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Acyclovir-resistant (ACV-R) herpes simplex virus (HSV) disease in patients with hematologic malignancy (HM) and hematopoietic-cell transplant (HCT) recipients

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Background

- Before routine prophylaxis, >70% of patients undergoing HCT had HSV outbreaks.[1]
- Acyclovir (ACV), the first treatment for HSV, became commercially available in 1983; yet ACV resistance was reported even before it became available.[1]
- Prevalence of ACV-R HSV is about 5% in immunocompromised patients and up to 30% in HCT recipients.[2]
- Treatment is difficult, particularly when it does not respond to high-dose ACV and typically requires therapy with foscarnet or cidofovir, both of which have significant toxicities.
- Some studies suggest HCT recipients with ACV-R HSV may have high mortality[3,4]
- We observed significant morbidity and mortality among HCT patients with ACV-R disease at our center and undertook this study to more carefully review ACV-R outcomes at our center.

Methods

- We retrospectively identified 19 adult HM patients and HCT recipients who developed symptomatic ACV-R HSV disease from 1/1/2006 to 3/1/2018.
- HCT recipients typically receive 1 year of ACV prophylaxis after HCT, or longer in those with graft-versus-host disease.
- Clinical, microbiological and treatment details were collected.

Cohort Characteristics (n = 19)

Baseline Characteristics	Patients N=19 (%)
Median Age, years [range]	50 [31-77]
Male sex	15 (79)
Heme Malignancy	4 (21)
CLL	3 (16)
NHL	1 (5)
Allogeneic HCT	15 (79)
Cord blood HCT	3 (16)
Median time from HCT, months	9.2 [1-60]

HSV Characteristics	Patients N=19(%)
Location of HSV	
Oral	13 (68)
Perineal	4 (21)
Oral and Perineal	1 (4)
Trunk	1 (4)
Virus Type	
HSV1*	16 (84)
HSV2*	4 (21)
Lab-confirmed resistance†	15 (79)

* One patient had concurrent confirmed resistant HSV-1 and HSV2 infection in two distinct anatomic locations
† Resistance confirmed by culture-based phenotypic resistance testing

Disclosures

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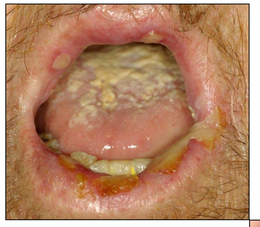
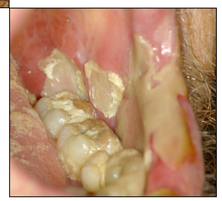
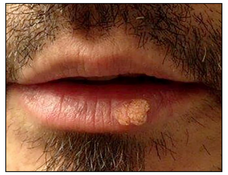


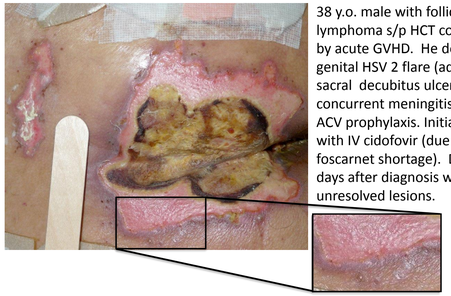
48 y.o. male s/p HCT with extensive chronic GVHD of the mouth, eyes, skin, and liver who developed oral HSV on prophylactic ACV. Treated with IV foscarnet without resolution of HSV

The patient died 44 days after diagnosis of ACV-R HSV from GVHD, GI bleeding and respiratory failure.





41 y.o. male with ALL s/p HCT with extensive chronic GVHD who developed a verrucous lip lesion on ACV prophylaxis. Lesion was excised and was pathologically identified as **herpes vegetans.** It recurred and was treated with topical cidofovir without resolution. It spread to involve buccal and palatal mucosa. He was treated IV foscarnet without resolution. Patient developed multiple coinfections and died 117 days after diagnosis with HSV.

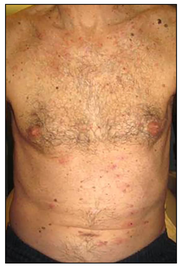


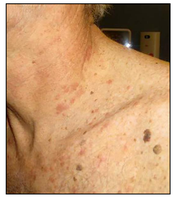
38 y.o. male with follicular lymphoma s/p HCT complicated by acute GVHD. He developed genital HSV 2 flare (adjacent to sacral decubitus ulcer) with concurrent meningitis while on ACV prophylaxis. Initially treated with IV cidofovir (due to foscarnet shortage). Died 94 days after diagnosis with unresolved lesions.

Comorbidities

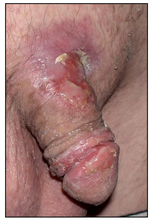
Comorbidity	Patients (%)
Graft-versus-host disease (N=15)	10 (67)
acute GVHD	3 (20)
chronic GVHD	7 (47)
Systemic Steroids (N=19)	12 (63)
Coinfection† (N=19)	10 (53)

† Including EBV viremia (2), bacteremia (3), thrush (2), skin and soft tissue infection (2), norovirus (1), bacterial bronchitis (1),mycobacterial joint infection (1)





65 y.o. male with CLL treated with alemtuzumab developed HSV ulcers across his neck and chest while on ACV prophylaxis. Treated with foscarnet, and improved, but relapsed when he was switched to high-dose valacyclovir and was subsequently treated with oral brincidofovir.



51yo male with T-cell prolymphocytic leukemia s/p HCT. He developed genital HSV ulcers while on ACV prophylaxis. Treated with topical cidofovir then IV foscarnet with resolution of lesions. Died 382 days after diagnosis of HSV from PTLD.

Treatment and Toxicities

Characteristic	Episodes N=27 (%)
Primary therapy	
Foscarnet	20 (74)
Cidofovir	4 (15)
IV Acyclovir	1 (4)
High dose oral valacyclovir	2 (7)
Lesion healed	23 (85)
Median time to healing, days [range]	36 [10-88]
Toxicities of treatment	
Acute kidney injury attributed to foscarnet	4 (15)
Nephrogenic diabetes Insipidus	1 (4)

Outcomes and Mortality

- 19 patients experienced 27 episodes of ACV-R HSV in this cohort (1 patient with 6 recurrences, 2 patients with 1 recurrence each).
- 14 (74%) survived 21 episodes; Median time to resolution per episode was 36 days (range, 10-88) after treatment started
- 5 patients (26%) died before resolution of ACV-R HSV, a median of 81 days (range, 23-117) after starting treatment
- 7 patients with resolution of ACV-R HSV subsequently died, a median of 139 days (range, 27-382) after treatment started
- Among HCT recipients 5 of 15 (33%) died within 12 weeks of diagnosis

Conclusion

ACV-R HSV disease is an uncommon complication of HM and allogeneic HCT. While ACV-resistant HSV did not cause death in this cohort, death within 12 weeks of infection was common.

References

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