Research Article

Stem Cell & Regenerative Medicine

Mesenchymal Stem Cells Transplantation in Hematological Patients with Graft-Versus-Host Disease: Characteristics and Risk Factors for Infectious Complications

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Received: 02 June 2017; **Accepted:** 19 June 2017

Citation: Igor Stoma, Igor Karpov, Svetlana Krivenko, et al. Mesenchymal Stem Cells Transplantation in Hematological Patients with Graft-Versus-Host Disease: Characteristics and Risk Factors for Infectious Complications. Stem Cells Regen Med. 2017; 1(1): 1-6.

ABSTRACT

Background: *The role of MSCs in infection prevention and treatment is still discussed in transplant and hematological patients. The spectrum and risk factors for infections after MSCs transplantation in patients with GVHD have not been studied before.*

Objective: *to determine the risk factors and characteristics of infectious complications in patients received mesenchymal stem cell transplantation as a treatment for GVHD.*

Methods: *A prospective observational study was performed to evaluate the risk factors and characteristics of infectious complications after MSCs transplantation in adult patients having GVHD. Forty episodes of MSCs transplantation in patients with GVHD after allogeneic HSCT were enrolled in the study. MSCs were given at a median dose of 1.44 (interquartile range 1.02-1.97) mln cells/kg per infusion at 76 days (interquartile range 34-185 days) after HSCT. Data relating to age, gender, date and type of transplantation, characteristics of MSCs, infectious agents and antimicrobial therapy and prevention regimens were prospectively collected in all of the enrolled patients. The episode of proven infectious complication after MSCs transplantation was set as a primary outcome.*

Results: *There were totally 40 cases of MSCs transplantation in patients with acute or chronic GVHD. Among the registered infectious episodes were viral infections (CMV-associated disease, EBV-associated disease), invasive pulmonary aspergillosis, bacterial bloodstream infections and pneumonia. Progression of main disease was shown to be a risk factor for developing aspergillosis and HSCT from unrelated donor recently was main independent risk factor for bacterial infectious complications. Patients with acute form of GVHD showed a trend to have an increased risk of developing CMV-disease. Cryopreservation of MSCs has shown no significant impact on risk of infections after MSC transplantation.*

Conclusion: *Viral infections (CMV-disease, EBV-viremia), invasive pulmonary aspergillosis, bacterial bloodstream infections and pneumonia are common complications in adult patients received MSCs transplantation due to GVHD. Risk factor for invasive pulmonary aspergillosis is progression of main disease, and unrelated HSCT mainly increases risk of bacterial infectious complications after MSC transplantation in patients with GVHD, while cryopreservation of MSCs has shown no significant impact on risk of infections after MSC transplantation.*

Keywords
Mesenchymal stem cell transplantation, Infectious complications, Risk factors, Graft-versus-host disease.

Introduction
Mesenchymal stem cells (MSCs) - are multipotent adult stem cells that are found in multiple tissues, including umbilical cord, bone marrow and fat tissue. This sells are well known for repairing tissue, supporting hematopoiesis, and modulating immune and inflammation response. MSC are approved and widely used in patients with hematological diseases, hematopoietic stem cell transplant (HSCT) recipients, which have poor graft function and graft-versus-host disease (GVHD). GVHD is one of the most common serious complication of allogeneic HSCT and remains a leading cause of mortality in HSCT recipients all over the world [1-3].

Currently, the role of MSCs in infection prevention and treatment is still discussed in transplant and hematological patients. Some of the recent studies showed that MSC transplantation increased the risk of infectious complications by suppressing T-cell response and secreting VEGF and IL-6 [4-6]. However, other published studies showed that the incidence of infections did not increase after MSC transplantation treatment for GVHD and engraftment failure [7-10].

Methods
Setting and design
Republican center for hematology and bone marrow transplantation is a national clinical and research center for adult patients situated in Minsk, Republic of Belarus. Clinical departments are based in 9th clinical hospital of Minsk, which is one of the largest teaching hospitals in Belarus performing more than a hundred HSCT every year. This center has 150 beds including intensive care unit for patients with various hematological diseases and patients undergoing HSCT. Center also includes: microbiology laboratory, laboratory of bone marrow separation and freezing, laboratory of cellular biotechnology, HLA-typing laboratory and clinical diagnostics laboratory.

