



Comparison of Varicella-zoster Infections in Pediatric Cancer Patients Versus Other Immunocompromised Patients

Çocuk Kanser Hastaları ile Diğer İmmün Yetmezlikli Hastalardaki Varisella-Zoster Enfeksiyonlarının Karşılaştırılması

Mustafa Asım Yörük¹(ID), Emine Olcay Yasa²(ID)

¹ Clinic of Pediatrics Hematology Oncology, Yeditepe University Hospital, İstanbul, Turkey

² Clinic of Pediatrics, Medeniyet University Göztepe Training and Research Hospital, İstanbul, Turkey

Cite this article as: Yörük MA, Yasa EO. Comparison of varicella-zoster infections in pediatric cancer patients versus other immunocompromised patients. J Pediatr Inf 2022;16(1):e27-e34.

Abstract

Objective: This study aims to compare the clinical features of varicella and herpes zoster infections in cancer patients with chronic immunocompromised patients.

Material and Methods: Medical records of 144 immunocompromised patients between the ages of 0 and 18 were examined. The patients were divided into two groups. Group A consisted of cancer patients, while Group B consisted of patients with non-cancer immunodeficiency. Data were collected showing the complications associated with varicella-zoster virus, length of hospital stay, vaccination status, acyclovir, intravenous immunoglobulin, antibiotic therapy, and disease outcomes.

Results: Of 144 children patients, 55 (38.2%) were in Group A and 89 (61.8%) were in Group B. Acute lymphoblastic leukemia (54.5%) in Group A and neurological disorders (33.8%) in Group B were the underlying primary disease. Seventeen of those with herpes zoster disease were in Group A, and 83 of those with varicella disease were in Group B. Chickenpox/herpes zoster was observed more in the spring (70.4%) in Group B and in the summer season in Group A (53.1%). The median duration of the rash was nine (3-36) days in chickenpox and 10 (8-12) days in herpes zoster. There was no significant difference between the two groups in terms of CRP positivity and antibiotic treatment ($p > 0.05$). 38.1% of the patients in Group A and 5.6% of the patients in Group B were neutropenic ($p < 0.05$). There were complications in 54 patients in Group A and 25 patients in group B. Among the complications, secondary bacterial infection/sepsis was seen more in Group A than in Group B. There was a statistically significant difference between the groups in the distribution

Öz

Giriş: Bu çalışmada kanser hastalarındaki suçiçeği ve herpes zoster enfeksiyonlarının klinik özelliklerinin immün yetmezlikli kronik hastalarla karşılaştırılması amaçlanmaktadır.

Gereç ve Yöntemler: 0-18 yaşları arasındaki 144 immün yetmezlikli çocuk hastanın tıbbi kayıtları incelendi. Hastalar iki gruba ayrıldı. Grup A kanser hastalarından oluşurken, Grup B kanser dışı immün yetmezlikli hastalardan oluşuyordu. Varisella zoster virüs (VZV) ile ilişkili komplikasyonlar, hastane yatış süreleri, aşılanma durumları, asiklovir, intravenöz immünglobulin, antibiyotik tedavisi ve hastalığın sonuçlarını gösteren veriler toplandı.

Bulgular: Çalışmamızdaki 144 çocuk hastanın 55 (%38.2)'i Grup A ve 89 (%61.8)'u Grup B'deydi. Grup A'da akut lenfoblastik lösemi (%54.5), Grup B'de nörolojik bozukluklar (%33.8) altta yatan birincil hastalıktı. Herpes zoster hastalığı olanların 17'si grup A'da, altısı Grup B'de; suçiçeği hastalığı olanların 38'i Grup A'da, 83'ü Grup B'deydi. Suçiçeği/herpes zoster Grup B'de ilkbaharda (%70.4), Grup A'da yaz mevsiminde (%53.1) daha fazla gözlenmiştir. Döküntü süresi suçiçeğinde ortalama 9 (3-36) gün, herpes zosterde ortalama 10 (8-12) gündü. İki grup arasında CRP pozitifliği ve antibiyotik tedavisi açısından anlamlı bir fark yoktu ($p > 0.05$). Grup A'da hastaların %38.1'i ve Grup B'de %5.6'sı nötropenikti ($p < 0.05$). A grubunda 54 hasta ve B grubunda 25 hastada komplikasyon vardı. Komplikasyonlar içinde ikincil bakteriyel enfeksiyon/sepsis bulgusu Grup A'da Grup B'ye göre daha fazlaydı. Gruplar arası asiklovir kullanımının dağılımında ve asiklovir kullanım süresi arasında istatistiksel olarak anlamlı fark vardı ($p < 0.05$). Gruplar arasında hastane kalış süresi A grubunda daha uzundu ($p < 0.05$).

