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Antiviral prophylaxis: herpes simplex virus type 1, herpes simplex virus type 2, varicella zoster virus

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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ÖGHO Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie
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Antiviral prophylaxis: herpes simplex virus type 1, herpes simplex virus type 2, varicella zoster virus

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Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

Reactivation of viral disease is a major complication of antineoplastic therapy in patients (pat.) with solid tumors or hematologic malignancies. Human herpesviruses (herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus-6 (HHV-6)) and hepatitis viruses (hepatitis B, hepatitis C, hepatitis E) are relevant in this regard due to persistence or chronic infection. Incidence and severity of viral disease depends primarily on the degree of cellular immunosuppression. Targeted drug prophylaxis can be an effective strategy to prevent symptomatic viral reactivation.

The guideline "Management of herpesvirus reactivations in patients with solid tumors and hematologic malignancies" was developed by the Working Group on Infections of the DGHO (AGIHO) for the diagnosis, prophylaxis and therapy of these patients [1]. It is based on a systematic literature search, a uniform assessment of the strength of evidence, and a consensus-building process.

This is a summary of the most important recommendations for antiviral prophylaxis for patients in hematology and oncology who are not undergoing cellular therapy (autologous or allogeneic stem cell transplantation, CAR T-cell therapy) but are being treated with conventionally dosed chemotherapy or monoclonal antibodies or specific inhibitors. This version supplements and updates the current version [2]. Evidence criteria are presented in Onkopedia in the chapter "Infections in the outpatient cancer care ".

2 Background

Most clinical manifestations of viral diseases result from reactivation of latent infections. The risk of disease by reactivation increases with intensity and duration of T-cell suppression.

The most common pathogens are herpes simplex viruses (HSV-1 and HSV-2)), varicella zoster virus (VZV) and hepatitis B virus (HBV). Reactivation of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) plays a minor role outside of allogeneic stem cell transplantation.

However, the importance of viral infections of the respiratory tract has been increasingly recognized in recent years. These are mostly exogenously acquired primary infections. They are associated with an increased rate of secondary complications such as bacterial pneumonia with significant morbidity and mortality.

3 Pathogenesis

Human herpesviruses persist after primary infection throughout life. Reactivation can occur in the presence of immunosuppression or other trigger factors and lead to local or systemic disease.

Reactivation of HSV-1, HSV-2 and VZV is relatively common in patients with solid tumors or hematologic neoplasms or during therapy. A comparable risk exists for the reactivation of HBV in patients who have been infected before and show persistence of viral replication.

The risk of viral reactivation depends on the type of malignancy, tumor therapy, and individual factors such as age, comorbidity, comedication, remission status and prior therapy.

4 Clinical presentation

Reactivation of HSV-1, HSV-2 may be asymptomatic. Most symptomatic reactivations are herpes labialis, herpes stomatitis and herpes genitalis.

Reactivation of VZV usually results in the clinical picture of shingles (herpes zoster). Depending on the severity of immunosuppression, this can affect several dermatomes or may be disseminated.

HSV-1, HSV-2, and VZV reactivation during severe immunosuppression may be accompanied by organ manifestations associated with high morbidity and mortality. An overview is given in Table 1.

Table 1: Clinical presentation of reactivation of HSV-1, HSV-2, VZV.

	HSV-1	HSV-2	VZV
Reactivation	asymptomatic Herpes labialis Stomatitis[1] Herpes genitalis Esophagitis [1] Hepatitis [1] Colitis [1] Pneumonitis [1] Encephalitis Keratitis	asymptomatic Herpes genitalis Hepatitis [1] Meningitis Encephalitis	Herpes zoster Zoster sine herpete (visceral herpes zoster) Herpes zoster, disseminated [1] Hepatitis [1] Pancreatitis [1] Pneumonitis [1] Meningoencephalitis Cerebral vasculopathy Keratitis, uveitis, retinitis

Legend:
[1] in immunocompromised patients

5 Diagnostic tests

5.1 Diagnostic tests for herpes viruses

Serologic testing for HSV or VZV (HSV IgG or VZV IgG) can confirm a previous infection. Since the current seroprevalence in adults is about 90% due to high rates of primary infection in childhood (partly asymptomatic) antiviral prophylaxis is adequate for most patients in the given indication as protection against reactivation - even without prior serological testing.

There is no indication for regular screening with PCR for reactivation by HSV-1, HSV-2 or VZV.

6 Antiviral prophylaxis against reactivation of herpes viruses in patients with solid tumors and hematologic neoplasms (patients with stem cell transplantation and cellular therapy not included here)

The indications for antiviral pharmacological prophylaxis in patients with solid tumors and hematologic neoplasms are summarized in Figure 1 (regarding HSV-1 and HSV-2) and in Figure 2 (regarding VZV).

The strength of recommendation (SoR) and quality of evidence (QoE) is described in Table 2.

Recommendations for antiviral prophylaxis are based on the risk for symptomatic viral reactivations.

Although vaccination is available for the prevention of VZV reactivation (Shingrix®), the evidence is still insufficient to stop prophylaxis in patients at higher risk.

Aciclovir is commonly used and has been best studied for antiviral pharmacological prophylaxis. The dosages that have been used are inconsistent.

For prophylaxis of reactivations of HSV-1 and HSV-2 aciclovir is usually given at a dose of 400 mg orally twice daily.

For prophylaxis of VZV reactivation, dosages of 400 mg orally daily to thrice daily are used.

Evidence for valaciclovir from studies is limited; in clinical practice, it is used in doses of 250 mg or 500 mg orally twice daily for antiviral prophylaxis.

