typing from DNA extracted from a blood sample and buccal swab sample for the 66 patients. It follows that blood samples from a patient with transfusion history may be used for HLA typing instead of samples obtained from buccal swabs. The study was preliminary and focused only on adult patients with hematologic diseases (ALL, AML, CML, MDS, multiple myeloma, DLBCL, hemophagocytic lymphohistiocytosis, NKT cell lymphoma and severe aplastic anemia).

Summary

Although HSC has been used for quite a long time now, during this congress some very important issues were presented: reports on hematopoietic cells collection, preparation and storage, summarizing the results of many years of experience. One example is a study on apheresis procedures, as well as on the adverse reactions related to growth factor G-CSF injected prior to HSC collection and to ACD-A used during apheresis (The Hematology Clinic of the University of Skopje). This center performed allogeneic transplantation mainly for acute myeloid leukemia, which accounted for 55.8% of all transplants [8]. The results of a paper summarizing the difficulties in collecting PBSC from low weight donors (The National Institute in Taipei, Taiwan) shows that the long-standing practice helps to perform complex procedures that enable sufficient collection of PBSCs, despite even low donor's body weight [9]. Hematopoietic cells and lymphocytes are the source of material for numerous novel applications. An example is the "Immuno-Cluster" international cooperative project to develop a treatment protocol for triple-negative breast cancer, in which the cryopreserved PBSCs or DLI cells have been found most potent for the production of a cancer vaccine [6].

Reports from the ISBT congress indicate that application of hematopoietic cells is extended. Centers worldwide strive to improve PBSC transplantation procedures and introduce new technologies for more effective treatment of numerous disorders (not only hematologic).

Conflict of interest: none declared

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