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Invasive fungal diseases in patients after allogeneic hematopoietic stem cell transplantation?

N.I. Zubarovskaya, E.V. Semenova, N.V. Stancheva, V.N. Vavilov, I.V. Kazantsev, Yu.G. Vasilieva, N.N. Klimko, B.V. Afanasyev

R.M. Gorbacheva Memorial Institute of Children Hematology and Transplantation, St. Petersburg Pavlov State Medical University, St. Petersburg, Russia

Correspondence: Natalia Zubarovskaya, Memorial R.M. Gorbacheva Institute of Children Hematology and Transplantation, St. Petersburg Pavlov State Medical University, 6/8, Tolstoy str., St. Petersburg, 199044, Russia, Tel.: +7-812-499-68-19, Fax: +7-812-234-06-16, E-mail: zoubarov@mail.ru

Summary

Background: The aim of the study was to determine the risk factors and incidence of invasive fungal diseases (IFD) in patients after allo-HSCT.

Materials and patients: In our department 221 allo-HSCTs from related, unrelated and haploidentical donors were performed between October 2000 and June 2008. In the study were enrolled 131 patients younger than 21 and 90 patients older than 21 years old after allo- HSCT. In 87 (37%) patients allo-HSCT was conducted in non-remission.

Results: The incidence of IFD after allo-HSCT remains high. Depending on donor characteristics (HLA-matched related, unrelated or haploidentical donor) it is 28%, 35%, and 38% respectively. Looking at age it is 32% for patients ≤21 years, and 27% for patients >21 years. In the RIC regimen group IFD was diagnosed in 34% of younger (≤21 years) patients and 31% of older (>21 years); and for the MC group it amounted to 32% for younger ($p>0.05$) and 17% for elder age groups ($p<0.05$). Neither the rate of IFD in both age groups, the source of HSC and/or rate of post-transplant engraftment were found to independently exert influence on the incidence of IFD following allo-SCT.
In multifactor analysis was noticed correlation between HSC sources and age.
IFD incidence was 1.8-fold higher in elder relapsed patients after related allo-HSCT with RIC ($p<0.05$). Contrariwise, in this group the incidence of IFD was low in patients that underwent HSCT in remission and received PBSC ($p<0.05$). The influence of transplant type was also noticed in the younger (≤21 years) group: the probability of IFD development was much higher in relapsed patients after BM allo-HSCT with RIC ($p<0.05$). It was noticed that the disease stage, grade I–IV mucositis ($p<0.05$), and extensive cGVHD ($p<0.05$) were the most prominent risk factors for IFD development. When these factors are present no difference was seen in groups with different conditioning regimens and HSC sources.
In patients >21 years IFD incidence increased by inclusion of ATG in the conditioning regimen ($p<0.05$).

Conclusions: The main risk factors that influence the incidence of IFD after allo-HSCT in all age groups are the stage of the disease, mucositis development, and extensive form of cGVHD. After diagnosis of IFD 12-weeks OS is 50%. IFD impairs 5-years OS after allo-HSCT.

Keywords: allogeneic stem cell transplantation, invasive mycoses, risk factors of invasive mycoses

Introduction

Hematopoietic stem cell transplantation (HSCT) is one of the most efficient methods in the treatment of hematological and oncological disorders. Each year, some 25,000 autologous HSCTs (auto-HSCT) and 15,000 allogeneic HSCTs (allo-HSCT) from donors with different degrees of HLA compatibility (related, unrelated, and haploidentical donors) are performed worldwide.

In spite of the advances in the treatment of allo-HSCT, infectious complications, especially invasive fungal diseases (IFD) remain one of the main causes of high morbidity and mortality in the allo-HSCT recipients cohort [3], with one of the most significant factors being the difficultly of diagnosis in the early (up to 100 days from HSCT) and the late (more than 100 days) post-HSCT periods [17]. IFD develop in 5–18% of allo-HSCT recipients, while after auto-HSCT the incidence of fungal infections is much lower, i.e., 1.1% [4]. The overall mortality from IFD in the first year after diagnosis is 70–93%. Most are diagnosed postmortem.

The incidence of IFD is influenced by the HLA-compatibility between donor and recipient. In related allo-HSCT the incidence of IFD is 3.7%, and when the donor and recipient are partially matched it rises to 5.9% [6]. This distinction is caused by the profound and prolonged immunosuppression that is employed as "graft-versus-host" disease (GVHD) prophylaxis [7].

