

# Greater Efficacy of Cidofovir Than of Foscarnet for the Treatment of Acyclovir-Resistant Herpes Simplex Virus Infection After Allogeneic Hematopoietic Stem Cell Transplantation

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**Abstract:** Herpes simplex virus (HSV) infection is a common problem in patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Severe HSV infections can cause pneumonia, encephalitis, meningitis and other lesions, thus requiring caution. Acyclovir is the drug of choice for the prevention of HSV infection. Acyclovir resistance caused refractory HSV infection which is a severe complication after allo-HSCT. Cidofovir may be effective for acyclovir-resistant patients; however, the efficacy of systemic cidofovir administration for acyclovir-resistant patients after allo-HSCT remains unknown. We describe a 67-year-old female patient with multiple ulcers and erosions of the periocular, perioral, and oral mucosa after haploidentical allo-HSCT. Poor results were observed after the treatment of acyclovir and foscarnet. In particular, an adverse effect of low potassium and renal damage has been observed with foscarnet. Genetic testing suggested an acyclovir-resistant herpes simplex virus type 1 (HSV1) infection with T287M mutation of gene *UL23*. The patient's infection was cured after intravenous treatment with cidofovir. Systemic administration of cidofovir may be useful for patients with acyclovir-resistant HSV1 infection after haploidentical allo-HSCT.

**Keywords:** herpes simplex virus, cidofovir, allogeneic hematopoietic stem cell transplantation, resistance

## Introduction

Despite systemic acyclovir (ACV) prophylaxis, herpes simplex virus (HSV) infections still occur in patients undergoing allogeneic hematopoietic stem cell transplantation. HSV infections often involve skin and mucosal lesions in the oropharynx, genitals, and perigenital areas and, in severe cases, may also lead to pneumonia, encephalitis, meningitis, or lesions in other organs and tissues.<sup>1,2</sup> In particular, central system infections caused by HSV may lead to long-term sequelae with very poor prognosis. Patients with immunodeficiency are often characterized by extensive and prolonged disease. There is also a greater likelihood of viral dissemination leading to organ and tissue involvement beyond the primary focus. Intravenous acyclovir remains the treatment of choice for severe herpes simplex virus infections.<sup>3</sup> Frequent ACV use increases the chances of acyclovir-resistant HSV infection. Acyclovir resistance should be suspected in patients who worsen despite adequate therapy with acyclovir, individuals with multiple episodes of recurrent HSV, and highly immunocompromised individuals. Intravenous foscarnet may be considered in cases of resistance to acyclovir, valaciclovir or famciclovir. However, many reports of cross-resistance between foscarnet and acyclovir exist.<sup>4</sup> Cidofovir may be effective in patients with multidrug-resistant HSV infection,<sup>5,6</sup> possibly because cidofovir has much lower cross-resistance with acyclovir.<sup>5</sup> However, only case reports on the use of cidofovir for patients with acyclovir-resistant HSV

infection after allo-HSCT have been published; in particular, no study has investigated the efficacy of cidofovir in those experiencing acyclovir-resistant HSV infection after haploidentical allo-HSCT.

