Treatment of herpes zoster with brivudin in immunocompromised children

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Research Article

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Abstract

Purpose: Herpes zoster (HZ) is caused by endogenous reactivation of latent varicella-zoster virus (VZV) that persists in sensory ganglia after primary infection. The incidence and severity of HZ increases during immunosuppression. Especially immunocompromised patients are at high risk of developing a cutaneous rash and suffering from delayed healing of lesions. Bromovinyl deoxyuridine (brivudin), one of the most potent oral inhibitors of VZV replication, is widely used in therapy of HZ in adult patients, particularly in Europe. In this study, we investigated the efficacy of brivudin in immunocompromised children to provide an outpatient treatment option.

Methods: In this prospective study, we included 64 immunocompromised pediatric patients with a median age of 14 years. Forty-seven patients received immunosuppressive therapy as part of hematopoietic stem cell transplantation and 17 patients as part of chemotherapy. Primary diagnosis was made clinically by examining the nature and the localization of the skin lesions. Laboratory confirmation was conducted based on the detection of VZV DNA in vesicle fluid and blood samples. Brivudin was administered orally at a single dose of 2-5 mg/kg per day. We monitored the patients' response for the full time of treatment and observed the time of full crusting of lesions, loss of crusts, and any adverse effects that occurred.

Results: Patients received medication for 7-21 days (median: 14 days). All children responded promptly to antiviral treatment and recovered completely from their HZ infections without complications.Crusting of lesions was reached after 3-14 days (median: 6 days). Full healing of skin lesions was ascertained within 7-21 days (median: 12 days). Overall, brivudin therapy was well tolerated. No clinical side effects during or after the treatment were observed. High compliance was achieved due to the once-daily dosing regimen. All patients were treated in an outpatient manner.

Conclusion: Oral brivudin was a very effective and well-tolerated therapy in immunocompromised children with HZ infection. The oral administration offers potential for outpatient treatment of HZ in these patients.

Introduction

Hematopoietic stem cell transplantation (HSCT) is an important curative treatment option for hematological malignancies, solid tumors, and genetic diseases. However, the success of HSCT is still compromised by complications. Herpes zoster (HZ) is a common and serious complication after HSCT. Especially, latent varicella-zoster virus (VZV) can reactivate and results in HZ because of the immunosuppressive conditions. Berman et al. (2006) showed that among 90 VZV seropositive children and adolescents, who underwent allogeneic HSCT, the incidence of infection was 54% by 12 months and 69% by 60 months after HSCT.

During primary infection, VZV manifests as varicella (chickenpox). Subsequently, the virus enters into a state of latency and persists in the dorsal root, cranial, and enteric ganglia (Chen et al., 2011).

Endogenous reactivation of VZV leads to HZ infection, a painful skin rash with a dermatomal distribution. The mechanism controlling the latency of VZV is not clearly understood. However, it is known that the reactivation is accompanied by a weakened VZV-specific T-cell response (Oxman, 2009). The natural decline in T-cell function with age (immunosenescence) is the most important factor influencing VZV reactivation in otherwise healthy individuals. It has already been demonstrated that a severely weakened immune system caused by disease-induced immunosuppression or by immunosuppressive therapy predisposes to a higher rate of VZV reactivation and a severe course of the disease (Buchbinder et al., 1992). Specifically, regarding children, HZ develops frequently in patients with weakened immune systems. A Danish study provides further evidence that nearly one-third of seropositive children experienced HZ infection during primary chemotherapy. The risk of getting sick was related to the intensity of the treatment (Sørensen et al., 2011).

Currently, the drug of choice for antiviral treatment of VZV infections in children is acyclovir. Many studies showed that therapy with intravenous acyclovir in patients with normal renal functions (500 mg/m^2 every eight hours) reduces the duration of viral replication and stops disease progression (Balfour et al., 1983; Meyers et al., 1984; Serota et al., 1982). However, the terminal elimination half-life of approximately three hours at intravenous application necessitates high doses, frequent administration, and hospitalization (Laskin et al., 1982). Moreover, acyclovir is poorly absorbed after oral administration with a bioavailability of only 20% (de Miranda & Blum, 1983). Therefore, in children, an orally given drug would be preferred to provide an outpatient treatment.

It was previously demonstrated that in cell culture studies brivudin proved to be 200 to 1000 times more effective in inhibiting VZV replication than acyclovir or penciclovir (Andrei et al., 1995). A double-blind, randomized study comparing oral brivudin and oral acyclovir showed similar results. Both drugs were administered for seven days. Brivudin presented a similar safety profile and a significant improvement in efficacy in immunocompetent patients with HZ (Wassilew et al., 2003).

