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Delay of Alternative Antiviral Therapy and Poor Outcomes of Acyclovir-Resistant Herpes Simplex Virus Infections in Recipients of Allogeneic Stem Cell Transplant

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Abstract

Acyclovir is commonly used to prevent and treat herpes simplex virus (HSV) reactivation after hematopoietic cell transplant (HCT), and only few reports have been published on acyclovir-resistant HSV in HCT recipients. We reviewed the medical records of patients with a microbiologic diagnosis of acyclovir-resistant HSV by plaque reduction test who received an HCT from 2002 through 2014. A total of 4028 HCTs were performed during the study period, and 18 of the recipients met the diagnostic criteria for acyclovir-resistant HSV. All cases had undergone allogeneic HCTs. Most patients were in the pre-engraftment period or on systemic corticosteroid therapy for graft-versus-host disease (GVHD). The median time between diagnosis and susceptibility testing was 15 days, and antiviral therapy was changed at a median of 27 days. Patients required prolonged therapy (~ 80 days), and many had serious complications including renal failure and hospitalization. In conclusion, acyclovir-resistant HSV infection is more likely during the period of profound deficit in T-cell–mediated immunity and is associated with

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significant morbidities. Higher doses of acyclovir prophylaxis might be needed for patients with history of HSV during pre-engraftment or GVHD treatment. In patients who do not respond or progress after 1-week of acyclovir therapy, testing for drug-resistant HSV and early switch to an alternative antiviral should be considered.

Keywords

HSV infection; acyclovir-resistance; stem cell transplant

Background

Hematopoietic cell transplant (HCT) is used to treat a wide range of hematologic malignancies and some non-malignant conditions [1]. The conditioning regimen usually ablates the recipient's humoral and cellular immunity, which is recovered slowly as the recipient's marrow is repopulated with donor cells [2]. Owing to this weak cellular immunity, viral infections, including those caused by herpes simplex virus (HSV), are common after HCT.

In an earlier era, over 70% of HCT recipients experienced HSV reactivation, and the use of acyclovir prophylaxis has brought that rate down to 12% [3, 4]. However, there is concern that the widespread use of acyclovir prophylaxis, especially at low doses, may promote the emergence of acyclovir-resistant HSV infection [5, 6]. In contrast with the general population, in whom the incidence of acyclovir-resistant HSV cases is 0.5%–6% [7, 8], the reported incidence of acyclovir-resistant HSV infections in HCT recipients ranges from 7% to as high as 36%, [9–13] [14].

Herein, we reviewed all cases of microbiologically confirmed acyclovir-resistant HSV infections in HCT recipients cared for at our center and identified patterns in infection course, treatment strategies, and outcomes that could help in management of these resistant infections.

Study design

We identified all HCT recipients with microbiologically confirmed acyclovir-resistant HSV treated at our institution January 2002 through December 2014. The Institutional Review Board at our institution approved this study and a waiver of informed consent.

For patients undergoing HCT at our institution and independently of varicella zoster or herpes virus serostatus, prophylaxis is administered in the form of 500 mg of oral valacyclovir daily, [15, 16] starting at day −1 before transplant (or the intravenous equivalent of 5 mg/kg every 12 or 24 hours, if oral intake was limited because of mucositis), and until 6 months after transplant or until the patient was off all significant immunosuppression. For those patients with history of HSV or VZV reactivation, valacyclovir was given at 500 mg oral twice a day for prophylaxis. These recommendations are specific to our institution and may not be standard practice in others.

Acyclovir-resistant HSV infections were defined by the development of ulcerated or vesicular lesions clinically consistent with HSV infection with cultures positive for HSV and confirmed acyclovir-resistant HSV isolate on phenotypic analysis. Antiviral susceptibility testing was done by plaque reduction test (ARUP Laboratories, Salt Lake City, UT). [17, 18]. In brief, after media aspiration, 0.2 mL of virus was added to each of the three wells at a concentration that would produce 20–30 plaques per well. The virus was absorbed for 1 hour while the plates were rocked every 15 minutes to evenly distribute the media. Antiviral drugs were diluted in minimal essential medium (MEM) with Earle's salts supplemented with 2% fetal bovine serum, l-glutamine, penicillin, gentamicin, and 0.01% gamma globulin (GAMMAGARD). Antivirals were added to plates in duplicate in concentrations of 300–0.1 μM. Cells were stained with 1% crystal violet in 20% methanol. Plaques were counted using a stereomicroscope, and the concentration of the antiviral drug that reduced plaque formation by 50% (IC50) was interpolated from the experimental data using a modified version of the software MacSynergy II. [17] IC50 values for testing on the resistant strain PAAr5 and the susceptible strain HSV-F have been published previously by the Clinical Laboratory Standards Institute. [18]