Correspondence Address/Yazışma Adresi

Mustafa Asım Yörük

Yeditepe Üniversitesi Hastanesi,
Pediyatrik Hematoloji Onkoloji Kliniği,
İstanbul-Türkiye

E-mail: dryoruk@gmail.com

Received: 08.10.2019

Accepted: 08.06.2021

Available Online Date: 09.06.2022

©Copyright 2022 by Pediatric Infectious Diseases and Immunization Society.
Available online at www.cocukenfeksiyon.org

of acyclovir use and the duration of acyclovir ($p < 0.05$). The length of hospital stay between groups was longer in group A ($p < 0.05$).

Conclusion: Varicella zoster infections are one of the important causes of mortality and morbidity in pediatric oncology patients. The frequency of herpes zoster is higher in cancer patients compared to other immunodeficient patients and close monitoring is required. At least one complication can often be seen in immunocompromised patients who become ill with varicella zoster virus, and it is possible to prevent complications or to decrease their severity by starting acyclovir/antiviral therapy without delay. Cancer patients require a longer period of acyclovir treatment than other immunocompromised VZV patients. Initiation of acyclovir/antiviral therapy by hospitalization of cancer patients with varicella zoster virus infection and other immunodeficient patients without delay will decrease the complications and mortality rates of varicella zoster virus. Multidisciplinary follow-up of pediatric infection specialists, pediatric hematology-oncology specialists and other specialists who follow immunocompromised patients will reduce the morbidity and mortality of VZV infections in these patient groups.

Keywords: Leukemia, immunocompromised, varicella, herpes zoster

Introduction

Varicella is one of the most common diseases in childhood. Varicella-zoster virus (VZV) causes two different pictures: chickenpox and herpes zoster. Chickenpox is caused by the transmission of the virus to people who are not immune. Herpes zoster is a recurrent infection of VZV that remains latent after primary infection in the organism. Children with cancer have a higher risk for herpes zoster than the normal population; leukemia is the one with the highest risk among cancer types (1). Varicella-zoster virus infections are potentially life-threatening for cancer patients receiving chemotherapy, or immunocompromised patients receiving corticosteroids. Several studies report elevated incidence rates of herpes zoster in persons with immunocompromising conditions ranging up to 10 times more than the general population for individuals with stem cell or bone marrow transplants (2-4). Unlike the immunocompetent patients, crusted lesions can be contagious in pediatric hematology-oncology patients (5). Immunocompromised patients exposed to varicella may experience significant morbidity and a 7% mortality rate (5). VZV infections are one of the most important causes of mortality and morbidity in pediatric hematology-oncology patients. Morbidity and mortality of VZV infection decrease with the initiation of acyclovir treatment in the early phase of the disease (6).

Varicella virus infection can cause complications and requires hospitalization (1). The most common complications in children were a secondary bacterial infection (23%), neurological (19.1%), and respiratory system (17.5%) complications (7). Chemotherapy causes zoster eruptions in approximately one-quarter of children with acute lymphoblastic leukemia (ALL) (8).

In this study, we aimed to determine the clinical characteristics of chickenpox and herpes zoster infections in cancer patients and to compare the complication rates, length of

Sonuç: Pediatrik onkoloji hastalarında varisella zoster enfeksiyonları mortalite ve morbiditenin önemli nedenlerinden biridir. Kanser hastalarında diğer immün yetmezlikli hastalara göre herpes zoster sıklığı suçiçeğinden daha fazla olup yakın izlem gerekmektedir. Varisella zoster virüsü ile hastalanan immün yetmezlikli hastalarda sıklıkla en az bir komplikasyon görülebilmekte olup komplikasyonların önlenmesi ya da şiddetinin azalması asiklovir/antiviral tedaviye vakit geçirmeden başlanmasıyla mümkündür. Kanser hastaları, immün yetmezlikli diğer VZV hastalarına göre daha uzun bir süre asiklovir tedavisi gerekmektedir. Varisella zoster virüs enfeksiyonlu kanser hastaları ve diğer immün yetmezlikli hastaların vakit geçirmeden hastaneye yatırılarak asiklovir/antiviral tedavi başlanması varisella zoster virüsüne ait komplikasyonları ve ölüm oranlarını azaltacaktır. Pediatrik enfeksiyon uzmanları, pediatrik hematoloji-onkoloji uzmanları ve immün yetmezlikli hastaları tedavi eden diğer branş hekimlerinin multidisipliner izlemi bu hasta gruplarında VZV enfeksiyonlarına ait morbidite ve mortaliteyi azaltacaktır.

Anahtar Kelimeler: Lösemi, immün yetmezlik, suçiçeği, herpes zoster

hospital stay, use of acyclovir, and treatment results with other chronic immunodeficient patients.

Materials and Methods

Six-year hospital records of 144 immunocompromised children aged 0 to 18 years who were treated in the pediatric infectious diseases unit with the diagnosis of chickenpox or herpes zoster infection were analyzed retrospectively.