An observational study was performed to estimate the possible modern risk factors for infections in patients receiving MSCs transplant as a treatment for GVHD. Diagnosis of GVHD was made according to the literature criteria defined by the Consensus Workshop [11,12]. Patients were included in the MSCs transplantation list, if they developed a GVHD after an allogeneic HSCT. Patients were excluded from the study if they had severe organ insufficiency and/or any abnormality in vital signs. The period of observation for patients received MSCs transplant was set up to one year in the study.

Proven case of infection after the MSCs transplantation was taken as a primary outcome in the study. As a covariates included in analysis were taken: age and gender characteristics, type of allogeneic HSCT (related/non-related), primary disease, main disease progression, level of neutropenia on the first day of infectious complication, type of GVHD (acute/chronic), source, amount and characteristics of MSCs, immunological characteristics of patients with GVHD. Among concurrent diseases of patients included in the study were diabetes mellitus, chronic gastritis and chronic cystitis (each registered only in a single patient).

The study was approved by the Scientific and Ethical Committees of Republican center for hematology and bone marrow transplantation in Minsk, Republic of Belarus.

Data collection
Epidemiological, clinical and laboratory data were prospectively collected in each adult patient with GVHD undergoing MSCs transplantation from September 2010 to September 2016. Cultures for bacterial and fungal infections were obtained with standard precautions from all patients with fulfilled criteria of febrile neutropenia or other signs of infection (including biomarkers as procalcitonin, presepsin, C-reactive protein, galactomannan) after MSCs transplantation, with identification and *in vitro* antibiotic susceptibility testing being performed with standard means. As a criteria of febrile neutropenia were taken: single oral temperature measurement of >38.3πC or a temperature of >38.0πC sustained over a 1-h period in a patient with absolute neutrophil count (ANC) of <500 cells/mm^3 or an ANC that is expected to decrease to <500 cells/mm^3 during the next 48 hours [13]. The diagnostic criteria of viral infections (CMV, VZV, EBV, HSV) during the study were defined by published recommendations from the Infectious Diseases working party of the EBMT and guidelines from European Conference on Infections in Leukemia [14,15]. Diagnostic criteria of infections caused by *Aspergillus spp.* and *Candida spp.* were defined by Practice Guidelines for the Diagnosis and Management of Aspergillosis [16], and Clinical Practice Guideline for the Management of Candidiasis [17].

Transplantation procedure and management of infections
HSCT was performed according to institutional protocols. Briefly, the most frequent myeloablative conditioning regimens were busulfan and cyclophosphamide (BuCy), cyclophosphamide and total body irradiation (Cy+TBI). GVHD prophylaxis regimens included cyclosporine, methotrexate and tacrolimus. All patients received methylprednisolone combined with calcineurin inhibitors as first-line treatments for acute GVHD. Anti-thymocyte globulin was administered in cases of unrelated donors.

MSCs were isolated and cultivated from bone marrow aspirates and adipose tissue by standard laboratory techniques. Immunologic characteristics of MSCs were evaluated with flow cytometry with expression of antigens: $CD45^-$ $CD34^-$ $CD90^+$ $CD105^+$ $CD13^+$ (Beckman Coulter).

Standard antibacterial prophylaxis in was based on fluoroquinolones (mainly ciprofloxacin 0.5 g BID orally) starting from the initiation of conditioning regimen until the time, when level of neutrophils in peripheral blood exceeds 500 cells/mm3. No routine antibacterial prophylaxis against *Streptococcus pneumoniae* was administered. The institution's standard protocols of initial empirical antibiotic

therapy for febrile neutropenia included cephalosporins (cefepime or cefoperazone/sulbactam) or carbapenems (imipenem/cilastatin or meropenem) depending on risk group of a patient with an addition of vancomycin in case of possible infection caused by gram-positive pathogens [18]. Antifungal prophylaxis with fluconazole was prescribed to non-neutropenic patients and micafungin was used as antifungal prophylaxis in patients undergoing allogeneic HSCT with neutropenia. Prophylaxis against *Pneumocystis jirovecii* with trimethoprim-sulfametoxazole was administered to all patients until the immunologic recovery after HSCT. Prophylaxis of infections caused by herpes simplex viruses was performed by acyclovir. Real time quantitative polymerase chain reaction (PCR) was used for monitoring CMV and EBV DNA levels in HSCT patients weekly during the pre-engraftment period and after MSCs transplantation, with ganciclovir used as first line pre-emptive therapy in case of possible active CMV infection. CMV-DNA and EBV-DNA were monitored twice a week until GVHD was resolved or until the end of antiviral therapy.

