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STEM CELL TRANSPLANTATIONS: «FAMICORD GROUP» OWN EXPERIENCE

ABSTRACT

The umbilical cord blood is now a renowned source of stem cells that can be used for hematopoietic stem cell transplantation. Because of cord blood advantages, including immediate availability and higher degree of acceptable HLA mismatch, the number of patients who received such treatment is constantly growing. The limitations of cord blood usage still exist, however laboratory and clinical trials all over the world try to overcome that barriers. Owing to international cooperation of stem cell banks, umbilical cord-derived stem cells from FamiCord Group were used in clinical trials of hematopoietic stem cell transplantations. Ten transplantations, including one autologous, took place in Poland, while the other three were carried out in Hungary. The most common indication was acute leukemia, however among children with hematologic diseases there were also patients with histiocytosis, chronic granulomatous disease or hypoxic ischaemic encephalopathy. Currently many scientists explore the possibilities of umbilical cord stem cell potential clinical usage with promising results.

KEY WORDS: cord blood stem cells, hematopoietic stem cell transplantation.

The hematopoietic stem cell transplantation with umbilical cord blood (UCB-HSCT) as a source is a rapidly developing method that enables finding a donor for larger group of patients. Up to date, over 25000 hematopoietic stem cell transplantations (HSCT) with umbilical cord blood (UCB) as a source of cells have been performed. The UCB is nowadays in the scientific spotlight because of its advantages: no adverse effects on the stem cell donor, immediate availability, greater degree of HLA disparity, low risk of pathogen transmission and relatively low risk of developing graft-versus-host disease (GvHD).

On the other hand, limitations of UCB usage still exist. The limited number of cells results in poorer homing and engraftment that puts patients at susceptibility of developing life-threatening infections due to prolonged neutropenia [1, 2]. However, many new procedures are now in the phase of a clinical trial with the objective to overcome those limitations [3]. That can be achieved by increasing the number of infused *CD34*⁺ cells (double umbilical cord blood transplantation), enhancing homing (dipeptidylpeptidase IV inhibitors, complement *C3a*), *ex vivo* expansion of stem cells with growth factors and cytokines, influencing bone marrow microenvironment (intra-bone infusion, co-transplantation with mesenchymal stem cells), promoting undifferentiated state of progenitor cells (*Notch* ligand, nicotinamide, copper chelators, aryl hydrocarbon receptor antagonists) or other methods such as manipulations with α -1,3-fucosyltransferase VI and prostaglandin *E2* [4-12].

The UCB collection is an easy and safe procedure with no risk to the donor. The blood is collected to the special kit by the umbilical cord puncture from the navel-string vessel after the omphalotomy. The collected cells are processed and cryopreserved in a liquid nitrogen and they can be applied even after 23,5 years [13]. The preliminary evaluation of umbilical cord blood as a biological material for transplantation

is based on the obtained volume and number of leukocytes in a microliter. However, an unequivocal assessment can be done after determining the exact number of *CD34*⁺ cells.

The first attempt of umbilical cord blood transplantation was undertaken in 1970, in a boy treated due to leukemia. Eight units of cord blood had been transplanted in intervals of about dozen days with preceding chemotherapy based only on encorton and 6-mercaptopurine, without any kind of preparative regimen [14]. The first successful transplantation was conducted by *E. Gluckman* at the initiative of *H. Broxmeyer* and *J. Kurtzberg*. The patient was a 5-year-old boy with Fanconi anemia, he received his new-born sisters' cord blood [15]. Nowadays the patient still remains in a good health condition. The first unrelated allogeneic stem cell transplantation was carried out five years later in two patients with high risk leukemia [16]. However, the first autologous HSCT was conducted in Brasil: the recipient was a girl with neuroblastoma, whose cord blood was preserved with the objective of treating her older brother suffering from leukemia [17].