Patients who were diagnosed with chickenpox or herpes zoster and were immunosuppressive up to one month before diagnosis were included in the study. Immune suppressive condition; cancer patients receiving chemotherapy, patients with congenital or acquired immunodeficiency, and patients with chronic disease receiving corticosteroids, immunosuppressive, or chemotherapeutics were accepted as immunodeficient patients. Complications due to varicella-zoster virus infection were defined as bacterial superinfection of the skin occurring within 14 days after the onset of VZV infection, or as neurological (encephalitis, meningitis, cerebellitis), hematological, pulmonary, gastrointestinal, and osteoarticular complications.

The patients were divided into two groups according to their underlying diseases. Group A consisted of patients with immunosuppression due to hematological or oncological diseases (ALL, acute myeloid leukemia (AML), solid tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, immunosuppressed immune thrombocytopenic purpura (ITP), and other immunocompromised hematological disorders).

Other hematological disorders were congenital neutropenia, cyclic neutropenia, hemophagocytic syndrome, Schwachmann - Diamond syndrome, and histiocytosis receiving chemotherapy or corticosteroids. Group B consisted of patients with immunosuppression due to other causes (newborn babies, neurological, rheumatologic, nephrological, genetic, and cardiovascular diseases).

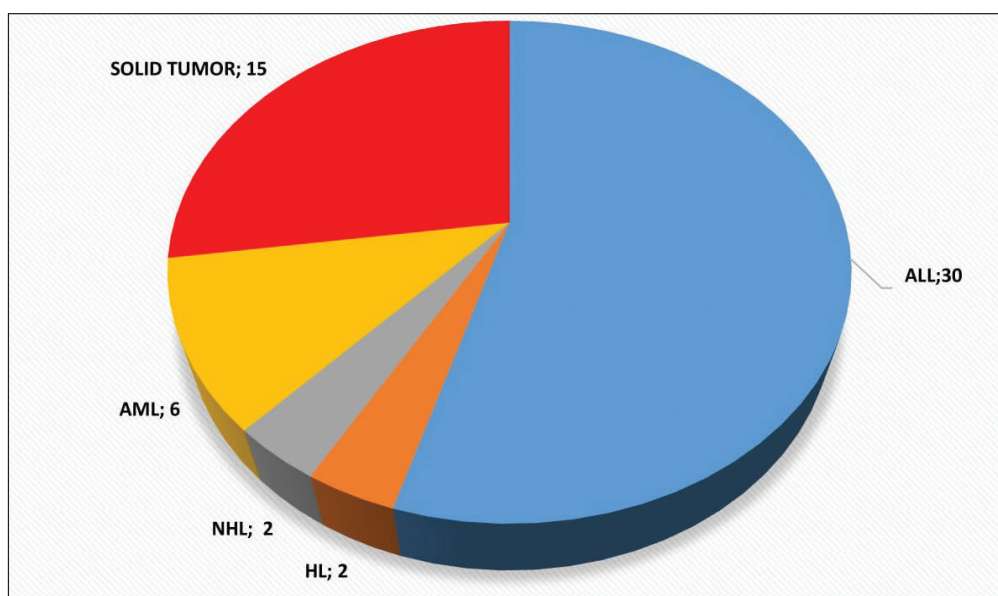


Figure 1. Distribution of patients in Group A.

ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, NHL: Non-Hodgkin lymphoma, HL: Hodgkin lymphoma.