In this prospective study, we aimed to investigate the clinical outcome of VZV infections in children with hematological malignancies, solid tumors, and genetic diseases who were treated with brivudin. Pediatric patients would clearly benefit from an oral antiviral drug with high potency which could provide an outpatient treatment.

Patients And Methods

Patients

In this prospective study, we analyzed 64 immunocompromised children suffering from HZ in the period from January 2004 to December 2019 at the Department of Pediatrics, Jena University Hospital, Jena, Germany. All patients received immunosuppressive treatment due to hematological malignancies, solid tumors, and genetic diseases (Table 1). The vesicular exanthema was localized on thoracic and abdominal dermatomes in 32 patients (50.0%). In 23 patients (35.9%) HZ lesions were localized on the

extremities. Nine patients (14.1%) showed the typical rash on the head. In all patients the rash was limited to one, two or three dermatomes. There was no evidence of cutaneous or visceral dissemination. We excluded patients who received treatment with 5-fluorouracil and its prodrugs within the last four weeks. A detailed characterization of the study population is presented in Table 1.

Table 1
Characteristics of patients (*n* = 64)

Characteristics	Total no. (%)	Allogeneic transplantation (*n* = 45)	Autologous transplantation (*n* = 2)
Median age of the patients (years)	14		
Sex of the patients			
Male	36 (56.2)	26	1
Female	28 (43.8)	19	1
Diseases			
Hematological diseases	32 (50.0)	19	-
ALL			
AML	9 (14.0)	7	-
CML	3 (4.7)	3	-
JMML	1 (1.6)	1	-
MDS	6 (9.4)	6	-
Solid tumors	7 (10.9)	3	2
Genetic diseases	6 (9.4)	6	-

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CML* chronic myeloid leukemia, *JMML* juvenile myelomonocytic leukemia, *MDS* myelodysplastic syndrome

Methods

The diagnosis of HZ was performed by clinical examination. Typical skin manifestations included unilateral vesicular lesions within one to three adjacent dermatomes. Burning pain usually preceded the rash. To confirm the clinical diagnosis, vesicular fluid was investigated in 34 patients and blood samples were collected from 16 patients. These samples were analyzed for the presence of VZV DNA using the polymerase chain reaction (PCR) (Sauerbrei et al., 1999).

Brivudin Treatment

Following the diagnosis, treatment with brivudin was immediately initiated in all patients. Brivudin was administered orally for a minimum of seven days. Duration of therapy was determined individually and extended up to 21 days depending on how well the vesicular rash regressed. All patients received brivudin once daily at a minimum of 2 mg/kg and a maximum of 5 mg/kg. To monitor the patients' response to the drug, we examined all patients for at least three weeks. During this period, we documented the time to full crusting of lesions, loss of crusts. Complications or adverse effects were also recorded.

Results

We investigated the course of HZ in 64 patients treated with brivudin, of whom 36 patients (56.2%) were males and 28 patients (43.8%) were females during a period of 16 years. All patients reported a painful, burning, and itchy feeling in the involved dermatome before the typical vesicular lesions became visible. Some patients also experienced hyper- or paresthesia. In the following days, patients described the pain to be more intense. Unilateral and dermatomal distributed lesions were visible and developed into taut blisters filled with serous fluid. All analyses of the fluid of lesions (34 out of 34 samples) showed positive results. Furthermore, VZV DNA was detected in 93.8% of the patients in whom the blood samples were tested (15 out of 16 samples). The PCR results are presented in Table 2.

Table 2
PCR results

Sample	Positive results (%)
Fluid of the lesion	34 of 34 patients (100.0)
Blood	15 of 16 patients (93.8)

The first dose of brivudin was started immediately after diagnosis of HZ. Thirty patients (46.9%) were treated for one week and 26 patients (40.6%) were treated for two weeks. Eight patients (12.5%) received the drug for three weeks. In addition to therapy with brivudin, we prescribed supportive treatment consisting of drying preparations (zinc oxide paste), antipruritics (dimetindene), and analgesics (ibuprofen, metamizole, or paracetamol). Sixteen patients (25.0%) did not need any additive treatment. All other patients clearly took advantage of additional drying preparations. Eight patients (12.5%) received medication to reduce itching and only four patients (6.3%) took pain-alleviating medication.

