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Viral infections after hematopoetic stem cell transplantation in children with acute lymphoblastic leukemia: the Polish experience

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Abstract

Introduction: Allogeneic hematopoetic stem cell transplantation (allo-HSCT) is one of the therapeutic options in pediatric acute lymphoblastic leukemia (ALL). Most previous analyses have concerned the reactivation of viruses in the entire population of children after allo-HSCT, regardless of the disease entity being an indication for transplantation. In our report, we aimed to evaluate the occurrence, etiology, risk factors and clinical outcome of viral infections in pediatric patients with ALL.

Material and methods: 83 post-HSCT ALL patients from 2020 through 2021 were analyzed for infections with polioma BK virus (BKV), cytomegalovirus (CMV), Epstein-Bárr virus, severe acute respiratory syndrome coronavirus 2, adenovirus, respiratory syncytial virus, norovirus, rotavirus, influenza, human herpes virus-6, parainfluenza and rhinovirus.
Results: Viral infections were detected after 41% of the transplantations. The viruses most commonly detected were BKV (26.2%) and CMV (23.8%). The analyzed potential risk factors for viral infections were total body irradiation (TBI), graft-versus-host disease, complete remission status, and donor type. Overall survival in the investigated group was 0.815.
Conclusions: Complications occurred more frequently in patients without TBI and we did not confirm the impact of other factors. Viral infections in children with ALL after allo-HSCT remain a significant problem. Our results highlight the importance of frequent monitoring and anti-viral prophylaxis.
Key words: hematopoetic stem cell transplantation, viral infections, pediatric ALL, post-transplant infectious complications

Introduction

Allogeneic hematopoetic stem cell transplantation (allo-HSCT) is one of the therapeutic options in pediatric acute lymphoblastic leukemia (ALL). Severe myelo- and lymphoablation, delayed immunoreconstitution, and the need for enhanced immunosuppression in the case of graft-versus-host disease (GvHD), all promote opportunistic infections, including viral infections [1–5].

Such complications result in longer immune recovery, intensive antiviral treatment, and longer hospitalization. Viremia post-HSCT is usually caused by virus reactivation of cytomegalovirus (CMV), Epstein-Barr virus (EBV), adenovirus (ADV), BK Polyomavirus (BKV), herpes simplex virus-1, -2 (HSV-1, HSV-2), varicella zoster virus (VZV), and human herpes virus-6, -7 (HHV-6, HHV-7) [4, 6–8].

This experience has led to frequent viral load monitoring and the use of prophylactic acyclovir for HSV, preemptive rituximab for EBV, and preemptive therapy for CMV [1, 9, 10].

The aim of this multi-center retrospective analysis was to characterize the frequency, type, risk factors and outcome of viral infections after HSCT in children with ALL.

Material and methods

In this retrospective cohort study, the clinical records and medical charts of 83 children (aged 0.5–17.5 years) diagnosed with ALL who underwent allo-HSCT in five pediatric transplantation centers from 2020 through 2021 were analyzed. The mean age on the day of the stem cell infusion was 8.7 ± 4.4 years. The disease status was first complete remission (CR1) in 74.7%, 24.1% of the patients received transplant in >CR1, and 1.2% were qualified as partial responders. For 16.9%, a matched family donor (MSD) was available. Most patients (72.3%) underwent HSCT from human leukocyte antigen (HLA)-identical unrelated donors [matched unrelated donor (MUD)] and 6.0% from mismatched unrelated donors (MMUD, ≤9/10). For 3.6% of the patients, the donor was a haploidentical family member. All patients received a myeloablative conditioning regimen, and in 56 patients (67.5%) the conditioning was based on total body irradiation (TBI).

The general characteristics of the analyzed patients are set out in Table I.

