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Pediatric Transplantation

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ORIGINAL ARTICLE

Varicella-Zoster Virus Reactivation After Pediatric Allogeneic Hematopoietic Stem Cell Transplantation, Single-Center Experience of Acyclovir Prophylaxis

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Received: 15 April 2024 | **Revised:** 13 June 2024 | **Accepted:** 15 June 2024

Funding: The authors received no specific funding for this work.

Keywords: acyclovir prophylaxis | hematopoietic stem cell transplantation | herpes zoster | varicella-zoster virus

ABSTRACT

Background: Varicella-zoster virus (VZV) reactivation is the most common infectious complication in the late posthematopoietic stem cell transplantation (HSCT) period and is reported as 16%–41%. Acyclovir prophylaxis is recommended for at least 1 year after HSCT to prevent VZV infections. However, studies on the most appropriate prophylaxis are ongoing in pediatric patients.

Methods: Patients who underwent allogeneic HSCT between January 1, 1996 and January 1, 2020 were retrospectively analyzed to outline the characteristics of VZV reactivation after allogeneic HSCT in pediatric patients using 6 months acyclovir prophylaxis.

Results: There were 260 patients and 273 HSCTs. Median age was 10.43 (0.47–18.38), and 56% was male. Median follow-up was 2325 days (18–7579 days). VZV reactivation occurred in 21.2% ($n = 58$) at a median of 354 (55–3433) days post-HSCT. The peak incidence was 6–12 months post-HSCT (43.1%). Older age at HSCT, female gender, history of varicella infection, lack of varicella vaccination, low lymphocyte, CD4 count, and CD4/CD8 ratio at 9 and 12 months post-HSCT was found as a significant risk for herpes zoster (HZ) in univariate analysis, whereas history of varicella infection and low CD4/CD8 ratio at 12 months post-HSCT was an independent risk factor in multivariate analysis.

Conclusions: Tailoring acyclovir prophylaxis according to pre-HCT varicella history, posttransplant CD4 T lymphocyte counts and functions, and ongoing immunosuppression may help to reduce HZ-related morbidity and mortality.

1 | Introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment option for many malignant and nonmalignant disorders. Infections are one of the leading causes of morbidity and mortality. Varicella-zoster virus (VZV) reactivation is the most common viral disease in the late posttransplant period, and the reported incidence varies between 16% and 41% [1].

VZV reactivation presenting as herpes zoster (HZ) is caused by the reactivation of the latent virus in the dorsal ganglion cells and is associated with decreased T-lymphocyte functions.

Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; CB, cord blood; CSA, cyclosporin; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; IV, intravenous; MTX, methotrexate; PB, peripheral blood; TBI, total body irradiation; VZV, varicella-zoster virus.

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Although HZ has a benign course in healthy children, serious complications similar to adults including disseminated disease, postherpetic neuralgia, and widespread cutaneous disease and visceral dissemination, such as pneumonia, hepatitis, and encephalitis, have been reported in immunosuppressed children. HZ in an immunosuppressed patient, especially after HSCT, requires inpatient treatment increasing the hospital stay as well as the treatment cost [2]. The main approach to prevent VZV infection post-HSCT is acyclovir prophylaxis. Although there are ongoing studies on the use of HZ vaccine in adults post-HSCT, acyclovir prophylaxis remains to be the only option for pediatric patients [3].

The prospective studies on the use of acyclovir for VZV prevention were conducted on adults and there is less information on the use of acyclovir in the pediatric postHSCT population. The duration of acyclovir used to prevent HZ after HSCT in pediatric patients remains unclear. There are no prospective studies and published retrospective studies are scarce. We retrospectively evaluated the incidence and characteristics of VZV infections for pediatric patients who underwent allogeneic HSCT at Ankara University Children's Hospital to understand the role of acyclovir prophylaxis given for 6 months post-HSCT on VZV infections in pediatric HSCT patients.

2 | Materials and Methods

Patients who received allogeneic HSCT between January 1, 1996 and January 1, 2020 at Ankara University Pediatric Bone Marrow Transplant Unit were evaluated retrospectively. Autologous HSCT and patients with immunodeficiency were excluded. Acyclovir prophylaxis was administered routinely for all allogeneic HSCT patients at 1200–1500 mg/m^2/day intravenously (IV) for the first month post-HSCT and continued until the end of immunosuppressive treatment at 30–40 mg/kg/day orally.

