

REVIEW

Vaccination for herpes zoster in patients with solid tumors: a position paper on the behalf of the Associazione Italiana di Oncologia Medica (AIOM)

P. Pedrazzoli^{1,2†}, A. Lasagna^{2*†}, I. Cassaniti^{3†}, A. Ferrari², F. Bergami³, N. Silvestris⁴, E. Sapuppo^{4,5}, M. Di Maio⁶, S. Cinieri⁷ & F. Baldanti^{3,8}

¹Department of Internal Medicine and Medical Therapy, University of Pavia, Pavia; ²Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia; ³Molecular Virology Unit, Department of Microbiology and Virology, Fondazione IRCCS Policlinico San Matteo, Pavia; ⁴Medical Oncology Unit, Department of Human Pathology "G. Barresi", University of Messina, Messina; ⁵School of Specialization in Medical Oncology, University of Messina; ⁶Department of Oncology, University of Turin, Division of Medical Oncology, Ordine Mauriziano Hospital, Turin; ⁷Medical Oncology Division and Breast Unit, Senatore Antonio Perrino Hospital, ASL Brindisi, Brindisi; ⁸Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy



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Herpes zoster (HZ) is the infectious reactivation of the varicella-zoster virus. HZ is more frequent in immunocompromised subjects, including patients with cancer. HZ complications can even last for years with a consequent delay in treatment of the underlying malignancy and with an unfavorable impact on quality of life. Nowadays, HZ is a vaccine-preventable disease: the recent approval of adjuvanted glycoprotein E-based recombinant zoster vaccine has changed preventive perspectives in immunocompromised subjects. Recombinant zoster vaccine induced both strong humoral and cellular immune responses also in immunocompromised patients. The question is, therefore, to which categories of cancer patients we should recommend HZ vaccination. Based on a careful review of the available data present in the literature, including recommendations and expert opinions, we report the position of the Associazione Italiana di Oncologia Medica on HZ vaccination in adult patients with solid tumors, thus providing clinical practice advice in a field where clear-cut information is missing.

Key words: herpes zoster, reactivation, cancer, RZV, vaccine

INTRODUCTION

Herpes zoster (HZ), known also as shingles, is the infectious reactivation of the varicella-zoster virus (VZV). Due to the wide range of clinical manifestations, delayed life complications, and long duration, HZ may be defined as a complex neurocutaneous disease. HZ is a potential cause of additional morbidity in subjects who are immunocompromised, such as patients with cancer, and cutaneous and visceral dissemination may lead to serious and life-threatening complications. Moreover, this condition is not infrequent. Indeed, the incidence of HZ in patients with solid tumors is ~15 cases per 1000 person-years and 30 cases in patients with hematological malignancies.¹⁻³ Finally, a controversial association between HZ and an increased cancer risk has also been postulated.⁴

Nowadays, HZ is a vaccine-preventable disease. The clinical and economic consequences of HZ in patients with cancer impose a greater awareness by the oncologist about the safety, efficacy, timing, and cost–benefit analysis of vaccinating patients with cancer on active therapy against HZ.

Vaccination might also prevent severe HZ complications and bacterial super-infections that might require a dose reduction and delays in treatment of the underlying cancer.

In this position paper, we will report:

- The epidemiology of HZ in patients with cancer and the risk of reactivation according to the different types of oncological treatments.
- The current and emerging evidence on the prevention of HZ by available vaccines.
- Associazione Italiana di Oncologia Medica (AIOM) recommendations.

*Correspondence to: Dr Angioletta Lasagna, Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Piazzale C. Golgi 19, 27100 Pavia, Italy. Tel: +39-0382502287; Fax: +39-0382501601
E-mail: a.lasagna@smatteo.pv.it (A. Lasagna).

[†]Equal contributions.

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MATERIALS AND METHODS

A web-based search of Medline/PubMed library data published from 2000 to December 2021 was carried out by associating 'Herpes Zoster' with 'cancer' OR 'chemotherapy' OR 'immunotherapy' OR 'radiotherapy' OR 'autologous

hematopoietic stem cell transplant' and 'adjuvanted recombinant vaccine'. The authors selected >100 papers. The references of each paper were reviewed to identify additional studies. Other than the authors, a panel of experts in the field of virology selected by the board of AIOM provided additional information which helped greatly in clarifying the biological and clinical issues on which clear-cut information was missing or available data were conflicting.