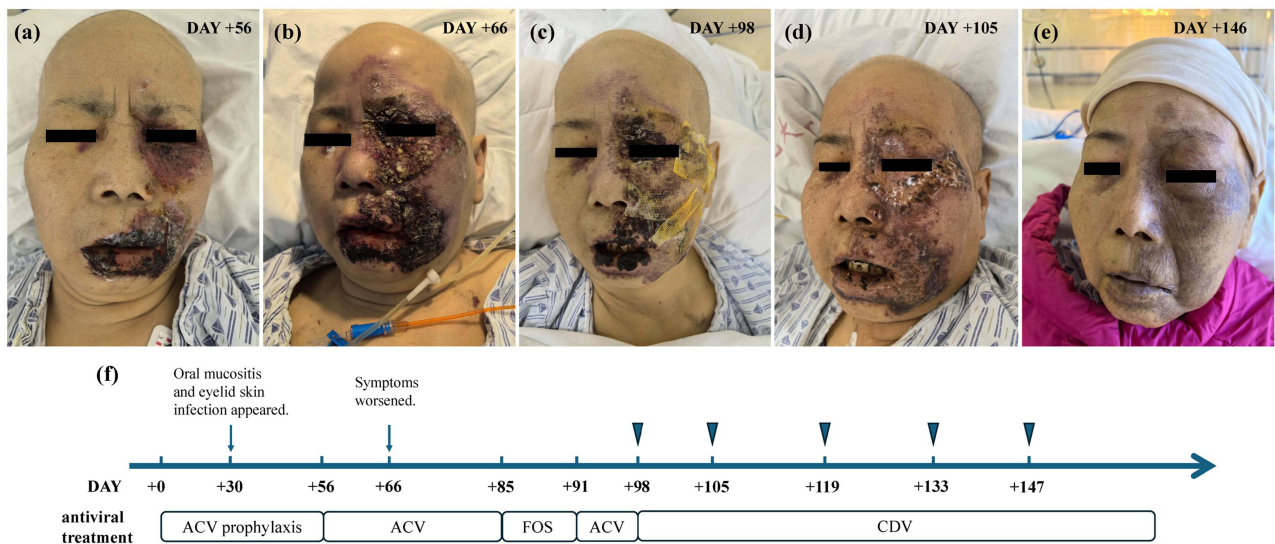
This paper reports that a patient with refractory HSV infection after haploidentical allo-HSCT was successfully treated with intravenous cidofovir.

## Case Presentation

A 67-year-old female was diagnosed with T-cell acute lymphoid leukemia (T-ALL) in April 2024. After the first course of inductive chemotherapy and two rounds of consolidation, the patient received HLA 5/10-matched haploidentical allo-HSCT from her daughter in September 2024. The conditioning regimen used before allo-HSCT included busulfan (0.8 mg/kg every 6 h for 3 days), fludarabine (30 mg/m<sup>2</sup>/d for 5 days), cyclophosphamide (1 g/m<sup>2</sup>/d for 2 days) and antithymocyte globulin (2.5 mg/kg for 4 days).

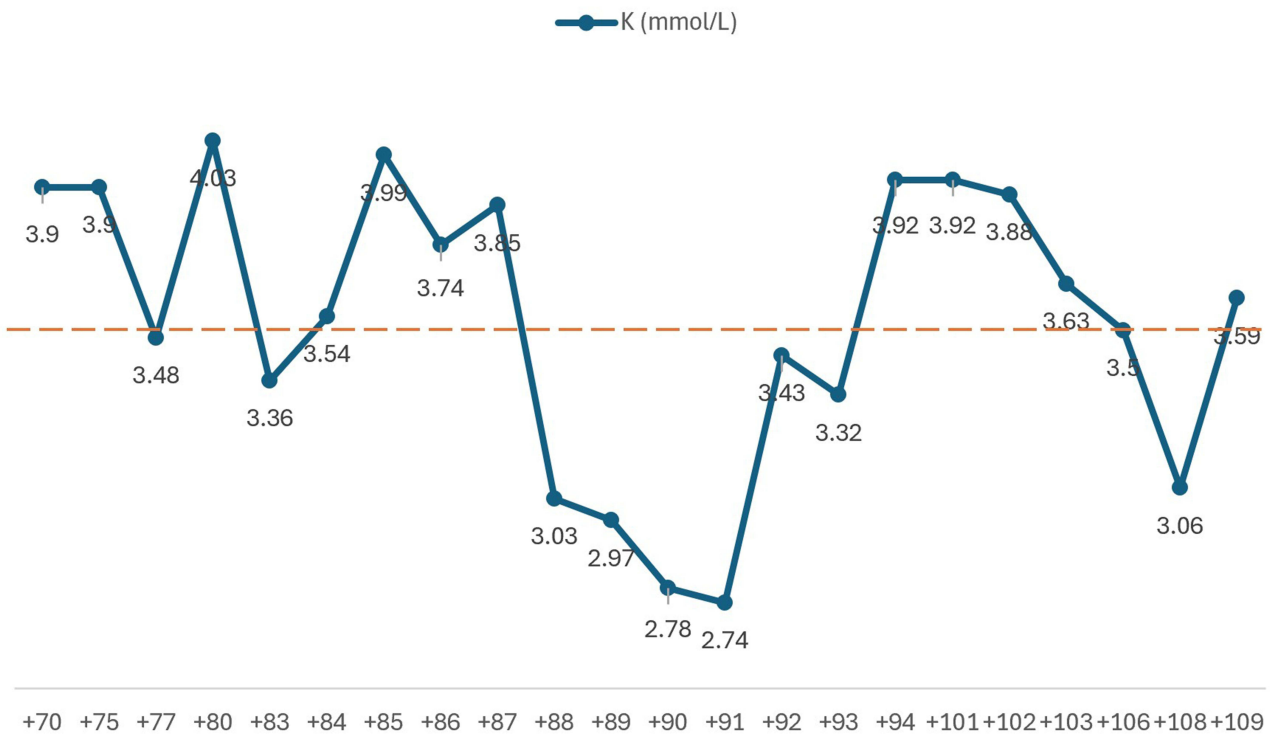
One month after HSCT, the patient presented with multiple ulcers and erosions of the periocular, perioral, and oral mucosa (Figure 1) despite prophylaxis with acyclovir (0.4 g bid) from Day +1. The plasma PCR assay for HSV1 was positive, with a cycle threshold value of 23. No improvement was observed after treatment with acyclovir (250 mg every 8 h i.v.), and her oral mucositis continued to worsen (Figure 1a and b). Treatment with foscarnet (40 mg/kg every 8 h i.v.) was started on Day +84. Ganciclovir eye ointment was also given for external application. However, the patient presented elevated serum creatinine, low potassium (Figure 2), low calcium and low magnesium, presumably as an adverse effect of renal damage and electrolyte imbalance caused by foscarnet. Based on these concerns, treatment was changed to acyclovir (500 mg every 8 h i.v.) after 6 days of foscarnet use. During this time (Day +84 to Day +97), the patient's mucositis increased in extent and degree (Figure 1c).