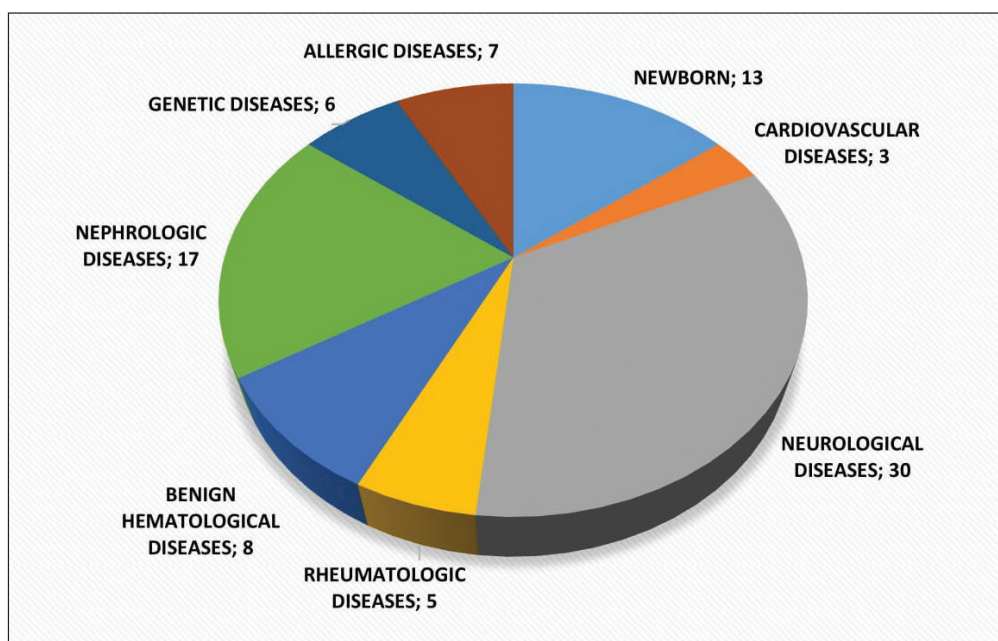


Figure 2. Distribution of patients in Group B.

Information on gender, age, underlying diseases, presenting symptoms, complications related to varicella-zoster virus and duration of hospitalization, vaccination history, acyclovir treatment, intravenous immunoglobulin administration, antibiotic therapy, intensive care unit stay, and hospitalization results (intensive care unit need or death) were retrospectively scanned from the hospital medical information system. The dose of acyclovir was intravenous (1500 mg/m²/day) in 3 divided doses. Acyclovir treatment was scheduled for seven days but was extended if the rash persisted.

The data were analyzed using the SPSS 25.0 (Statistical Packages of Social Sciences) program on the computer. The compliance of the data to normal distribution was evaluated with the Kolmogorov-Smirnov test. Descriptive statistics were presented as mean $\pm$ standard deviation, median, minimum and maximum value for continuous variables, and as frequency and percentage for categorical variables. The Mann-Whitney U test was used to compare the data of two independent groups that were not normally distributed. For the analysis of the difference between categorical variables, the Chi-square

test, and Fisher's exact probability test was used. $p < 0.05$ was considered statistically significant.

Written informed consent/permission was obtained from each patient or their legal guardian before the treatment. The study was approved by the institutional ethics committee (2019/0068).

Results

Of the 144 immunocompromised children included in the study, 55 (38.2%) were in Group A and 89 (61.8%) were in Group B. Acute lymphoblastic leukemia (54.5%) was the most common disease in Group A, followed by solid tumors (27.3%). Neurological disorders (mostly epilepsy and West syndrome) (33.8%) were the most common primary diseases in group B, followed by nephrological diseases (mostly nephrotic syndrome) (19.1%).

Patient characteristics according to the groups are given in Table 1 and clinical features are given in Table 2. Patient characteristics according to chickenpox and herpes zoster are given in Table 3.

The median age of the 144 children included in the study was four years (range 16 days to 17 years) and the male/female ratio was 1.57. Chickenpox/Herpes zoster ratio was 2.2 in Group A, 13.8 in Group B, and 5.2 in all patients. There was a statistically significant difference between the distribution of diseases between the groups ($p < 0.05$). Of those with herpes zoster disease, 17 were in Group A, and six were in Group B; 38 of those with chickenpox were in Group A and 83 were in Group B. The median age was three years (16 days-7 years) in chickenpox patients and eight years (2-17 years) in herpes zoster patients. Chickenpox was seen in all subgroups except Hodgkin lymphoma in Group A, while it was seen in all subgroups in Group B. While herpes zoster was seen in all subgroups in Group A, it was not seen in the neonatal period, in those with neurological, rheumatological, and cardiovascular diseases in Group B. There was a statistically significant difference in the seasonal distribution of varicella/herpes zoster between the groups ($p < 0.05$). In the spring, VZV infections were observed more in Group B than in Group A. In the summer season, VZV infections were observed more in Group A than in Group B. None of the patients were vaccinated against chickenpox.

Table 1. Patient characteristics

	Group A (n= 55) (% in group) (% in category)	Group B (n= 89) (% in group) (% in category)	Total (n= 144) (% in total)	p
Age	1 year-16 years (median 6 years)	16 days-17 years (median 3 years)	16 days-17 years (median 4 years)	$p < 0.05$
Male/Female	31/24 (1.29)	57/32 (1.78)	88/56 (1.57)	$p > 0.05$
Varicella/Herpes zoster	38/17 (2.2)	83/6 (13.8)	121/23 (5.2)	$p < 0.05$
Seasonal Distribution				
Spring	16 (29.1) (29.6)	38 (42.7) (70.4)	54 (37.5)	$p < 0.05$
Summer	17 (30.9) (53.1)	15 (16.9) (46.9)	32 (22.2)	
Fall	11 (20) (55)	9 (10.1) (45)	20 (13.9)	
Winter	11 (20) (28.9)	27 (30.3) (71.1)	38 (26.4)	
Diseases				
ALL	30 (54.5)	-	30 (54.5)	-
AML	6 (11)	-	6 (11)	-
Solid tumor	15 (27.3)	-	15 (27.3)	-
Hodgkin lymphoma	2 (3.6)	-	2 (3.6)	-
Non-Hodgkin lymphoma	2 (3.6)	-	2 (3.6)	-
Newborn period	-	13 (14.6)	13 (14.6)	-
Neurological diseases	-	30 (33.8)	30 (33.8)	-
Rheumatologic diseases	-	5 (5.6)	5 (5.6)	-
Nephrological diseases	-	17 (19.1)	17 (19.1)	-
Genetic diseases	-	6 (6.7)	6 (6.7)	-
Cardiovascular diseases	-	3 (3.4)	3 (3.4)	-
Allergic diseases	-	7 (7.8)	7 (7.8)	-
Benign hematological diseases	-	8 (9)	8 (9)	-