To evaluate patients’ response to the treatment, we focused on the time to crusting of the lesions. This allowed us to confirm that the process of healing had begun. Full crusting occurred within a median time of six days (Fig. 1). Fifty patients (78.1%) showed full crusting within the first week of treatment. In all remaining patients (21.9%), full crusting occurred during the second week. Our second hallmark of patients’ response to brivudin was the time to complete healing of lesions. This was observed between the 7th and the 21st day of treatment. Eleven pediatric patients (17.2%) showed complete healing within the first week, 39 patients (60.9%) during the second and 14 patients (21.9%) during the third week. The

results of the course of the disease are demonstrated in Table 3 and Fig. 1. Figure 2 shows a HZ infection on the left scrotum and its complete healing after seven days of brivudin therapy.

Table 3
Course of the disease

	Crusting (%)	Complete healing (%)
First week	50 patients (78.1)	11 patients (17.2)
Second week	14 patients (21.9)	39 patients (60.9)
Third week	-	14 patients (21.9)

In summary, brivudin was very well tolerated. Interestingly, one patient showed a special course of disease, briefly summarized as follows. At the age of 14 years, he received the VZV vaccination, as he had not suffered from chickenpox yet. Three weeks later, he was diagnosed with acute myeloid leukemia (AML). It can be assumed that he was already ill at the time of the vaccination. Since his immune system was weakened and he was further immunosuppressed by chemotherapy, he suffered from chickenpox 4 weeks after the diagnosis of AML. Since then, the VZV persisted in his dorsal root and cranial nerve ganglia. Four months after bone marrow transplantation his VZV-specific cellular immunity declined, which led to HZ only 59 days after transplantation. This happened again at a similar interval of 56 days after his second HSCT. The VZV DNA taken from the fluid of the lesions and blood was tested and showed that only the vOka DNA of the live attenuated Oka vaccine was found. This means that the patient suffered two times from vaccine-associated HZ because he was vaccinated shortly before his diagnosis of AML and start of chemotherapy.

Finally, we did not observe any myelo-, hepato- and nephrotoxic side effects during the treatment with brivudin. None of the patients treated with brivudin suffered from postherpetic neuralgia.

Discussion

Our results demonstrate the highly beneficial effects of treating HZ with brivudin in immunocompromised children. The course of HZ is self-limiting in otherwise healthy patients (Gross et al., 2020). Therefore, antiviral therapy is usually not indicated in immunocompetent children. If risk factors are already known and complications could occur during the course of the disease, antiviral therapy is indicated. This requires careful consideration of whether the potential benefits outweigh the potential risks.

Previously published data have shown that brivudin is significantly more effective in inhibiting VZV replication than comparable nucleoside analogues such as acyclovir, famciclovir, or penciclovir (Andrei et al. 1995). These results were confirmed by Wassilew et al. (2003) who compared the efficacy and safety of oral brivudin and acyclovir in a double-blind randomized study with immunocompetent patients.

Another small Belgian study with four immunocompromised patients showed excellent treatment results. All patients showed regression of the lesions within the first days and full recovery without any adverse effect (de Clercq et al., 1980). Additionally, patients suffered only from little or no side and long-term effects and reported a significantly lower level of pain when receiving treatment with brivudin (Wutzler et al., 1995).

Apart from enhanced effectiveness, the convenience for patients is much higher with brivudin and patient compliance hence induced. Compared to acyclovir, brivudin can be taken per os as a single dose once daily. This is due to greater potency and long plasma elimination half-life (Wassilew et al., 2003). In contrast, acyclovir is an intravenous antiviral drug, which must be given three times daily for at least five days. The oral alternative of acyclovir, which needs to be administered five times daily, is poorly absorbed by the body. This requires hospitalization of immunocompromised children.

Treatment with a nucleoside analogue should be started as early as possible to reduce complications and adverse effects. Schmader (2001) showed that an early antiviral treatment significantly decreases intensity of pain and increases regression of lesions in elderly. Based on this knowledge, we administered the drug as soon as possible. In our cohort, treatment was started immediately after the onset of rash in all 64 children. During and after treatment, we could not observe any liver-, kidney- or myelotoxicity.

A secondary aim of early treatment was to reduce the incidence of postherpetic neuralgia which is defined as the persistence of dermatomal pain of more than three months. None of our patients reported pain beyond the three-month mark. Standard treatment recommends brivudin therapy for seven days. Several studies already showed that there is no clinical relevance to limit therapy to seven days. Antiviral medication should be continued if crusting and healing has not completed after the 7th day of therapy.

