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CHALLENGING CLINICAL CASE

Salvage Treatment of Refractory HSV Oral Lesions with Pritelivir in Allogeneic Hematopoietic Cell Transplant Recipients

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ABSTRACT We present two allogeneic hematopoietic cell transplantation recipients (HCTr) treated with pritelivir for acyclovir-resistant/refractory (r/r) HSV infection based on the expanded access program of the pritelivir manufacturer. Outpatient treatment with pritelivir was administered, with partial response by week 1 of treatment and complete response by week 4 of treatment in both patients. No adverse events were noted. Pritelivir appears to be an effective and safe option for the management of acyclovir-r/r HSV infections in highly immunocompromised patients in an outpatient setting.

KEYWORDS resistant/refractory HSV infection, allogeneic hematopoietic cell transplant, pritelivir

Allogeneic hematopoietic cell transplantation (HCT) recipients (r) may develop acyclovir-resistant or refractory herpes simplex virus (r/r HSV) infections (1). The prevalence of r/r HSV infection after an allogeneic HCT is estimated between 4.1 and 10%, with some studies reporting rates as high as 36% (2–4). In a French study conducted in 3,357 patients with HSV infection between 1999 and 2002, 0.35% of immunocompetent and 3.5% of immunocompromised subjects had an acyclovir-resistant HSV infection, with the highest rate reported in HCT recipients (10.9%) (5). Exposure to prolonged (val)acyclovir-based prophylaxis at variable doses and with potentially suboptimal oral absorption in cases of severe gastrointestinal tract (GIT) mucositis or graft versus host disease (GvHD) may select for acyclovir-resistant HSV, as shown in a recent cohort of 532 patients with 17% prevalence of acyclovir-resistant strains (6). Acyclovir-resistant HSV infections may present with recurrent, longer-lasting, larger, deeper, and more extended ulcerations in typical or atypical areas, and treatment options remain limited (2, 7). Acyclovir and other nucleoside analogs block ongoing DNA chain elongation through inhibition of viral DNA polymerase, but multiple phosphorylations, the first by the viral thymidine kinase, are required (8). Mutations in the viral thymidine kinase (UL23 gene) are the most important mechanisms of acyclovir resistance (95%), followed by viral DNA polymerase (UL30 gene) mutations, which are less common (5%) (9–11). Foscarnet is a pyrophosphate analog that inhibits the cleavage of pyrophosphate from the nucleoside triphosphate and remains the only approved option for the treatment of acyclovir-resistant HSV strains (12–14). However, foscarnet administration is challenging due to multiple adverse events, including nephrotoxicity, electrolyte abnormalities, and mucosal ulceration and the fact that it can only be administered intravenously, often requiring patient admission to the hospital (15). Moreover, mutations in the DNA polymerase (UL54 gene) can coexist with thymidine kinase mutations, conferring resistance to foscarnet, ganciclovir, and acyclovir as well as cidofovir (16). The increasing pool of highly immunocompromised hosts, prevalence of r/r HSV infections, and limited treatment options point to the urgent need of new classes of safe and effective antiviral compounds with activity against r/r HSV infections.

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Pritelivir is a helicase-primase inhibitor, a new class of antiviral molecules that block *de novo* synthesis of viral DNA; it does not require activation by viral thymidine kinase (17, 18). Pritelivir has activity against both HSV-1 and HSV-2, including acyclovir-resistant HSV strains, but it does not have any activity against other herpesviruses (e.g., varicella-zoster virus [VZV], Epstein-Barr virus [EBV], cytomegalovirus [CMV], and human herpesvirus 6 [HHV-6]) (19, 20). Multiple *in vitro* studies have demonstrated the potent activity of pritelivir against acyclovir-resistant strains (21, 22). In addition, *in vivo* animal models have confirmed the potency of pritelivir in comparison to acyclovir against recurrent HSV infections (23–25). Resistance to pritelivir may occur due to mutations in the UL5 (helicase) and/or the UL52 gene (26, 27). However, thus far, no pritelivir-associated mutations have been described in immunocompetent subjects receiving daily therapy of pritelivir for up to 28 days (28). Pritelivir has been administered for compassionate use in the context of the Expanded Access Program supported by AiCuris. However, there is a paucity of clinical data on pritelivir administration in real life. Herein, we present two cases of acyclovir r/r HSV-1 infections in allogeneic HCTr at our institution.