Table I. Patients' general characteristics

Variable	N	% of all patients
Number of patients with ALL	83	
Age at HSCT, years, average ± SD	83	8.69 ± 4.35 Range: 0.57–17.62
Sex		
Female	37	44.6
Male	46	55.4
Donor type		
MMFD	3	3.6
MMUD	5	6.0
MSD	15	18.1
MUD	60	72.3
Remission status		
>CR1	20	24.1
CR1	62	74.7
PR	1	1.2
Conditioning regimen		
TBI-based	56	67.5
Non-TBI	56	67.5
Deaths	11	13.3
Deaths from infection	4	4.8

ALL — acute lymphoblastic leukemia; HSCT — hematopoetic stem cell transplantation; SD — standard deviation; MMFD — mismatched family donor; MMUD — mismatched unrelated donor; MSD — matched sibling donor; MUD — matched unrelated donor; CR1 — first complete remission; PR — partial remission; TBI — total body irradiation

The analysis was performed in the R statistical package, version 4.0.5. Nominal variables are presented as the number of patients or the number of infections with % frequency. Quantitative variables are presented as mean ± standard deviation (SD) or as median (first quartile; third quartile) with range. The survival rate was calculated taking into account the 95% confidence level [confidence interval (CI)], and Kaplan-Meier survival curves were determined.

Results

The number of viral infections in the analyzed cohort was 84 diagnosed across 34 patients. The average age was 8.47 years (SD ± 4.78) and the group consisted of 13 girls and 21 boys. Among the children with viremia, 50% received TBI. In 82.4%, transplantation from MUD was performed, while MMUD, MSD and haploidentical donor transplant were performed in 5.9% of each. Out of five fatal cases, three (8.8%) were caused by an infectious complication. The diagnostic material was mostly blood plasma (50.6%), followed by nasal swab, urine, and feces (22.9%, 18.1%, and 8.4%, respectively). The characteristics of patients with viral infections are set out in Table II.

Table II. Characteristics of patients with viral infections

Variable	**N**	**% of all patients**
Number of patients	34	
Age at HCST, years, average ± SD		8.47 ± 4.78 Range: 0.57–17.52
Sex		
Female	13	38.2
Male	21	61.8
TBI		
No	17	50.0
Yes	17	50.0
Donor type		
MMFD	2	5.9
MMUD	2	5.9
MSD	2	5.9
MUD	28	82.4
CR		
>CR1	9	26.5

Variable	N	% of all patients
CR1	24	70.6
PR	1	2.9
Conditioning regimen		
TBI-based	17	50.0
Non-based	17	50.0
Deaths	5	14.7
Deaths from infection	3	8.8
Number of viral infections	**84**	
Diagnostic material		
Feces	7	8.4
Urine	15	18.1
Blood plasma	42	50.6
Nasal swab	19	22.9
Treatment		
None	25	30.1
Symptomatic	21	25.3
Anti-virals	37	44.6
Time from HSCT to viral infection, days, median	83	+28 (from +4 to +85)
GvHD before viral infection		
No	65	81.3
Yes	15	18.8

HSCT — hematopoetic stem cell transplantation; SD — standard deviation; TBI — total body irradiation; MMFD — mismatched family donor; MMUD — mismatched unrelated donor; MSD — matched sibling donor, MUD — matched unrelated donor; CR1 — first complete remission; PR — partial remission; GvHD — graft-versus-host disease

Table III. Etiology of viral infections

Virus type	N	% of viral infections
BKV	22	26.2
CMV	20	23.8
SARS CoV-2	10	11.9
EBV	9	10.7
ADV	7	8.3
RSV	6	7.1
Norovirus	3	3.6
Rotavirus	3	3.6
Influenza	1	1.2

Virus type	N	% of viral infections
HHV-6	1	1.2
Parainfluenza	1	1.2
Rhinovirus	1	1.2

BKV — BK poliomavirus; CMV — cytomegalovirus; SARS CoV-2 — severe acute respiratory syndrome coronavirus 2; EBV — Epstein Barr virus; ADV — adenovirus; RSV — respiratory syncytial virus; HHV-6 — herpes simplex virus