Indications for UCB-HSCT are the same as those for bone marrow or peripheral blood stem cell transplantation. *European Bone Marrow and Blood Transplantation Group (EBMT)* published its first two reports without distinguishing the type of source for HSCT [18, 19]. For the first time, in 2002, *EBMT* report officially distinguished three stem cell (SC) sources and described conditions which have to be fulfilled when cord blood is chosen as a cell source for HSCT [20]. Cord blood as an alternative stem cell source is used for treating a variety of malignant or non-malignant diseases as well as hematologic disorders. The penultimate *EBMT* report in 2006 confirmed that the recommendations for UCB-HSCT are the same as for bone marrow or peripheral blood hematopoietic stem cell transplantation [21]. According to *Gratwohl study*, main causes of

UCB-HSCT in Europe were due to non-malignant disorders (leading in the group of related transplantations), acute leukemia (leading in the group of unrelated transplantations) and lymphoproliferative diseases [22].

Nowadays, the number of patients after UCB transplantations continues to increase. According to *Eurocord* data, 8007 patients have been treated with UCB-HSCT until the end of 2011 year, using 10651 cord blood units. The number of transplantations worldwide exceeded 25000 procedures until the end of 2012 [23].

The *FamiCord Group* donated cord blood units for 13 umbilical cord hematopoietic stem cell transplantations. We would like to share our experience concerning clinical use of umbilical cord blood-derived stem cells.

RESULTS

The first transplantation of *FamiCord Group* was also a first transplantation in Poland with umbilical cord blood from a private bank (*The Polish Stem Cell Bank – PBKM S.A.*). The procedure was carried out in March 2007, in the Department and Clinic of Pediatric Oncology, Hematology and Bone Marrow Transplantation of Wrocław Medical University. The patient was an 8-year-old girl treated due to IV stage of neuroblastoma. She was diagnosed in 2003, however in 2006 she presented with bone marrow relapse. The number of SC collected from patient's younger sister cord blood was insufficient for the patient's weight. The missing cells were obtained from the bone marrow of the same donor on the day of the transplantation. The patient was conditioned with treosulfan and cyclophosphamide. The stem cells were HLA-matched and blood group-matched, the UCB-HSC viability equaled appropriately 90 and 98% in the two cord blood units. The neutrophil engraftment ($>0.5 \cdot 10^9/L$) was observed after 16 days, however the platelet level reached $>50 \cdot 10^9/L$ in 30 days. The patient developed skin type of GvHD that ceased after immunosuppressive therapy with corticosteroids and *CellCept*. On the +23th day after the procedure, the patient manifested symptoms of BKV-positive haemorrhagic cystitis that required intensive therapy. The girl underwent urinary tract catheterization, bladder rising as well as treatment with ciprofloxacin and *Vistide*. The patient was discharged in good general condition +58 days after the HSCT [24].

The second transplantation was conducted in the Department of Pediatric Hematology and Oncology of Collegium Medicum in Bydgoszcz, Mikolaj Kopernik University, Poland. The recipient was a 5-year-old girl with an early relapse of acute lymphoblastic leukemia. The stem cells were collected in 2007 from a sibling donor, processed and cryopreserved in PBKM S.A. The donor turned out to be HLA-matched and ABO-unmatched. The procedure took place in January 2008, with the Busilvex-cyclophosphamide-based conditioning. Neutrophils engrafted on +19th day, platelets on +30th. No adverse effects were noticed after transplantation, patient did not develop GvHD. The recipient was discharged in a good general condition +48 days after transplantation [25].

