Incidence of Infectious Complications in Children With Acute Lymphoblastic Leukemia Treated With Hematopoietic Stem Cell Transplantation

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ABSTRACT

Objective. We analyzed incidence and profile of infections in children with acute lymphoblastic leukemia (ALL) treated with hematopoietic stem cell transplantation (HSCT) in Polish pediatric HSCT departments, over a 2-year period.

Patients and Methods. Hospital records of 67 patients, who underwent allogeneic HSCT for ALL, were analyzed retrospectively for microbiologically documented infection: bacterial infection (BI), viral infection (VI), and fungal infection (FI). The majority of patients (40/67; 59.7%) underwent HSCT from matched unrelated donors (MUD).

Results. In total, 84 BI in 31 patients, 93 VI in 50 patients, and 27 FI in 22 patients were diagnosed. No differences were found in the frequency of occurrence of BI according to the type of transplant ($P = .16$); the occurrence of VI was statistically more frequent in MUD transplant recipients as compared with matched sibling donors (MSD) and mismatched related donors (MMFD; $P = .001$) and there was a trend in MUD patients for the higher occurrence of FI in comparison with MSD and MMFD transplants ($P = .08$). Regarding disease status, the occurrence of BI, VI, and FI was statistically more frequent in children who underwent transplantation in their first complete remission (CR1), rather than those who underwent transplantation in ≥CR2 ($P < .05$). In conclusion, infectious complications are an important cause of morbidity in children with ALL treated with allogeneic HSCT and the incidence of infections is high in this group of patients.

INFECTIONS are an important cause of morbidity and mortality in patients treated with hematopoietic stem cell transplantation (HSCT). Patients undergoing allogeneic HSCT are at particular risk of having infectious complications, both in the early (<100 days) and late (>100 days) post-transplantation periods [1,2]. The risk of infections following HSCT is attributed to the use of conditioning regimens and immunosuppressive therapy, which cause severe impairment of the immune system [3–5]. We present the results of the analysis of incidence and profile of infections in children with acute lymphoblastic leukemia (ALL) treated with allogeneic HSCT in Polish pediatric HSCT centers.

PATIENTS AND METHODS

Hospital records of 67 consecutive children, who underwent allogeneic HSCT for ALL over the period of 2 years, were analyzed. Data concerned the type of infection, fever episodes, infection treatment, and clinical outcome. Infection was defined as isolation

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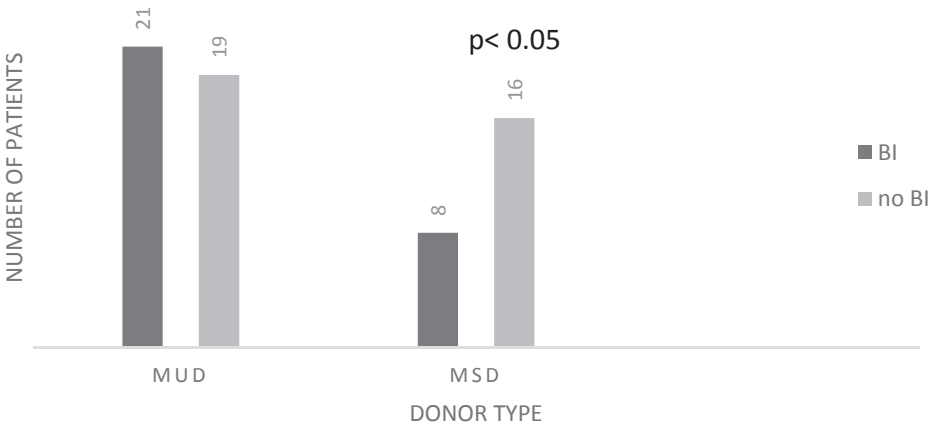

Fig 1. The frequency of BI according to donor type. Abbreviations: BI, bacterial infections; MUD, matched unrelated donor; MSD, matched sibling donor.