(This case will be presented as an oral presentation [abstract number 00346] during the 33rd European Congress of Clinical Microbiology and Infectious Diseases—ECCMID 2023 in Copenhagen on 16 April 2023 [Session: 1-h Case Session, Virulent Viruses, 11:00 a.m. Hall F].)

CASE PRESENTATIONS

Case 1. A 35-year-old patient with a history of acute lymphoid leukemia type B (ALL-B) Philadelphia$^+$ received an allogeneic HCT from an unrelated human leukocyte antigen (HLA)-compatible donor after myeloablative conditioning with etoposide and fractionated total body irradiation (12 Gy; posttransplant day [PTD] 0). The patient developed severe cutaneous acute GvHD grade 4 stage IV on PTD 35, followed by a generalized severe chronic GvHD form (mouth/muscle/skin/eyes), which was treated with different combinations of immunosuppressive therapy, including the following compounds: high-dose corticosteroids, tacrolimus, ciclosporin, mycophenolate mofetil (MMF), ruxolitinib, etanercept, extracorporeal photopheresis, tocilizumab, and ibrutinib.

On PTD 177, the patient developed the first HSV-1 episode, presenting as severe stomatitis with multiple oral lesions while on primary HSV prophylaxis with valacyclovir 500 mg twice daily orally (p.o.). Molecular testing confirmed the presence of HSV-1 on an oral swab, with a cycle threshold (C_T) of 23, and gene sequencing showed the presence of T556A and D672N polymorphisms in the predicted HSV-1 DNA polymerase. A specific mutation was not detected, but the deletion of a base in position 1060 suggested potential acyclovir resistance, which was subsequently confirmed by phenotypic culture testing. The patient was treated successfully with foscarnet at 40 mg/kg three times daily intravenously (i.v.) for 21 days and modification of immunosuppression (Table 1). Secondary prophylaxis with valacyclovir 500 mg twice daily p.o. was restarted on PTD 199 (results for acyclovir resistance testing were not yet available). On PTD 219, the patient developed a second episode of HSV-1 stomatitis (HSV-1 PCR was positive by oral swab, C_T 21) and was treated with foscarnet at 40 mg/kg three times daily i.v. for 5 days and was switched to cidofovir at 5 mg/kg once weekly i.v. for three weekly doses with foscarnet mouth wash because of foscarnet-induced genital ulcerations. Cidofovir was continued as secondary prophylaxis at 5 mg/kg once every other week until a third episode of HSV-1 stomatitis was diagnosed on PTD 270 (tested HSV-1 positive by oral swab, C_T 22), which was successfully treated with a 15-day course of foscarnet at 40 mg/kg three times daily i.v. Foscarnet resistance was excluded during this third episode by additional DNA polymerase gene sequencing. Secondary prophylaxis with cidofovir at 5 mg/kg every other week i.v. was restarted on PTD 287 until a fourth HSV-1 stomatitis episode was diagnosed on day 374 (HSV-1 PCR positive, C_T 23); cidofovir was continued as therapy once a week at 5 mg/kg i.v. for 15 days and then as secondary prophylaxis every other week, with the last dose administered on PTD 429. A treatment request for pritelivir in the context of an expanded access program was submitted to the manufacturer (AiCuris) for the treatment of this episode, but pritelivir

TABLE 1 History of infections due to herpes simplex virus 1 (HSV-1) before the initiation of pritelivir