The third transplantation was the first autologous one. It was performed in a 16-month-old child with hypoxic-ischemic encephalopathy after cardiac arrest 7 months before. The recent experimental results showed that human umbilical cord blood derivatives transplantation can be proposed as a new treatment for a stroke. The procedure was approved by Review Board of Ethics Committee and carried out by Children's Memorial Health Institute in Warsaw. The patient was in a permanent vegetative state with a severe epileptic seizures and an unsatisfying drug control. The cells from the autologous umbilical cord blood were neurologically restricted by a 10-day culture in neurogenic conditions. To enable engraftment tracking with MRI, the cells were labeled with iron oxide nanoparticles. The patient received three serial injections into lateral ventricle of the brain containing $1,2 \cdot 10^6$ cells/0,5 ml with 1 month intervals. There were no adverse effects apart from transient fever not exceeding 38°C. The MRI examination showed hypointense areas appearing immediately after injection that persisted up to 4 months after the procedure. The neurological state of

the child has slightly improved during 6 month follow-up: he responded to the mother voice through smiling, the seizures were reduced by 50 %, the nystagmus was less pronounced and the spasticity was milder. Although the child still was severely impaired, it no longer fulfilled the diagnostic criteria of a vegetative state. There is a strong need of further studies that will determine benefits coming from this approach [26].

The fourth transplantation of umbilical cord blood from *PBKM S.A.* took place in January 2009, in the Department of Paediatric Haematology, Oncology and Transplantation of Medical University of Lublin. The recipient was a 5-year-old boy treated due to myelodysplastic syndrome with monosomy of chromosome 7. The cord blood was collected in April 2008 from 6/6 HLA-matched and blood group-matched younger brother. The patient underwent conditioning with treosulfan, cyclophosphamide and melfalan. He received $0,75 \cdot 10^5$ $CD34^+$ cells/kg body weight. The neutrophil engraftment was noticed on +28th day, the platelet on +34th day. The chimerism study showed 100 % of donor origin. No adverse effects were observed during peritransplant period and the patient was discharged in a good general condition [27].

The fifth transplantation of *FamiCord Group* was a first one from Hungarian private stem cell bank. It took place in September 2010. The recipient was a 1,5-year-old girl with *MLL* gene rearrangement, treated according to high risk group of the *ALL IC-BFM 2002* Protocol. The donor was her younger sister. After the procedure, chimerism study showed 95% cells of donor origin and further 100%.

The sixth transplantation took place in the Department and Clinic of Pediatric Oncology, Hematology and Bone Marrow Transplantation of Wrocław Medical University, on January the 7th, 2011. The patient was a 12-year-old girl with Fanconi anemia. The conditioning regimen was composed of busulfan, fludarabine, anti-thymocyte globulin and muromonab-CD3. She received HLA-matched and ABO-matched stem cells from her younger brother's umbilical cord blood in the dose of $3,98 \cdot 10^6$ $CD34^+$ cells/kg body weight. Neutrophil recovery was achieved on +18th day and primary results showed complete chimerism of donor origin. The peritransplant period was complicated by BKV-associated hemorrhagic cystitis and asymptomatic CMV reactivation. However, a mixed chimerism with an increasing number of autologous cells was observed and therefore, on the +139th day posttransplant, the patient received donor lymphocyte infusion with the cell dose of $1 \cdot 10^6$ $CD3$ cells/kg body weight.

The seventh transplantation was the second one from a public bank in Hungary. It was carried out on April the 14th, 2011. The patient was a girl with trisomy 21, treated due to thrombocytopenia since birth and diagnosed with MDS that transformed into minimally differentiated acute myeloid leukaemia after 3 months. The patient was treated according to *AML-BFM-98* protocol and archived remission, however minimal residual disease persisted. The girl was qualified for HSCT and her brother turned out to be HLA-identical donor, therefore his stored cord blood have been planned as a SC source. The busulphan-fludarabine-cyclophosphamide-based conditioning was applied. The HSCT was performed with $CD34^+$ cell dose of $6,8 \cdot 10^5$ /kg body weight. No early adverse effects were observed. With lower grade of expected GvHD after UCB-HSCT, the child received only cyclosporine, without methotrexate as a GvHD prophylaxis. High fever was observed on the +7th day after transplantation, and the antibiotic therapy was changed from the empiric to the aimed one. The girl received also antihypertensive treatment due to headaches connected with high blood pressure. Neutrophil engraftment was observed on +14th day, however the patient received parenteral filgrastim in the meantime. The patient developed skin lesions of stage I GvHD and thus received methyl-prednisone with gradually decreasing doses and topical tacrolimus. The treatment was discontinued at +44th posttransplantation day, since no dermatological symptoms persisted. The patient received also inhalative bronchodilators from +29th day post-HSCT, due to the signs of obstructive disease of lower respiratory tract. The patient was discharged in a good clinical condition on +50th day after transplantation.