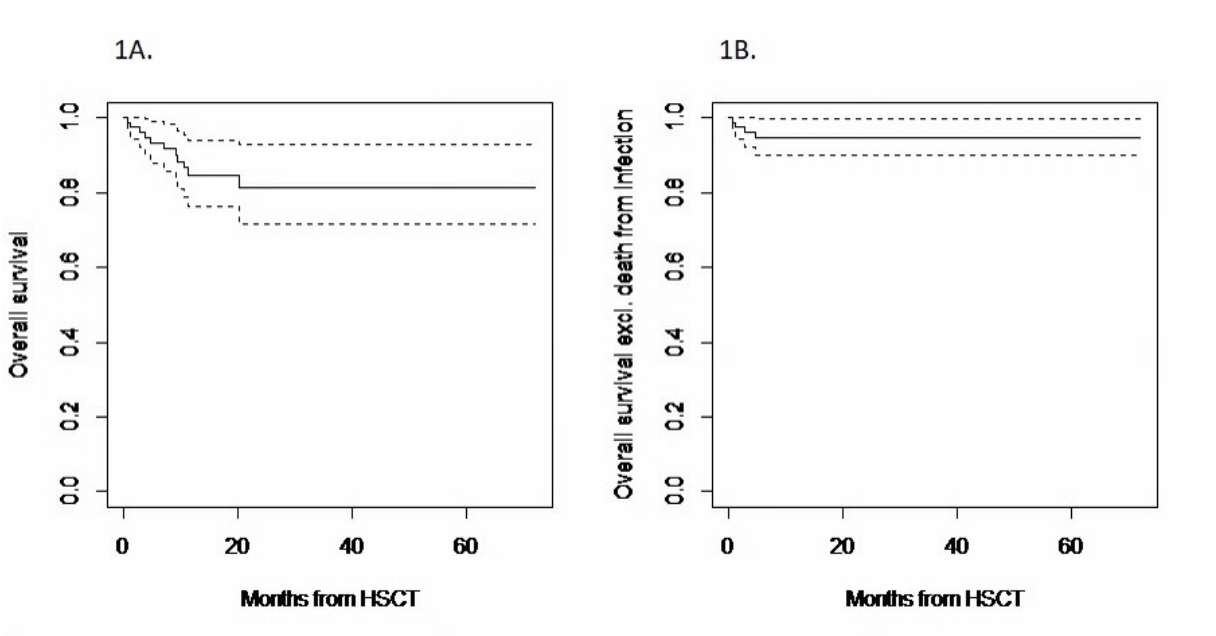

Figure 1A. Overall survival of analyzed group; **B.** Overall survival of analyzed group excluding death from infection; HSCT — hematopoetic stem cell transplantation

In the analyzed group, 44.6% of the patients received specific antiviral agents, and 25.3% required symptomatic treatment only. Complications occurred from day +4 to day +85 from transplantation (median 28 days). In 18.8% of the cases, GvHD preceded the occurrence of a viral infection.

The most commonly detected virus was BKV (26.2%). The etiology included also CMV (23.8%), while the third most common cause was severe acute respiratory syndrome novel coronavirus 2 (SARS-CoV-2 — 11.9%). Other detected pathogens were EBV (10.7%), ADV (8.3%), respiratory syncytial virus (RSV), norovirus, rotavirus, influenza, HHV-6, parainfluenza, and rhinovirus (*see* Table III).

The overall survival (regardless of cause of death) was 0.815 (95% CI: 0.715–0.928). When considering only deaths due to infection, this was 0.947 (95% CI: 0.898–0.999) (*see* Figure 1).

Viral pathogens were detected twice as frequently in the group without TBI (63%) than in the group with TBI (30.4%). The difference between the groups was statistically significant (p = 0.010). In the non-TBI group, conditioning was based mostly on treosulfan (32.4%), then busulfan (8.8%), melphalan (5.9%), and cyclophosphamide (2.9%).

There was no statistically significant relationship between the occurrence of infections (any and particular types) and GvHD or CR (p >0.05 in each case).

The statistical relationships between viral infections and TBI, GvHD, and CR status are set out in Table IV.

Table IV. Statistical relationships between total body irradiation (TBI), graft-versus-host disease (GvHD), complete remission (CR) status, donor type, and viral infections

Variable	**Yes**	**No**	***p***
	N [%]		
TBI	17 (30.4)	17 (63.0)	**0.010**
GvHD	21 (36.8)	10 (45.5)	0.656
>CR1	9 (45.0)	24 (38.7)	0.813

Discussion

In our report, we have assessed the occurrence, etiology, risk factors and clinical outcome of viral infections in pediatric patients with ALL after allo-HSCT. Most previous studies have concerned the reactivation of viruses in the entire population of children who underwent the procedure, regardless of the disease entity being an indication for transplantation.