VZV AND HZ

VZV is a ubiquitous alphaherpesvirus with double-stranded DNA.^{5,6} Its primary infection causes varicella (chickenpox); after this phase, the virus is transferred in the latent form to ganglia nervous tissue (dorsal root ganglia, cranial nerve ganglia such as the trigeminal ganglia, and autonomic ganglia).⁶ During this latency phase, reactivation of the virus can sometimes arise, but it remains subclinical thanks to the immune system. In the case of diminished cell-mediated immunity, the virus reactivates in a clinically evident form, giving rise to a secondary infection known as HZ or shingles.⁷

Diagnosis of HZ is typically clinical with pain and pruritic unilateral and dermatomal rash, with impact on sleep quality and social activities. HZ presents a prodromal phase with mild general symptoms such as burning pains and/or sensory disturbances in the area from one to three adjoining dermatomes. Then skin erythema appears followed by peculiar grouped papules developing to vesicles.⁸

Clinical diagnosis can be confirmed by a laboratory test with the dosage of serum antibodies against VZV and the determination of VZV-DNA with the PCR technique.⁵ In particular, vesicular PCR is the most sensitive and specific test for diagnosing HZ, but it can only be used for patients with cutaneous lesions.⁹ Salivary VZV DNA testing is useful for diagnosing VZV infections without skin rash,^{9,10} but further larger studies are needed to evaluate the usefulness of salivary VZV DNA-specific PCR analysis as a routine diagnostic test.

Antiviral therapy

Antiviral therapy is recommended for patients with HZ, particularly for immunocompromised subjects, and/or those aged ≥ 50 years, and/or those with lesions involving the face or eye, severe rash, or other complications of HZ, with the optimal timepoint within 72 h after diagnosis.⁵

The duration of skin symptoms and pain can be reduced by oral guanosine analogues: acyclovir, famciclovir, and valacyclovir.¹¹ A meta-analysis of four double-blind, randomized, placebo-controlled trials of acyclovir (800 mg five times daily per os) has demonstrated acceleration of pain resolution.¹² Valacyclovir is the prodrug of acyclovir, and after oral uptake, it is converted into acyclovir. The dosage is 1000 mg three times per day, with a consequently better compliance.⁵ The dosage of famciclovir is 500 mg orally three times per day.⁵ Two randomized clinical trials have shown superiority of valacyclovir over

acyclovir considering the duration and severity of pain, but they have not shown any differences about the resolution of skin symptoms.^{13,14}

The main complication of HZ is postherpetic neuralgia (PHN): this is a chronic pain disorder caused by damaged nerve fibers in the affected nerve root due to necrosis and scarring from the viral infection.¹⁵ Chen and colleagues¹⁶ have reviewed all the randomized, controlled trials of antiviral treatment for preventing PHN. The authors have demonstrated that both acyclovir and famciclovir have not statistically significantly reduced the incidence of PHN when compared with placebo.¹⁶

Cidofovir or foscarnet should be used only in acyclovir-resistant cases.¹⁷ Resistant viruses are selected under antiviral drugs typically in immunodeficient patients with an impaired immune response.¹⁸ Clinicians should suspect resistant viral strains if there are no clinical improvements after a cycle of 10 (–21) days of antiviral medication (mostly acyclovir).¹⁹ Amenamevir is a drug of a novel class of antiviral agents, the helicase-primase (HP) inhibitors.²⁰ HP is involved in the initial phase of DNA synthesis and amenamevir is effective against acyclovir-resistant mutants.²¹ A randomized, controlled, double-blind study has demonstrated non-inferior efficacy of amenamevir (400 mg once daily for 7 days) compared with that of valacyclovir (3000 mg daily dose) for the treatment of HZ in immunocompetent Japanese patients.²⁰

Immunological aspects of HZ

As reported by Jones et al.²² all the peripheral blood mononuclear cell (PBMC) subsets [monocytes, B cells, and natural killer (NK) T cells] are infected with VZV. T-lineage cells and NK cells appear to be more able to withstand the viral infection over a long period due to their slight increases in surface VZV-glycoprotein E (gE) expression.²² Latent VZV is maintained in a subclinical state in neural ganglia due to T-cell-mediated immunity.²³ So far, the decline of the VZV-specific response, in particular T-cell response, with age and immunosuppression, might be related to increased incidence and severity of HZ.²³⁻²⁵ Thus, the role of VZV-specific T-cell response in high-risk subjects should be considered.^{26,27}

