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Case Report

Improvement of refractory acyclovir-resistant herpes simplex virus type 1 infection by continuous acyclovir administration

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ABSTRACT

Resistant herpes simplex virus type 1 (HSV-1) infection is sometimes fatal for immunocompromised patients. Here, we report 10-year-old girl receiving hematopoietic stem cell transplantation developed refractory HSV-1 infection, which was persisted to intermittent acyclovir (ACV) or foscarnet (FOS) administrations but was improved by continuous ACV administration. The isolates from the lesion were identified with low susceptibilities to ACV and FOS by plaque reduction assay due to *DNA pol* gene mutation. Continuous ACV administration overcomes the efficacy of intermittent administration and could be the best option to treat severe HSV-1 infectious patients.

1. Introduction

Acyclovir (ACV) and its derivatives have become the first line treatment option for herpes simplex virus (HSV) infections. However, resistant HSV infections occur relatively frequently in immunocompromised patients, especially hematopoietic stem cell transplantation (HSCT) recipients, and are associated with persistent, severe and sometimes fatal diseases [1–3]. This resistance is due to either clinical or virological resistance, or both, although it is difficult to distinguish between them clinically. Clinical resistance is related to the host's immunocompromised status, while virological resistance is mostly related to mutations in the thymidine kinase (TK) gene of the HSV, conferring ACV resistance, or by DNA polymerase mutations (DNA pol), conferring foscarnet (FOS) resistance [4]. Here, we report a 10-year-old girl with refractory acute monocytic leukaemia (AMoL) who developed mucosal HSV type 1 (HSV-1) infection that was persistent virologically ACV-sensitive, but was refractory to intermittent ACV administration. The HSV-1 subsequently obtained cross-resistance to ACV and FOS due to mutation in the *DNA pol* gene after switching to FOS, although the mucosal lesion gradually improved with continuous ACV administration.

2. Case report

A 10-year-old girl who was admitted with gingival swelling and persistent fever was diagnosed with AMoL. She had also developed an ulcer on her lower lip that tested positive for HSV-1 by polymerase chain reaction assay. The infection initially responded well to intermittent ACV administration, 30 mg/kg/day, during chemotherapy with valacyclovir as a prophylaxis (Fig. 1). Though induction chemotherapy did not induce complete remission (CR), salvage

Abbreviations: ACV, Acyclovir; HSV-1, Herpes simplex virus type 1; HSCT, Hematopoietic stem cell transplantation; TK, Thymidine kinase; DNA pol, DNA polymerase; FOS, Foscarnet; AMoL, Acute monocytic leukaemia; CR, Complete remission; CBT, Cord blood transplantation; GVHD, Graft versus host disease; EC_{50}, Effective concentrations for 50%.

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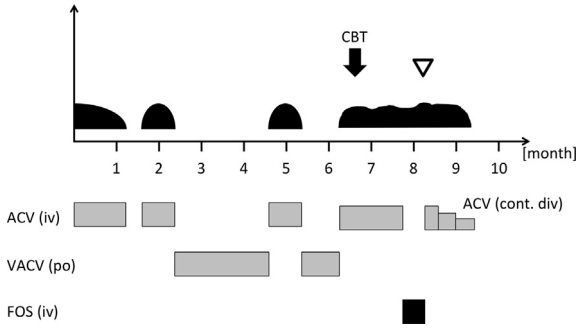

Fig. 1. Clinical course of HSV-1 infection in a cord blood transplantation recipient. HSV-1, herpes simplex virus type 1; CBT, cord blood transplantation; ACV, acyclovir; VACV, valacyclovir; FOS, foscarnet; cont. div, continuous drip infusion into vein; iv, infusion into vein; po, per os; black graph, the emergence of HSV infection (ulceration); inverted triangle, the time point of virus isolation.

therapy successfully achieved CR, followed by cord blood transplantation (CBT). The myeloablative regimen consisted of total body irradiation (12 Gy), cyclophosphamide (60 mg/kg for 2 days) and cytarabine (60 mg/kg for 2 days). Tacrolimus (the target dose: 15 ng/mL) and short-term methotrexate therapy (15 mg/m^2 (day 1) and 10 mg/m^2 (day 3, 6 and 11)) were used as prophylaxis against graft-versus-host disease (GVHD) without administration of corticosteroids due to free from developing GVHD. Since the mucosal HSV-1 infection was not cured despite white blood cell recovery (achieved on day 24), we changed the anti-viral therapy from ACV to FOS. However, the size of ulcer got increased despite FOS administration for 10 days. The next treatment options in this situation would be continuous ACV administration or cidofovir, but cidofovir has not been approved yet in Japan. Therefore, a continuous infusion of ACV 30 mg/kg/day was administered. After the initiation of continuous infusion of ACV resulted obviously in improvement in the mucosal infection, and the lesion was completely cured with 6 weeks of continuous intravenous administration of ACV. Although her immune status had been recovering, the cure of HSV infection was predominantly result of the efficiency of continuous ACV administration. During her clinical course, she had not developed any other virus reactivation without HSV-1.