The eighth recipient was a 5-year-old boy with an early bone marrow relapse of a pre-B acute lymphoblastic leukemia. The donor was his 6/6 HLA-matched younger brother. The procedure took place in the Department and Clinic of Pediatric Oncology, Haematology and Bone Marrow Transplantation, Medical University in Wrocław, on June the 30th, 2010. The boy was conditioned with TBI and etoposide. GvHD prophylaxis consisted only of cyclosporine A. The number of CD34+ infused cells equaled $2,26 \cdot 10^5$ CD34+ cells/kg body weight with leukocyte viability of 98%. Neutrophil engraftment was noticed on +20th day, platelet – on +39th. Chimerism studies showed 98% cells of donor origin. The boy developed hepatomegaly, edema and tachycardia consistent with periengraftment syndrome. The symptoms subsided with corticosteroids therapy. However, the boy developed cyclosporine A-related toxicity and *Staphylococcus haemolyticus* infection.

The ninth transplantation took place in the Department of Paediatric Oncology, Hematology and Transplantology of University of Medical Sciences in Poznań, on September the 28th, 2011. The patient was a 3-year-old boy treated due to histiocytosis. The transplantation was performed with cord blood collected from his HLA-matched younger brother. The number of infused cells equaled $32 \cdot 10^5$ CD34+ with cell viability of 99%. At the time of writing, over nearly 2 years after transplantation, the patient is alive and remains in complete remission of disease.

The tenth patient was a 7-year-old boy with chronic granulomatous disease (CGD), who presented with pneumonia, otitis, laryngitis and chronic lymphadenopathy at the age of 2. Multiple granulomas in lungs and intestines had been detected and the diagnose of CGD was established. The donor was his 9/10 antigen HLA-matched younger brother. Preparation, freezing and storage of CB unit was done in 2007, at PBKM S.A. in Warsaw. The patient underwent conditioning that consisted of busulfan, fludarabine and alemtuzumab. The procedure was carried out on November the 24th, 2011. The boy received $5,8 \cdot 10^7$ leukocytes/kg body weight with 98% viability. The neutrophils engrafted on +26th day post-HSCT. The peritransplant period was uneventful apart from CMV asymptomatic reactivation. The neutrophil oxidative burst test, characteristic of CGD, performed on day +63 was negative, which confirmed the cure of the disease. No signs of acute graft versus host disease were observed. The patient is alive and remains in complete remission.

The eleventh transplantation took place in the Pediatric Oncology and Stem Cell Transplantation Department of University Teaching Hospital in Miskolc, in Hungary, on May 29th, 2012. The patient was a 2,5-year-old boy with aplastic anemia.

The twelfth patient was a 7-year-old boy suffering from severe aplastic anemia. The procedure took place in the Department of Pediatric Oncology, Hematology and Bone Marrow Transplantation in Wrocław, on January the 30th, 2013. The cord blood from patients younger sister was prepared, cryopreserved and stored at Polish Stem Cell Bank.

The patient was conditioned with busulfan, fludarabine and *Mab-Campath-1H* and transplanted with HLA-matched cord blood that was cryopreserved 3 weeks before. The neutrophil engraftment occurred on +26th day. The peritransplantation period was complicated with asymptomatic CMV reactivation and mild skin GvHD that subsided with steroid treatment. The patient remains in complete disease remission.