In the last few years allo-HSCT has become a treatment option for many more patients [8] due to the practical application of conditioning regimens with reduced intensity and toxicity [5], implementation of new immunosuppressive drugs, and more effective regimens of treatment for acute GVHD (aGVHD) and chronic GVHD (cGVHD) [8]. The treatment of IFD in patients with GVHD is complicated by the fact that in most clinical situations sufficient response to antifungal therapy can be achieved only by diminishing the intensity of immunosuppression [8], and this option is often unacceptable.

IFD has a different etiology and in general the incidence of IFD caused by mold fungi such as *Aspergillus fumigatus*, *Fusarium* species, and *Zygomycetes* species [4] has increased. This can be attributed not only to the actual increase in number of mold infections after allo-HSCT, but also to the development of better diagnostic tools [10].

In spite of this general increase of IFD, Zygomycetes spp. infection is diagnosed in less than 2% of the cases [11]. The incidence of invasive candidiasis has decreased from 77% to 42%, but at the same time invasive aspergillosis (IA) rates increased from 13% to 29% [4]. Currently, the most common etiological agents of invasive candidiasis are *C. albicans, C. tropicalis, C. glabrata, C.parapsilosis and C. krusei*.

In summary, infectious complications, along with relapses of the disease and GVHD, remain one of the most significant factors that determine the effectiveness of allo-HSCT in the treatment of hematologic, oncologic, and congenital diseases [1,2].

Research purpose. To determine the etiology, incidence, and risk factors of IFD in patients suffering from different hematological diseases who underwent allo-HSCT (a single center experience).

Materials and methods

Between October 2000 and June 2008, 221 patients (pts) underwent allo-HSCT in the R. M. Gorbacheva Memorial Institute of Children Hematology and Transplantation (ICHT) (former BMT Clinic) of Saint Petersburg's State Pavlov Medical University (SPbSMU). The age range of patients was from 1 to 66 years; 131 of the patients were younger than 21 years, and 90 of them were older than 21.

In most of the cases, if the family member was HLA-compatible, related allo-HSCT was performed. For the other patients an unrelated donor was searched for and activated in the international donor database. In the absence of fully-matched donors haploidentical HSCT (haplo-HSCT) was performed (usually from the patient's mother). Overall, 135 pts underwent unrelated allo-HSCT, 77 pts related allo-HSCT, and 9 pts haplo-HSCT.

Allo-HSCT was performed in 91 pts with acute lymphoblastic leukemia (ALL), 57 pts with acute myeloid leukemia (AML), 2 pts with acute biphenotypic leukemia (BiAL), 25 pts with chronic myelo- and lymphoproliferative disorders (CMPD, CLPD), 1 pt with hypereosinophilic syndrome (HES), 11 pts with severe aplastic anemia (AA), 8 pts with congenital disorders, 5 pts with Hodgkin's lymphoma (HL), 11 pts with non-Hodgkin's lymphoma (NHL), 6 pts with myelodysplastic syndrome (MDS), 1 with primary myelofibrosis (MF), and 3 pts with solid tumors.

Allo-HSCT was performed in cases of remission (134 pts), and also in patients with relapse and progression (87 pts) of their disease (Table 1).

For 86 recipients (39%) myeloablative conditioning (MC) regimens were used, containing busulfan 16 mg/kg, and cyclophosphamide 120 mg/m^2 [11]. Allo-HSCT in 135 pts (61%) was performed after a reduced-intensity conditioning (RIC) regimen of fludarabine 150 mg/m2, and busulfan 8 mg/kg or melphalan 140 mg/m^2 [12].

In 67 pts the source of the hematopoietic stem cells (HSC) was bone marrow (BM), and in 142 pts peripheral blood stem cells (PBSC) were used. In 12 pts a combination of both sources were used due to insufficient CD34+/kg value after the first cell procurement. The total value of CD 34+/kg ranged from 3.0 to 8.0 x 10/^{6}kg.

The EBMT criteria were used for the assessment of hematopoietic recovery after allo-HSCT: neutrophils at 0.5x10^9/l for at least 3 days without any granulocyte colony-stimulating factor (G-CSF) administration, trombocytes 20x10^9/l for at least 3 days without transfusions.

For aGVHD prophylaxis cyclosporine A at 3mg/kg from D-1 in combination with a short course of methotrexate 10 mg/m^2 was given on D+1, +3 and +6, or, in other cases, mycophenolate mophetil (MMF) 30 mg/kg from D+1. Another regimen was the combination of tacrolimus 0.03 mg/kg from D-1 and MMF 30 mg/kg from D+1. Anti-thymocyte globulin (ATG) or alemtuzumab were added in unrelated allo-HSCT and haplo-HSCT, and quite rarely, related allo-HSCT cases.

