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Original article

Feasibility of co-transplantation of umbilical cord blood and third-party mesenchymal stromal cells after (non)myeloablative conditioning in patients with hematological malignancies

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ABSTRACT

Umbilical cord blood (UCB) is an alternative source of stem cells for patients lacking a 9/10 or 10/10 HLA identical donor. However, after UCB transplantation, time to engraftment and immune recovery are prolonged, increasing the risk of fatal complications. Mesenchymal stromal cells (MSC) can support hematopoietic engraftment and have immunosuppressive effects.

The primary objective of this phase I/II multicenter study was to determine the feasibility and safety of UCB transplantation with co-infusion of third party MSC, as assessed by treatment related mortality (TRM) at day 100. Secondary objectives were engraftment, immune recovery, occurrence of graft versus host disease (GVHD), infections, disease free survival, relapse incidence and overall survival.

Eleven patients were grafted according to this protocol. Allogeneic transplantation after co-infusion appears feasible with 18 % TRM at day 100. Engraftment data show a median time of 16 days to neutrophil and 27 days to platelet recovery, which is shorter than what is usually reported after UCB transplantation. Only 1 episode of acute GVHD was reported.

In conclusion, MSC and UCB co-transplantation is feasible and might help overcome some of the drawbacks of UCB transplantation.

Introduction

Allogeneic stem cell transplantation is a standard treatment modality for various high-risk malignant and non-malignant hematological disorders [1]. Typically, stem cells will be collected from an HLA-compatible donor – either an HLA-identical sibling or a matched unrelated donor. However, approximately 30 % of patients will not have such a donor available [2]. For these patients, alternative donor sources such as haplo-identical related donors or umbilical cord blood (UCB) stem cells are considered [1]. There are some advantages to the use of UCB transplantation: firstly, the cells are readily available from a donor bank, secondly HLA compatibility requirements are less stringent and thirdly the incidence of acute or chronic graft-versus-host disease (GVHD) is limited [3–5]. However, there are some possible drawbacks to UCB as a source of stem cells. Time to hematopoietic and immune recovery is delayed resulting in an increase in infectious complications and increased transplant related morbidity and mortality [5]. Although for UCB transplantation, a lower mononuclear cell number is needed, one

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unit often does not contain enough cells to be able to transplant the average adult. This barrier has been overcome by the introduction of double UCB transplantation [6]. In 2005 Barker and colleagues reported outcome data of 21 patients treated with a double UCB transplantation in a phase 1/2 trial. None of the patients experienced graft failure and they observed a higher engraftment rate than previous studies with single cord blood units [7]. Cell dose correlates with non-relapse mortality, therefore strategies to increase cell dose such as double UCB transplant are mostly adopted in the treatment of adult patients [6].

Mesenchymal stromal cells (MSC) are non-hematopoietic multipotent cells that can be expanded ex-vivo from the bone marrow and several other tissues [8]. They can support and facilitate hematopoietic engraftment [9–11]. Because of their immunosuppressive qualities there is great interest to use these cells in the treatment and/or prevention of GVHD. Many groups have reported data on the use of MSC in the treatment of both acute and chronic GVHD. MSC do not express HLA class II and are therefore less susceptible to immune recognition, thus allowing the use of third party MSC for clinical applications. Preliminary reports have shown that co-transplantation of MSC and hematopoietic stem cells can improve engraftment and might lower the risk for GVHD occurrence [11–14].

Because of the need to overcome slow engraftment and high TRM in the setting of UCB transplantation, the Belgian Hematology Society designed a pilot study to investigate the feasibility and safety of combining MSC infusion with UCB infusion at the time of transplantation. The primary objective of the study was to evaluate the feasibility and safety of such an approach.

Materials and methods

Study design

We describe here a single arm, multicenter phase I-II pilot study. The aim of this study was to include 20 patients. A stopping rule of true rate of non-relapse mortality exceeding 40 % at day 100 was defined.

Patients lacking $a \geq 9/10$ HLA matched donor and with adequate UCB units available (either single or double cord) were eligible. At least a 4/6 match and minimally 3×10^7 total nucleated cells (TNC) in the graft(s) were required. If necessary, to reach a sufficient cell dose, double UCB transplantation was performed.