The thirteenth transplantation of *FamiCord Group* took place in the Department of Paediatric Oncology, Hematology and Transplantology of University of Medical Sciences in Poznań on March the 6th, 2013. The preparation, cryopreservation and banking had been done by Polish Stem Cell Bank. The recipient was a 3-year-old girl with acute myeloblastic leukemia in first remission. The cord blood was donated by her HLA-matched and group-matched younger brother 4 months earlier. The cell viability was 98%. Neutrophils hematological recovery was noticed on +16th post-transplantation day, however platelets engrafted on +30th day. Up to date, the girl is in complete disease remission in good overall clinical condition.

The *FamiCord Group* transplantations were the first procedures with a SC source coming from a private bank both in Poland and Hungary. Moreover, it was a first and second time in Poland to use cord blood combined with bone marrow from the same donor (in children). This kind of procedure is considered safe and effective, moreover, the bone marrow harvesting is much less traumatic for a donor, because only a supplementary number of CD34+ has to be collected [29]. Among *FamiCord Group* transplantations there were two with contaminated at the day of delivery cord blood (in Poland with *Propionibacterium acnes* and in Hungary with *Streptococcus agalactiae*). No serious adverse effects and no evidence of bacteria in recipient's peripheral blood were observed.

There are many studies concerning HSCT with contaminated stem cell products, however the final decision about transplantation lies in the hands of a transplant center and is made individually for each patient. The choice about banking an infected cord blood portion is made by parents after a consultation with a doctor, who provides them with information about the type of microbe and its antibiogram in a case of bacterial contamination. The reported results of HSCT with contaminated stem cell product remains good for a majority of procedures [30]. *Klein et al.* study analyzed the clinical outcomes of hematopoietic stem cell transplantations of contaminated products in years 1990–2004. A total number of 35 patients received infected material with coagulase-negative *Staphylococcus* as a predominant species isolated, the transplantation was preceded by prophylactic antibiotic therapy. All patients had benign post-transplant courses apart from one patient with *Pseudomonas* bacteremia who died because of complications [31]. The *Kamble et al.* and *Kelly et al.* studies suggest that prophylactic antibiotic therapy might be unnecessary due to very rare clinical consequences following HSCT with contaminated blood products [32, 33].

CONCLUSIONS

THE UMBILICAL CORD BLOOD IS A WELL-ESTABLISHED SOURCE OF HEMATOPOIETIC STEM CELLS AND ITS UTILITY STILL INCREASES. THE UCB IS CONSIDERED AS AN ALTERNATIVE CELL SOURCE IN PATIENTS WHO LACK MORE CONVENTIONAL DONORS OR FOR PATIENTS TAKING PART IN PROSPECTIVE CLINICAL TRIALS. THE GROWING NUMBER OF STUDIES CONFIRMS CORD BLOOD STEM CELLS EFFICACY AND SAFETY [28].

THE FIELD OF UCB-HSCT IS STILL RELATIVELY NEW. FURTHER STUDIES EXPLORING POSSIBILITIES OF ENHANCING CORD BLOOD USAGE AND ANALYZING OUTCOMES IN SPECIFIC GROUP OF PATIENTS SHOULD BE CARRIED OUT. AS FOR NOW, THERE ARE MORE THAN 400 CLINICAL STUDIES ALL OVER THE WORLD INVESTIGATING USAGE OF CORD BLOOD DERIVATIVES, CONSTANTLY LOOKING FOR NEW POSSIBILITIES [34]. THE STUDIES INVOLVING STEM CELL EXPANSION, DOUBLE UMBILICAL CELL TRANSPLANTATION OR UCB-HSCT WITH REDUCED INTENSITY CONDITIONING MAY EXPAND CORD BLOOD USAGE INTO ADULT POPULATION [35]. IN THE FUTURE THERE MIGHT EVEN EXIST A POSSIBILITY OF AN INTRAUTERINE ALLOGENEIC STEM CELL TRANSPLANTATION AFTER PRENATALLY ESTABLISHED DIAGNOSIS (IN UTERO HEMATOPOIETIC CELL TRANSPLANTATION – IUHCT) [36].

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