Corticosteroids (1–3 mg/kg of prednisolone or methylprednisolone) with gradual tapering were used as the first line of treatment of aGVHD or cGVHD. For aGVHD with intestinal involvement,

topical steroids (budesonide) were added to the therapy scheme at the rate of up to 9 mg/day. As a second line of immunosuppression TNF-б blockers (infliximab, etanercept), and IL-2 receptor blockers (daclizumab) were used; cGVHD was treated with anti-CD20 antibodies (rituximab). The grade of aGVHD and cGVHD were defined according to international criteria [16].

Characteristic:	1-21 y.o.	>21 y.o.	Total:
Gender			
Female	n=74	n=57	n=131
Male	n=57	n=33	n=90
Primary disease:			
AML	n=29	n=29	n=58
ALL	n=65	n=26	n=91
BiAL	n=2	-	n=2
CMPD	n=8	n=16	n=24
CLPD	-	n=1	n=1
NHL	n=4	n=6	n=10
HL	n=1	n=4	n=5
AA	n=3	n=3	n=6
MDS	n=1	-	-
HES	-	n=1	n=1
MF	n=8	-	n=8
Congenital disorders			-
Others	n=1	n=2	n=3
Stage of disease:			
Remission	n=81	n=53	n=134
Relapse	n=50	n=37	n=87
Transplant cell source			
Bone marrow	n=43	n=24	n=67
Peripheral blood	n=78	n=64	n=142
Peripheral blood and bone marrow	n=10	n=2	n=12
Stem cell donors			
Related	n=79	n=55	n=55
Unrelated	n=41	n=34	n=34
Haplodentical	n=8	n=1	n=1
Conditioning regimen			
Myeloablative	n=63	n=23	n=86
Reduced intensity	n=68	n=67	n=135

Table 1. Characteristics of the patients who underwent allo-HSCT

Patients' examination before allo-HSCT and in the early post-transplant period

Pre-transplant examination of patients included serological screening for the following infections: cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus type 1 and 2 (HSV), and toxoplasmosis. Additionally, bacteriological and mycological studies (evaluation of blood, urine, stool and pharyngeal smear cultures) were performed on all patients.

In the early post-transplant period (up to D+100), the CMV status was monitored by PCR. Fungal infection monitoring was performed once a week by testing the galactomannan level via a latex-agglutination test (Enzyme-Linked Immunosorbent Assay, Platelia Aspergillus, Bio Rad) and, if the results were stable negative the test was performed bi-weekly. Early diagnostics of IM were performed using chest CT scans.

If any signs of infection were discovered, the microbiological, mycological (including galactomannan assay), and virological studies were repeated. To determine the localization of infection, chest X-ray or CT scan, abdominal US-scan, MRT or CT brain scans were performed.

In certain cases bronchoscopy with a study of bronchoalveolar lavage (BAL) cultures, or ophtalmoscopy with pupil dilatation were done.

Prophylaxis against infectious complications in allo-HSCT recipients

Allo-HSCT recipients were treated in wards with HEPA-filtered air. Selective decontamination was conducted from D-7 to D-1, then from D+1 up until recovery of granulocyte count of $0.5x10^9$/l, and included the following antibacterial drugs: Ciprofloxacin 10 mg/kg/day, metronidazole 30 mg/kg/day; non-absorbing antibiotics per os (80 mg gentamycin 80 and 50000 units of amphotericin-B in form of water suspension).

All patients received trimethoprim/sulfametoxasol (5 mg/kg/day trimethoprim) as Pneumocystis carinii infection prophylaxis, which continued after engraftment until the completion of immunosuppressive therapy.

For herpes viral infection prophylaxis all patients received zovirax (5 mg/kg) from D-7 until D-1, then from D+1 until the end of immunosuppressive therapy.

Ganciclovir (5 mg/kg) was used for CMV infection prophylaxis in the patients with more than 10^3 copies by polymerase chain reaction (PCR).

The choice of antifungal drug for prophylaxis against IFD was based on anamnesis data on previous fungal infections, duration and severity of chemotherapy-induced neutropenia prior to allo-HSCT, and the type and stage of disease. Different generations of azoles were prescribed in 212 recipients test subject group: fluconazole (400 mg/day in adults, 6 mg/kg/day in children) in 155 pts, itraconazole (200 mg/day in adults, 8 mg/kg/day in children) in 19 pts, and voriconazole (6 mg/kg/day the 1st day, then 4 mg/kg/day in adults and 14 mg/kg/day in children) in 37 pts. For primary prophylaxis 4 pts received caspofungin (70 mg/kg/day the 1st day, then 50 mg/kg/day, no age adjustments were used). In one of the patients with resistant soft tissues IFD caused by a. flavus and a. fumigatus, caspofungin (70 mg/kg/day the 1st day, then 50 mg/kg/day) and posaconazole (800 mg/day) were given as secondary prophylaxis before haplo-HSCT.