Transplant candidates between 15 and 60 years old could be included after informed consent. Patients were excluded in case of previous allogeneic stem cell transplantation, progressive malignant disease, significant organ damage (creatinine clearance $<$ 60 mL/min, AST/ALT $>$3x ULN and/or bilirubin $>$3 mg/dL, LVEF $<$50 %, DLCO $<$ 50 %), significant psychiatric or neurological disorder. Patients with an uncontrolled infection, HIV infection or pregnancy were also excluded from participation in this trial.

Patients were followed for 12 months after transplantation.

The study was approved by the Ethics Committees of the participating centers.

Study objectives

The primary objective of this study was to determine the feasibility of UCB HSCT with co- infusion of third-party mesenchymal stem cells as assessed by the treatment-related mortality at d100 after transplant.

Secondary endpoints were overall survival, relapse incidence, disease-free survival, hematopoietic recovery, immune recovery, infections, and incidence of acute and chronic GVHD.

Treatment plan

Investigators could opt for either myeloablative or reduced intensity conditioning. As myeloablative conditioning, cyclophosphamide 120 mg kg^{-1} (days −5 and −4) and total body irradiation (TBI) 12 Gy in 6 fractions (day −3, −2 and −1) were prescribed. GVHD prophylaxis consisted of antithymocyte globulin (ATG) (Thymoglobulin®) 7,5 mg kg^{-1} (days −4, −3 and −2) and cyclosporin A. Reduced intensity conditioning consisted of cyclophosphamide 50 mg kg^{-1} (day −6), Fludarabine 200 mg/m^2 (day −6 until −2) and TBI 2 Gy (day −1). Graft-versus-host disease prophylaxis consisted of ATG (Thymoglobulin®) 7,5 mg kg^{-1} (days −4, −3 and −2), cyclosporin A and mycophenolate mofetil.

Supportive care was performed according to local guidelines. Post-transplant G-CSF 5 μg/kg was administered daily until ANC was above 1000/μL for 3 consecutive days. Prophylactic anti-infectious therapy consisted of fluconazole or posaconazole, acyclovir and SMX/TMP.

GVHD was graded according to the Glucksberg criteria [15].

MSC expansion and co-infusion

Bone marrow collection and MSC expansion were performed at the Laboratory of Cell and Gene Therapy (LTCG) at the university of Liege as described previously [16]. After administration of 2 mg kg^{-1} methylprednisolone and an antihistaminic drug, thawed MSC were administered at a dose of 1–2 $\times$ 10^6/kg recipient weight at least one hour before administering the UCB. In case of double UCB, the 2nd UCB was administered 1 hour after the first.

Engraftment and immune reconstitution

Neutrophil engraftment was defined as the first of 3 consecutive days of absolute neutrophil count (ANC) $>$500/μL. Platelet engraftment was defined as a platelet count of $>$20,000/μL without transfusion support.

Chimerism studies (total white blood cells and CD3 positive cells) were performed on the day leucocyte count exceeded 1000/μL and further on day 40, 100, 180 and 365 after transplant. Bone marrow chimerism analysis was performed every 3 months during the first year post transplant. Flowcytometry based lymphocyte subset analyses (CD3, CD4, CD8, CD19, CD45RA, CD45RO and CD56) were performed on day 30, 60, 100, 180 and 365 after transplant.

Results

Patient characteristics

Between January 2011 and February 2017, 11 patients out of 13 potentially eligible patients were grafted according to protocol. One patient was excluded due to disease progression at admission for transplantation, and there was 1 screening failure. Median age of the included patients was 43 years (range 20–66 years); of these patients 6 were male and 5 females. One 66-year-old patient was included after waiver by the principal investigator, this was documented in the case report form. The majority of patients underwent an allogeneic stem cell transplantation for acute leukemia ($n = 8$). An overview of the patient characteristics is presented in Table 1.