During the period of severe neutropenia (ANC<100 cells/mm^3) all patients were isolated in single rooms with positive pressure, laminar air flow and high-efficiency particulate air filtration. After the ANC exceeded 100 cells/mm^3 some of the clinically stable patients were moved to the intensive care department with 2 patients in a room and positive air pressure.

Statistical analysis

Methods of non-parametric statistics for categorical (Chi-squared or Fisher's exact tests) and quantitative (Mann-Whitney U-test, Odds Ratio, Kruskal-Wallis test) were used in statistical analysis. The distribution of the variable was determined by the Shapiro-Wilk test. Multivariate analysis was performed by means of logistic regression methods for categorical variables with $p \leq 0.2$ in previously performed univariate analysis. Data processing and analysis was performed using MedCalc Statistical Software v. 17.2 (MedCalc Software bvba, Ostend, Belgium), and results were regarded as statistically significant when $p<0.1$.

Results

During the study period there were totally 40 procedures of MSCs transplantation performed in patients with GVHD. Median time from HSCT to MSCs transplantation was 76 days (interquartile range 34-185 days). The median number of MSCs transplantations per patient was 2 with interquartile range from one to three and maximum number of 5 transplantation procedures per patient.

Tables 1 and 2 show the baseline demographic and clinical characteristics of the patients and MSCs transplants in the study.

Baseline characteristics		Absolute number of MSCs transplants (n=40), %
Age	Years, Median, Interquartile range	34 (30-42)
Sex	Female	28 (70.0)
Type of allogeneic HSCT	Related	17 (42.5)
	Unrelated	23 (57.5)
Primary disease	Acute myeloid leukemia	13 (32.5)
	Hodgkin's lymphoma	10 (25.0)
	Chronic myeloid leukemia	9 (22.5)
	Myelodysplastic syndrome	6 (15.0)
	Acute lymphocytic leukemia	2 (5.0)
Primary disease stage	Progression	19 (47.5)
	Remission	21 (52.5)
Level of neutropenia	100-500 cells/mm^3	6 (15.0)
	>500 cells/mm^3	34 (85.0)
MSCs donor type	Related	14 (35.0)
	Unrelated	26 (65.0)
MSCs source	Bone marrow	14 (35.0)
	Adipose tissue	26 (65.0)
Passage of MSCs	P1	6 (15.0)
	P2	25 (62.5)
	P3	6 (15.0)
	P4	3 (7.5)
Cryopreservation of MSCs		32 (80.0)
Type of GVHD	Acute	31 (77.5)
	Chronic	9 (22.5)
GVHD involved organs	Gastrointestinal	15 (37.5)
	Liver	13 (32.5)
	Skin	12 (30.0)

Table 1: Demographical and clinical baseline characteristics of patients, transplants and GVHD in the study.

MSC transplant characteristics	Median (interquartile range)
Amount of cells per infusion (mln/kg)	1.44 (1.02-1.97)
Vitality of MSC (%)	97.0 (95.0-98.0)
MSCs cultivation time (days)	22 (19.5-28.5)

Table 2: Laboratory characteristics of MSCs transplants in the study (n=40).