Invasive fungal diseases was classified according to EORTC/MSG 2005 criteria based on host risk factors, clinical presentations, and infectious agent identification. The host risk factors considered were congenital immunodeficiency, immunosuppressive therapy by calcinerim inhibitors, long courses (more than 3 weeks) of steroids, prolonged (more than 10 days) neutropenia (ANC<$0,5x10^9$/l) and previous therapy with monoclonal antibodies (MABs), б-TNF inhibitors or antilymphocyte globulin. Fever was considered

non-specific to fungal infections; it was regarded as a host factor. Based on these criteria, all IFD was divided into three forms: possible , probable , and proven. For verification of IFD (proven IFD) the fungal culture or a biopsy specimen with fungal mycelium visible by light microscopy had to be obtained from normally sterile tissue. Probable IFD was characterized by the presence of host factors, characteristic lesions on chest, brain or sinus CT scan, and/or characteristic changes discovered by abdominal US-scan or fundoscopy. For probable IFD the following criteria were used: fungal mycelium detectable by light microscopy in a normally non-sterile tissue specimen (sinus mucosa or BAL) and/or positive culture from sinus aspirate or BAL, positive Aspergillus antigen in blood, spinal fluid or BAL.

Possible IFD was characterized by the presence of host factors and characteristic clinical findings with no according laboratory confirmation [13].

Statistics

Fisher's exact test, the chi-quadrat test and the Mann-Whitney test were used for statistical data processing. Descriptive statistics methods were used for validation of continuous variables. Risks were calculated using likelihood ratios. Distinctions were considered reliable if error probability was below 0.05 ($p \leq 0.05$).

Results

Patients with possible, probable and proven IFD were included in the analysis. The occurrence of IFD between October 2000 and July 2008 amounted to 60/221 (27%) in the early post-allo-HSCT period and 8/221 (4%) in the late post-allo-HSCT period.

After allo- HSCT according to the EORTC/MSG definitions 2005 was diagnosed in 27 patients possible IFD, in 38 patients probable and in 3 patients proven (Fig.1).

Probable aspergillosis involving the lungs was diagnosed in 32 pts; one patient had simultaneous lung and brain lesions, and lungs and sinus lesions occurred in 3pts. One post-haplo-HSCT patient had lung lesions caused by A. fumugatus and Cryptococcal CNS infection.

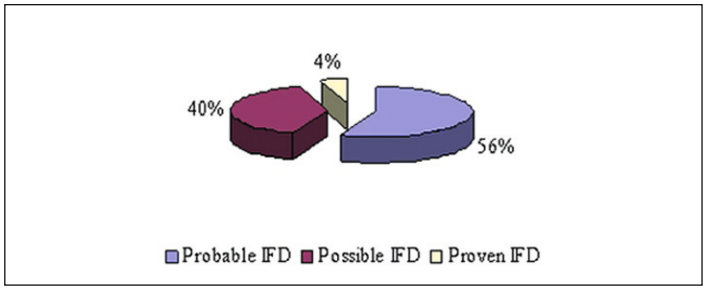

Figure 1. IFD according to the EORTC/MSG definitions in patients after allo-HSCT

Possible aspergillosis with lung involvement was diagnosed in 24 pts; combined involvement of lungs and sinus in 3 pts.

Chronic disseminated candidiasis (CDC) was revealed in 2 pts, and C. krusei was detected in one patient. Candidemia was caused by C. parapsilosis in 3 pts.

In 25 pts IFD was diagnosed before allo-HSCT treatment. In all of these cases the necessary degree of infection control was obtained prior to allogeneic transplant procedure. IFD reactivation after allo-HSCT was noted in 10 of 25 (40%) pts.

The most common target organ of possible and probable IFD was the lung. Lung involvement was found in 51% of IFD patients younger than 21 (HR=10; 95% confidence range, 5.6–21.3 $P<0.05$), and 49% of IFD patients older than 21 (HR=11; 95% confidence range, 5.6–21.3 $P<0.05$). The other targeted organs were the sinuses: 6/68 (8%) of patients, and the brain: 2/68 (3%) of patients.