The immune evasion pathway triggered by VZV infection may be due to the ability of infected immune cells to transmit virus together with the induction of programmed death-ligand 1 (PD-L1) expression in PBMCs. It has been demonstrated that VZV-infected PBMCs have from 2- to 14-fold induction in PD-L1 expression levels compared with those uninfected.²² The enhanced CD8+ T-cell effector function is able to block PD-L1 and reduce virus dissemination and widespread disease associated with VZV.²³

HZ complications may be cutaneous, visceral, neurological, and ocular and they are more frequent in immunocompromised subjects, such as patients with cancer.⁶ PHN can be refractory to analgesic treatment and neuroleptics and can last for years.¹¹ A recent meta-analysis systematically evaluated the risk factors of PHN. Decrease in

cell-mediated immunity with advancing age, acute severe pain in the HZ phase, presence of a prodromal phase, and severe rash were independent risk factors of PHN.²⁸ Moreover, PHN can severely compromise quality of life, with disordered sleep, chronic fatigue, weight loss, anorexia, anxiety, and depression.²⁹

Vaccination against VZV has been increasingly encouraged in these frail subjects.

HZ VACCINE

Mechanism of action

Live-attenuated vaccine for the prevention of HZ (ZVL) is not recommended for immunocompromised subjects due to the high risk of associated complications, including multi-organ failure and death.^{30,31}

Recently, the approval of an adjuvanted gE-based recombinant vaccine combined with a novel adjuvant (AS01B) (RZV, Shingrix, GlaxoSmithKline, Wavre, Belgium)³² has changed preventive perspectives in immunocompromised subjects, including cancer patients. gE plays a central role in HZ and is an important target for immune responses: this vaccine is able to induce sustained antigen-specific cellular and humoral immune responses against HZ.³³

The efficacy of RZV has no significant variation according to age, in contrast with ZVL, which showed lower efficacy among subjects aged ≥ 70 years (37.6%).^{34,35} The age-independent efficacy of RZV is a very important issue, since the incidence of HZ and severity of its complications are higher among older adults with more medical needs.³⁴ Vaccine administration at a dosage of 0.5 ml into the deltoid muscle is normally carried out in two doses at month 0 and month 1 or 2, and if the second dose is delayed, we need to administer it as soon as possible without repeating the first dose.^{34,35}

The most common side-effects observed after RZV were pain at the injection site (68.7%) and fatigue (32.9%).³⁵ The overall frequency and severity of the solicited reactions did not increase significantly after the second dose of vaccine.³⁵

In subjects aged ≥ 60 years vaccinated with two RZV doses, humoral and cell-mediated responses were maintained through 10 years after vaccination and are predicted to persist over 20 years after the initial vaccination. The available data show that, 10 years after the initial vaccination, the anti-gE antibody geometric mean concentration and mean gE-specific CD4+ T cells expressing more than two activation markers (including interferon- γ , interleukin 2, tumor necrosis factor- α) have remained 6.0- and 3.5-fold, respectively, above pre-vaccination levels.³⁶ Data suggested that the adjuvant AS01 formulation increases the immunogenicity of the RZV vaccine by a sustained stimulation of the cell-mediated response.³⁷

On 23 July 2021, the Food and Drug Administration approved RZV for the prevention of HZ in adults who have or might have an increased risk of HZ due to immunosuppression.³⁸

RZV and co-administration with other types of vaccine

The Centers for Disease Control and Prevention's general best practice guidelines for immunization affirm that RZV can be co-administered, at different anatomic sites, with other vaccines.³⁹ There is no evidence for interference in the immune response in the case of concomitant administration of RZV with Fluarix Quadrivalent (influenza vaccine).⁴⁰ A clinical trial to evaluate the concomitant administration of RZV with 23-valent pneumococcal polysaccharide vaccine (PPSV23, Pneumovax 23) is ongoing. To date, the efficacy and safety of co-administration of RZV and adjuvanted influenza vaccine (Fluad) have not been demonstrated.⁴¹ Importantly, no increased incidence of HZ has been recognized as a problem in clinical practice after these inactivated vaccines.