Data collected included demographic data, transplant data, conditioning regimen, corticosteroid use, GVHD, and outcomes including 1-year survival. The first day of clinical manifestation of HSV infection was designated as the day when typical HSV lesions were identified. Clinical response to therapy was defined as total resolution or significant improvement of the HSV infection within 2 weeks of therapy.

Descriptive statistics were used to summarize patients' data. Continuous data were presented as medians and interquartile ranges (IQRs). Categorical data were presented as frequencies and percentages. In addition, a Kaplan-Meier overall survival curve was estimated for 1 year after HCT. All data analyses were performed using SAS version 9.3 (SAS Institute Inc.).

Results

Baseline patient characteristics

A total of 4028 allogeneic HCTs were performed at our center between 2002 through 2014, and among the recipients, the incidence of laboratory-confirmed acyclovir-resistant infections was 0.4% (18 patients). The median age at diagnosis was 47 years (range: 17–63 years). Antithymocyte globulin was part of the conditioning regimen in 14 cases (78%). Most patients had neutropenia and lymphocytopenia at the time of diagnosis. Clinical and demographic characteristics are summarized in Table 1.

Clinical Presentation of acyclovir resistant HSV

Twelve patients had oral/labial HSV infections identified as HSV1, and six patients had genital/perineal HSV infections identified as HSV2. The median time from transplant to the first episode of acyclovir-resistant HSV infection was bimodal, with early presentation at a median of 10.5 days (IQR: 1–31 days) and late presentation at a median of 89.5 days (IQR: 41–735 days) (Table 2). Seventeen of the 18 patients were on valacyclovir or parenteral

acyclovir for prophylaxis before diagnosis. The median duration of previous acyclovir exposure was 12 months (range: 2–28 months).

Nine cases of acyclovir-resistant HSV infection (50%) occurred pre-engraftment, seven had a diagnosis of GvHD requiring systemic corticosteroids at least 1 month before diagnosis of the acyclovir-resistant HSV infection, and the remaining Two patients received a cord blood transplantation and anti-thymocyte globulin (ATG). Acute GVHD was classified as grade 1 in two patients, grade 2 in three patients, and grade 3–4 in four patients. The sites of GvHD included the skin in 8 (66%) patients, gastrointestinal tract in 5 (42%) patients, liver in 1 (8%) patient, and eyes in 3 (25%) patients, with 5 patients having more than one site involved. One-third of the patients had their steroid doses tapered after the diagnosis of HSV infections.

Susceptibility testing

Acyclovir resistance was suspected and susceptibility analyses ordered at a median of 15 days after HSV infection was clinically diagnosed (IQR: 0–96 days). The median IC50 for all isolates was 39 μg/mL (IQR: 6–48 μg/mL). Importantly, four patients had acyclovir-susceptible HSV infections within 3 months before acyclovir-resistant isolates were identified. For the 12 foscarnet-susceptible isolates, the median IC50 was 62 μg/mL (IQR: 12–100 μg/mL). Six patients displayed foscarnet resistance, with an MIC (minimum inhibitory concentration) of >200 μg/mL, and these patients had been exposed to foscarnet within the previous month.

Management and outcomes

Five (28%) patients had a clinical response within two weeks of therapy, and 13 (72%) patients had slow or no clinical responses at 2 weeks (i.e., had no clinical improvement and/or had new lesions).