In the group of patients we studied, a complication in the form of a viral infection after allo-HSCT occurred more often in boys, in patients transplanted from an unrelated donor, and in the first remission of ALL. However, the differences between the groups were not statistically significant. The median age at viral onset was ≥8 years.

Tsoumakas et al. [7], in a multivariate analysis, defined that when the recipient was ≥8 years and the transplantation came from a related donor, the patients were more prone to EBV, ADV and BKV infection.

In the study by Yamada et al. [11], the following risk factors for viremia were determined: a CMV seronegative donor (for CMV reactivation as well as for EBV, BKV, HHV-6), age ≥5 years at

the time of transplantation, the use of myeloablative conditioning, and no use of cyclophosphamide after transplantation.

The diagnosis of aGvHD especially in stage ≥II and the onset of chronic GvHD are important risk factors for viral infections. This is due to the need for intensified immunosuppression. Moreover, the very occurrence of GvHD leads to a delay in the reconstitution of the immune system after allo-HSCT [1, 12]. In our analysis, GvHD was not related to the occurrence of viremia, although the follow-up was relatively short.

Analyzing the conditioning regimen, we encountered viremia less frequently in patients who underwent TBI. The difference between the TBI and the non-TBI group was statistically relevant. In contrast, in a retrospective analysis by Düver et al. [8], no significant association was found for TBI conditioning. Another study revealed TBI to be an independent risk factor for high CMV or EBV DNA levels [13]. Our observation could be related to the small number of patients in our study group. Moreover, a relatively large group received non-TBI conditioning (50%).

The reactivation of viral infections with viruses like BKV, CMV, and EBV is a relevant complication after HSCT, as we confirmed in our retrospective study [7, 8]. In our analysis, the reactivation of BKV was most frequently observed, followed by CMV. SARS-CoV-2 was the third most common factor of infection, which underlines the importance of the pathogen nowadays. However, we observed neither a severe nor a fatal clinical course of coronavirus infection. Less frequently detected viruses were ADV and RSV, followed by norovirus and rotavirus.

Düver et al. [8] evaluated that HHV-6, EBV, CMV, and ADV were the most common etiological factors of viral load; a higher number of HSV infections (10.3%) and VZV (15%) were also found.

In another study, concerning both autogeneic and allogeneic transplantation, the most frequently identified virus was CMV (38%), then BKV, EBV, and ADV. Other viruses such as HHV-6, HHV-7, HSV, and VZV were of marginal importance [7].

Other studies have revealed that coronavirus occurred with a frequency of 3-6%, which was lower than we observed in our report. SARS-CoV-2 was first detected in late 2019, and so there is still a lack of multicenter analyses on its prevalence in children after allo-HSCT [14–17]. Studies on RSV after allo-HSCT put its frequency at 2–17% of transplantations, yet there are very few analyses of RSV, parainfluenza and rhinovirus in pediatric patients [18–21].

Due to the recommendation to use acyclovir prophylaxis in the guidelines, we did not analyze the viral load of HSV and VZV [22]. The selection of donors in terms of the serological status for CMV and EBV contributed to the reduction of the reactivation frequency of these viruses. Frequent monitoring of PCR viral load levels made it possible to reduce the need for causative treatment and thus lower the risk of antiviral treatment side effects. Careful selection of donors for

HLA compatibility reduced the risk of GvHD, but this complication is still a significant factor in the development of infection. Mortality due to viral infections remains unacceptably high [5, 22].

Our study has several limitations. The study group contained a relatively small number of patients and the duration of follow up was limited. Factors such as recipient/donor serostatus, the type of GvHD prophylaxis, the use of T-cell depletion, the time of immunoreconstitution, and GvHD stage were not included in our analysis.

Conclusions

In conclusion, our report describes the epidemiology and risk factors of viral infections after allo-HSCT in children with ALL. In the studied group, TBI was not conducive to viremia. Complications occurred more frequently in patients who received chemotherapy-based conditioning. GvHD, CR1 status and donor type did not impact the rate of infections. The third most commonly detected viral pathogen was SARS-CoV-2, which underscores its relevance in patients after allo-HSCT. Frequent monitoring and the assessment of risk factors, together with tailoring immunosuppressive and antiviral therapy, are all crucial. Further studies regarding viral complications in this group of pediatric patients could reveal more specific management strategies.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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