Case Series: Varicella-Zoster in Patients with Acute Lymphoblastic Leukemia. Lesson Learned from Managing Outbreak in Resource Limited Facility

Abstract

Chicken pox is a self-limited exanthematous disease that primarily affects children. Varicella zoster virus (VZV) has been considered to be the causative agent. VZV infections manifest as varicella and herpes zoster usually cause mild infections, without any severe complications in immunocompetent children [1]. However, in certain individuals with immunocompromised status, the infection may show the disseminated form, and the complications; including bacterial superinfections, central nervous systems problems, coagulopathies may potentially fatal and disabling [1,2]. Even though varicella vaccine has been widely introduced in the world, it is only a handful of Indonesian could afford the vaccine, as Indonesian national vaccination program did not include varicella vaccine into the program.

Introduction

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Acute lymphoblastic leukemia (ALL) as the most common childhood malignancy brings some severe immunocompromised conditions for the patients. Children with ALL are susceptible to varicella infections leading to serious mortality and morbidity [3,4]. Various factors contribute in ALL patients’ susceptibility towards VZV infections. Immune system impairment and long-term steroid usage are suspected as possible causes. Reactivation of dormant virus due to immunocompromised state, particularly after chemotherapy treatment, triggered viral infections. Administration of high-dose steroids reported to play as important risk factor in immunocompromised patients by impairing T cell and neutrophil function, mimics general signs and symptoms of inflammation [4,5].

Diagnostic of VZV infection in ALL patients would be difficult because of atypical presentation and overlapping symptoms with other secondary concomitant infections. Microbiological examination combined with contact preventive measures and patient isolation are important things to do [4]. To date, Ayclovir and varicella-zoster immune globulin (VZIG) as antiviral treatment are known to be able to decrease the mortality rate of immunocompromised patients suffered from VZV infection. Vaccination as preventive approach has significant role in preventing severe complications and death. One research about vaccination efficacy in children with ALL showed justifiable effectiveness and remarkable reduction in mortality [6].

In Indonesia, management of VZV infection in children with ALL remains challenging due to limited epidemiological data, no published therapeutic and vaccination guidelines designed...

Keywords: VZV infections; ALL; Malignancy; Immunocompromised patients; Indonesia; Cohorting

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Dian K Nurputra1, Anindian S Rahmawati1, Ratni Indrawanti2, Pudjo H Widjajanto3, Eggi Argun4, Ida Safitri1, Sutaryo2, Sri Mulatsih**

1Department of Child Health, Faculty of Medicine, Universitas Gadjah Mada, Indonesia
2Division of Tropical Medicine, Department of Child Health, Faculty of Medicine, Universitas Gadjah Mada, Indonesia
3Division of Hemato-oncology, Department of Child Health, Faculty of Medicine, Universitas Gadjah Mada, Indonesia

*Corresponding author: Sri Mulatsih MD. Ph.D, Division of Hemato-oncology, Department of Child Health, Faculty of Medicine, Universitas Gadjah Mada, Jl. Kesehatan No.1, Bulaksumur-Sleman, D.I. Yogyakarta-Indonesia, Tel: +6281249816246; Email: smulats@gmail.com

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specifically for ALL, neither in local nor national level. This study was purposed to investigate VZV infections and explore the possibilities of available treatments for children with ALL treated in paediatric ward, Dr. Sardjito General Hospital, Yogyakarta.

Cases

All patients with acute lymphoblastic leukemia hospitalized with VZV-infections in the pediatric cancer and pediatric infectious ward of the Sardjito General Hospital during short outbreak in November to December 2017 were included consecutively and their medical charts were reviewed for hospitalization, treatment, treatment duration, occurrence of complications, and outcome. The identified patient cohort was further divided into subgroups with either an ALL underwent chemotherapy in induction phase or maintenance phase, or another malignancy. The data; local hospitalization, treatment, and complication rates of VZV infections could be calculated. Furthermore, rate and severity of VZV-related complications were compared among ALL children. Acquired data were then compared to a review of the literature. Keywords for literature search were varicella zoster virus infection, leukemia, children, malignancy and complications.