Microbiological data concerning the causes of infectious complications after has shown the major impact of viral infections (mainly CMV) and fungal infections (invasive pulmonary aspergillosis). There were no bloodstream infections caused by *Candida spp.* registered in the study what may be explained by broad use of micafungin as a prophylaxis antifungal regimen in allogeneic HSCT recipients. Bacterial infections were mostly presented by bloodstream infections (caused by *K. pneumoniae*, *E. faecalis, E. coli*) and *pneumonia*. The period of observation for patients received MSCs transplant was set up to one year in the study, but all of the infectious episodes occurred during the

100-day period after MSCs transplantation. Not all of the patients in the study had serious prolonged febrile episodes, some of the infectious diseases episodes (17/42.5%) were associated with low fever for a short time period. It is interesting to underline that 85% of patients in the study did not have neutropenia at the onset of infectious complication. Table 3 and Picture 1 show the spectrum of infections registered in patients received MSCs transplantation as a treatment of GVHD in the study.

Pathogen		Absolute number	Frequency of infection, %
Viral infections	CMV	12	30.0
	EBV	4	10.0
Bacterial infections	Bloodstream infection	8	20.0
	Pneumonia	5	12.5
Fungal infections	Invasive pulmonary aspergillosis	11	27.5

Table 3: Causes of infections in patients received MSCs transplant as a treatment of GVHD.

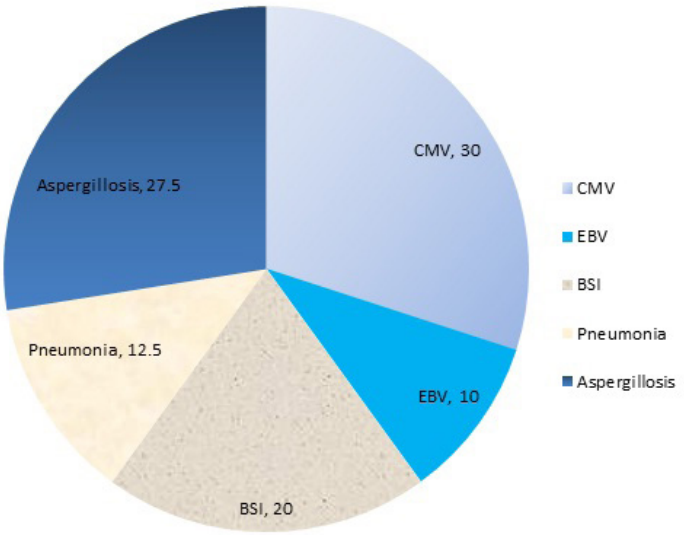

Figure 1: Causes of infectious complications after MSCs transplantation, %.

Therefore, among the causes of infections in patients with GVHD after MSCs transplantation were CMV-disease and invasive pulmonary aspergillosis. In the risk factor analysis part of the study all of the covariates were included in the univariate analysis. Risk factors, which have shown statistical significance ($p<0.2$) in univariate analysis, subsequently were checked for independency in multivariate analysis performed by means of logistic regression. Results of multivariate analysis are shown in Table 4.

Patients with acute form of GVHD showed a trend to have an increased risk of developing CMV-disease (OR 12.18; 95% CI 0.65-22.84; p=0.1092), and younger patients in the study had also a higher chance of CMV reactivation (reciprocal OR 0.89; 95% CI 0.79-0.99; p=0.1092). The immunological basis for increased risk of CMV-disease in acute GVHD should be further investigated on larger groups of patients. Progression of main diseases was found to be a main independent risk factor for development of invasive pulmonary aspergillosis (OR 5.24; 95% CI 1.77-15.21; p=0.0792). And it was proven that as in published studies on risk factors in HSCT [19], the patients with hematopoietic stem cell transplant from unrelated donor remain high risk for bacterial infections even after MSCs transplantation (OR 4.57; 95% CI 1.44-42.67; p=0.0018).

Risk factor		Odds ratio	95% confidence interval	*P*
Aspergillosis	Age	0.82	0.65-1.03	0.0792
	Progression of main disease	5.24	1.77-15.21	
	Chronic GVHD	8.51	0.53-23.70	
	Adipose-tissue derived MSCs	1.37	0.10-19.59	
CMV	Age	0.89	0.79-0.99	0.1092
	Progression of main disease	0.18	0.02-1.60	
	Adipose-tissue derived MSCs	4.57	0.82-25.59	
	Acute GVHD	12.18	0.65-22.84	
Bacterial infections	HSCT from unrelated donor	4.57	1.44-42.67	0.0018
	MSCs from bone marrow	4.40	0.81-23.78	

Table 4: Results of multivariate analysis of risk factors for infectious complications in patients received MSCs transplantation as a treatment of GVHD after allogeneic HSCT.