The management of acyclovir-resistant HSV with antiviral therapy was complex and is summarized in Table 2. All patients were initially treated with high-dose oral valacyclovir (1000 mg every 8 hours) or intravenous acyclovir (5–10 mg/kg every 8 hours) without a response and then were transitioned to foscarnet and/or cidofovir (topical or intravenous). The mean time to transition of antiviral therapy was 27 days (IQR: 10–70 days) in both groups but 9 days (IQR: 2–46) in the rapid responders, in contrast to 28 days (IQR: 7–96) in the slow and non-responders (p=0.15). Treatment with antiviral therapy was prolonged, reaching a median of 80 days in patients with good clinical responses and 100 days in patients with poor clinical responses. Combination antiviral strategies were used in most patients (n=12) and included intravenous foscarnet combined with topical therapy (either cidofovir 1% once daily or imiquimod) in five patients, intravenous foscarnet with topical acyclovir in two patients, and parenteral and topical cidofovir in two patients. The duration of topical cidofovir varied between patients and ranged between 5 and 58 days with close follow-up of their renal function. Because of the common use of various combination strategies, we were unable to determine whether there was a difference in outcomes by treatment strategy. Recurrent HSV infection occurred in four patients (22%), all of whom

had foscarnet-resistant HSV infection, an underlying diagnosis of GvHD, and were treated with parenteral or topical cidofovir therapy.

Of the whole cohort, nine patients (50%) died within 1 year after HSV infection, and none of those nine had clinical responses. Causes of death included bacterial infections (n=4), heart failure (n=1), graft failure with diffuse alveolar hemorrhage (n=1), unknown causes (n=2), and HSV hepatitis with disseminated infection (n=1).

Adverse events

Complications derived from acyclovir-resistant HSV infection and its treatment included hospitalization in nine (50%) patients, acute kidney injury secondary to antivirals in nine (50%) patients, and hemodialysis subsequent to kidney injury in four (22%) patients.

Other infections

Cytomegalovirus reactivation was documented in eight patients (40%), and two of them had end-organ disease. Hemorrhagic cystitis due to BK virus occurred in five patients (28%).

Discussion

This study is one of the largest case series to date of acyclovir-resistant HSV infections after HCT. All the cases were among allogeneic HCT recipients. The pattern of these infections was bimodal: most occurred either in the pre-engraftment period, when mucosal damage is maximal as a consequence of chemotherapy and/or radiotherapy from the conditioning regimen; or in patients with GvHD on steroid treatment, most of whom received ATG as part of conditioning. In addition, the incidence of acyclovir-resistant HSV infection reported in our cohort was much lower than previously reported in other HCT studies [6, 9, 19, 20]. However, we note that acyclovir resistance can be underdiagnosed in our cohort; as only patients with a high index of suspicion for resistance and whom the provider chose to test had specimens tested for resistance.

Most of these infections occurred during the use of acyclovir or valacyclovir as prophylaxis against HSV. Timely resistance testing and prompt change of antiviral therapy was more common in patients with good clinical responses, although not statistically significantly more common, likely owing to our small numbers. There was one death related to resistant HSV infection in a patient with disseminated HSV infection and hepatitis. Complications associated with the need for prolonged antiviral therapy, including hospitalization and renal failure, were common, which parallels recent data from Japan showing an association between acyclovir-resistant HSV and poor prognosis in patients after stem cell transplant (14).

Delayed clearance of HSV from mucocutaneous lesions, taking weeks rather than days owing to lack of T-cell–mediated immunity (i.e. secondary to ATG [21] and/or steroids use [22]), may lead to large areas of involved tissues with persistent replication under the selective pressure of low doses of acyclovir, selecting for acyclovir-resistant strains [23, 24]. Several lines of evidence highlight the importance of cell-mediated immunity (CD4+ and CD8+ T cells) in providing protection from HSV reactivation as well as healing of

established lesions,[25] and studies in haploidentical transplant recipients have correlated healing of HSV lesions with recovery of CD4+ and CD8+ T cells. [11] Different phenotypes of thymidine kinase (TK) and DNA polymerase mutations have been described as conferring acyclovir resistance [26]. The most common phenotype is absent or deficient TK in the HSV strain [26–28], probably selected by the prolonged use of low dose acyclovir, as seen in our patients who received prophylaxis with acyclovir or valacyclovir for a median of 12 months before the diagnosis of acyclovir-resistant infection. Although we did not perform genotypic testing (i.e., polymerase chain reaction and sequence analysis), dual resistance to foscarnet and acyclovir was seen in six of our patients, probably owing to the simultaneous occurrence of mutations in the *pol* genes [29] and HSV TK, and all of those patients had been exposed to foscarnet within the month prior to HSV infection. Moreover, in our cohort, few patients responded to either intravenous foscarnet or high-dose intravenous acyclovir despite having isolates that were phenotypically resistant to either antiviral therapy. This observation was reported previously with higher doses of acyclovir and may be explained by the mixed population of wild-type and mutant HSV isolates [28, 30, 31].