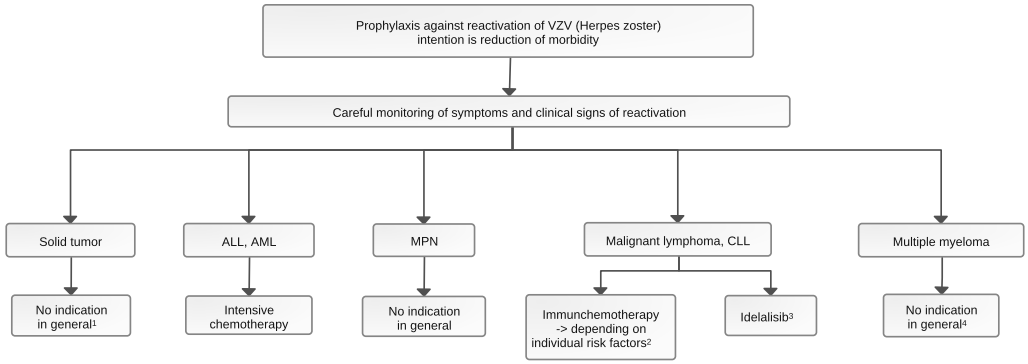
For both drugs, maximum doses must be calculated depending on renal function.

Table 2: Evidence for pharmacological prophylaxis against reactivation of HSV-1, HSV-2, and VZV.

Indication	Virus	SoR	QoE	Comment
Solid tumor	HSV-1, HSV-2	D	III	
Exception may be: head and neck tumor and radiochemotherapy	HSV-1, HSV-2	C	IIr	
Solid tumor	VZV	D	III	
Exception may be: prednisolone equivalent > 10 mg daily, for > 14 days	VZV	C	IIu	
AML, ALL; intensive chemotherapy	HSV-1, HSV-2 VZV	B B	I, IIr IIr	
MPN **MPN; ruxolitinib**	HSV-1, HSV-2 VZV	C B	IIu IIru	
Lymphoma, CLL; immunochemotherapy	HSV-1, HSV-2, VZV	B	IIu	individual risk assessment
Lymphoma, CLL; idelalisib	HSV-1, HSV-2, VZV	B	III	(Figure 1 and 2)
Lymphoma, CLL; BTK/BCL2 inhibitors	VZV	C	III	advanced therapy
Multiple Myeloma	HSV-1, HSV-2	*	*	
Multiple Myeloma; proteasome inhibitors	VZV	A	IIu	
Multiple Myeloma; lenalidomide, anti-CD38-Ab	VZV	C	IIt	

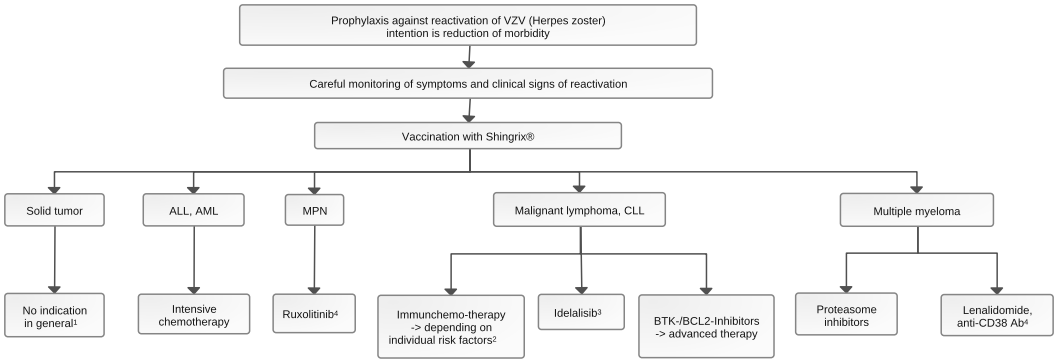
Legend:
** assessment difficult, as aciclovir has been used widely in patients treated with proteasome inhibitors as pharmacological prophylaxis against reactivation of VZV*

Figure 1: Indications for drug prophylaxis against HSV-1 and HSV-2 reactivation



Legend:
[1] exception may be: head and neck tumor treated with radiochemotherapy.
[2] risk factors: aged > 60 years, cumulative prednisolone equivalent > 2500 mg/m^2 BSA, > 1st line of therapy, therapy with bendamustine, maintenance therapy with anti-CD20 antibody, history of febrile neutropenia or HSV/VZV reactivation
[3] mandatory antiviral prophylaxis against CMV reactivation
[4] assessment difficult, as aciclovir has been used widely in patients treated with proteasome inhibitors as pharmacological prophylaxis against reactivation of VZV

Figure 2: Antiviral prophylaxis against reactivation of VZV (herpes zoster primarily)



Legend:
[1] exception may be: prednisolone equivalent > 10 mg daily for longer than 14 days.
[2] risk factors: aged > 60 years, cumulative prednisolone equivalent > 2500 mg/m^2 BSA, > 1st line of therapy, therapy with bendamustine, maintenance therapy with anti-CD20 antibody, history of febrile neutropenia or HSV/VZV reactivation
[3] mandatory antiviral prophylaxis against CMV reactivation.
[4] risk factors: ≥ 2nd line of therapy, prior treatment with steroids, history of VZV reactivation, CD4 count < 200/ul

9 References

1. Henze L, Buhl C, Sandherr M et al. (2022) Management of herpesvirus reactivations in patients with solid tumours and hematologic malignancies: update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO) on herpes simplex virus type 1, herpes simplex virus type 2, and varicella zoster virus. Ann Hematol 101(3): 491-511. DIO:10.1007/s00277-021-04746-y.
2. Sandherr M et al: Antiviral prophylaxis in patients with solid tumours and haematological malignancies - Update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Ann Hematol 2015 94(9): 1441-50. DOI:10.1007/s00277-015-2447-3.

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16 Disclosure of Potential Conflicts of Interest

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