Acyclovir-resistant herpes simplex virus pneumonia post-unrelated stem cell transplantation: A word of caution


Abstract: HSV causes serious complications in immunocompromised patients, especially SCT recipients. Although ACV is an effective antiviral prophylaxis, the emergence of ACV resistance is a growing problem. The authors describe two cases of fatal ACV-resistant HSV in two pediatric patients following unrelated donor SCT. Despite the in vitro sensitivity of the HSV isolates to foscarnet, both patients failed to respond to foscarnet therapy. Other antiviral therapies should be considered in those patients who fail to show rapid clinical improvement.

SCT is an established therapeutic modality that may be life-saving. HSV infection is one of the most common viral infections following SCT. HSV reactivates in 70-80% of SCT patients who are seropositive and who had not received ACV prophylaxis (1). Most infections involve the oral cavity and can lead to decreased oral intake and severe pain (2). Prior to ACV prophylaxis, HSV accounted for 5% of pneumonia post-transplant and some were fatal (3). ACV prophylaxis is considered the standard of care for seropositive patients and is capable of reducing HSV reactivation in more than 90% of the patients (2). We report on two patients who developed ACV-resistant HSV with subsequent fatal pneumonia.

Case report

Case 1

An eight-yr-old with ALL in third complete remission underwent a second matched unrelated donor SCT using reduced intensity preparative regimen with intravenous busulfan (0.8 mg/kg/dose for eight doses), fludarabine (30 mg/m²/dose for six doses) and thymoglobulin (2.5 mg/kg/dose for four doses). GVHD prophylaxis was with cyclosporine and mycophenolate mofetil. Grade 2 acute GVHD was diagnosed on day +20 and she was started on 2 mg/kg/day of steroids. She was seropositive for HSV prior to the first SCT a year earlier and had continued on ACV prophylaxis at a dose of 600 mg/m²/dose orally every 12 h or 250 mg/m²/dose intravenously every 12 h when she was not able to tolerate oral medications. On day +10, she developed an oral lesion suspicious for HSV and subsequently ACV dosing was increased from prophylactic twice a day dosing to treatment dosing, 250 mg/m²/dose intravenously every eight h. A viral culture done on day +10 was positive for HSY type I. As a result of the progression of the lesion, therapy was changed to foscarnet 60 mg/kg/dose intravenously every 12 h four days later. Sensitivity testing by plaque reduction assays showed that the HSV isolate to be resistance to ACV and sensitive to foscarnet. Despite in vitro sensitivity to foscarnet, the lesions spread and
involved the eyes and the entire mouth. The dose of foscarnet was increased to 90 mg/kg/dose without clinical response. The patient developed pneumonia and respiratory failure requiring mechanical ventilation on day +50 post-transplant. A bronchoalveolar lavage was positive for HSV. All other infectious workup was negative. Despite aggressive supportive care, the patient died day +110 post-transplant of respiratory failure. An autopsy of the lungs revealed extensive involvement of the lung with HSV (Fig. 1).

Case 2
A 16-yr-old girl with a diagnosis of severe aplastic anemia with prior history of one episode of HSV mouth lesion treated successfully with oral valacyclovir for seven days with complete resolution of the lesions two months prior to transplant. She underwent an unrelated cord blood transplant which was mismatched at HLA A and B with total nucleated cell dose of 3.7 x 10^9/kg. Conditioning regimen was intravenous busulfan (0.8 mg/kg/dose x 16 doses), cyclophosphamide (50 mg/kg/dose x four doses) and ATG (30 mg/kg/dose x three doses). GVHD prophylaxis was tacrolimus and mycophenolate mofetil. Hyper-acute GVHD developed at day +11 and she was started on 2 mg/kg/day of steroids. She had neutrophil engraftment at day +15 post-transplant. On day +16 post-transplant, she developed a blister on the lip that was HSV type I positive by culture while on ACV prophylaxis of 250 mg/m²/dose intravenously every 12 h. Despite changing the ACV dose to treatment doses, the lesions progressed and she was empirically changed to foscarnet 60 mg/kg/dose intravenously every 12 h. HSV sensitivities were obtained by plaque reduction assays found to be resistant to ACV and sensitive to foscarnet. The patient developed high fever and cytopenia. All infectious workup was negative except for blood that was positive for HSV by qualitative PCR. The lesions spread to the nose, face and oropharynx. The patient required endotracheal intubation for airway management. Despite continued therapy with foscarnet, she had progressive cytopenia (despite full donor chimerism in the bone marrow) and pneumonia. A bronchoalveolar lavage was positive for HSV. The patient died on day +70 post-transplant of respiratory failure. An autopsy of her lungs revealed extensive pneumonia with HSV recovered from the lung tissue by PCR.

Discussion
Prior to ACV prophylaxis lung tissue submitted for post-mortem virus isolation, HSV pneumonitis was diagnosed in 16 of 183 samples for SCT recipients (none had a premortem diagnosis) (3). With the use of ACV prophylaxis post-SCT, the incidence of viral shedding ranges from 0.9% to 2.5% of the patients (2, 4). Among those shedding HSV, only 11% were ACV resistant and all those patients received allogeneic transplants and were on ACV prophylaxis (4). ACV-resistant HSV has been associated with significant morbidity and mortality in SCT patients (5–7). In a recent study, factors associated with development of ACV-resistant HSV include recipients of allogeneic donor SCT and presence of acute GVHD (6). Both of our

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**Fig. 1.** (a) Low-power H&E photomicrograph of lungs showing classic changes of intra-alveolar hemorrhage, type II pneumocytes hyperplasia with fibrin within alveolar spaces consistent with an organizing pneumonia (original magnification 200x). (b) High-power magnification of an immunohistochemical stain against herpes simplex virus type I with a large cytoplasmic herpetic inclusion decorated with brown counter stain (original magnification 400x).
patients had unrelated donor SCT and both patients were on steroid therapy for acute GVHD. Our second patient developed persistent viremia detected in the blood that was associated with severe cytopenia. Foscarnet remains the main salvage therapy for patients with ACV-resistant HSV and both of our patients failed to respond clinically to foscarnet therapy despite both isolates being sensitive to foscarnet. In both cases, the foscarnet dose was increased to 90 mg/kg/dose intravenously every 12 h without clinical response. Although there are few reports in the literature of ACV-resistant HSV post-transplant, most patients seem to respond to foscarnet and few patients died as a direct result of the HSV infection. Cidofovir is another potential therapy for patients with ACV- and foscarnet-resistant HSV, although it is associated with significant renal toxicity (7). None of our patients isolates were tested for cidofovir sensitivity. It is important for transplant physicians to monitor clinical response and to consider other therapies early including cidofovir or combination therapy once patients develop ACV-resistant HSV and fail to show improvement to prevent the development of pneumonitis.

References