Valacyclovir which is the l-valyl ester of acyclovir, has a bioavailability of >50%, which is three to five times greater than acyclovir [15]. Valacyclovir oral dose of 500 mg daily have been effective in preventing recurrent oral and genital herpes infections [32]. However, in HCT recipients, drug-resistant HSV infections have been reported with low doses of antiviral prophylaxis [11], such as seen in our cohort of patients.

Various strategies have been proposed to reduce the incidence of HSV reactivation and resistant HSV infections [23] [30]. Erard *et al.* assessed HCT recipients with resistant HSV after acyclovir prophylaxis for 30 days, 1 year, and >1 year after HCT and found that the rate of resistant HSV was lower in those who received long-term prophylaxis (>1 year) with higher doses of acyclovir than in those who received shorter prophylaxis or lower doses [23]. This difference could be explained by the fact that the use of a lower dose may be insufficient to inhibit HSV replication in some patients, leading to selection of acyclovir-resistant isolates. A prospective trial comparing high-dose acyclovir prophylaxis or the equivalent dose of valacyclovir to the regular dose in HCT recipients in the pre-engraftment period, with mucositis, or on high-dose steroids would be worth exploring. Furthermore, new therapeutic agents for drug-resistant HSV are in development, including ASP2151 (amenamevir) and monoclonal antibodies, which will need to be evaluated in transplant recipients [33, 34].

Some of the limitations of our study are the small sample size and its lack of controls, which preclude a multivariate analysis of risk factors. In addition, we included only patients who had their HSV isolates tested for resistance; therefore, we could not accurately determine the true incidence of acyclovir-resistant infection in this population. Lastly, genotypic analysis of different mutations in the TK and DNA polymerase genes conferring resistance to acyclovir and foscarnet were not obtained. Such test would be less subject to interpretation bias and reproducibility than phenotypic analysis and may correlate better with response to therapy.

In summary, patients with breakthrough HSV infections with acyclovir-resistant strains after HCT may have extensive and severe mucocutaneous disease that requires prolonged therapy. In HCT recipients, persistent HSV lesions that do not respond to or that progress after 1 week of acyclovir therapy, especially during the pre-engraftment period and during treatment with systemic corticosteroids, should be managed aggressively with a low threshold of early resistance testing. A switch to an alternative antiviral therapy must be considered if there is a lack of improvement or if new lesions occur after a week of therapy. Future directions in the management of acyclovir-resistant HSV infection should include the widespread use of genotypic assays, including next-generation sequencing, which will provide more complete information on mechanisms of resistance in a manner readily applicable at bedside.

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Table 1

Demographics and Clinical Characteristics of 18 Patients with Acyclovir-Resistant HSV Infections