RZV is safe and should be encouraged despite the ongoing COVID-19 pandemic: in fact, COVID-19 infection and COVID vaccines may trigger HZ as recently reported in some case reports.⁴²⁻⁴⁴ COVID-19 infection may induce a decrease of CD4+ T cells, CD8+ T cells, B cells, and NK cells, and this dysregulation of the immune system, associated with mental stress, might cause the reactivation of VZV.⁴² So, in this pandemic context, HZ vaccination seems even more crucial in preventing HZ complications in patients who are infected with SARS-CoV-2.

It is well known that inactivated vaccines for hepatitis A, influenza, rabies, and Japanese encephalitis may cause HZ. Eid and colleagues⁴³ have reported HZ 6 days after the messenger RNA COVID-19 vaccine. Two cases of HZ after 24 and 2 days were reported in breast cancer-operated women.⁴⁴ Thus, COVID vaccination may induce a cascade of antigenic-mediated immunological events triggering latent VZV reactivation.⁴⁵

HZ IN CANCER PATIENTS

The correlation between cancer and HZ is quite strong [relative risk 2.17; 95% confidence interval (CI) 1.86-2.53] and is caused by the reduction in immune efficiency produced by the cancer itself and by the active therapies.⁴⁶ Qian and colleagues⁴⁷ have demonstrated that the diagnosis of cancer is associated with a 40% higher risk of developing HZ in an Australian population-based prospective cohort study. Moreover, the risk of HZ seems to be higher among patients with cancer receiving chemotherapy compared with those who did not.⁴⁷ Conversely, Lai et al.⁴⁸ have found that there is a statistically higher risk of subsequent cancer among subjects with a diagnosis of HZ for ≥ 1 year. Hansson and colleagues⁴⁹ have estimated the association between 21 of the most common specific hematological and solid tumors and a subsequent HZ risk. Cancer was positively associated with HZ risk [adjusted odds ratio (OR) 1.29, 95% CI 1.27-1.32]. This association was strong for hematological malignancies (OR 2.46, 95% CI 2.33-2.60). For 11 of 18 solid tumors evaluated, they found a positive association between central nervous system cancer and HZ (adjusted OR 2.31, 95% CI 1.85-2.88); followed by lung (adjusted OR 1.50, 95% CI 1.33-1.69), oral (adjusted OR

1.41, 95% CI 1.11-1.79), and esophageal (adjusted OR 1.41, 95% CI 1.13-1.76) cancers. Modest associations have been found for stomach, colorectal, breast, ovarian, prostate, kidney, and bladder cancers (adjusted ORs in a range 1.10-1.30). No evidence of associations between salivary, larynx, cervix, uterus, testicular, or thyroid cancers, or melanoma and HZ has been demonstrated.⁴⁹

HZ and chemotherapy

Patients with cancer undergoing chemotherapy have a high and well-known risk of HZ.^{3,6} The immunogenicity of RZV has been studied in this population.⁵⁰ In a phase II/III observer-blind, multicenter study, patients with solid tumors were randomized (1 : 1) to receive two doses of RZV or placebo 1-2 months apart. The patients were stratified (4 : 1) according to the time gap between the vaccine and the start of a chemotherapy cycle [first dose of RZV vaccine 8-30 days before the start (PreChemo) or at the start (± 1 day) of a chemotherapy cycle (OnChemo)].⁵⁰ Both the RZV-PreChemo group and the RZV-OnChemo group developed a robust RZV humoral immune response, but it was higher in the RZV-PreChemo group. The impact of cell-mediated immune responses is unclear in the absence of efficacy data or the immunologic correlation to a clinical protection. Efficacy trials will be very important to assess the impact of RZV in patients with solid tumors during chemotherapy. However, humoral and cell-mediated immune responses persisted 12 months after RZV.⁵⁰

Solicited general symptom such as fatigue, myalgia, headache, gastrointestinal symptoms and fever was reported by 81.3% RZV and 66.4% placebo recipients. This frequency in both arms was higher than in immunocompetent recipients, probably due to the general symptoms associated with the underlying cancer.⁵⁰

HZ and autologous hematopoietic stem cell transplant

In autologous hematopoietic stem cell transplant (HSCT), a procedure with limited indications in solid tumors,⁵¹ the incidence of HZ ranges from 16% to 30%.⁵² Antiviral prophylaxis (AP) with low-dose acyclovir is commonly used in patients after HSCT.⁵³ There is an inverse relationship between the duration of AP and the incidence of HZ: patients with AP prescription duration of >1 year had one-third the risk of HZ when compared with those with AP prescription duration <3 months.⁵⁴