Clinical history[a]	Case 1		Case 2	
Primary HSV prophylaxis	Valacyclovir 500 mg/12 h p.o.		Valacyclovir 500 mg/12 h p.o.	
First HSV episode, PTD	171		98	
Treatment	Start	End	Start	End
Valacyclovir 1 g/8 h p.o., PTD			98	105
Foscarnet 40 mg/kg/8 h i.v., PTD	177	198	106	116
Treatment duration in total, days	21		18	
Immunosuppression	Tocilizumab, photopheresis	Ibrutinib, tocilizumab, photopheresis	Tacrolimus	Tacrolimus
Prednisone dose, mg/24 h	80	70	60	40
Secondary prophylaxis PTD[b]			117	128
Valacyclovir 500 mg /12 h p.o., PTD	199	219		
Second HSV episode, PTD	219		128	
Treatment				
Foscarnet 40 mg/kg/ 8 h i.v., PTD	220	225		
Cidofovir 5 mg/kg QW i.v., PTD[c]	226	246	128	142
Treatment duration in total, days	26		14	
Immunosuppression	Ibrutinib	Ibrutinib	Tacrolimus	Tacrolimus
Prednisone dose, mg/24 h	100	100	20	10
Secondary prophylaxis PTD[b]	247	270	142	146
Third HSV episode, PTD	270			
Treatment, foscarnet 40 mg/kg/8 h i.v., PTD	271	286		
Treatment duration in total, days	15			
Immunosuppression	Photopheresis	Tacrolimus, photopheresis		
Prednisone dose, mg/24 h	55	50		
Secondary prophylaxis PTD[b]	287	374		
Fourth HSV episode, PTD	374			
Treatment, cidofovir 5 mg/kg QW i.v., PTD	375	381		
Treatment duration in total, days	7			
Immunosuppression	Photopheresis	Photopheresis		
Prednisone dose, mg/24 h	50	50		
Secondary prophylaxis PTD[b]	381	443		

[a]HCT, hematopoietic cell transplant; GvHD, graft versus host disease; PTD, posttransplant day; p.o., orally; i.v., intravenous; QW, once weekly.
[b]Secondary prophylaxis included administration of cidofovir 5 mg/kg every other week i.v.
[c]Foscarnet mouth wash was also administered daily with i.v. cidofovir from PTD 226 to 246.

eventually arrived at our institution after completion of treatment for this fourth episode. However, a fifth stomatitis episode was diagnosed (confirmed by positive HSV-1 PCR, C_T 24) on PTD 444 (Fig. 1a).

TREATMENT WITH PRITELIVIR AND OUTCOME

As pritelivir was already at the hospital pharmacy, therapy with pritelivir 100 mg once daily p.o. was started on PTD 445 until PTD 478 (Table 2). After 7 days of pritelivir therapy, the tongue ulcerative lesions significantly improved (Fig. 1b), with complete resolution of all lesions attained by 34 days of therapy (Fig. 1c). The therapy with pritelivir was well tolerated, and no major adverse events were reported by the patient. No secondary prophylaxis was started after treatment with pritelivir since the immunosuppression was reduced. A recurrent episode of HSV-1 stomatitis was detected after stopping pritelivir at PTD 562, which was treated succesfully with cidofovir i.v. for 2 weeks. Follow-up ended at PTD 743.

Case 2. A 42-year-old patient received an allogeneic HCT from a haploidentical donor for myelodysplastic syndrome. The patient developed acute GIT GvHD grade 2 stage I on PTD 22 and was treated with corticosteroids (2 mg/kg once daily). Primary HSV prophylaxis consisted of valacyclovir 500 mg twice daily p.o. On PTD 98, the patient developed a breakthrough-valacyclovir HSV-1 infection (HSV-1 PCR positive by oral swab, C_T not available), which was initially treated with high-dose valacyclovir at 1 g three times daily p.o. However, molecular testing confirmed the presence of acyclovir-resistant HSV-1 by sequencing of the thymidine kinase gene (R281STOP) on PTD 105. Treatment was changed to foscarnet at 40 mg/kg three times daily i.v. for a total