3. Discussion

To analyze the susceptibility of the offending virus to antiviral agents, aspirate samples were obtained simultaneously from three vesicular lesions three days after starting continuous infusion of ACV, and isolates were obtained from each sample by inoculating them into Vero cell cultures. Susceptibilities of the three isolates to ACV and FOS were determined using plaque reduction assays and were expressed as the effective concentrations for 50% (EC_{50}) plaque reduction (Table 1). In isolates 1 and 3, FOS EC_{50} results decreased to 4.1-fold and 3.2-fold relative to the data of wild type HSV, whereas ACV EC_{50} results decreased to 8.1-fold and 7.8-fold relative to that of wild type HSV. While, in isolate 2, there was no difference in each EC_{50} compared to the data for wild type HSV. Next, the *TK* and *DNA pol* genes of HSV-1 were sequenced directly from the purified HSV genome according to the manufacturer's procedures (ABI PRISM 3100 DNA sequencer). No mutations in the *TK* gene were observed in any of the isolates. While analysis of the *DNA pol* gene from isolates 1 and 3 identified a single amino acid substitution of serine at position 724 to asparagine (S724N), which was previously reported to confer cross resistance to ACV and FOS [5,6], no mutations in *TK* and *DNA pol* genes were identified from isolate 2. These data suggested that resistance of the HSV-1 infection to intermittent ACV administration was not due to virological resistance related to TK gene mutation, but was a state of clinical resistance induced by CBT, which was proved by the existence of non-mutated isolate 2. Moreover, as previously reported [7], we also found that the DNA pol mutants emerged after a short period of FOS administration and were mixed with wild type viruses. Laboratory diagnosis of virological resistance to antiviral agents is assessed using plaque reduction assay or genotypic assay [4]. However, these tests are not widely used in clinical practice since they are time consuming and costly. Our experience suggests that since the use of anti-viral drugs is associated with a substantial risk of development of drug resistance or obtains selective advantage, unconsidered treatment alteration need to be avoided [1,8]. Further, for confirmation of virological resistance, multiple samples should be obtained from the lesion.

Table 1
Virological characterization of HSV-1 isolates from vesicular lesions.

	Susceptibility (μg/ml)		mutation	
	ACV	FOS	TK	DNA polymerase
Isolate 1	1.08 ± 0.51	65.00 ± 13.90	no	S724N
Isolate 2	0.24 ± 0.03	11.42 ± 1.14	no	no
Isolate 3	1.04 ± 0.56	51.58 ± 16.49	no	S724N
Wild type 7401H	0.133 ± 0.02	16.00 ± 0.96	no	no

Susceptibility (EC_{50}) was expressed as the mean ± SD of three independent experiments. ACV, acyclovir; FOS, foscarnet; TK, thymidine kinase.

One interesting aspect of this case is that continuous ACV administration was predominantly effective, even though some HSV-1 strains obtained from this patient had mutations in the *DNA pol* gene. In a previous study, similar to our case, administration of ACV by continuous infusion was reported to be effective even in virologically ACV-resistant HSV cases [9]. The detailed mechanisms why ACV could overcome drug-resistance strain remain unclear, but to increase intracellular ACV concentration would be a rational explanation referred to the effectiveness of continuous ACV administration. In fact, we demonstrated that the intracellular half-life of ACV after a single dose was extremely short (0.3 hrs) compared to its serum half-life (2.5 hrs) [10]. It strongly suggested that intracellular ACV concentration could be kept only by continuous infusion of ACV. Although not commonly administered, a continuous infusion of ACV might be the ideal therapeutic option as the initial treatment for patients in a clinically resistant state, as well as for the patients residing in the countries where cidofovir has not been approved.

In conclusion, continuous ACV infusion is the best option to treat HSV-1 infection in immunocompromised individuals with adequate renal function. Prospective clinical studies on continuous ACV infusion are warranted to evaluate the efficacy and safety of continuous ACV infusion.

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Conflicts of interest

None.

Authorship statement

I state that all the authors meet the criteria of ICMJE authorship criteria.

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