When looking at CT-scans results, specific lesions were revealed in 12 pts, in 32 cases signs of IFD were nonspecific, in 7 cases changes were not revealed; in 18 pts a CT-scan was not done. The ELISA-test was performed on 35pts only: galactomannan was positive in 27 pts and negative in 8 pts.

In the younger (≤21 years) patients, IFD was found in 12/43 (28%) pts after related allo-HSCT, in 28/80 (35%) pts after unrelated allo-HSCT, and in 3/8 (38%) pts after haplo-HSCT (Fig. 2).

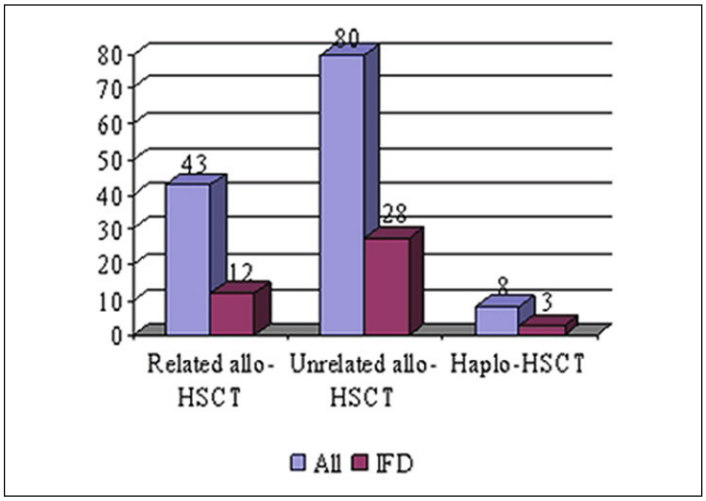

Figure 2. Incidence of IFD after allo-HSCT in patients ≤21 years old

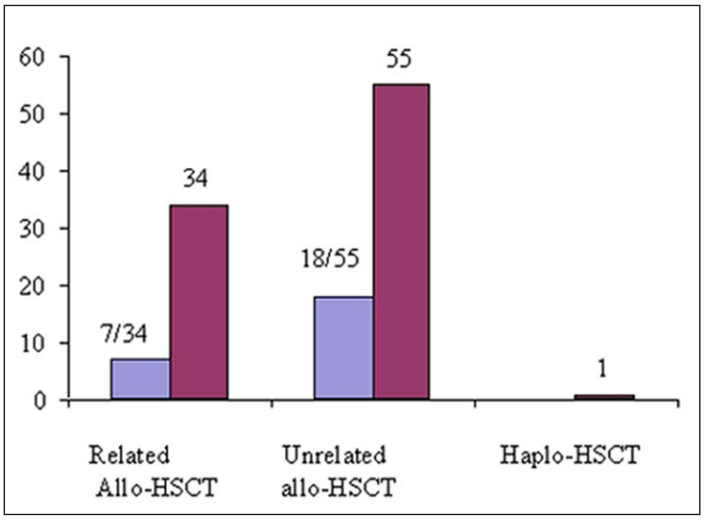

Figure 3. Incidence of IFD after allo-HSCT in patients >21 years old

In older (>21 years) patients, IFD was found after related allo-HSCT in 7/34 (20%) pts and in 18/55 (33%) pts after unrelated allo-HSCT;

the one patient who was treated with haplo-HSCT did not develop IFD (Fig. 3).

In the case of younger patients (≤21 years) who were given RIC and allo-HSCT, IFD was diagnosed in 20/63 (32%) cases and in 4/23 (17%) pts in the older group (>21 years). IFD was diagnosed in 23/68 (34%) cases in the younger patients' group, and in 21/67 (31%) of older patients who were given MC. The median of IM diagnosis after allo-HSCT with RIC was at D+88 (day 13–740) and at D+ 86 (day 1–940) after allo-HSCT combined with MC.

The characteristics of patients with IFD are shown in Tables 2 and 3.

IFD developed in 1/2 (50%) patients who received cells from a mixed source. The comparison didn't show up as statistically valid (p>0.05).

Multivariate analysis revealed the influence of the following risk factors on the probability of IFD development in younger (≤21 years) patients. These factors are allo-HSCT conducted in relapse, and the usage of RIC regimens before allo-HSCT with BM (HR=0.4; 95% confidence range, 0.21–0.76, p<0.05). The incidence of IFD was noticeably lower in the group of patients older than 21 who were transplanted in remission using a HLA-compatible related donor with MC where PBSC was the HSC source than in groups of patients with any other risk factors (HR=1.59; 95% confidence range, 1.01–2.51, p<0.05).