Characteristic	Total patients N=18	Clinical response N=5	No response N=13
Median age, years (range)	47 (17–73)	46 (17–64)	47 (23–73)
Male, no. (%)	10 (56)	3 (60)	7(54)
Race/ethnicity, no. (%)			
White	13 (72)	2(40)	11(85)
African American	1 (6)	0	1 (8)
Hispanic	3 (17)	2(40)	1 (8)
Middle Eastern	1 (6)	1(20)	0
Underlying hematologic condition, no. (%)			
Acute myeloid leukemia/myelodysplastic syndrome	7 (39)	1(20)	6 (46)
Hodgkin lymphoma	3 (17)	1(20)	2 (15)
Non-Hodgkin lymphoma	1 (6)	1(20)	0
Acute lymphocytic leukemia	4 (22)	2(40)	2 (15)
Chronic myeloid leukemia	3 (17)	0	3 (23)
Disease status at time of transplant, no. (%)			
Complete remission	10 (56)	4(80)	6 (46)
Partial remission or not in remission	8 (44)	1(20)	7 (54)
Type of transplant, no. (%)			
Matched related donor	5 (28)	1(20)	4 (31)
Matched unrelated donor	9 (50)	4(80)	5 (38)
Haploidentical	1 (6)	0	1 (8)
Cord blood	3 (17)	0	3 (23)
Conditioning regimen, no. (%)			
Myeloablative	9 (50)	2(40)	4 (31)
Reduced-intensity	8 (45)	2(40)	8 (62)
Nonmyeloablative	1 (6)	1(20)	1 (8)
Antithymocyte globulin	14 (78)	1(20)	13 (93)
Diagnosis of GvHD	12 (67)	2 (40)	10 (77)
Steroids at >20 mg within 8 weeks of HSV infection	10 (56)	3 (60)	7 (54)
Median ALC at time of HSV diagnosis (range) cells/mL	90 (0 – 5,470)	180 (0 –5,470)	60 (0–3,250)

HSV, Herpes virus infection. GVHD, Graft vs host disease. ALC, absolute lymphocyte count.

Table 2

Treatment Strategies Used for Acyclovir-Resistant HSV Infections

Time from HCT to HSV infection diagnosis (days)	Time from HCT to resistance (days)	Site of infection	Antiviral prophylaxis	Treatment	Total duration of antiviral therapy	Response to Therapy at 2 weeks	Treatment-related side effects
300	300	Anal	Oral valacyclovir prophylaxis [1]	Oral valacyclovir treatment[3] dose	80 days	Yes	None
9	49	Oral	Oral valacyclovir prophylaxis [1]	IV acyclovir treatment dose[4] for 21 days, followed by some resolution then oral valacyclovir, followed by IV foscarnet treatment dose[5] for 40 days + topical cidofovir[7] for 58 days	119 days ** (adjusted for renal function)	No	Renal failure
84	180	Anal	Oral valacyclovir prophylaxis [1]	Oral valacyclovir treatment[3] dose for 10 days, followed by IV foscarnet for 60 days treatment[5] and maintenance for 40 days[6*]+ topical cidofovir[7] for 40 days.	150 days ** (adjusted for renal function)	No	Renal failure, dialysis, need for hospitalization
94	110	Oral	Oral valacyclovir prophylaxis [1]	Oral valacyclovir treatment[3] for 40 days, then IV foscarnet treatment[5] for 20 days, followed by IV cidofovir x1[8]	60 days (adjusted for renal function)	Yes	None
46	52	Anal	Oral valacyclovir prophylaxis [1]	Oral valacyclovir treatment[3] dose for 10 days, followed by IV foscarnet treatment[5] for 60 days	70 days ** (adjusted for renal function)	No** * (no response at 2 weeks of therapy, eventual response)	Renal failure, hospitalization
1	58	Genital	Oral valacyclovir prophylaxis [1]	IV acyclovir[4] for 14 days, followed by oral valacyclovir treatment[3] dose with exacerbation for 30 days, followed by IV foscarnet treatment[5] for 50 days with topical acyclovir	94 days ** (adjusted for renal function)	No	Renal failure, dialysis, hospitalization
7	89	Oral	Oral valacyclovir prophylaxis [1]	IV acyclovir treatment[4] for 28 days, followed by IV foscarnet treatment[5] for 18 days	46 days	Yes	None