Table 1: Patient Characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (Years)</th>
<th>Nutritional Status (WHO-Z Score)</th>
<th>Onset of VZV Exanthema before Admission</th>
<th>Organ Involvement</th>
<th>Onset and Type of Antiviral Therapy</th>
<th>Underlying Disease, Point of Therapy</th>
<th>Stratification/ Stadium</th>
<th>Duration of Antiviral Therapy</th>
<th>Final Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.S.</td>
<td>Female</td>
<td>2</td>
<td>0.4Z</td>
<td>4 days</td>
<td>Skin</td>
<td>On day one, acyclovir p.o</td>
<td>Retinoblastoma on chemotherapy weeks 9</td>
<td>Bilateral (stadium II-III)</td>
<td>Acyclovir po 4 days, continue with acyclovir IV 6 days, acyclovir po 2 days</td>
<td>Alive, no sequele</td>
</tr>
<tr>
<td>M.N.</td>
<td>Male</td>
<td>3.5</td>
<td>1.24Z</td>
<td>5 days</td>
<td>Skin</td>
<td>On day two with Acyclovir po</td>
<td>ALL on maintenance phase week 34</td>
<td>HR</td>
<td>Acyclovir po for 4 days continued with IV 6 days</td>
<td>Alive, no sequele</td>
</tr>
<tr>
<td>M.A</td>
<td>Male</td>
<td>4</td>
<td>1.05Z</td>
<td>7 days</td>
<td>Skin</td>
<td>On day 2, Acyclovir po</td>
<td>ALL on induction phase week 5</td>
<td>HR</td>
<td>Acyclovir po Acyclovir IV 5 days</td>
<td>Alive, no sequele</td>
</tr>
<tr>
<td>H.D.</td>
<td>Male</td>
<td>4</td>
<td>-0.0Z</td>
<td>2 days</td>
<td>Skin</td>
<td>On Day 1, Acyclovir po</td>
<td>ALL on induction phase week 3</td>
<td>SR</td>
<td>Acyclovir IV 5 days</td>
<td>Alive, no sequele</td>
</tr>
<tr>
<td>S</td>
<td>Male</td>
<td>8</td>
<td>-1,82Z</td>
<td>2 days</td>
<td>Skin, Lung, Liver</td>
<td>On day 2, using Acyclovir IV</td>
<td>ALL on maintenance phase Week 72</td>
<td>HR</td>
<td>Acyclovir IV 1 day</td>
<td>Death</td>
</tr>
<tr>
<td>L</td>
<td>Female</td>
<td>4</td>
<td>0.08Z</td>
<td>3 days</td>
<td>Skin, Lung</td>
<td>No Acyclovir</td>
<td>ALL on induction phase weeks 6</td>
<td>SR</td>
<td>Acyclovir IV not yet administrated</td>
<td>Death</td>
</tr>
<tr>
<td>D.J.</td>
<td>Male</td>
<td>10</td>
<td>1.12Z</td>
<td>2 days</td>
<td>Skin</td>
<td>On day 1, Acyclovir po</td>
<td>ALL on maintenance week 16</td>
<td>HR</td>
<td>Acyclovir po 3 days, continued with IV 5 days</td>
<td>Alive, no sequele</td>
</tr>
<tr>
<td>R.A.</td>
<td>Female</td>
<td>4</td>
<td>-0.44Z</td>
<td>4 days</td>
<td>Skin</td>
<td>On day 2, Acyclovir po</td>
<td>Teratoma maligna on chemotherapy weeks 4</td>
<td>-</td>
<td>Acyclovir po 3 days, continued with IV 5 days</td>
<td>Alive, no sequele</td>
</tr>
</tbody>
</table>

ALL: Acute lymphoblastic Leukemia; HR: High Risk Stratification; SR: Standard Risk

Results

A total of 8 children of ALL with VZV-infections have been admitted into at paediatric ward and paediatric cancer ward of the Sardjito General Hospital between November 01, 2017 and December 31, 2017. The median age of these 8 children was 3.8 years (range: 2 to 10 years old). Out of the 8 admitted children, 6 have suffered from ALL as their underlying disease, one suffered from retinoblastoma and other from teratoma malignant. Three patients from six received high-dose chemotherapy during induction phase (Table 1). Drugs used during induction phase were high dose methotrexate following intratechal methotrexate, high dose prednisone. On the other hand, drugs used in maintenance phase were per oral 6-mercaptopurine dan per oral methotrexate.

Patients and/or guardians of children treated in our hospital have been asked for informed consent to scientific analysis and agreed upon anonymized publication of their medical data in accordance with the Declaration of Helsinki. The ethical committee of the Universitas Gadjah Mada has determined that for analysis and publication of single centre case series, such informed consent is sufficient and no specific review of retrospective data analysis projects are required.
VZV-infection was the prime indication for admission in all cases. None of the patients were treated on outpatient basis and all received intravenous acyclovir as antiviral immediately after the admission. It is noted that 7 from 8 (92%) had started oral acyclovir from the previous referral hospital. None of them had received varicella zoster vaccination before. One patient who passed away got acyclovir injection on day two after symptoms appeared. One patient never had chance to get acyclovir treatment. Clinical manifestations of VZV infections in our patients were classic polymorphism skin lesion, ranged from hyperemic papules, vesicles and pustules that distributed all over body. The representative pictures of the lesion were shown in Figure 1. All six of them did not suffer from any severer complication after being treated in the hospital. Two of them suffered from pneumonia since the admission and finally passed away.

