



**2<sup>nd</sup>  
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# **Recommendations for HSV management in patients with leukemia**

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# MANAGEMENT OF HSV INFECTION AND DISEASE IN PATIENTS TREATED FOR LEUKEMIA

- Recommendations for patients with leukemia treated by chemotherapy alone or by high-dose conditioning followed by hematopoietic stem cell transplantation (HSCT)

# EPIDEMIOLOGY OF HSV INFECTION AND DISEASE IN PATIENTS WITH LEUKEMIA

- Up to 80% of adult patients with leukemia are HSV seropositive (II).
- HSV infection in patients with leukemia results in most cases from reactivation of latent virus, whereas primary infection is unusual (II).
- Both HSV types 1 and 2 are a common cause of HSV disease (HSV type 1 more frequent)(II).

# EPIDEMIOLOGY OF HSV INFECTION AND DISEASE IN PATIENTS WITH LEUKEMIA

- The incidence of HSV infection among HSV seropositive patients receiving chemotherapy for acute leukemia was 61% and 66%, respectively, in two large series (I).
- The incidence of HSV infection among HSV seropositive HSCT recipients is about 80% (II).
- The majority of HSV infection occur during the first 4 weeks after HSCT (II).

# CLINICAL MANIFESTATIONS OF HSV DISEASE IN PATIENTS WITH LEUKEMIA

- The most frequent clinical manifestations of HSV disease are mucocutaneous lesions.
- The sites of mucocutaneous HSV lesions are the oro-facial region in 85-90% of cases and the genital area in 10-15% (I).
- Esophageal HSV disease is present in about 10% of patients with upper gastro-intestinal symptoms (II).
- Uncommon HSV disease manifestations are pneumonia (2-3% of patients in the absence of prophylaxis), hepatitis, meningitis, encephalitis, and bone marrow suppression (III).

# MONITORING FOR AND DIAGNOSIS OF HSV INFECTION

- Patients with leukemia should be tested for HSV serology before induction chemotherapy or HSCT for risk stratification of HSV reactivation (BII).
- Serological results are not helpful in confirming the diagnosis of HSV reactivation during immunosuppressive treatment (DIII).
- Routine surveillance for HSV infection by culture or PCR during chemotherapy or after HSCT is not required (CIII).

# MONITORING FOR AND DIAGNOSIS OF HSV INFECTION

- Virus culture is one of the standard methods for detection of HSV in clinical specimens, and usually yields results within 48 hours of inoculation (III).
- Virus culture is required for testing of antiviral drug resistance (III).

# DIAGNOSIS OF HSV DISEASE

- The diagnosis of mucocutaneous HSV disease can often be made on clinical grounds and may be confirmed by appropriate diagnostic techniques (BIII).
- In the presence of severe mucositis following chemotherapy or irradiation, the diagnosis of oropharyngeal HSV disease is difficult and identification of virus by appropriate diagnostic techniques is required (BIII).
- HSV PCR in CSF is indicated in the diagnosis of HSV meningitis and encephalitis (AII).

# PREVENTION OF HSV DISEASE: HSV SERONEGATIVE PATIENTS

- Primary HSV infection in patients treated for leukemia is unusual, and antiviral drug prophylaxis is thus not recommended in HSV seronegative leukemic patients during chemotherapy or after HSCT (DIII).

# PREVENTION OF HSV DISEASE: HSV SEROPOSITIVE PATIENTS

- HSV seropositive patients undergoing allogeneic HSCT for acute leukemia should receive antiviral drug prophylaxis (AI).
- HSV seropositive patients treated for acute leukemia by chemotherapy alone should be considered for antiviral drug prophylaxis (BIII).
- Intravenous or oral acyclovir (AI), or oral valaciclovir (BIII) should be given prophylactically for 3-5 weeks after start of chemotherapy or after HSCT, and for longer periods of time in children treated for acute leukemia.