ALL: Acute lymphoblastic leukemia, AML: Acute myeloblastic leukemia.

Table 2. The clinical features

	Group A (n= 55) (% in group) (% in category)	Group B (n= 89) (% in group) (% in category)	Total (n= 144) (% in total)	p
Symptoms				
Rash	43 (78.2) (44.3)	54 (60.7) (55.7)	97 (67.3)	p< 0.05
Fever, rash	8 (14.5) (36.4)	14 (15.7) (63.6)	22 (15.3)	p> 0.05
Fever, rash, convulsion	0 (0) (0)	5 (5.6) (100)	5 (3.5)	p> 0.05
Fever, rash, vomiting	0 (0) (0)	4 (4.5) (100)	4 (2.8)	p> 0.05
Pain, rash	4 (7.3) (66.7)	2 (2.2) (33.3)	6 (4.2)	p> 0.05
Rash, unconsciousness	0 (0) (0)	3 (3.4)	3 (2.1)	p> 0.05
Rash, imbalance	0 (0) (0)	2 (2.2)	2 (1.4)	p> 0.05
Clinical Features				
Duration of rash	5-35 days (median 10 days)	3-36 days (median 9 days)	3-36 days (median 9 days)	
Neutropenia	21 (38.1) (80.7)	5 (5.6) (19.3)	26 (18)	p< 0.05
C-reactive protein (+)	25 (45.5) (37.9)	41 (46.1) (62.1)	66 (45.8)	p> 0.05
Complications	54 (98.1) (68.3)	25 (28) (31.7)	79 (54.8)	-
Skin infection	7 (12.7) (63.6)	4 (4.5) (36.4)	11 (7.6)	
Neurological	0 (0) (0)	4 (4.5) (100)	4 (2.8)	
Respiratory	2 (3.6) (22.2)	7 (7.9) (77.8)	9 (6.3)	
Secondary bacterial infection/sepsis	43 (78.2) (84.3)	8 (9) (15.7)	51 (35.4)	
Ocular involvement	2 (3.6) (50)	2 (2.2) (50)	4 (2.8)	
No complication	1 (1.8) (1.5)	64 (71.9) (98.5)	65 (45.1)	
Acyclovir treatment	52 (94.5) (44.1)	66 (74.2) (55.9)	118 (81.9)	p< 0.05
Duration of acyclovir treatment	0-24 days (median 9 days)	0-10 days (median 7 days)	0-24 days (median 7 days)	p< 0.05
Antibiotic treatment	25 (47.2) (37.9)	41 (46.1) (62.1)	66 (46.5)	p> 0.05
Intravenous immunoglobulin	0 (0) (0)	1 (1.1) (100)	1 (0.69)	
Duration of hospitalization	4-15 days (median 8 days)	1-36 days (median 7 days)	1-36 days (median 7 days)	p< 0.05
Need for pediatric intensive care unit	0 (0) (0)	1 (1.1) (100)	1 (0.69)	-
Death	0 (0) (0)	1 (1.1) (100)	1 (0.69)	-

When only the patients with rash findings were considered, there was a statistically significant difference in the distribution of rash between the groups ($p < 0.05$). There was no statistically significant difference between the groups in patients with other symptoms accompanying rash (fever, convulsion, vomiting, pain, confusion, balance disorder) ($p > 0.05$). The median duration of the rash was 9 (3-36) days in chickenpox and 10 (8-12) days in herpes zoster.

There was no statistically significant difference between the two groups in terms of CRP positivity and antibiotic treatment ($p > 0.05$). 38.1% of the patients in Group A and 5.6% of the patients in Group B were neutropenic, and there was a statistically significant difference between the two groups ($p < 0.05$). At least one complication due to VZV was observed in 79 of 144 patients; 54 of the patients with complications were

in Group A and 25 were in Group B. The most common complication is secondary bacterial infection/sepsis; It was seen at a rate of 78.2% in Group A and 9% in Group B. The distribution of secondary bacterial infection/sepsis between groups is significant, and it is more in Group A than in Group B. Neurological complications were seen in four patients in Group B but none in Group A. There was no statistically significant difference between the groups in terms of other complications (skin infection, pneumonia, eye involvement) observed in the study group ($p > 0.05$). The distribution of cases without complications between the groups was significant and it was less in Group A than in Group B. There was a statistically significant difference in the distribution of acyclovir use between the groups and the duration of acyclovir use ($p < 0.05$). There were more acyclovir users in Group A than those in Group B.