Type of IM	IM before HSCT	Day <+100	Day >+100	Target organ	Radiographic findings	Laboratory data
Possible IM	n=2	n=13	n=3	Lung: n=14, Lung and sinuses: n=2	Non-specific: n=9, No changes: n=5, No data: n=1	Positive AA: n=5, Negative AA: n=1, No test conducted: n=10
Probable IM	n=3	n=21	n=5	Lung: n=22, Lungs and sinuses: n=1, Lungs and CNS: n=1, Lungs and CNS: (cryptococcosis): n=1, Lung, spleen, soft tissue lesions: n=1	Non-specific: n=10, Specific: n=6, No changes: n=2, Was not carried out: n=8	Positive AA: n=14, Negative AA: n=3, No test conducted: n=7, C. krusei-positive urine culture
Proven IFD	n=1	n=1	-	-	-	C. parspsilosis-positive blood culture
Total:	n=6	n=35	n=8	n=43	n=43	n=43

Table 2. IFD characteristics in patients ≤21 years

Type of IFD	IFD before HSCT	Day <+100	Day >+100	Target organ	Radiographic findings	Laboratory data
Possible IFD	n=1	n=10	n=1	Lung: n=10, Lung and sinuses: n=1	Non-specific: n=9, No data: n=3	Positive AA: n=3, Negative AA: n=2, No test conducted: n=6
Probable IFD	n=2	n=12	n=1	Lung: n=10, Lung and sinuses: n=2, Liver: n=1	Non-specific: n=4, Specific: n=6, Was not carried out: n=3	Positive AA: n=4, Negative AA: n=5, No test conducted: n=4
Proven IFD	n=1	n=1	-	-	-	C. parspsilosis-positive peripheral blood culture
Total:	n=4	n=23	n=2	n=25	n=25	n=25

Table 3. IM characteristics in patients >21 years

In allo-HSCT recipients >21 years old the incidence of IFD was 1.8-fold higher after allo-HSCT with RIC than in patients who had undergone an MC regimen (hazards ratio (HR)=1.2; 95% confidence range, 1.01–1.6, p<0.05). In the group of elder patients, the incidence of IM after related allo-HSCT was higher in patients given an RIC regimen in relapse (HR=0.5; 95% confidence range, 0.3–0.9, p <0.05).

Different grades of mucositis influence the frequency of IFD occurrence in both age groups (HR=2.1; 95% confidence range, 1.2–3.8, p<0.05 for patients ≤21 years; HR=2.1; 95% confidence range, 1.2–3.8, p<0.05 for patients >21 years).

When looking at the source of HSC, the following incidence rates of IFD were observed: for BM recipients ≤21 years it amounted to 12/43 (28%) pts; for the patients of the same age group that received PBSC it was 27/78 (35%). IFD was diagnosed in 4/10 (40%) pts that received HSC from a mixed (BM and PBSC) source. In the elder age group the incidence of IFD amounted to 4/24 (16%) of patients that received BM, 20/64 (31%) of PBSC recipients, and

The introduction of ALG into the conditioning regimen for patients of the elder (>21 years) age group increased the possibility of IFD (HR=0.7; 95% confidence range, 0.59–0.88, p<0.05). In the younger (≤21 years) age group this difference was not statistically valid.

The rate of engraftment after allo-HSCT had no effect on the incidence and time of diagnosis of IFD in either age group. In patients ≤21 years the engraftment was noted on D+19±8 (from D+13 to D+46); in patients >21 years on D+16±4 (from D+9 to D+29) (p>0.05).

In patients ≤21 years with grade I–III aGVHD IFD developed in 17/66 (26%) cases; in 5/13 (46%) pts with grade IV aGVHD and 4/26 (15%) pts with an extensive form of cGVHD. In patients with an extensive form of cGVHD the incidence of IFD was significantly higher (HR= 2.1; 95% confidence range, 1.3–3.4, p<0.05). In patients >21 years IFD developed in 12/45 (27%) cases with grade I–III aGVHD, and in 2/11 (18%) pts with grade IV aGVHD. IFD also developed in 2/13 (15%) pts with extensive cGVHD following aGVHD.