Time from HCT to HSV infection diagnosis (days)	Time from HCT to resistance (days)	Site of infection	Antiviral prophylaxis	Treatment	Total duration of antiviral therapy	Response to Therapy at 2 weeks	Treatment-related side effects
224	27	Oral	Oral valacyclovir prophylaxis [1]	Oral valacyclovir treatment[3] dose 10 days, then IV acyclovir treatment[4] for 14 days, followed by IV foscarnet treatment[5*] 20 days, foscarnet maintenance [*] 10 days, plus topical cidofovir[7]/ imiquimod for 8 days	62 days ** (adjusted for renal function)	No	Renal failure, hospitalization
4	85	Anal, hepatitis	Oral valacyclovir prophylaxis [1]	Oral valacyclovir treatment[3] dose for 18 days with topical cidofovir[7] for 5 days	18 days	Yes	None
16	44	Oral and genital HSV pneumonitis	Oral valacyclovir prophylaxis [1]	Oral valacyclovir treatment[3] dose for 28 days, followed by IV acyclovir treatment[4] for 8 days, followed by IV foscarnet treatment/ maintenance[5*] for 50 days +topical cidofovir[7] /imiquimod 42 day.	128 days** (adjusted for renal function)	No	Renal failure
85	17	Oral	Oral valacyclovir prophylaxis [1]	IV acyclovir treatment[4] for 4 days, followed by IV foscarnet treatment[5] for 4 days	8 days	No	Hospitalization
18	90	Oral	IV Acyclovir prophylaxis [2]	Oral valacyclovir treatment[3] for 8 days, then IV acyclovir treatment[4] for 15 days, then IV foscarnet treatment[5*] for 60 days, then IV cidofovir x1[8]	84 days ** (adjusted for renal function)	No** [*] (no response at 2 weeks of therapy, eventual response)	Renal failure
14	19	Oral	IV Acyclovir prophylaxis [2]	IV acyclovir treatment[4] for 40 days, then foscarnet treatment[5] for 30 days, then IV cidofovir (once a week for 33 days) plus topical cidofovir[7]	103 days ** (adjusted for renal function)	No** [*] (no response at 2 weeks of therapy, eventual response)	Renal failure
31	44	Oral	Oral valacyclovir prophylaxis [1]	Oral valacyclovir treatment[3] dose for 14 days, then IV acyclovir for 7 days followed by foscarnet treamtent[5] for 10 days	31 days	Yes	None
5	17	Oral	IV Acyclovir prophylaxis [2]	Oral valacyclovir treatment[3] dose for 15 days, followed by IV	49 days	No	None

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Time from HCT to HSV infection diagnosis (days)	Time from HCT to resistance (days)	Site of infection	Antiviral prophylaxis	Treatment	Total duration of antiviral therapy	Response to Therapy at 2 weeks	Treatment-related side effects
				acyclovir treatment[4] for 5 days, then IV foscarnet treatment[5] for 25 days, then topical acyclovir for 40 days			
41	90	Genital/anal	IV Acyclovir prophylaxis [2]	IV acyclovir treatment[4] for 25 days, then IV foscarnet treatment[5] for 100 days, followed by topical cidofovir[7]/imiquimod on-off for 80 days	205 ** (adjusted for renal function)	No	Renal failure
735	741	Oral/cornea	Oral valacyclovir prophylaxis [1]	IV acyclovir treatment[4] 5 days, followed by IV foscarnet treatment[5] for 20 days then IV cidofovir for 600 days, plus topical cidofovir[7]	625 days ** (adjusted for renal function)	No*** (no response at 2 weeks of therapy, eventual response)	Renal failure
12	19	Oral/oropharyngeal Pneumonitis	Oral valacyclovir prophylaxis [1]	IV acyclovir treatment[4] for 14 days, then IV foscarnet treatment[5*] for 200 days, cidofovir IV on-off for 100 day +, cidofovir topical[7] for 60 days	321 days ** (adjusted for renal function)	No*** (no response at 2 weeks of therapy, eventual response)	Renal failure, dialysis, hospitalization

[1] Oral valacyclovir prophylaxis –used per internal standard of care practices. [15, 16]

[2] IV acyclovir prophylaxis used at 5mg/kg every 12 hours [35]

[3] Valcyclovir treatment dose used at 1 gram oral every 8 hours [15]

[4] IV acyclovir treatment dose used 5 to 10 mg /kg iv q 8 hours [35, 36]

[5] Foscarnet treatment dose used at 40 mg/kg/dose every 8 to 12 hours [37, 38]

[6] Foscarnet maintenance dose used at 90 mg/kg once daily- used on a patient with concomitant CMV infection

[7] Topical cidofovir dose used at 1% to 3% once daily [39]

[8] IV cidofovir dose used at 5mg/kg weekly[40, 41]

[*] Indicates received foscarnet for concomitant CMV therapy