The randomized clinical trial ZOE-HSCT demonstrated the reduction of the incidence of HZ in autologous stem cell transplant recipients with a two-dose course of RZV administered 50-70 days after transplant compared with placebo.⁵⁵ RZV induced both strong humoral and cellular immune responses. RZV was well tolerated and most symptoms were mild and transient, with a median duration of up to 3 days. The overall frequency of solicited general symptoms was 75% after vaccine and 51% after placebo, similar to the frequency reported in clinical trials in immunocompetent recipients.^{34,35}

HZ and immunotherapy

Data on HZ are less available among patients with cancer during therapy with immune checkpoint inhibitors (ICIs).⁵⁶ It could be speculated that the increased T-cell function due to the ICIs should reduce the VZV reactivation. Limited clinical data, however, does not allow exclusion of the risk of HZ.

To the best of our knowledge, there are few cases of ICI-treated patients with documented HZ: a patient with lung cancer developed VZV encephalitis 5 days after the 31st cycle of nivolumab monotherapy⁵⁷ and a patient with metastatic adenocarcinoma of the lung during nivolumab reported HZ.⁵⁸

A potential risk factor for HZ during immunotherapy may be the use of high-dose steroids for the management of immune-related adverse events, because dexamethasone has a well-known direct suppressive role on T-cell function.⁵⁹ On the other hand, ICIs might induce an exaggerated host inflammatory response on the host immunity, similar to immune reconstitution inflammatory syndrome, and so they may cause reactivation of chronic infections such as VZV.⁶⁰

To date, no clinical trial is ongoing to evaluate the efficacy, immunogenicity, and safety of RZV in patients with cancer undergoing immunotherapy.

HZ and radiotherapy

Relatively few studies have evaluated the occurrence of HZ after radiotherapy (RT).

HZ typically occurred within the first 2 years after the completion of RT.^{61,62} In a propensity score-matched retrospective cohort study, patients with cancer who had received RT showed a significantly higher risk of HZ than the non-RT group (hazard ratio, 2.59, 95% CI 1.84-3.66); moreover, the anatomic relation between the RT field and HZ was evaluated.⁶³ RT may cause HZ due to impairment of local cellular immune response mechanisms.⁶¹

A serologic screening for VZV might be recommended before RT to determine whether prophylactic therapy is required during and after treatment and to differentiate between the RT-related dermatological adverse events necrosis and herpetic infection.⁶²

In a retrospective cohort analysis of data from Tokyo Metropolitan Cancer and Infectious Diseases Center, Shimizuguchi and colleagues⁶³ reported a significantly higher risk of HZ development in the RT group (versus the non-RT group) (hazard ratio, 2.59; 95% CI 1.84-3.66). In a retrospective study of patients with breast cancer who had received postoperative RT, Dunst et al.⁶¹ observed that 3.7% of patients developed HZ, typically within the first 2 years after RT. This relationship between HZ and RT in patients with breast cancer was also observed in a large matched-pair study: the RT group had a 1.51-fold higher risk of HZ than the non-RT group within 5 months of RT completion.⁶⁴

In a population-based study, the authors have demonstrated that gynecological cancer patients receiving RT and CT had the highest cumulative risk of HZ compared with the

non-RT group (1.68-fold higher risk of HZ; 95% CI 1.16-2.36, $P = 0.009$).⁶⁵

This increased risk of HZ has also been confirmed in patients with head/neck cancer (18.55 versus 9.06 per 1000 person-years, $P = 0.03$) and persisted within the first 2 years and then diminished.⁶⁶

AIOM RECOMMENDATIONS

To date, after the above reported review of available evidences, AIOM recommendations about the topic are the following:

- Oncologists should be aware of the need to screen every patient with cancer who is a candidate for oncological active therapy, for VZV, in the absence of local seroprevalence data. There are significant differences in VZV seroepidemiology across the world according to socio-economic status.⁶² It is preferable to obtain serological tests before vaccination, but this is not a mandatory requirement.
- RZV is safe and efficacious in frail subjects, including patients with cancer.
- In the absence of definitive data on the immunogenicity of the vaccine for different types of cancer and therapy, clinical judgment is recommended when determining which patients are candidates for vaccination for HZ.
- Systemic therapies associated with lymphopenia or profound neutropenia lasting ≥ 7 days may be related to a higher risk of reactivation of VZV, so RZV should be offered to these patients. In those patients with severe lymphopenia due to chemotherapy, the need to start a prophylactic virostatic treatment before RZV might be discussed with virologists and infectious disease colleagues, because the vaccine's efficacy might be clearly compromised in these conditions.
- Patients with polycomorbidities,⁶⁷ the elderly (≥ 65 years) and those with a life expectancy >3 months, irrespective of the type of cancer and of type of active therapy and RT, may benefit from the vaccine.
- Definitive data of HZ during ICIs and/or target therapy are unavailable. For this reason, vaccination can be recommended in this patient population based on what has been previously stated.
- For disease-free patients >5 years following active treatment and patients who have surgery not requiring additional treatment, HZ vaccination should be considered according to recommendations for the general population.
- The ideal time to administer the vaccine in patients undergoing active treatment is still unclear. Preferably, vaccination should be scheduled 2-3 weeks before the start of oncological therapies in order to avoid the phase of leucopenia in case treatment has already begun. It is generally recommended to check the general vaccination status of patients before starting cancer therapy.
- It can be co-administered with other vaccines, including COVID-19 and flu vaccines, but, preferably, we suggest performing the vaccinations at different times (2 weeks

Table 1. Recommendations and statements on the use of vaccination for herpes zoster in patients with solid tumors

1. Oncologists should be aware of the need to screen every patient with cancer who is a candidate for oncological active therapy, for VZV, in the absence of local seroprevalence data. It is preferable to obtain serological tests before vaccination, but this is not a mandatory requirement.
2. Recombinant vaccine for the prevention of HZ (RZV) is safe and minimally invasive. It reduces the likelihood of HZ in immunocompromised subjects, including patients with cancer.
3. In the absence of definitive data on the immunogenicity of the vaccine for different types of cancer and therapy, clinical judgment is recommended when determining which patients are candidates for vaccination for HZ.
4. Chemotherapies that cause lymphopenia/profound neutropenia for ≥ 7 days may be associated with a higher risk of reactivations of VZV, so RZV should be offered to these patients. In those patients with severe lymphopenia due to chemotherapy, the need to start prophylactic virostatic treatment before RZV might be discussed with virologists and infectious disease colleagues because the vaccine's efficacy might be clearly compromised in these conditions.
5. Patients with polycomorbidities, the elderly (≥ 65 years) and those with a life expectancy >3 months, irrespective of the type of cancer and of type of active therapy, may benefit from the vaccine.
6. Definitive data of HZ during ICIs and/or target therapy are unavailable. For this reason, the recommendation for vaccination should be given based on the patient's general condition, life expectancy, and age.
7. For disease-free patients >5 years following active treatment and patients who have surgery not requiring additional treatment, HZ vaccination should be considered according to recommendations for immunocompetent recipients.
8. The ideal time to administer the vaccine in patients undergoing active treatment is still unclear. Preferably, vaccination should be scheduled 2-3 weeks before the start of oncological therapies in order to avoid the phase of leucopenia in case treatment has already begun. It is generally recommended to check the general vaccination status of the patients before starting the cancer therapy.
9. It can be co-administered with other vaccines, including COVID-19 and flu vaccines, but, preferably, we suggest performing the vaccinations at different times (2 weeks apart), to avoid the risk of accumulation of adverse events (i.e. fever).
10. Well-designed prospective clinical trials about the assessment and duration of the humoral and cell-mediated response elicited by vaccination in larger cohorts of patients with cancer, undergoing different types of treatment, will be useful in order to establish evidence-based guidelines.

HZ, herpes zoster; ICIs, immune checkpoint inhibitors; RZV, recombinant zoster vaccine; VZV, varicella-zoster virus.

apart) to avoid the risk of accumulation of adverse events (e.g. fever).

- Further prospective clinical trials about the role of RVZ, including assessment of the humoral and cell-mediated response elicited by vaccination in larger cohorts of patients with cancer undergoing different types of treatment, are required in order to better define evidence-based guidelines. Moreover, the duration of protection is unknown in patients with cancer, so well-designed prospective studies will help us to clarify this aspect.

A summary of the AIOM recommendations is reported in [Table 1](#).