Data regarding VZV reactivation were collected from the charts and directly from the families by phone calls. Age; gender; underlying disease; HLA compatibility; relationship between the donor, stem cell source, conditioning regimen, antithymocyte globulin (ATG), and total body irradiation (TBI) use; graft versus host disease (GVHD) prophylaxis; duration of immunosuppressive treatment; GVHD status; immune reconstitution by leukocyte; CD4 T lymphocyte and CD8 T lymphocyte counts at post-HSCT 6, 9, 12, 18, and 24 months; duration of acyclovir use; and varicella serology/history of disease or vaccination were recorded as variables. Myeloablative conditioning was defined as fractionated TBI ≥8 Gy, single TBI ≥5 Gy, >6.4 mg/kg of IV busulfan, or ≥150 mg/m^2 of melphalan [4]. GVHD prophylaxis was discontinued at approximately the sixth month in benign diseases and at approximately the fourth month in malignant diseases. The white blood cell, total neutrophil, total lymphocyte, CD4 T lymphocyte and CD8 T lymphocyte counts, and CD4/CD8 ratios at 6, 9, 12, 18, and 24 months after HSCT were recorded. Patients who received two HSCTs were noted but were not excluded from being able to see if there was an impact of the second HSCT on VZV occurrence. The time to second HSCT was median 40.47 months (1.64–87.67 months). Each HSCT was evaluated individually for statistical analysis.

2.1 | Statistical Analysis

Mean standard deviation, median, minimum, and maximum values were given in descriptive statistics for continuous data; percentage values were given in discrete data. Kolmogorov Smirnov test was used to examine the conformity of the data to the normal distribution. Mann–Whitney *U* test was used to compare continuous data in two groups. Chi-square and Fisher's exact tests were used for group comparisons (cross tables) of nominal variables. The factors affecting the development of HZ post-HSCT were examined with multivariate logistic regression. IBM SPSS Statistics 20 program was used in the evaluations and the statistical significance limit was accepted as $p < 0.05$.

3 | Results

In total, 260 patients received 273 HSCTs between November 1997 and January 2020. Patient and transplant characteristics of the cohort is given in Table 1. In the median follow-up period of 6.4 years (18 days–20.8 years), the incidence of HZ was 21.2% (*n*: 58). The median age at the time of HZ infection was 13.81 years (3.03–27 years). Time to HZ infection was median 345 days (55–3433 days) post-HSCT. Most of the patients with HZ infection had a history of varicella infection before HSCT (86.2%). In most of the cases, HZ infection presented after the cessation of acyclovir (94.8%) and median time to HZ infection after acyclovir cessation was median 158 days (20–3239 days). All HZ infections recorded were after the first HSCT. Thoracic region was the most common site for HZ (31%) followed by lumbar in 22.4%. HZ was disseminated in 19% (*n*: 11) of cases. The most common complication was secondary bacterial skin infections (13.8%; 8/58). HZ was treated with IV, oral, and IV followed by po acyclovir in 48.3%, 25.9% oral, and 20.7% of cases. The median time for hospitalization was 8 days (2–20 days). There was no HZ infection-related death in our cohort. Characteristics of the patients with and without HZ are summarized in Table 2.

Only 5.2% (*n*: 3/58) of the patients had HZ while on acyclovir prophylaxis. On the other hand, 94.8% (*n*: 55) experienced HZ after the cessation of acyclovir prophylaxis. The period, in which HZ was most experienced post-HSCT, was 6 months to 1 year post-HSCT (43.1% [*n*: 25]), followed by 1 year to 2 years (24.1% [*n*: 14]) and the first 6 months (13.8% [*n*: 8]) post-HSCT (Figure 1). The incidence of HZ after 2 years post-HSCT was 0.7–1% per year. Eight patients (13.8%) had HZ infection within the first 6 months, and in 5/8 patients, acyclovir prophylaxis was discontinued prematurely for different reasons. From 6 months to 18 months post-HSCT, 33 patients had HZ infection. In 23 (69.7%) of these patients, the last CD4 count before HZ infection was below 500/μL. In contrast, none of the patients who had HZ infection after 18 months had a CD4 count <500/μL. The risk of HZ infection approached to normal population after 2 years and CD4 count was not found to be a risk factor for HZ infection in

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TABLE 1 | Patient and transplant characteristics of the cohort.