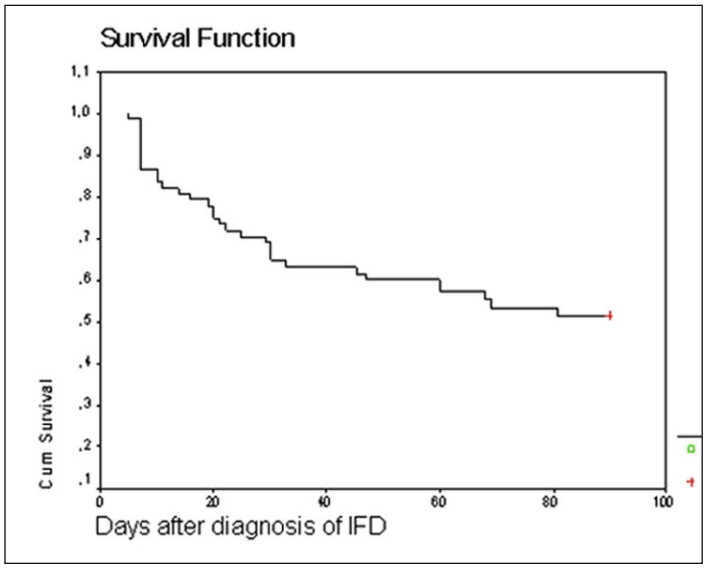

Figure 4. 12- weeks OS after diagnosis of IFD in patients after allo- HSCT

Log Rank <0.05

The influence of IFD on 5-year (OS) after allo-HSCT in both age groups was 40% (without IFD) and 18% (with IFD) (Fig.5).

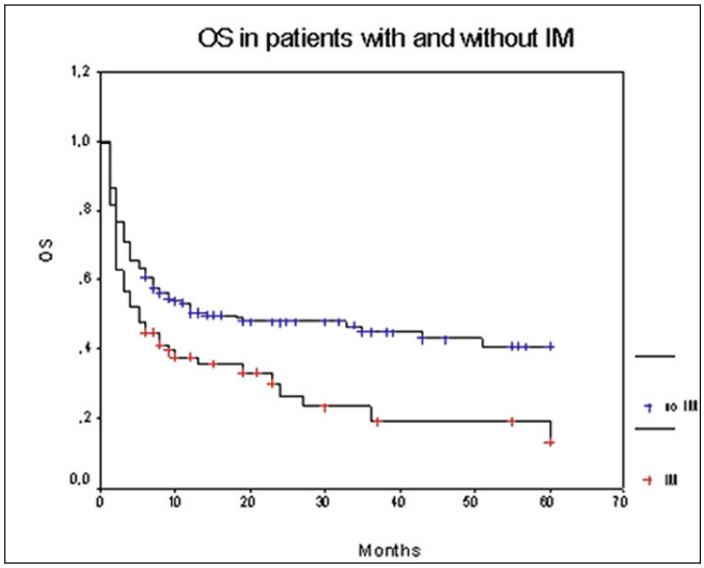

Figure 5. 5-years OS in patients after allo-HSCT with and without IM

In the elder (>21 years) group of patients the following incidence of IFD depending on antifungal prophylaxis was observed: under fluconazole in 29/94 (30%) pts, under itraconazole in 2/8 (25%) pts, under voriconazole in 13 of 25 (52%) pts; and no IFD developed in patients that received prophylaxis with caspofungine (2 pts) or posaconazole (1pt). For the younger group the IFD incidence under fluconazole was in 19 of 61 (31%) pts, under itraconazole in 2 of 11 (18%) pts, under voriconazole in 3 of 12 (25%) pts and no IFD cases emerged under prophylaxis with caspofungine (0/2). The difference of IFD incidence between these age groups had no statistical significance (p>0.05).

The 12-weeks overall survival (OS) after diagnosis of IFD in patients after allo-HSCT is 50%.

Conclusion

The incidence of IFD after allo-HSCT remains high. Depending on donor characteristics (HLA-matched related, unrelated or haploidentical donor) it is 28%, 35%, and 38% respectively.

Looking at age it is 32% for patients ≤21 years, and 27% for patients >21 years. The overall IFD incidence is slightly higher than in similar studies [15], but this may be explained by the characteristics of the groups analyzed. In our study 87/221 (39%) pts underwent allo-HSCT in relapse, and this proved to be a risk factor.

Despite the fact that age above 10 years was considered a risk factor for IFD development in both early and late periods after allo-HSCT [14], in this study the age was not an independent risk factor of IFD. In the RIC regimen group IFD was diagnosed in 34% of younger (≤21 years) patients and 31% of older (>21 years); and for the MC group it amounted to 32% for younger (p>0, 05) and 17% for elder age groups (p<0.05). Neither the rate of IFD in both age groups, the source of HSC and/or rate of post-transplant engraftment were found to independently exert influence on the incidence of IFD following allo-SCT.