Table 3. Varicella and herpes zoster patient characteristics

	Varicella (n= 121) (84%)	Herpes Zoster (n= 23) (16%)
Age	16 days – 17 years (median 3 years)	2-17 years (median 8 years)
Male/Female	74/47 (1.57)	14/9 (1.55)
Seasonal Distribution		
Spring	46 (38%)	8 (34.8%)
Summer	24 (19.8%)	8 (34.8%)
Fall	16 (13.2%)	4 (17.4%)
Winter	35 (29%)	3 (13%)
Diseases		
ALL	24 (19.8%)	6 (26%)
AML	2 (1.7%)	4 (17.4%)
Solid tumor	11 (9%)	4 (17.4%)
Hodgkin lymphoma	-	2 (8.7%)
Non-Hodgkin lymphoma	1 (0.8%)	1 (4.4%)
Newborn period	13 (10.7%)	-
Neurological diseases	30 (24.8%)	-
Rheumatologic diseases	5 (4.1%)	-
Nephrological diseases	14 (11.6%)	3 (13%)
Genetic diseases	6 (5%)	-
Cardiovascular diseases	3 (2.5%)	-
Allergic diseases	5 (4.2%)	2 (8.7%)
Benign hematological diseases	7 (5.8%)	1 (4.4%)

ALL: Acute lymphoblastic leukemia, AML: Acute myeloblastic leukemia.

When all patients were included, the median hospital stay was seven days, which was eight days in Group A and seven days in Group B. There was a statistically significant difference between the median values of hospital stay between the groups ($p < 0.05$). The median value of Group A was higher than that of Group B. Only one of our patients needed treatment in the intensive care unit. The patient was in Group B (spinal muscular atrophy patient), hospitalized to the intensive care unit on the third day of the rash, and recovered. One juvenile rheumatoid arthritis patient was admitted to the hospital on the fifth day of his rash and died of sepsis.

Discussion

In our study, herpes zoster was more common in Group A and chickenpox in Group B ($p < 0.05$). Zoster rash occurs in approximately one-quarter of children with acute lymphoblastic leukemia (ALL) receiving chemotherapy (8). Herpes zoster that develops in pediatric patients with acute lymphoblastic leukemia occurs as a result of intensive chemotherapy and indicates the relationship between childhood cancer and herpes zoster (9). The higher prevalence of herpes zoster in cancer patients

is due to cellular immunosuppression due to chemotherapy, stress, surgery, or radiotherapy (10).

Although it is generally a self-limiting disease, VZV can potentially cause serious complications, including secondary bacterial infections (mainly in the skin), respiratory complications (viral or bacterial pneumonia), and neurological complications (7). In our study, 54.8% of the patients had at least one complication and the most common complication was secondary bacterial infection/sepsis (35.4%). In our study, cancer patients were hospitalized as soon as chickenpox and herpes symptoms developed; in Group B patients with complications or extensive rash were hospitalized. Complications due to varicella-zoster virus and especially skin infections are the most common reasons for hospitalization (11). There was no statistically significant difference between the two groups in terms of the incidence of complications ($p > 0.05$). In Diniz's study, the leading causes of hospitalizations were bacterial complications (77.7%), viral complications (11.4%), and the main bacterial complications were skin infection and pneumonia (12). Skin infection was detected in 7.6% of our patients. Risk factors for bacterial skin infection may include the use of nonste-

roidal anti-inflammatory drugs or topical agents (13,14). Since nonsteroidal anti-inflammatory drugs or topical agents were not used in our patients, the incidence of skin infections was found low.

The most common (38.3%) complications of the varicella-zoster virus are neurological disorders (15). When all patients were evaluated in the VARICOMP study, neurological complications were 19.1% and 6.8% in the presence of underlying disease (7). In our study, neurological complications were observed in four children (2.8%), all patients were in Group B. Pneumonia (8 bacterial, 1 viral) was detected in 6.3% of our patients. Two patients were in the cancer group and seven patients were in the other immunodeficient group. The incidence of pneumonia in our study was similar to the prevalence rates of varicella pneumonia previously reported (16-18). Eight of our patients with varicella pneumonia were younger than 10 years old and one was older than 10 years old. The median age was 4 (1-13) years. Varicella pneumonia is most common in children younger than 10 years old. The median age in children with varicella pneumonia was found to be three years and four months (2 months-10 years) (19). The fact that acyclovir treatment was started without delay at the time of the diagnosis of chickenpox/herpes zoster infection in the cancer patients group reduces the frequency of pneumonia and neurological complications related to VZV.