	***n* = 273**
Age at HSCT (year) (median)	10.43 (0.47–18.37)
Gender, *n* (%)	
Female	120 (44)
Male	153 (56)
Underlying disease, *n* (%)	
Thalassemia major	109 (39.9)
Acute leukemia	77 (28.5)
Fanconi aplastic anemia	22 (8.1)
Other	65 (23.5)
HSCT number, *n* (%)	
First HSCT	258 (94.5)
Second HSCT	15 (5.5)
Donor status, *n* (%)	
Matched sibling	207 (75.8)
Matched family	30 (11)
Matched/well matched unrelated	27 (9.9)
Haplo	9 (3.3)
Stem cell source	
Bone marrow	184 (67.4)
Peripheral blood	75 (27.5)
Cord blood	5 (1.8)
Different combinations	9 (3.3)
Conditioning regimen, *n* (%)	
Myeloablative	241 (88.3)
Non-myeloablative	32 (11.7)
ATG use, *n* (%)	
Yes	135 (49.5)
No	138 (50.5)
TBI use, *n* (%)	
Yes	26 (9.5)
No	247 (90.5)
GVHD prophylaxis	
CSA + MTX	176 (64.5)
CSA	77 (28.2)
Different combinations	20 (7.3)
Acute GVHD (grade I–IV), *n* (%)	
Yes	71 (26)
No	202 (74)
Chronic GVHD, *n* (%)	
Yes	45 (16.5)
No	228 (83.5)
Duration of acyclovir prophylaxis, days (median)	184 (11–1408)
VZV serology, *n* (%)	
Positive	10 (3.7)
Negative	4 (1.4)
Unknown	259 (94.9)
History of VZV infection pre-HSCT, *n* (%)	
Yes	108 (39.6)
No	148 (54.2)
Unknown	17 (6.2)
History of VZV vaccination, *n* (%)	
Yes	33 (12.1)
No	240 (87.9)
Post-HSCT mortality, *n* (%)	
0–100 days	13 (4.8)
101–365 days	14 (5.1)
>365 days	21 (7.7)

Abbreviations: ATG, antithymocyte globulin; CSA, cyclosporin; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; MTX, methotrexate; TBI, total body irradiation; VZV, varicella-zoster virus.

this late period. The evolution of the cellular recovery is summarized in Table 3. Although immunosuppressive therapy was given for more than 6 months in 27.6% (*n*: 16) of the patients who developed HZ, in 75% (*n*: 12) of patients, acyclovir prophylaxis was discontinued before the immunosuppressive therapy for different reasons.

In univariate analysis, older age at the time of HSCT, female gender, history of chickenpox, no varicella vaccination, low lymphocyte and CD4 counts and CD4/CD8 ratio at 9 and 12 months were statistically significant risk factors for HZ infection but only low CD4/CD8 ratio at 12 months and history of varicella infection was found to be an independent risk factor in multivariate analysis (OR: 3.695; 95% CI: 1.3–10.1; $p = 0.011$).

A subgroup analysis was performed for the patients who survived at least 100 days post-HSCT. None of the patients had HZ within 100 days so the frequency of HZ was 22.6% (*n*: 58/257). Univariate analysis showed similar results with the whole cohort with older age of the patient, previous varicella infection before HSCT and the absence of varicella vaccination, low CD4 T lymphocyte count, and ratio of CD4/CD8 T lymphocyte count at the 9 and 12 months being a risk factor for the development of HZ infection. On multivariable analysis, similar to

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TABLE 2 | Characteristics of the patients with and without HZ and the univariate analysis.