CONCLUSIONS

Patients with cancer are frail subjects and they are more likely to get HZ and its complications with a consequent delay in treatment of the underlying malignancy. Some 30% of patients with HZ hospitalized for complications are

immunocompromised.⁶⁸ The available recommendations approved by health authorities all over the world underline the increased risk of HZ in immunocompromised individuals, including those with cancer.⁶⁹ The approval of RZV has also changed preventive perspectives in immunocompromised subjects.

To date, only a few countries have included HZ vaccination for immunocompromised patients in the national recommendations and in reimbursement systems, so not all patients are able to follow the recommendations or afford the vaccine. In light of the increased risk of reactivation and severe complications from HZ, however, it is advocated that health systems worldwide include this vaccine into the therapeutic reimbursement system for patients with cancer.

In the absence of available data on the immunogenicity of the vaccine for different types of cancer and therapy, the recommendation for HZ vaccination should be given based on the patient's general condition, life expectancy, age, and the potential multiple lines of oncological treatment. Well-designed prospective clinical trials about the assessment of the humoral and cell-mediated response elicited by vaccination in larger cohorts of patients with cancer, undergoing different types of treatment, will be useful in order to establish evidence-based guidelines.

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DISCLOSURE

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REFERENCES

- Galetta KM, Gildea D. Zeroing in on zoster: a tale of many disorders produced by one virus. *J Neurol Sci*. 2015;358(1-2):38-45.
- Rosamilia LL. Herpes zoster presentation, management, and prevention: a modern case-based review. *Am J Clin Dermatol*. 2020;21(1):97-107.
- Kawai K, Yawn B. Risk of herpes zoster in cancer patients and the promise of new vaccines. *J Infect Dis*. 2019;220(1):1-2.
- Sim JH, Cho HS, Kim YD, et al. The association between herpes zoster and increased cancer risk: a nationwide population-based matched control study. *Curr Oncol*. 2021;28(4):2720-2730.
- Gershon AA, Breuer J, Cohen JI, et al. Varicella zoster virus infection. *Nat Rev Dis Primers*. 2015;1:15016.
- Kennedy PGE, Gershon AA. Clinical features of varicella-zoster virus infection. *Viruses*. 2018;10(11):609.
- Freer G, Pistello M. Varicella-zoster virus infection: natural history, clinical manifestations, immunity and current and future vaccination strategies. *New Microbiol*. 2018;41(2):95-105.
- Sauerbrei A. Diagnosis, antiviral therapy, and prophylaxis of varicella-zoster virus infections. *Eur J Clin Microbiol Infect Dis*. 2016;35(5):723-734.
- Park SY, Kim JY, Kim JA, et al. Diagnostic usefulness of varicella-zoster virus real-time polymerase chain reaction analysis of DNA in saliva and plasma specimens from patients with herpes zoster. *J Infect Dis*. 2017;217(1):51-57.
- Gershon AA, Chen J, Gershon MD. Use of saliva to identify varicella zoster virus infection of the gut. *Clin Infect Dis*. 2015;61:536-544.
- Saguil A, Kane S, Mercado M, Lauters R. Herpes zoster and post-herpetic neuralgia: prevention and management. *Am Fam Physician*. 2017;96(10):656-663.
- Wood MJ, Kay R, Dworkin RH, Soong SJ, Whitley RJ. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. *Clin Infect Dis*. 1996;22(2):341-347.
- Beutner KR, Friedman DJ, Forszpaniak C, Andersen PL, Wood MJ. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. *Antimicrob Agents Chemother*. 1995;39:1546-1553.
- Lin WR, Lin HH, Lee SS, et al. Comparative study of the efficacy and safety of valaciclovir versus acyclovir in the treatment of herpes zoster. *J Microbiol Immunol Infect*. 2001;34:138-142.
- Ilyas S, Chandrasekar PH. Preventing varicella-zoster: advances with the recombinant zoster vaccine. *Open Forum Infect Dis*. 2020;7(7):ofaa274.
- Chen N, Li Q, Yang J, Zhou M, Zhou D, He L. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2014;2:CD006866.