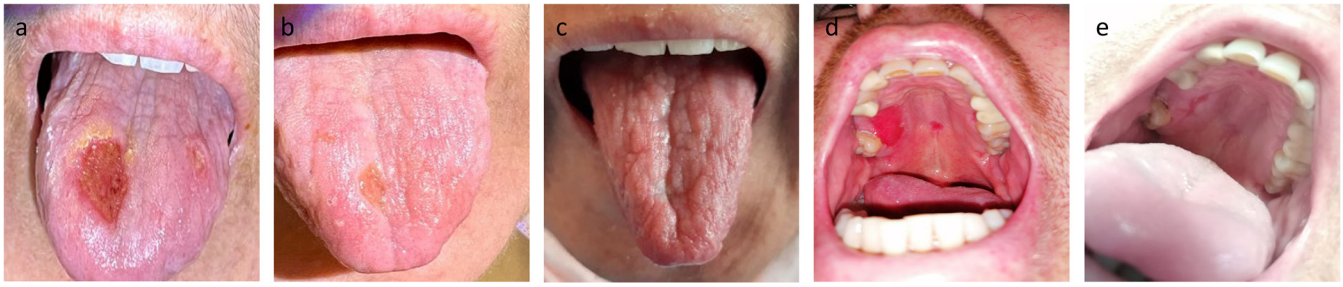

FIG 1 (a to c) First case of an allogeneic hematopoietic cell transplant (HCT) recipient with acyclovir-resistant/refractory HSV-1 (r/r HSV-1) stomatitis with multiple tongue ulcers diagnosed on posttransplant day (PTD) 444 (a), with clear improvement of the tongue lesions after 7 days of therapy with pritelivir on PTD 451 (b) and complete resolution of the tongue lesions on PTD 478 after 34 days of pritelivir therapy (c). (d and e) Second case of an allogeneic HCT recipient with r/r HSV-1 stomatitis associated with lesions on the hard palate on posttransplant day (PTD) 146 (d) with almost complete resolution of the hard palate lesion after 15 days of pritelivir therapy by PTD 161 (e).

duration of 10 days with complete clinical response (Table 1). Secondary prophylaxis with cidofovir at 5 mg/kg every other week i.v. was initiated on PTD 117. On PTD 128 and 11 days after completion of the treatment with foscarnet of the first episode, HSV-1 stomatitis recurrence was diagnosed based on an oral swab positive for HSV-1 by PCR, leading to administration of treatment-dose cidofovir at 5 mg/kg once every week i.v. for 2 weeks with complete resolution of the oral lesions. On PTD 146, 9 days after the second dose of cidofovir, the patient developed a third episode of stomatitis associated with multiple ulcerative painful lesions of the hard palate (Fig. 1d), which was diagnosed by an oral swab that tested positive for HSV-1 by PCR testing.

CHALLENGE QUESTION

What treatment options would you consider at this point?

1. Foscarnet local administration
2. Foscarnet i.v.
3. Cidofovir i.v.
4. Pritelivir p.o.
5. Combination treatment with pritelivir p.o. and foscarnet i.v.

TREATMENT WITH PRITELIVIR AND OUTCOME

Treatment with pritelivir 100 mg once daily p.o. was initiated on PTD 146 after approval by the Expanded Access Program by AiCuris for compassionate use (Table 2). The patient had a partial clinical response within 1 week and an almost complete resolution of the oral lesions by 2 weeks after pritelivir initiation (Fig. 1e). After a 30-day course of treatment with pritelivir, the infection resolved completely, and no secondary prophylaxis was initiated, considering that immunosuppression had been tapered off. The pritelivir was well tolerated, and no adverse events or relapses were noted. Follow-up ended at PTD 243.

COMMENTARY

We report two complex cases of acyclovir-resistant HSV-1 infections in allogeneic HCT recipients that were successfully treated with a new helicase-primase inhibitor, pritelivir, as salvage therapy. The increasing pool of highly immunocompromised hosts who remain on (val)acyclovir primary prophylaxis for a long duration has led to higher rates of acyclovir-r/r HSV infections, with only i.v.-administered, potentially nephrotoxic treatment options currently available (3, 4, 6, 9). New effective and safe alternative treatment options are urgently needed.