Survival and GVHD

TRM at day 100 was 18 % and 36 % at day 365, overall mortality was 45 % at 12 months. At 12 months after transplantation 1 disease relapse was observed. The causes of death of the five patients during the study period were disease relapse; toxoplasmosis and invasive aspergillosis combined with a herpetic cerebral vasculitis; posterior reversible encephalopathy syndrome and multi-organ failure (MOF); euthanasia after suffering a CMV reactivation, pneumocystis pneumonia and MOF after veno-occlusive disease; and toxic encephalitis.

During the follow-up period of 12 months only 1 case of GVHD was reported: acute GVHD grade II.

Table 1
Overview of the characteristics of all patients included in the trial. (M = male, F = female, AML = acute myeloid leukemia, CR = complete remission, MDS = myelodysplastic syndrome, DLBCL = diffuse large B-cell lymphoma, RIC = reduced intensity conditioning, MAC = myeloablative conditioning, UCB = umbilical cord blood).

Median age (range)	43years (20–66years)
M/F	6/5
Underlying disease	
Acute leukemia	**8**
AML CR1	3
AML CR2	4
ALL CR1	1
MDS	**1**
DLBCL	**2**
Transplantation	
RIC/MAC	**4/7**
Single/double UCB	**2/9**
Median cell dose UCB (range)	**4,25 (3,06–5,79) x 10^7 TNC/kg**

Engraftment and immune reconstitution

Engraftment data show a median time of 16 days to neutrophil recovery (range 7–36 days) and a median of 27 days to platelet recovery (range 18–38) (Table 2). Six of the 11 patients grafted with MSC and UCB reached day 365 of these 5 could be evaluated for donor chimerism, chimerism analysis at day 365 was not performed for 1 patient All 5 evaluable patients showed full donor chimerism (Table 2). There was no graft failure 1 year after transplant in this trial.

Immunophenotyping to determine lymphocyte subsets was not performed regularly and insufficient data are therefore available on B-, T- and NK cell recovery to allow analysis. At day 30, 6/7 evaluable patients had a lymphocyte count > 200/μL. Total lymphocyte count (Table 2) was >500/μL 6 months after transplant in all patients still alive at that timepoint.

Infections

Table 3 provides an overview of infections reported in this study. Of the 11 patients grafted with MSC and UCB cells, 6 presented with viral infectious complications. CMV infection was most commonly reported: 5 episodes in 4 patients. EBV reactivation was observed in 3 patients and was complicated by post-transplant lymphoproliferative disorder (PTLD) in 1 patient. This patient finally succumbed to PTLD refractory to multiple lines of treatment >3 years after the MSC-UCB co-infusion. For 32 infectious complications, a causative microbiological agent could be identified, in 41 % of cases it was a viral infection.

Table 2
Overview of the outcome parameters in this trial. *median (range).

TRM at day 100	18 %
TRM at 12 months	36 %
Overall survival at 12 months	55 %
Disease relapse	1/11
GVHD	1/11
Engraftment data:	
Neutrophil engraftment	16 days (7–36 days)*
Platelet engraftment	27 days (18–38 days)*
Graft failure	0
Chimerism at 12 months	5/6 complete donor chimerism (6 patients reached day 365)
Timepoint (days)	**Lymphocyte count (/mm^3)**
100	700 (354–1648)* (n = 9/9)
180	1170 (600–2735)* (n = 7/8)
365	2220 (1230–2718)* (n = 4/6)

Table 3
Overview of infections reported in this study population.

Pathogens	Incidence
Bacteria	14 episodes
Fungal	5 episodes
Viral	13 episodes
CMV	5 episodes
EBV	3 patients (1 PTLD)

Discussion

Umbilical cord blood is an alternative source of stem cells for patients requiring a hematopoietic stem cell transplantation who do not have a matched sibling or unrelated donor.

In this phase I/II trial, we have investigated whether allogeneic transplantation after co-infusion of MSC and UCB transplantation is feasible and safe, using TRM at day 100 as the primary outcome.

MSC have been studied extensively in the context of hematopoietic stem cell transplantation. They have shown promise in the prevention of GVHD when co-transplanted in a cohort of non-myeloablative transplanted patients, without compromising the graft-versus-tumor effect compared to a historic matched cohort [17]. Additionally, MSCs have demonstrated efficacy in treating steroid-refractory acute GVHD, however, optimal dosing and administration schedules should still be explored [18]. Furthermore, MSC infusion might also play a role in addressing poor graft function, leading to enhanced hematological function post-allogeneic hematopoietic stem cell transplantation subsequent to a single intravenous administration of MSCs, as demonstrated by Servais et al. [19].