# PREVENTION OF HSV DISEASE: HSV SEROPOSITIVE PATIENTS

- The intravenous route is preferred in patients who develop chemotherapy- or irradiation-induced mucositis which impedes intake of oral medication (CIII).
- Allogeneic HSCT recipients who develop graft-versus-host disease or receive immunosuppressive treatment, including steroids, usually require a prolonged HSV prophylaxis (BII).

# PREVENTION OF HSV DISEASE: RECOMMENDED REGIMENS

- Acyclovir 250 mg/m<sup>2</sup> or 5 mg/kg q12h iv (AI)
- Acyclovir from 3x200 mg/d to 2x800 mg/d po (AI)
- Valaciclovir 2x500 mg/d po (AI)

# THERAPY OF HSV DISEASE

- Intravenous acyclovir remains the therapy of choice for severe mucocutaneous or visceral HSV disease (AI).
- Oral acyclovir, valaciclovir, or famciclovir may be considered as alternative for less serious manifestations of HSV disease (CIII).
- Firm recommendation for therapy of HSV pneumonia or HSV meningitis and encephalitis cannot be made since data on antiviral treatment of these conditions in leukemic patients are limited (CIII).

# THERAPY OF HSV DISEASE: RECOMMENDED REGIMENS

## Mucocutaneous or esophageal disease

- Acyclovir 250 mg/m<sup>2</sup> or 5 mg/kg q8h iv for 7-10 d (AI)
- Acyclovir from 5x200 mg/d to 5x400 mg/d po for 10 d (AI)
- Famciclovir 2x500 mg/d po for 10 d (BIII)
- Valaciclovir 2x 500 mg/d po for 10 d (BIII)

## Pneumonia, hepatitis, meningitis, encephalitis

- Acyclovir 500 mg/m<sup>2</sup> or 10 mg/kg q8h iv for 14-21 d (AIII)

# HSV RESISTANCE TO ANTIVIRAL DRUGS

- The emergence of resistant HSV strains that cause disease unresponsive to antiviral drugs is reported with increasing frequency in patients with hematologic malignancy (III).
- Retrospective data of acyclovir prophylaxis after HSCT show a 2-year probability of acyclovir-resistant HSV disease of 1.3% with 30 days of acyclovir, of 0.2% with 1 year of acyclovir, and of 0% with acyclovir given for more than 1 year. Thus, the longer the duration of acyclovir prophylaxis the lower the probability of HSV resistant disease (II).

# HSV RESISTANCE TO ANTIVIRAL DRUGS

- The mechanism of resistance in the vast majority of clinical HSV strains isolated to date is a deficiency in viral thymidine kinase resulting in reduced activation of acyclovir in HSV-infected cells (III).
- Acyclovir-resistant HSV isolates are usually susceptible to antiviral agents, such as foscarnet and cidofovir, that do not require viral thymidine kinase for activation (III).
- In several cases, multidrug-resistant HSV strains causing disease have been documented (III).
- If HSV disease is unresponsive to antiviral therapy given at maximum dose, resistance testing should be performed (CIII).

# HSV RESISTANCE TO ANTIVIRAL DRUGS: ALTERNATIVE TREATMENT REGIMENS

## Resistance to acyclovir or famciclovir

- Foscarnet 60 mg/kg q12h iv or 40 mg/kg q8h iv for 7-21 d or until complete healing (BIII)
- Topical trifluridine 5% ophthalmic solution q8h\* (CIII)
- Topical cidofovir gel 0.3% or 1% once daily\* (CIII)

*\*For accessible cutaneous lesions*

# HSV RESISTANCE TO ANTIVIRAL DRUGS: ALTERNATIVE TREATMENT REGIMENS

## Resistance to foscarnet

- Cidofovir 5 mg/kg once a week for 2 weeks, then once every 2 weeks\* (BIII)
- Topical trifluridine 5% ophthalmic solution q8h<sup>†</sup> (CIII)
- Topical cidofovir gel 0.3% or 1% once daily<sup>†</sup> (CIII)

*\*Combined with probenecide and iv hydration*

*†For accessible cutaneous lesions*