	HZ ($n=58$)	No HZ ($n=215$)	p
Age at HSCT (year) (median)	12.22 (2–18.07)	9.32 (0.47–18.38)	0.002
Gender, *n* (%)			
Female	33 (57)	87 (40)	0.025
Male	25 (43)	128 (60)	
Underlying disease, *n* (%)			
Non-malignant	35 (60)	122 (57)	0.623
Malignant	23 (40)	93 (43)	
HSCT number, *n* (%)			
First HSCT	57 (98)	201 (93)	0.206
Second HSCT	1 (2)	14 (7)	
Donor status, *n* (%)			
Matched sibling	49 (85)	158 (74)	—
Matched family	6 (10)	24 (11)	
Matched/well-matched unrelated	3 (5)	24 (11)	
Haplo	0	9 (4)	
Conditioning regimen, *n* (%)			
Myeloablative	48 (83)	193 (90)	0.141
Non-myeloablative	10 (17)	22 (10)	
ATG use, *n* (%)			
Yes	30 (52)	105 (49)	0.696
No	28 (48)	110 (51)	
TBI use, *n* (%)			
Yes	6 (10)	20 (9)	0.810
No	52 (90)	195 (91)	
Acute GVHD, *n* (%)			
Yes	17 (29)	54 (25)	0.518
No	41 (71)	161 (75)	
Chronic GVHD, *n* (%)			
Yes	11 (19)	34 (16)	0.566
No	47 (81)	181 (84)	
VZV serology of the patient ($n=14$), *n* (%)			
Positive	2 (100)	8 (67)	—
Negative	0	4 (33)	
History of VZV infection pre-HSCT, *n* (%)			
Yes	50 (86)	58 (29)	0.000
No	7 (12)	141 (71)	
Unknown	1 (2)	0	
History of VZV vaccination, *n* (%)			

(Continues)

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TABLE 2 | (Continued)

	HZ ($n=58$)	No HZ ($n=215$)	p
Yes	2 (3)	31 (14)	0.023
No	56 (97)	184 (86)	
GVHD prophylaxis duration, days (median)	183 (81–2956)	181 (18–1576)	0.073
Duration of acyclovir prophylaxis, days (median)	186 (38–317)	183 (11–1408)	0.972
Duration of IVIG, days (median)	154 (95–7415)	152 (13–3841)	0.147

Abbreviations: ATG, antithymocyte globulin; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; TBI, total body irradiation; VZV, varicella-zoster virus.



FIGURE 1 | Distribution of posttransplant HZ development according to years after HSCT. HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster.

the analysis of the whole cohort, history of varicella infection and CD4/CD8 T cell ratio were the independent risk factors for HZ.

4 | Discussion

HZ is the most common viral disease in the late posttransplant period and in this single-center experience using acyclovir prophylaxis for 6 months following allogeneic HSCT, the incidence of HZ was 21.2%. The lowest rate of HZ infection was during the first 6 months while the patients were on acyclovir prophylaxis (13.1%). The HZ incidence was reported as high as 31% in HSCT recipients without acyclovir prophylaxis in the literature [5]. Acyclovir prophylaxis 800 mg twice daily for 1-year post-HSCT decreased the HSV incidence to 5.2% in a double-blind controlled trial by Boeckh et al., whereas the HSV incidence was 26% in the placebo group (HR, 0.16; 95% CI, 0.035–0.74; $p=0.006$) [6]. The acyclovir prophylaxis duration is very variable between HSCT centers and the rate of HZ infection is consistently reported to be low in patients during the period of acyclovir use. The duration of acyclovir prophylaxis in these studies varies between 3 months and 1 year [7, 8]. Lower incidence of HZ infections with longer acyclovir was documented in a meta-analysis reporting the incidence of HZ as 2.1% and 15.4% in the groups using prophylaxis for at least 1 year and <1 year, respectively, with a pooled RR of 0.23 (95% CI, 0.04–1.39) [9]. In our study, HZ incidence was highest in the 6 months-1 year post HSCT (43.1%), immediately after the cessation of acyclovir prophylaxis. During this period acyclovir was discontinued despite the ongoing immunosuppressive treatment for different reasons in 16.5% (n: 45/273) of patients. The HZ incidence was lower 1–2 years post-HSCT in our study (23.1%) at and approached to the normal population after 2 years post-HSCT. Increased HZ risk has been reported with ongoing immunosuppression [6, 10, 11] regardless of time after HSCT and increased HZ from 6 months to 1 year period in our study could be partly related to the immature discontinuation of acyclovir.