IFD incidence was 1.8-fold higher in elder relapsed patients after related allo-HSCT with RIC (p<0.05). Contrariwise, in this group the incidence of IFD was low in patients that underwent HSCT in remission and received PBSC (p<0,05). The possible reason for this could be the population structure of G-CSF-stimulated donor PBSC, which alleviates immune reconstitution [9]. The influence of transplant type was also noticed in the younger (≤21 years) group: the probability of IFD development was much higher in relapsed patients after BM allo-HSCT with RIC (p<0.05). It was noticed that the disease stage, grade I–IV mucositis (p<0.05), and extensive cGVHD (p<0.05) were the most prominent risk factors for IFD development. When these factors are present no difference was seen in groups with different conditioning regimens and HSC sources.

In patients >21 years IFD incidence increased by inclusion of ATG in the conditioning regimen (p<0.05). Agents such as ATG, steroid-depressed function of immunocompetent cells (macrophages, granulocytes, monocytes and T-cells) and decreased production and secretion of pro-inflammatory cytokines (TNF, IFN-r, IL-2) secretion [9].

Our study revealed that IFD impairs the OS in patients after allo-HSCT in both age groups, but especially in patients older than 21 years.

In conclusion, the main risk factors that influence the incidence of IFD after allo-HSCT in all age groups are the stage of the disease, mucositis development, and extensive form of cGVHD.

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Инвазивные микозы у пациентов после аллогенной трансплантации гемопоэтических стволовых клеток

Н.И. Зубаровская, Е.В. Семенова, Н.В. Станчева, В.Н. Вавилов, И.В. Казанцев, Ю.Г. Васильева, Н.Н. Климко, Б.В. Афанасьев

Резюме

Цель исследовани: Определить частоту ИМ у пациентов после алло-ТГСК, выявить факторы риска, способствующие развитию ИМ.
Материалы и методы: С 2000г. по июнь 2008г. выполнена 221 алло-ТГСК от неродственного, родственного, частично совместимого (гаплоидентичного) донора. Из них до 21года - 131 пациентам, старше 21 года - 90 пациентам, медиана возраста составила 21 год (1-66 лет).У 87 пациентов (39,4%) алло-ТГСК произведена в рецидиве заболевания.
Результаты: Частота ИМ при алло-ТГСК составила 28%, 35% и 38% соответственно при использовании родственного, неродственного и гаплоидентичного доноров, а также 32% у пациентов до 21 года и 27% в группе пациентов старше 21 года. ИМ диагностирован соответственно у 32% и 17% пациентов с МРК (миелоаблативный кондиционирующий режим кондиционирования), у 34% и 31% с неМРК до 21 года и старше ($p>0,05$). В обеих группах источник ГСК, скорость восстановления кроветворения донора не имели самостоятельного воздействия при оценке вероятности возникновения ИМ у пациентов после алло-ТГСК.
Значение возраста и источника ГСК усиливалось при многофакторном анализе параметров, влиющих на развитие ИМ после алло-ТГСК. Проведение алло-ТГСК от родственного донора с неМРК в рецидиве заболевания увеличивало риск развития ИМ в 1,8 раза у пациентов старше 21 ($p<0,05$). Напротив, при алло-ТГСК в ремиссии ИМ развивался реже, особенно при использовании ПСКК ($p<0,05$).
Влияние трансплантата отмечено и в возрасте до 21 года, где вероятность развития ИМ была выше при проведении алло-ТГСК в рецидиве заболевания с МРК и КМ в качестве источника трансплнтата ($p>0,05$).
Установлено, что стадия заболевания, мукозит I-IV степени ($p<0,05$) и распространенная форма хронической РТПХ ($p<0,05$) являются наиболее значимыми отрицательными факторами. Их наличие создаёт условия для развития ИМ вне зависимости от режима кондиционирования и источника трансплантата.
В возрасте старше 21 года назначение АЛГ в режиме кондиционирования увеличивало вероятность развития ИМ ($p<0,05$). Общая 5-летняя выживаемость пациентов всех возрастных групп вне зависимости от стадии заболевания составила 40% и 18% при отсутствии и наличии ИМ, соответственно.
Заключение: Таким образом, наличие ИМ влияет на 5-летнюю ОВ пациентов. Основными факторами риска, влияющими на частоту ИМ после алло-ТГСК в возрастных группах до и старше 21 года являются стадия заболевания, развитие мукозита и распространенной формы хрРТПХ.

Ключевые слова: аллогенная трансплантация гемопоэтических стволовых клеток, инвазивный микоз, факторы риска развития инвазивного микоза