In our patient cohort, TRM at day 100 was 18 %. This compares favorably to the report of Laughlin and colleagues on single UCB transplantation in 2001 [5]. They found that 32 of 68 patients died in the first 3 months after transplanting due to conditioning toxicity and infections. In later reports, also including double UCBT, non-relapse mortality at 3 and 6 months varies between 14 and 22 % [7,20]. This improved survival between early and later UCB transplantation trials is attributed to improved patient selection, better supportive care, and infusion of higher cell doses [6]. In our – albeit small – study cohort, we found no excess TRM after MSC and UCB co-infusion compared to these earlier trials.

Delayed neutrophil and platelet engraftment as well as delayed immune recovery are of concern in UCBT, as this may lead to an increase in deleterious infectious and bleeding complications, and lead to increased TRM [20–24]. Also, cell dose is a factor that significantly impacts engraftment [6]. In our trial, most patients received a double cord blood transplantation, and all patients received a cell dose of at least 3×10^7 TNC/kg (single UCB dose was approximately $3{,}1 \times 10^7$ TNC/kg, for double UCB transplantation median cell dose was higher at $4{,}7 \times 10^7$ TNC/kg). Laughlin et al. reported neutrophil engraftment after a median of 27 days and platelet engraftment after a median of 58 days in a report on 68 single unit UCBT in 2001 [5]. Later studies show that neutrophil engraftment after double UCBT varies between 20 and 30 days, and median platelet recovery varies between 40 and 50 days [7,20,22,25]. Time to engraftment might be an important prognostic factor in UCBT. Brunstein and colleagues compared double UCBT to matched related, unrelated and mismatched unrelated donor transplant. They found that TRM was highest in the double UCBT, however this was only maintained if neutrophil recovery was delayed beyond 26 days [22]. Different strategies have been studied to improve engraftment after UCBT, thereby decreasing infectious complications. Anand et al. expanded UCB units with nicotinamide (NiCord) and compared this to single and double CBT. Nicotinamide inhibits differentiation and enhances the functionality of the haematopoietic progenitor cells during ex vivo expansion. They found accelerated neutrophil engraftment in the NiCord cohort with a median time to engraftment of 12,5 days versus 26

days in the control group. This correlated with less grade 2–3 infections in the NiCord treated patients [26]. Another approach that has been studied is co-transplantation of haploidentical stem cells (Haplo-Cord) and UCB. Van Besien and colleagues compared 97 patients treated with the Haplo-Cord protocol (single UCB + *T*-cell depleted haploidentical stem cells) to 193 patients treated with double UBCT. By day 30, 90 % of Haplo-Cord patients had attained neutrophil recovery versus 82 % of patients in the double cord group. There was a clear difference in platelet recovery: 58 % of Haplo-Cord patients had platelet recovery at day 30 compared to 12 % of double UCBT patients [27]. In our setting of co-transplantation of MSC and cord blood cells time to neutrophil and platelet recovery was clearly acceptable with a median of 16 and 27 days, respectively. There were no graft failures. Although this is a small cohort, this might indicate that co-infusion of MSC and UCB shortens time to engraftment, especially platelet engraftment.

Some authors argue that the speed of lymphocyte recovery is also linked to the risk of (fatal) infectious complications [28]. Unfortunately, lymphocyte phenotyping was not performed regularly in our study, therefore we do not have enough data on B- and T-cell recovery. We did find that total lymphocyte count returned to normal at 6 months after co-transplantation and nearly all patients evaluated at day 30 reached a lymphocyte count $> 200/\mu L$. Due to the small sample size we cannot confirm the benefit of a speedy lymphocyte recovery. Only one patient died of opportunistic infections after day +180, with a lymphocyte count of 1170/μL.