In varicella-zoster ocular involvement, initiating antiviral drugs within 72 hours from the onset of the rash is beneficial in preventing ocular involvement, and timely diagnosis and treatment limit visual morbidity (20). In our study, eye involvement was observed in 4 (2.8%) of the patients and they were treated with topical acyclovir in addition to intravenous acyclovir. Two of the patients were in Group A, and two of them were in Group B. As a result of the early initiation of antiviral therapy, no permanent sequelae developed in our patients.

In our study, varicella cases were most common in March, January, June, and May, as in the VARICOMP study (7). This seasonality is similar to that seen in other countries with temperate climates (21). There was a statistically significant difference in the seasonal distribution of varicella/herpes zoster between the groups ($p < 0.05$). It was observed more in Group B than Group A in the spring, and more in Group A than Group B in the summer.

There was a statistically significant difference between the two groups in terms of the incidence of neutropenia ($p < 0.05$). Neutropenia occurs in cancer patients due to chemotherapy. Neutropenia is a life-threatening feature in patients with chickenpox/herpes and acyclovir treatment should be started immediately.

There was no statistically significant difference between the two groups in terms of CRP positivity and antibiotic treatment. The median duration of rash in our patients was 9 (3-

36) days in chickenpox and 10 (8-12) days in herpes zoster. In healthy children with herpes zoster, the rash usually dries up within 7 to 10 days with crusting (22). In patients with a weak immune system, the rash lasts longer than in healthy children.

In our study, the duration of hospital stay was longer in cancer patients ($p < 0.05$). The more severe immune deficiency in cancer patients leads to longer hospital stays. Because ALL is the most common childhood cancer, it was the underlying primary disease (54.5%).

Acyclovir treatment rates and duration of acyclovir treatment were found to be higher in cancer patients ($p < 0.05$). Acyclovir treatment was initiated as soon as the diagnosis of varicella infection in cancer patients, and in Group B acyclovir treatment was begun after the hospitalization of patients with complications or common rash. Acyclovir treatment was not given to three of the patients in Group A because their rashes were crusty when they were seen.

Varicella-zoster virus causes high morbidity and is more common in healthy children less than five years of age. Therefore, routine vaccination should be mandatory (23). The morbidity and mortality of varicella-zoster virus infections decrease significantly by starting acyclovir treatment early in the course of the disease (6).

Conclusion

Varicella-zoster infections are one of the important causes of mortality and morbidity in pediatric oncology patients. The frequency of herpes zoster is higher in cancer patients compared to other immunodeficient patients and close monitoring is required. At least one complication can often be seen in immunocompromised patients with varicella-zoster virus, and it is possible to prevent complications or to decrease their severity by starting acyclovir/antiviral therapy without delay. Cancer patients require a longer period of acyclovir treatment than other immunocompromised VZV patients. Initiation of acyclovir/antiviral therapy by the hospitalization of cancer patients with varicella-zoster virus infection and other immunodeficient patients immediately will decrease the complications and mortality rates of varicella-zoster virus. Multidisciplinary follow-up of pediatric infectious diseases specialists, pediatric hematology-oncology specialists, and other specialists treating immunocompromised patients will reduce the morbidity and mortality of VZV infections in these patient groups.

Ethics Committee Approval: The ethical approval for this study was obtained from İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee (Decision no: 2019/0068, Date: 27.02.2019).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - All of authors; Design - All of authors; Supervision - All of authors; Data Collection and/or Processing - All of authors; Analysis and/or Interpretation - All of authors; Literature Review - All of authors; Writing - All of authors; Critical Review - All of authors.

Conflict of Interest: The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript

Financial Disclosure: The authors declared that this study has received no financial support.