Due to the absence of large cohort studies, brivudin is not currently approved for antiviral treatment of HZ in children. However, if risk factors are known or complications occur, it should be considered if the benefit of therapy (shortened duration and spread of symptoms, reduced intensity and duration of HZ-associated pain) is greater than the risks of therapy. Brivudin is contraindicated in immunocompromised patients who receive treatment with 5-fluorouracil or 5-fluoropyrimidine-containing drugs within the past four weeks or are planned to receive treatment within the next four weeks. Lethal drug interactions can occur if both drugs are taken.

Furthermore, we investigated whether the introduction of VZV vaccination affected the rate of HZ. Our study provides data of 64 patients in the period of January 2004 to December 2019. For further analyses, we divided this period into two equal periods of eight years. During the first eight years (January 2004 to December 2011), 47 patients were diagnosed with HZ and treated with brivudin. During the second period, only 17 cases of HZ were registered at the Department of Pediatrics, Jena University Hospital, Jena, Germany. This represents a decrease of VZV reactivations by 64%. This decrease could result from the universal varicella vaccination in childhood implemented in Germany in 2006 (STIKO Impfempfehlungen der Ständigen Impfkommission (STIKO. Epidem. Bull. 2004; 30: 235–250)). It is

recommended to vaccinate preferably between the 11th and 14th month of life (first vaccination) and between the 15th and 23rd month of life (second vaccination).

In conclusion, our findings confirm previous small studies on treating children suffering from HZ with brivudin (Benoit et al., 1985; Heidl et al., 1991; Rössig et al., 1998). Compared to those studies, we investigated a significantly larger cohort of patients and could demonstrate that immunocompromised children can be safely treated with brivudin. This group of patients benefits significantly from an outpatient treatment with a once-daily dosing regimen. Further studies in larger cohorts are necessary to confirm our results.

Declarations

Compliance with ethical standards

Conflict of interest The authors declare to have no potential conflicts of interest.

Ethical standard All procedures were in accordance with the ethical standards of the institutional research committee. The study was approved by the Jena University Hospital Ethics Committee (2021-2060). Informed consent was obtained from all individual participants, or the responsible persons included in the study.