Absolute lymphocyte count, CD4 T lymphocyte count and CD4/CD8 T lymphocyte ratio were significantly lower in patients who developed HZ at 9 and 12 months after transplantation ($p<0.05$) in our study. In addition, CD4/CD8 T lymphocyte ratio measured at the 12th month after transplantation was found to be an independent risk factor for the development of HZ post-HSCT in multivariate analysis. It was found that a one-unit increase in the patients' CD4/CD8 T lymphocyte ratio at 12 months reduced the development of HZ by 3.6 times ($p<0.05$). Low CD4/CD8 T lymphocyte ratio at 18 months post-HSCT had a borderline effect on HZ infection ($p=0.051$). Similar to our study, low CD4 count and low CD4/CD8 ratios were found to be associated with the development of HZ in the study by Aytaç et al. [7]. CD4 counts were not found to be a risk factor for HZ infection in the later period but T-cell function was not studied. In future studies, looking at parameters such as T-cell functions that may be at risk of infection in the late period may be helpful in terms of explaining the risks. Our study well documented the increased HZ risk with the premature cessation of acyclovir prophylaxis at 6 months, that is, before the sufficient CD4 T-cell recovery and/or while on immunosuppression. In current guidelines,

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TABLE 3 | Immunological and hematological values of patients with and without herpes zoster (HZ) at 6, 9, 12, 18, and 24 months post-HSCT.

	6 months		9 months		12 months		18 months		24 months	
	HZ ($n=58$)	No HZ ($n=215$)	HZ ($n=58$)	No HZ ($n=215$)	HZ ($n=58$)	No HZ ($n=215$)	HZ ($n=58$)	No HZ ($n=215$)	HZ ($n=58$)	No HZ ($n=215$)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
White cell count	5885 ± 2653	6280 ± 3779	7304 ± 3179	7524 ± 3466	7670 ± 2669	8260 ± 3365	7680 ± 2875	8046 ± 3159	7451 ± 1955	7787 ± 3230
Lymphocyte count	2085 ± 1310	2341 ± 1735	2580 ± 1528	2920 ± 1544*	2840 ± 1706	3310 ± 1522*	2932 ± 1501	3242 ± 1664	2862 ± 1137	3091 ± 1749
Neutrophil count	3044 ± 1702	3103 ± 2605	3767 ± 1800	3604 ± 2086	3904 ± 1782	3884 ± 2165	3858 ± 1733	3771 ± 2082	3660 ± 1399	3717 ± 1971
CD4 T-cell count	362 ± 241	432 ± 329	530 ± 316	639 ± 364*	667 ± 398	831 ± 416**	769 ± 371	902 ± 454	841 ± 354	899 ± 463
CD8 T-cell count	947 ± 663	1001 ± 832	1100 ± 773	1178 ± 765	1128 ± 697	1228 ± 732	1027 ± 624	1116 ± 712	951 ± 467	1021 ± 679
CD4/CD8	0.46 ± 0.29	0.52 ± 0.29	0.56 ± 0.38	0.65 ± 0.37*	0.67 ± 0.35	0.81 ± 0.45*	0.83 ± 0.32	0.92 ± 0.39	0.97 ± 0.36	1.00 ± 0.41

Abbreviations: HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster.
*$p<0.05$, **$p<0.01$.

prophylaxis with oral acyclovir (800 mg twice daily) or valacyclovir (500 mg once or twice daily) is recommended for seropositive allo-HSCT recipients, for 1 year, or longer in the presence of GVHD and immunosuppressive therapy [2]. More specific usage of prophylactic acyclovir was reported in a recent study reporting acyclovir prophylaxis for up to 4 weeks after discontinuation of immunosuppressive therapy and until CD4 T lymphocyte count recovery >250/μL which resulted in a low incidence of VZV infection post-HSCT (15.0%) [12].

The median time to HZ infection was 345 days post-HSCT in our study. HZ occurrence was reported to be sooner following HSCT in patients without acyclovir prophylaxis as shown by Kawasaki, Takayama, and Ohira, compared to studies with a median of 5 months after HSCT with a median of 9 weeks of prophylaxis [5, 8]. These findings suggest that acyclovir prophylaxis may shift the development of HZ infection to a later time after HSCT and that acyclovir prophylaxis is effective in preventing HZ infection in the early post-HSCT period.