All of our patients were reported to have good nutritional status, according to WHO Z-score classification. Six of them were then discharged with no change in their nutritional status.

Among 8 patients, two patients were passed away in emergency room, two patients were treated in the isolation room utilizing exhausting fan system, and one patient was in positive pressure room in pediatric cancer ward. Other three were treated in the common room utilizing “cohorting” management. The cohorting management was implemented by placing three beddings in room size 10x4 meters square with the distance between bedding more than 1 meter, separated using partition.

Discussion

In healthy children, it is not guaranteed that clinicians are very familiar with the clinical manifestation of varicella, but in the last several years, fewer cases have been met and diagnosed due primarily to the development of a safe and effective vaccine. However immunocompromised children tend to develop disseminated varicella with atypical presentation and internal organ involvement [1]. Disseminated varicella has higher mortality rate in immunocompromised children because longer healing process and progressive severe infections [1,2]. Interestingly, it is reported only 2 patients developed complicated varicella, manifesting as multi organ involvement in our study. These patients were in the induction phase of chemotherapy. Other patients developed only handful polymorphic lesion all over body, manifesting as similar as VZV-infected healthy children. Considering that patients with ALL or malignancies undergoing chemotherapy were in immunocompromised state, it was hypothesized that the reasons of milder manifestation of VZV in our patient were partly due to early introduction of acyclovir. Other half may be contributed by factors such as the recent immune condition, represented roughly by the absolute neutrophil count and nutritional state.

Acyclovir has an important role to decrease severity and mortality of varicella infection [2]. Early acyclovir administration has been beneficial to slow progression of disease and impair viral replication [1,3]. Some previous study stated that acyclovir alone was not sufficient to suppress varicella infection. Administration of varicella-zoster immunoglobulin (VZIG) combined with acyclovir were beneficial to treat patients with disseminated varicella infection [1,3]. VZIG may boost immune responses by enhancing NK cells and specific antibody against varicella zoster virus (VZV). Combination of VZIG and acyclovir will enhance antiviral effects of acyclovir [3]. VZIG prophylaxis can be considered for immunocompromised individuals who were significantly exposed to varicella during infectious period. However, there was insufficient evidence for VZIG as effective treatment of the disease. Public Health England recommended early treatment with high-dose oral acyclovir or systemic acyclovir as treatment for VZV in immunocompromised patients. Risk assessment and determination of immune status should be performed before administration of VZIG in immunocompromised patients [4]. Risk assessment performed here was in term of checking the CD4 and CD8 status.

Here, all patients received acyclovir as main therapy. Three patients received oral acyclovir continued with intravenous acyclovir, whereas two patients received intravenous acyclovir alone. None of our patients received VZIG as adjuvant therapy because of stock unavailability and no insurance coverage due to any established guideline. Here, we reported the benefit of giving oral acyclovir as initial therapy prior acyclovir intravenous injection. Established guidelines and studies mentioned that it is preferable to use acyclovir intravenous injection as soon as possible compared to per oral acyclovir in dealing with VZV infection. Interestingly, our study showed that early intervention using per oral acyclovir, in the later continued by intravenous acyclovir, and were quite helpful to prevent worsening complications. Children who got per-oral acyclovir on the same day when the symptoms manifested tend to develop milder symptoms. It was reported that the morbidity and mortality of VZV infections are reduced substantially by initiating acyclovir treatment early in the course of the disease [6].

Most frequently reported complications of VZV infections during chemotherapy and immunocompromised patients are interstitial or necrotizing pneumonia, viral hepatitis with acute liver failure, coagulopathies or bacterial super infections [7,8]. It was reported to be occurring in 20% of patient in immunocompromised [8]. Accordingly, our study reported that two from eight patients, suffered from pneumonia complications. There was one patient also suffered from low grade hepatitis,
shown by mild increase of AST and ALT, however no sign of liver failure. Most of our patients (83%) recovered completely without any sequelae, but one patient died due to severe pneumonia followed by sepsis and DIC. It was noticeable that patient S, who got severe pneumonia, suffered from low absolute neutrophil count (ANC). ANC of 0.2–0.5 × 10^9/L are associated with an increased risk of infections in most patients. ANC of 0.2 × 10^9/L or less (often referred to as “agranulocytosis”) carries a risk of severe, life-threatening infections with susceptibility to opportunistic organisms. These oft-quoted criteria were derived from clinical experience with neutropenia secondary to cancer chemotherapy [9]. Even though our study had insufficient data (no data on biopsy nor sputum culture), considering the result of low procalcitonin level (Table 2), there is a high possibility that the cause of his pneumonia may not be bacterial, suggesting that pneumonia in patient S may occur as varicella’s complication or fungal pneumonia leading to his demise.