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Figures

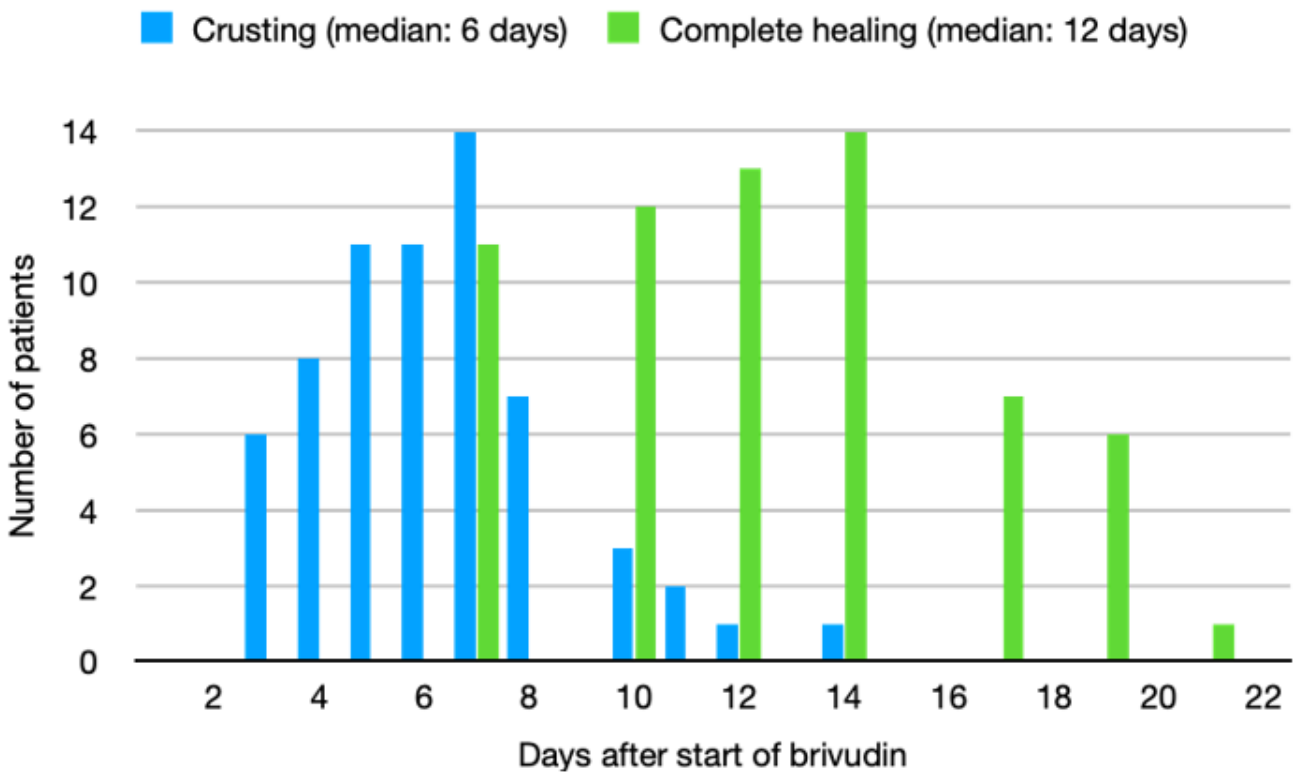

Figure 1

Course of the disease

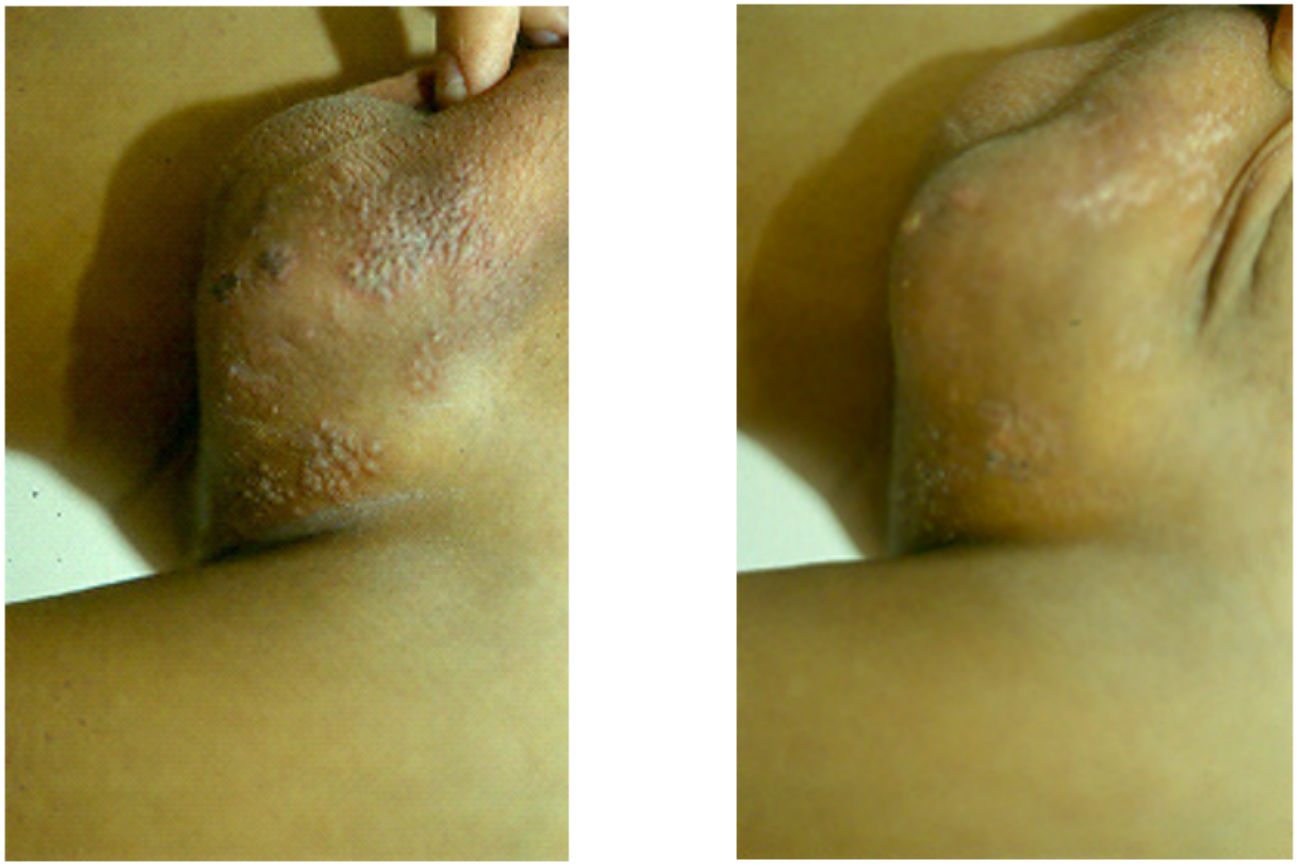

Figure 2

Herpes zoster on the left scrotum and complete healing of the herpes zoster lesions after 7 days of brivudin therapy (2 mg/kg/d)