Given the immunosuppressive qualities of MSC, there might be a concern for excess infectious complications. However, previous studies have shown that the use of MSC does not increase the risk for fatal infections per se [11]. In our study cohort we observed various infectious complications, viral infections accounting for 41 % of all causative agents identified and at the end of follow-up (median follow-up 12 months, range 1,5–12 months), 2 deaths were attributable to infection. This concurs with the data presented by Parody et al. they observed a higher incidence of infections in UCBT patients as compared to bone marrow or peripheral blood stem cell transplantation, but this did not result in a difference in infection related mortality between both groups [23]. In our small cohort co-infusion of MSC and UCB does not appear to be complicated by excess infectious episodes, however, this finding needs to be confirmed in a bigger cohort.

Since MSC could mitigate occurrence or severity of graft versus host disease and UCBT appears to induce less graft versus host disease than (mis)matched unrelated peripheral blood stem cell transplantation, this is also an interesting outcome parameter to study [11,29]. In our small cohort GVHD incidence was low despite HLA mismatching: only 1 patient developed grade II acute GVHD. We did not observe an excess relapse rate in this cohort of mainly high-risk patients.

In conclusion, this trial shows that allogeneic stem cell transplantation after co-infusion of MSC and UCB in the treatment of haematological disorders is feasible and safe. Additionally, our data suggest an acceptable haematopoietic recovery and a very low rate of GVHD, as compared to other published data. However, recruitment in this study was very slow, this is probably due to the introduction of post-transplantation cyclophosphamide and the progressive shift of cord to haplo-identical transplantation witnessed in the EBMT network over the past 10 years [30]. Considering the slow accrual rate in this trial at the start and the competition with haplo-identical donors in recent years, the BHS steering committee decided to stop the trial despite these encouraging results. However, in the current era UCB transplantation remains a valuable option: overall survival after UCB transplantation is similar compared with haploidentical and mismatched unrelated donors, stem cells are readily available for urgent transplants and some data suggest it is even better than mismatched donors in high-risk AML patients [31]. Our data show that co-infusion of MSC and UCB might overcome some of the drawbacks of UCB transplantation.

CRediT authorship contribution statement

Simon Planken: Formal analysis, Investigation, Methodology, Validation, Writing – review & editing, Writing – original draft. **Ann De Becker:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing, Writing – original draft, Supervision. **Tessa Kerre:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. **Hélène Schoemans:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. **Frédéric Baron:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. **Carlos Graux:** Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. **Ivan Van Riet:** Formal analysis, Investigation, Methodology, Validation, Writing – review & editing, Writing – original draft. **Chantal Lechanteur:** Investigation, Methodology, Validation, Writing – review & editing. **Etienne Baudoux:** Investigation, Methodology, Validation, Writing – review & editing. **Rik Schots:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing, Writing – original draft, Supervision. **Yves Beguin:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review & editing, Supervision.

Conflicts of interest

Helene Schoemans: reports having received personal fees from Incyte, Janssen, Novartis, Sanofi and from the Belgian Hematological Society (BHS), as well as research grants from Novartis and the BHS, all paid to her institution and not directly related to this work. She has also received non-financial support (travel grants) from Gilead, Pfizer, the EBMT (European Society for Blood and Marrow transplantation) and the CIBMTR (Center for International Bone Marrow Transplantation Research).

The other authors (SP, ADB, TK, FB, CG, IVR, CL, EB, RS, YB) didn't report any conflicts of interest.

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References

[1] Snowden JA, et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant 2022;57(8):1217–39.
[2] Tiercy JM. How to select the best available related or unrelated donor of hematopoietic stem cells? Haematologica 2016;101(6):680–7.
[3] Rocha V, et al. Graft-versus-host disease in children who have received a cord-blood or bone marrow transplant from an HLA-identical sibling. New Engl J Med 2000;342(25):1846–54.
[4] Gluckman E, et al. Outcome of cord-blood transplantation from related and unrelated donors. Eurocord transplant group and the European blood and marrow transplantation group. N Engl J Med 1997;337(6):373–81.
[5] Laughlin MJ, et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. New Engl J Med 2001;344(24):1815–22.
[6] Ballen K. Umbilical cord blood transplantation: challenges and future directions. Stem Cells Transl Med 2017;6(5):1312–5.
[7] Barker JN, et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood 2005;105(3):1343–7.
[8] Pittenger MF, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284(5411):143–7.
[9] Koç ON, et al. Rapid hematopoietic recovery after coinfusion of autologous-blood stem cells and culture-expanded marrow mesenchymal stem cells in advanced breast cancer patients receiving high-dose chemotherapy. J Clin Oncol 2000;18(2). p. 307-307.
[10] Majumdar MK, et al. Human marrow-derived mesenchymal stem cells (MSCs) express hematopoietic cytokines and support long-term hematopoiesis when differentiated toward stromal and osteogenic lineages. J Hematother Stem Cell Res 2000;9(6):841–8.
[11] De Becker A, Van Riet I. Mesenchymal stromal cell therapy in hematology: from laboratory to clinic and back again. Stem Cells Dev 2015;24(15):1713–29.