Acyclovir-resistant HSV1 became detectable in the oral swab, and genotyping confirmed the presence of a *UL23* resistance-associated mutation named T287M (Figure 3). From Day +98, the treatment was switched to i.v. cidofovir (5 mg/kg) once a week for 2 weeks and then every other week for one month (Figure 1f). The patient showed significant improvement after 2 injections of cidofovir (Figure 1d and e).



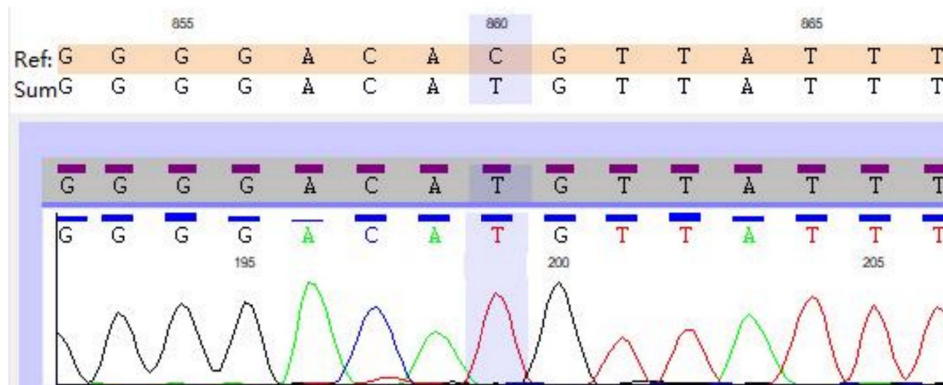
**Figure 1** Clinical course of HSV1 infection in this patient. ACV, Acyclovir; FOS, foscarnet; CDV, cidofovir; inverted triangle, the time point of intravenous cidofovir treatment. (a–e) Facial lesions in patients at different days; (f) Patient medication changes over the course of the infection.

## Electrolyte imbalance



**Figure 2** Electrolyte imbalance following foscarnet administration. Horizontal line, the lower limit for potassium, 3.5 mmol/L. Since the 5th day of switching to foscarnet (day +88), the patient experienced a significant decrease in blood potassium. And it rebounded significantly after discontinuation of the foscarnet (day +92).