References

- Lin HC, Chao YH, Wu KH, Yen TY, Hsu YL, Hsieh TH, et al. Increased risk of herpes zoster in children with cancer: a nationwide population-based cohort study. *Medicine (Baltimore)* 2016;95(30):e4037. [\[CrossRef\]](#)
- Gershon AA, Gershon MD, Breuer JD, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. *J Clin Virol* 2010;48(Suppl 1):S2-7. [\[CrossRef\]](#)
- Chen SY, Suaya JA, Li Q, Galindo CM, Misurski D, Burstin S, et al. Incidence of herpes zoster in patients with altered immune function. *Infection* 2014;42(2):325-34. [\[CrossRef\]](#)
- Forbes HJ, Bhaskaran K, Thomas SL, Smeeth L, Clayton T, Langan SM. Quantification of risk factors for herpes zoster: population based case-control study. *BMJ* 2014;348:g2911. [\[CrossRef\]](#)
- Manistarski M, Levin D, Dvir R, Berger A, Achipov S, Rosenfeld Keidar H, Grisaru-Soen, et al. Lessons from an outbreak of varicella infection in pediatric hemato-oncology patients. *Pediatr Infect Dis J* 2018;37(7):649-53. [\[CrossRef\]](#)
- Arvin AM. Antiviral therapy for varicella and herpes zoster. *Semin Pediatr Infect Dis* 2002;13(1):12-21. [\[CrossRef\]](#)
- Dinleyici EC, Kurugöl Z, Turel O, Hatpoglu N, Devrim I, Agin H, et al. VARICOMP Study Group: The epidemiology and economic impact of varicella-related hospitalizations in Turkey from 2008 to 2010: a nationwide survey during the pre-vaccine era (VARICOMP study). *Eur J Pediatr* 2012;171(5):817-25. [\[CrossRef\]](#)
- Sørensen GV, Helgestad J, Rosthøj S. Varicella-associated morbidity in children undergoing chemotherapy for acute lymphoblastic leukaemia. *Ugeskr Laeger* 2009;171(46):3350-4.
- Sørensen GV, Rosthøj S, Würtz M, Danielsen TK, Schröder H. The epidemiology of herpes zoster in 226 children with acute lymphoblastic leukaemia. *Pediatr Blood Cancer* 2011;57:993-7. [\[CrossRef\]](#)
- Hansson E, Forbes HJ, Langan SM, Smeeth L, Bhaskaran K. Herpes zoster risk after 21 specific cancers: population-based case-control study. *Br J Cancer* 2017;116:1643-51. [\[CrossRef\]](#)
- Dubos F, Hue V, Grandbastien B, Martinot A. Epidemiology of hospital admissions for paediatric varicella infections: a one-year prospective survey in the pre-vaccine era. *Epidemiol Infect* 2007;135(1):131-8. [\[CrossRef\]](#)
- Diniz LMO, Maia MMM, Oliveira YV, Mourao MSF, Couto AV, Mota VC, et al. Study of complications of varicella-zoster virus infection in hospitalized children at a reference hospital for infectious disease treatment. *Hosp Pediatr* 2018;8(7):419-25. [\[CrossRef\]](#)
- Lesko SM, O'Brien KL, Schwartz B, Vezina R, Mitchell AA. Invasive group A streptococcal infection and nonsteroidal anti-inflammatory drug use among children with primary varicella. *Pediatrics* 2001;107(5):1108-15. [\[CrossRef\]](#)
- Zerr DM, Alexander ER, Duchin JS, Koutsky LA, Rubens CE. A case-control study of necrotizing fasciitis during primary varicella. *Pediatrics* 1999;103(4 Pt 1):783-90. [\[CrossRef\]](#)
- Marchetto S, de Benedictis FM, de Martino M, Versace A, Chiappini E, Bertaine C, et al. Epidemiology of hospital admissions for chickenpox in children: an Italian multicentre study in the pre-vaccine era. *Acta Paediatr* 2007;96(10):1490-3. [\[CrossRef\]](#)
- Chi CY, Wang SM, Lin HC, Liu CC. Complications of varicella infection in children in southern Taiwan. *J Microbiol Immunol Infect* 2006;39(5):402-7.
- Koturoglu G, Kurugöl Z, Cetin N, Hizarcioglu M, Vardar F, Helvacı M, et al. Complications of varicella in healthy children in Izmir, Turkey. *Pediatr Int* 2005;47(3):296-9. [\[CrossRef\]](#)
- Kuchar E, Miskiewicz K, Szenborn L, Nitsch-Osuch A. Respiratory complications in children hospitalized with varicella. *Adv Exp Med Biol* 2013;788:97-102. [\[CrossRef\]](#)
- Bozzola E, Castelli Gattinara G, Bozzola M, Mirante N, Masci M, Rossetti C, et al. Varicella associated pneumoniae in a pediatric population. *Ital J Pediatr* 2017;43(1):49. [\[CrossRef\]](#)
- Kalogeropoulos CD, Bassukas ID, Moschos MM, Tabbara KF. Eye and periocular skin involvement in herpes zoster infection. *Med Hypothesis Discov Innov Ophthalmol* 2015;4(4):142-56.
- Grimpel E, Levy C, de La Rocque F, Cohen R, Soubeyrand B, Caulin E, et al (2007) Paediatric varicella hospitalizations in France: a nationwide survey. *Clin Microbiol Infect* 2007;13(5):546-9. [\[CrossRef\]](#)
- Cohen JL. Clinical practice: Herpes zoster. *N Engl J Med* 2013;369(3):255-63. [\[CrossRef\]](#)
- Guzman Laura KP, Perianez Vasco A, Falcon Neyra MD, Croche Santander B. Hospital admissions due to varicella in a tertiary hospital. *An Pediatr (Barc)* 2014;80(6):399-403. [\[CrossRef\]](#)