When patient- and disease-related risk factors are evaluated before HSCT in terms of HZ development, the presence of anti-VZV antibodies before HSCT is significantly associated with an increased incidence of VZV infection after HSCT [13] VZV serology was unknown in nearly 95% of the patients which was one of our study limitations. However, post-HSCT HZ infection was found to be significantly higher in patients with a history of varicella infection and past varicella infection was an independent risk factor on multivariate analysis. However, 12.1% of patients with HZ did not have a history of varicella in our study. The varicella infection history may not be reliable [14] and VZV serology may not be accurate. Kang et al. showed that pretransplant VZV serology was negative in 25% of patients who developed HZ [15] and failed to identify patients at risk of HZ. Current guidelines recommend acyclovir prophylaxis only for VZV seropositive patients. It should be kept in mind that patients with negative serology and without previous varicella infection history may be at risk for HZ infection and may benefit from acyclovir prophylaxis. Receiving varicella vaccine decreases the risk of HZ infection in non-HSCT patients [16, 17]. Duver et al. reported HZ incidence post-HSCT as 21.7% in patients without varicella vaccination while no vaccinated patient had a VZV reactivation [12]. In parallel to this finding, pretransplant varicella vaccination was found to be lower in patients with HZ compared to patients without HZ ($p=0.023$) in our study as well.

Although there are few studies reporting the cervical and lumbar dermatomes as the most common site for HZ [7, 8], thoracic dermatomes have been reported as the most common site of HZ infection both in HSCT [5, 13, 17, 18] and non-HSCT settings [19–21] in many as well as in our study. HZ was disseminated involving more than one dermatome in 19% and the most common complication was secondary bacterial skin infection with 13.8%, similar to Han et al. disseminated HZ developed in 24% of patients and secondary skin infection developed in 12% of patients [8].

In our study, the majority (69%) of patients with HZ were treated with IV acyclovir ± oral acyclovir, the median hospitalization period was 8 days, and no HZ-related mortality was observed. In the study by Han et al. who used acyclovir for a shorter period

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in the literature, 84.8% of the patients received IV treatment and the duration of hospitalization was reported as 12 days [8]. In a study by Asano-Mori et al. comparing long-term and short-term prophylaxis groups, 71% of patients with HZ in the short-term prophylaxis group and 21% of patients with HZ in the long-term prophylaxis group were hospitalized [17]. The effect of the duration of acyclovir prophylaxis on the clinical course of HZ in pediatric patients and its effect on the need for hospitalization and IV treatment is not clear, but longer acyclovir prophylaxis use could shift the HZ infection to a later time when immune system is better to control the disease.

In conclusion, acyclovir prophylaxis used for 6 months in this study resulted in a very low HZ risk during the time the patients were on acyclovir. The increase after the cessation of HZ after 6 months especially in the population who continued on immunosuppressive treatment underlines the importance of prophylaxis covering immunosuppressed times, regardless of VZV serology and history of varicella infection. Currently acyclovir prophylaxis is recommended for seropositive patients for the first year of HSCT. Acyclovir prophylaxis (2 × 20 mg/kg or 2 × 800 mg in adolescents) or valacyclovir (2 × 500 mg in adolescents) is recommended until day +365 for pediatric alloHSCT recipients for VZV seropositive patients [22]. As reported in this study and some others, it has to be kept in mind that VZV serology may not be solely useful for selecting the vulnerable population. It is also reported that there may be an increased risk of delayed VZV reactivation after discontinuing acyclovir (rebound) and optimal acyclovir dose and duration of the prophylaxis is still to be defined [9].

Author Contributions

G.A. and Elif Ince were responsible for designing the study, writing the protocol and report, conducting the research, screening potentially eligible studies, extracting and analyzing data, interpreting results, updating reference lists, and creating "Summary of findings" tables. Erdal Ince, T.I., E.C., F.D., H.O., H.F.C., and M.E. provided feedback on the report.

Acknowledgments

We thank all the patients and doctors who took part in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

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