Patients with acute form of GVHD showed a trend to have an increased risk of developing CMV-disease (OR 12.18; 95% CI 0.65-22.84; p=0.1092), and younger patients in the study had also a higher chance of CMV reactivation (reciprocal OR 0.89; 95% CI 0.79-0.99; p=0.1092). The immunological basis for increased risk of CMV-disease in acute GVHD should be further investigated on larger groups of patients. Progression of main diseases was found to be a main independent risk factor for development of invasive pulmonary aspergillosis (OR 5.24; 95% CI 1.77-15.21; p=0.0792). And it was proven that as in published studies on risk factors in HSCT [19], the patients with hematopoietic stem cell transplant from unrelated donor remain high risk for bacterial infections even after MSCs transplantation (OR 4.57; 95% CI 1.44-42.67; p=0.0018).

Higher vitality of MSC was associated with lower risk of developing CMV infection in conducted analysis (H=3.169, 1 d.f., p=0.072), while in case of patients with aspergillosis or bacterial infections no such associations were shown. Total amount of cells in transplant biological material used for infusion and adjusted to weight of the recipient had no association with infection risk in

the study (H=0.151, 1 d.f., p=0.697). In the performed analysis of possible impact of MSCs cryopreservation on incidence of infectious complications in post-transplantation period there were no associations found between any type of infections and cryopreserved MSCs being used (X2=0.152, p=0.696).

Discussion

MSCs transplantation has been included in medical practice worldwide as a possible treatment for GVHD since the first published article by Le Blanc et al. in 2004 [20]. Relation between MSCs transplantation and the risk of infections because of MSCs immunosuppression qualities were controversial [21–23]. There were studies published recently discussing the effects of MSCs transplantation on the host inflammatory immune response and possible direct antimicrobial activity of MSCs by means of secreting soluble factors [24]. Meisel et al. have discussed the possible mechanisms of antimicrobial activity of MSCs in studies with indoleamine 2,3-dioxygenase [4]. However, these data are mainly based on *in vitro* experiments and there is lack of information on spectrum and possible risk factors for infections in MSCs transplantation. In this study, we observed the spectrum of infectious complications and evaluated possible risk factors (recipient and transplant characteristics) for developing infections after MSCs transplantation in patients with GVHD. As the results of conducted analysis it was shown that patients with acute form of GVHD showed a trend to have an increased risk of developing CMV-disease, what corresponds with previous published studies on risk factors for CMV reactivation [26] and needs further studies to be explained in details as much as the possible impact of age on risk of CMV reactivation. Association between progression of main hematological diseases and risk of aspergillosis in GVHD patients after MSCs transplantation shown in the study should be taken into account when choosing the regimen of antifungal prophylaxis, with additional importance of prophylaxis with voriconazole in GVHD patients. Finally, the unrelated allogeneic HSCT should be defined as the most important risk factor for developing bloodstream infections and bacterial pneumonia in patients with GVHD and MSCs transplantation. Cryopreservation of MSCs has shown no significant impact on risk of infections after MSCs transplantation, while the level of *in vitro* vitality of MSCs was associated with their activity against CMV reactivation, what should be discussed in larger clinical studies.

Study limitations

The main limitation of our study was relatively small sample of MSCs transplantation cases, but concerning the cost of GVHD treatment, cost of every MSCs transplantation and HSCT procedure, even such numbers of observations may be important. Also, this study was conducted in one clinical center, but it is important to mention, that this center performs MSCs transplantation for patients from all parts of the country.

Conclusions

In conclusion, among the risk factors for infectious complications after MSCs transplantation are progression of main disease (for aspergillosis) and unrelated HSCT in the past history (for bacterial bloodstream infections and pneumonia). Patients with acute form of GVHD showed a trend to have an increased risk of CMV reactivation. Cryopreservation of MSCs has shown no significant impact on risk of infections after MSCs transplantation. Also, it was shown that in cases with higher level of *in vitro* vitality of MSCs the risk of CMV reactivation was lower, what should be checked in future larger studies.

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