BRIEF ARTICLES

Treatment of Acyclovir-Resistant Herpes Simplex Virus with Continuous Infusion of High-Dose Acyclovir in Hematopoietic Cell Transplant Patients

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Infection because of herpes simplex virus (HSV) that is resistant to acyclovir (ACV) poses treatment challenges in hematopoietic cell transplant (HCT) patients. We present a series of patients with ACV-resistant HSV following HCT who were successfully treated with continuous infusion high-dose ACV after failing standard treatment regimens for ACV-resistant HSV.

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KEY WORDS: Acyclovir, Drug resistance, Immunocompromised host, Hematopoietic stem cell transplantation

INTRODUCTION

In the immunocompromised population of allogeneic hematopoietic cell transplant (HCT) recipients, herpes simplex virus (HSV) remains a common viral infection in the first year after transplant despite the routine use of acyclovir (ACV) prophylaxis, with the potential for chronic and extensive mucocutaneous lesions and for progression to disseminated disease [1-3]. In contrast to immunocompetent patients, the combination of prolonged antiviral prophylaxis or treatment and impaired immune response can lead to the development of ACV resistance, which has been reported in up to 27% of allogeneic HCT recipients; lower levels have been reported in patients with HIV or hematologic malignancies, whereas resistance is very infrequent in immunocompetent patients [4-6]. The current ASBMT guidelines recommend that "a sufficiently high dose of acyclovir" be used to prevent the emergence of antiviral resistance [7].

Most mutations conferring ACV resistance occur in the viral thymidine kinase, rendering conventional dosing regimens of ACV and its analogs ineffective [8]. These viruses are typically sensitive to treatment with foscarnet (FOS) and cidofovir (CID); however, these drugs share substantial potential for nephrotoxicity, and resistance to FOS can develop quickly after relatively short periods of use [9,10].

We describe here a series of allogeneic HCT recipients with ACV-resistant HSV infection after HCT who failed treatment with 1 or more conventional antiviral therapies but responded to the administration of high-dose continuous infusion of ACV. All patients received antiviral prophylaxis with oral ACV 400 mg by mouth twice daily for at least 100 days after transplantation.

CLINICAL CASES

Case 1

Nine months following a T cell-depleted bone marrow transplant from an unrelated donor (URD) for acute myelogenous leukemia (AML) complicated by acute graft-versus-host disease (aGVHD) of the skin and gastrointestinal tract, a 37-year-old woman was admitted with high fever and a month-long history of severe genital ulcerations positive for HSV-2 by direct fluorescent antibody testing (DFA) and culture, which had progressed despite 400 mg of oral ACV 5 times per day, oral famciclovir, and 5 mg/kg intravenous (i.v.) ACV 3 times daily over a 1-month period. A plaque reduction assay (Viromed, Minnetonka, MN) indicated that the HSV-2 isolate was resistant to ACV and ganciclovir (GCV) but susceptible to FOS (see Table 1 and Figure 1). Replacing ACV with FOS resulted in a worsening of ulcerations and severe neutropenia, prompting discontinuation of FOS. After 5 doses of CID 5 mg/kg per week,

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Table 1. Summary of Case Reports

Case	Age, Sex	HCT Type*	GVHD	Immunosuppression		HSV Type; Location	MIC$_{50}$ (μg/mL)†			Failed Treatment Regimens‡	Cont. ACV Dose mg/kg/day	Outcome, Time to Response
				PRED	Other		ACV	GCV	FOS			
1	37 F	TCD URD MA	Skin, GI Grade 2	<0.5 mg/kg/day	CsA	HSV-2; Genitalia Naris	10	30	22	ACV PO FAM PO ACV IV FOS i.v. CID i.v.	30	Resolved 6 weeks
2	47 F	URD MA	Skin Grade 4	<0.5-2 mg/kg/day	TAC MMF	HSV-2; Genitalia, buttocks, thighs	>48	45	>200	ACV i.v. FOS i.v.	45	Resolved 2 months
3	55 F	URD MA	Skin Grade 2	50 mg/day	TAC MMF	HSV-1; OP	>48	30	>48	ACV i.v. FOS i.v.	30	Resolved 1 week
4	44 F	URD MA	Skin Grade 4	60 mg/day	TAC	HSV-1; OP	>48	30-50	>48	ACV i.v. FAM PO	30-50	Partially resolved§
5	54 M	MRD MA	None	None	CSA ATG	HSV-1; Naris	>48	30	>100	ACV PO FAM PO	30	Resolved 1 week
6	52 M	MRD NMA	Skin Grade 4	1 mg/kg/day	TAC	HSV-1; OP	48	48	100	ACV i.v.	30	Resolved 1 week

HCT indicates hematopoietic cell transplant; GVHD, graft-versus-host disease; PRED, prednisone (oral); HSV, herpes simplex virus; MIC, minimum inhibitory concentration; ACV, acyclovir; GCV, ganciclovir; FOS, foscarnet; CID, cidofovir; FAM, famciclovir; Cont., continuous; TCD, T cell depleted; URD, matched unrelated donor; MA, myeloablative; MRD, matched related donor; GI, gastrointestinal; CsA, cyclosporine; TAC, tacrolimus; MMF, mycophenolate mofetil; ATG, antithymocyte globulin, OP, oropharynx.

*All patients received allogeneic transplants and HSV prophylaxis with oral ACV 400 mg twice daily.

†For case 1, resistance testing performed by plaque reduction assay (Viromed, MN). For all other cases, resistance testing performed clinical isolates via dye uptake method by Focus Diagnostics (Cypress, CA). Breakpoints for resistance testing are 3 μg/mL for ACV and GCV and 100 μg/mL for FOS.

‡Dose ranges: ACV 400 mg by mouth 5 times daily to 10 mg/kg i.v. every 8 hours; CID 5 mg/kg weekly; FOS 40-50 mg/kg; FAM 1-3 g by mouth daily (in divided doses).

§Patient expired prior to resolution of lesions.