Table 2: Laboratory Profiles on selected patients.

<table>
<thead>
<tr>
<th>Laboratory Examination</th>
<th>M.N</th>
<th>M.A</th>
<th>N.S</th>
<th>H.D</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte</td>
<td>3.530</td>
<td>6.790</td>
<td>5.600</td>
<td>1.420</td>
<td>3.190</td>
</tr>
<tr>
<td>Hemogloblin</td>
<td>9.5</td>
<td>10.5</td>
<td>10.8</td>
<td>8.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Hematocrite</td>
<td>27.6</td>
<td>32.5</td>
<td>33.5</td>
<td>24.0</td>
<td>33.2</td>
</tr>
<tr>
<td>Thrombocyte</td>
<td>127,000</td>
<td>177,000</td>
<td>157,000</td>
<td>182,000</td>
<td>266,000</td>
</tr>
<tr>
<td>ANC</td>
<td>790</td>
<td>2,270</td>
<td>3,120</td>
<td>630</td>
<td>223</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.12</td>
<td>3.36</td>
<td>3.67</td>
<td>3.01</td>
<td>4.77</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>0.08</td>
<td>0.35</td>
<td>0.19</td>
<td>2.15</td>
<td>3.11</td>
</tr>
<tr>
<td>SGOT</td>
<td>Not examined</td>
<td>Not examined</td>
<td>Not examined</td>
<td>Not examined</td>
<td>522</td>
</tr>
<tr>
<td>SGPT</td>
<td>Not examined</td>
<td>Not examined</td>
<td>Not examined</td>
<td>Not examined</td>
<td>627</td>
</tr>
</tbody>
</table>

Previous reports mentioned that the complications of VZV-infections may be worsening during care in hospital due to series of secondary infections, including nosocomial infections. Good isolation system and minimal invasive care is reported to be necessary for limiting the potential of superinfection complication, burdening the recovery during VZV-infections in immunocompromised status [10]. During the outbreak, our hospital employed “patient cohorting” due to the limited availability of isolation room. During the implementation of cohorting there were no report of worsening condition of the patients, whether in the skin manifestation, no further other organ involvement, and no evidence of transmission of infected patient to other patients in hospital. It was reported that cohorting of patients according to presence or absence of specific pathogens, supported with strict hygienic precautions, medical services, environment control, able to lead a decrease in incidence and prevalence of acute or chronic infections, especially in immunocompromised [11]. Our study showed that even in the limited facilities, with no specific exhausting fan, nor fancy double-layered isolation room, the VZV-infections were still somehow manageable.

Interestingly, it is found out that the transmission of VZV-infections of our admitted patients was coming from one source and happened in a transit house. Transit house act as temporary stay, located near the hospital and run by private, for paediatric cancer patients during the waiting phase between chemotherapy sessions. Further investigations revealed that most patients did not show any sign of infections during their staying period prior to admission, speculating that the infections might be already in its incubation period. These data also provided the importance of educational handbook for parents or guardians containing information of warning sign of infections in patients with ALL. Education from medical officers regarding early sign identification was important to be carefully implemented. Taken together, these measures may provide early prevention and intervention system including acyclovir introduction to patients with ALL suffering from VZV-infection.

Finally, our study harboured several limitations such as no specific evidence to establish VZV-infections. The infections were diagnosed clinically and established by evaluating the good response to acyclovir treatment. Our study did not provide any pathological data including biopsy of skin etc as it is considered to be invasive and not necessary during the outbreak period. Our hospital did not have either specific guidelines to manage VZV-infections in patient with immunocompromised according to our limited facility. Thus, the study may able to provide basic data for establishment of specific recommendation or algorithm in VZV-infections management in patients with immunocompromised status.

In conclusion, VZV-infections in patient with immunocompromised status, such as patients with ALL or malignancy underwent chemotherapy, requires specific early measures and intervention which could be updated to the authorized guideline, build specifically to the properties and availability of each hospital.

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Conflict of interest

The authors declare no conflict of interest.

Patients consent form

All parents and guardians of the children included in this study have been asked for their consents and agreed upon anonymous publications.

References