[12] Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105(4):1815–22.
[13] Le Blanc K, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet 2008;371(9624):1579–86.
[14] Remberger M, Ringdén O. Treatment of severe acute graft-versus-host disease with mesenchymal stromal cells: a comparison with non-MSC treated patients. Int J Hematol 2012;96(6):822–4.
[15] Glucksberg H, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974;18 (4):295–304.
[16] Lechanteur C, et al. Clinical-scale expansion of mesenchymal stromal cells: a large banking experience. J Transl Med 2016;14(1):145.
[17] Baron F, et al. Cotransplantation of mesenchymal stem cells might prevent death from graft-versus-host disease (GVHD) without abrogating graft-versus-tumor effects after HLA-mismatched allogeneic transplantation following nonmyeloablative conditioning. Biol Blood Marrow Transplant 2010;16:838–47.
[18] Servais S, et al. Infusion of bone marrow derived multipotent mesenchymal stromal cells for the treatment of steroid-refractory acute graft-versus-host disease: a multicenter prospective study. Oncotarget 2018;9(29):20590–604.
[19] Servais S, et al. Multipotent mesenchymal stromal cells as treatment for poor graft function after allogeneic hematopoietic cell transplantation: a multicenter prospective analysis. Front Immunol 2023;14:1106464.
[20] Ballen KK, et al. Double unrelated reduced-intensity umbilical cord blood transplantation in adults. Biol Blood Marrow Transplant 2007;13(1):82–9.
[21] Rocha V, et al. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Engl J Med 2004;351(22):2276–85.
[22] Brunstein CG, et al. Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood. Blood 2010; 116(22):4693–9.
[23] Parody R, et al. Severe infections after unrelated donor allogeneic hematopoietic stem cell transplantation in adults: comparison of cord blood transplantation with peripheral blood and bone marrow transplantation. Biol Blood Marrow Transplant 2006;12(7):734–48.
[24] Szabolcs P, Cairo MS. Unrelated umbilical cord blood transplantation and immune reconstitution. Semin Hematol 2010;47(1):22–36.
[25] Rocha V, et al. Unrelated cord blood transplantation: outcomes after single-unit intrabone injection compared with double-unit intravenous injection in patients with hematological malignancies. Transplantation 2013;95(10):1284–91.
[26] Anand S, et al. Transplantation of Ex vivo expanded umbilical cord blood (NiCord) decreases early infection and hospitalization. Biol Blood Marrow Transplant 2017; 23(7):1151–7.
[27] van Besien K, et al. Reduced intensity haplo plus single cord transplant compared to double cord transplant: improved engraftment and graft-versus-host disease-free, relapse-free survival. Haematologica 2016;101(5):634–43.
[28] Burke MJ, et al. Early lymphocyte recovery and outcomes after umbilical cord blood transplantation (UCBT) for hematologic malignancies. Biol Blood Marrow Transplant 2011;17(6):831–40.
[29] Stagg J, Galipeau J. Mechanisms of immune modulation by mesenchymal stromal cells and clinical translation. Curr Mol Med 2013;13.
[30] Passweg JR, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European society for blood and marrow transplant activity survey report. Bone Marrow Transplant 2017;52(6):811–7.
[31] Holtan SG, et al. Optimizing donor choice and GVHD prophylaxis in allogeneic hematopoietic cell transplantation. J Clin Oncol 2021;39(5):373–85.