Our cases demonstrate that administration of pritelivir in highly immunocompromised patients with multiple recurrent r/r HSV-1 infection episodes was associated with favorable clinical outcomes. We documented complete clinical responses in both cases, and clinical responses were evident as fast as 7 days into treatment. This is

TABLE 2 Characteristics of infectious episodes due to herpes simplex virus 1 (HSV-1) treated with pritelivir[a]

Clinical history	Case 1		Case 2	
HSV infection diagnosis	Fifth HSV episode		Third HSV episode	
PTD	444		146	
Treatment	Start	End	Start	End
Pritelivir 100 mg/24 h p.o., PTD	445	478	146	176
Treatment duration in total, days	34		30	
Immunosuppression	Photopheresis	Photopheresis	Tacrolimus	Stopped PTD 174
Prednisone dose, mg/24 h	45	40	5	Stopped PTD 153
Secondary prophylaxis	None		None	

[a]PTD, posttransplant day; p.o., orally.

consistent with *in vitro* and animal model data showing a potent antiviral activity of this agent, even against acyclovir-resistant HSV strains (21, 24, 25). Data on the successful treatment of three allogeneic HCT recipients with recurrent genital HSV-2 infections have been reported (29, 30). A highly immunocompromised patient with severe GvHD was successfully treated with pritelivir after a long course of failed treatment with foscarnet for a genital infection with an acyclovir-r/r HSV-2 strain (29). In a second case report, two allogeneic HCT recipients presenting with foscarnet-refractory acyclovir-resistant HSV-2 genital infections were successfully treated with pritelivir (30).

Although foscarnet may be used for the treatment of r/r HSV infections, administration of this agent frequently requires the hospitalization of patients for i.v. administration, renal function monitoring, and electrolyte replenishment (16). In addition, patients may develop painful genital ulcers, as evidenced in case 1 presented herein, further limiting the use of this agent. Finally, although rare, foscarnet resistance may also emerge when treating r/r HSV infections with this agent (16). However, and despite a paucity of clinical efficacy data, off-label treatment with cidofovir may allow for outpatient management of such patients. However, cidofovir is not currently approved for the treatment of acyclovir-r/r HSV infections (31). Furthermore, cidofovir has been associated with significant adverse events, including nephrotoxicity, metabolic acidosis, and uveitis (32). Successful topical and intralesional use of cidofovir for acyclovir r/r HSV infections has been described in case reports, but its use in that form remains highly anecdotal (33, 34).

In contrast, pritelivir can be orally administered with minimal associated toxicities. Hence, patients with difficult-to-treat HSV infections may not require hospital admission for i.v. administration of foscarnet. In fact, for both episodes treated with pritelivir at our institution, patients remained outpatients and very much appreciated the fact that they did not have to be readmitted for another i.v.-administered antiviral treatment. This is quite pertinent, as allogeneic HCT recipients have already spent significant periods of time in the hospital, starting before their transplant for chemotherapy and other complications associated with their underlying hematologic malignancy and posttransplant. If additional subsequent admissions can be avoided, such as for the treatment of a mucosal viral infection without other significant repercussions, this would be beneficial for patient quality of life improvement and to reduce the burden on health care system resource utilization. Outpatient management was also possible due to the fact that pritelivir is well tolerated without major adverse events, as documented in our two patients who did not experience any toxicities.

In the first case, infection relapse was observed within 27 days after stopping treatment with pritelivir, considering the overall immunosuppression of this patient. This is in agreement with other case reports, which have shown relapse of HSV infection after pritelivir treatment completion (30). Data on secondary prophylaxis in acyclovir-r/r HSV infections are lacking, and there is no consensus on what to administer and for how long to prevent further relapses. Further studies to address this matter are required. Whether pritelivir may also be used as secondary prophylaxis in patients with multiple recurrences and persistent immunosuppression, at what dose, and for how long remain, at the time, unanswered questions (35).

In conclusion, acyclovir-r/r HSV infections may occasionally occur in severely immunocompromised patients, including allogeneic HCT recipients, and have been associated with multiple relapses and potentially toxic treatments for which hospitalization is frequently required. Our data and data from others suggest that pritelivir may be a well-tolerated and highly effective option for the treatment of acyclovir-r/r HSV strains. Although promising, more data from phase 3 clinical trials are required to better describe the efficacy and safety parameters of this agent and its position in clinical practice.

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