of any organism associated with symptoms, or presence of viral and fungal pathogens detected on pre-emptive screening. Colonization with no symptoms was not considered as infection. Bacterial infections (BI) were diagnosed based on microbiological identification of bacterial strain from cultures taken from peripheral blood, body fluid or other site of infection (skin or tissue lesions). Patients with fever without microbiological confirmation were excluded. Viral infections (VI) were diagnosed with the quantitative real-time polymerase chain reaction (PCR) method. For cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) screening, blood samples were collected once weekly in the post-transplantation period. Fungal infections (FI) were stratified as possible, probable, and proven according to European Conference on Infections in Leukaemia criteria and all were included into the analysis [4]. All patients received standard anti-infectious prophylaxis according to current European Society for Blood and Marrow Transplantation guidelines and center procedures [2]. Pre-emptive treatment was given based on the results of surveillance. All patients were followed up for at least 100 days or death, whichever occurred first.

The majority of patients (40/67; 59.7%) received stem cells from matched unrelated donors (MUD), 24/67 (35.8%) received stem cells from matched sibling donors (MSD), and 3/67 (4.5%) received stem cells from mismatched related donors (MMFD). Because of the small number, patients in the MMFD group were excluded from final statistical analyses. Regarding disease status, 34/67 patients (50.7%) underwent transplantation in first complete remission (CR1), whereas 33/67 (49.3%) underwent transplantation in more advanced disease (second or higher complete remission [≥CR2]).

Statistical analysis was performed using Statistica 10.0 software (Stat Soft. Inc, Krakow, Poland). The statistical differences were compared with Mann-Whitney U test for two groups and the Kruskal-Wallis and chi-square tests for more than two groups. Statistical significance was considered for $P < .05$.

RESULTS

At least one BI was documented in 31/67 ALL patients (46.3%); the total number of BI in this group was 84. Median age of children with BI was 7.2 years (range, 2.3–19). According to the type of transplant, no difference was found between the occurrence of BI and donor type (MUD vs MSD), as well as type of graft-versus-host disease (GvHD) prophylaxis (Cyclosporine + ATG vs Cyclosporine alone; $P < .05$; Fig 1). GvHD was diagnosed before the BI in 12/31 patients (38.7%), of which 10 underwent transplantation in CR1 and 2 in ≥CR2. The most commonly identified germs were as follows: *Clostridium difficile* (n = 20), *Escherichia coli* (n = 14), and *Staphylococcus* species (n = 13; Table 1). More than one BI was diagnosed in 22/31 (71%) patients. Median time from transplantation to occurrence of BI was 18 days (range, -7–+387), and 78/84 (92.9%) BI were diagnosed in the first 100 days after HSCT. Median time of antibiotic therapy was 33 days (range, 4–159).

At least one VI was diagnosed in 50/67 (74.6%) patients. In total, 93 VI were reported. Median age of patients with VI was 10 years (range, 2.3–19). The most common etiologic factors were as follows: CMV (n = 30), BK virus (BKV, n = 22), and EBV (n = 20). According to the type of transplant the occurrence of VI was statistically more frequent in MUD transplant recipients as compared with MSD ($P < .05$; Fig 2). In 22/50 patients (44%) GvHD was diagnosed, of which 18 underwent transplantation in CR1 and 4 in ≥CR2. Overall, 75/93 (80.6%) VI were diagnosed up to day +100. The most common etiologic factors of late infections (>day +100) were as follows: CMV (8/18), EBV (5/18), and varicella zoster virus (5/18). In two children VI were diagnosed and treated before HSCT, due to EBV-DNA-emia (1) and BKV infection (1). In 22/50 patients

Table 1. Identified Bacterial Strains in Patients With BI

Identified Bacterial Strain	Incidence	
Total	n = 84	%
Clostridium difficile	20	23.8
Escherichia coli	14	16.6
Staphylococcus epidermidis	8	9.5
Staphylococcus hemolyticus	3	3.6
Staphylococcus hominis	2	2.4
Enterobacter cloacae	11	13.1
Enterococcus faecium	11	13.1
Klebsiella pneumoniae	6	7.1
Klebsiella oxytoca	3	3.6
Enterobacter aerogenes	3	3.6
Proteus mirabilis	2	2.4
Pseudomonas aeruginosa	1	1.2