## HSV1-UL23: c.860C>T; P.T287M



**Figure 3** Diagram of the gene UL23 mutation site.

## Discussion

In the present study, a patient with acyclovir-resistant HSV infection after haploidentical allo-HSCT was cured with cidofovir, and this is the first case to demonstrate the efficacy of cidofovir in patients with this condition.

ACV has long been used as a prophylactic medicine for HSV infection in patients receiving bone marrow transplantation, thus posing a great challenge for HSV resistance to ACV. Some studies have shown that the rate of acyclovir resistance in patients undergoing allo-HSCT may be as high as 30%.<sup>7,8</sup>

In contrast to acyclovir, which derives its antiviral action from selective phosphorylation by viral thymidine kinase, cidofovir is a monophosphate nucleotide analog that targets the viral DNA polymerase and inhibits replication of the viral DNA strand, thereby reducing its proliferation.<sup>4,9</sup> Therefore, mutations that result in altered phosphorylase activity causing HSV resistance to ACV may not affect the efficacy of cidofovir.<sup>10</sup> Despite its nephrotoxicity, cidofovir still plays a role as an important option for patients with a poor response to ACV.<sup>11,12</sup> The other option, foscarnet, has more significant medication toxicity. It often manifests as nephrotoxicity, electrolyte disturbances, mucosal ulceration, nausea, vomiting, etc.<sup>13,14</sup> A study by Anton-Vazquez et al<sup>13</sup> demonstrated that a significant proportion of patients need to discontinue their antiviral therapy with foscarnet due to acute kidney injury. Considering the safety of the medication, cidofovir also has notable advantages.

Polymorphisms in the *tk* gene (gene *UL23*) of HSV-1 strains have been described extensively.<sup>15–17</sup> Often, the addition or deletion of nucleotides in long homopolymeric runs of Gs and Cs results in the formation of a premature stop codon downstream of the shift code, which further leads to a deficiency of enzymes.<sup>18</sup> Nucleotide substitutions in the *tk* gene leading to new codon production are less common than the former,<sup>19</sup> and our case presents an ACV-resistant mutation of the *UL23* gene named the T287M substitution located in nonconserved regions. The T287M mutation of the *UL23* gene detected in HSV2 isolates was previously reported to be sensitive to foscarnet.<sup>20</sup> In addition, Kawamura et al<sup>21</sup> reported that amenamevir was an effective treatment for a patient with the T287M mutation in HSV1. In the present study, we report for the first time that cidofovir could successfully cure patients with the T287M mutation of the *UL23* gene in HSV1.

Cidofovir has also been reported to be effective in patients with *UL23* mutations.<sup>6,22</sup> Mutations in the *tk* and *DNA pol* genes were previously identified in clinical isolates resistant to both ACV and foscarnet, leading to the hypothesis that they are associated with resistance to ACV and foscarnet, respectively.<sup>23–25</sup> Thus, both cidofovir and foscarnet may be effective against HSV1 infection in this patient. Discontinuation of foscarnet due to elevated creatinine may have contributed to the underutilization of its antiviral effect.

## Conclusion

This case report shows that cidofovir effectively treats HSV1 infection in patients after allo-HSCT. Despite ACV prophylaxis, our patient developed oral mucositis and eyelid skin soft tissue infection due to HSV1 infection. The use of high-dose acyclovir and foscarnet was ineffective. In our case, cidofovir had a better therapeutic effect. These findings suggest that clinicians may consider the intravenous use of cidofovir to treat patients with refractory HSV infections.

## Abbreviations

HSV, Herpes simplex virus; allo-HSCT, Allogeneic hematopoietic stem cell transplantation; ACV, Acyclovir; T-ALL, T-cell acute lymphoid leukemia; FOS, foscarnet; CDV, cidofovir; HLA, Human leukocyte antigen; PCR, Polymerase chain reaction.

## Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

As a case report, our paper did not require any referral to our institutional clinical ethics committee.

## Consent for Publication

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no competing interests in this work.

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