- Werner RN, Nikkels AF, Marinović B, et al. European consensus-based (S2k) guideline on the management of herpes zoster-guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), Part 2: treatment. *J Eur Acad Dermatol Venereol*. 2017;31(1):20-29.
- Balfour HH, Benson C, Braun J, et al. Management of acyclovir-resistant herpes simplex and varicella-zoster virus infections. *J Acquir Immune Defic Syndr*. 1994;7:254-260.
- Saint-Léger E, Caumes E, Breton G, et al. Clinical and virologic characterization of acyclovir-resistant varicella-zoster viruses isolated from 11 patients with acquired immunodeficiency syndrome. *Clin Infect Dis*. 2001;33:2061-2067.
- Kawashima M, Nemoto O, Honda M, et al. Amenamevir, a novel helicase-primase inhibitor, for treatment of herpes zoster: a randomized, double-blind, valaciclovir-controlled phase 3 study. *J Dermatol*. 2017;44(11):1219-1227.
- Shiraki K, Takemoto M, Daikoku T. Emergence of varicella-zoster virus resistance to acyclovir: epidemiology, prevention, and treatment. *Expert Rev Anti Infect Ther*. 2021;19(11):1415-1425.
- Jones D, Como CN, Jing L, et al. Varicella zoster virus productively infects human peripheral blood mononuclear cells to modulate expression of immunoinhibitory proteins and blocking PD-L1 enhances virus-specific CD8+ T cell effector function. *PLoS Pathog*. 2019;15(3):e1007650.
- Weinberg A, Levin MJ. VZV T cell-mediated immunity. *Curr Top Microbiol Immunol*. 2010;342:341-357.
- Arvin AM. Immune responses to varicella-zoster virus. *Infect Dis Clin North Am*. 1996;10(3):529-570.
- Weinberg A, Zhang JH, Oxman MN, et al. Varicella-zoster virus-specific immune responses to herpes zoster in elderly participants in a trial of a clinically effective zoster vaccine. *J Infect Dis*. 2009;200(7):1068-1077.
- Rondaan C, de Haan A, Horst G, et al. Altered cellular and humoral immunity to varicella-zoster virus in patients with autoimmune diseases. *Arthritis Rheumatol*. 2014;66(11):3122-3128.
- Cassaniti I, Ferrari A, Comolli G, et al. Characterization of varicella-zoster (VZV) specific T cell response in healthy subjects and transplanted patients by using Enzyme Linked Immunospot (ELISpot) assays. *Vaccines (Basel)*. 2021;9(8):875.
- Zhou H, Wang Z, Jin H, Chen X, Lei L. A systematic review and meta-analysis of independent risk factors for postherpetic neuralgia. *Ann Palliat Med*. 2021;10(12):12181-12189.
- Harbecke R, Cohen JI, Oxman MN. Herpes zoster vaccines. *J Infect Dis*. 2021;224(suppl 4):S429-S442.
- Alexander KE, Tong PL, Macartney K, Beresford R, Sheppard V, Gupta M. Live zoster vaccination in an immunocompromised patient leading to death secondary to disseminated varicella zoster virus infection. *Vaccine*. 2018;36(27):3890-3893.
- Costa E, Buxton J, Brown J, Templeton KE, Breuer J, Johannessen I. Fatal disseminated varicella zoster infection following zoster vaccination in an immunocompromised patient. *BMJ Case Rep*. 2016;2016:bcr2015212688.

32. Lecrenier N, Beukelaers P, Colindres R, et al. Development of adjuvanted recombinant zoster vaccine and its implications for shingles prevention. *Expert Rev Vaccines*. 2018;17(7):619-634.
33. Recombinant varicella zoster virus glycoprotein E antigen vaccine for prevention of herpes zoster and postherpetic neuralgia. *Aust Prescr*. 2021;44(5):173-174.
34. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med*. 2015;372(22):2087-2096.
35. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med*. 2016;375:1019-1032.
36. Hastie A, Catteau G, Enemu A, et al. Immunogenicity of the adjuvanted recombinant zoster vaccine: persistence and anamnestic response to additional doses administered 10 years after primary vaccination. *J Infect Dis*. 2021;224(12):2025-2034.
37. Didierlaurent AM, Laupèze B, Di Pasquale A, Hergli N, Collignon C, Garçon N. Adjuvant system AS01: helping to overcome the challenges of modern vaccines. *Expert Rev Vaccines*. 2017;16(1):55-63.
38. FDA. Vaccine SHINGRIX. 2022. Available at <https://www.fda.gov/vaccines-blood-biologics/vaccines/shingrix>. Accessed May 24, 2022.
39. Kroger AT, Duchin J, Vázquez M. General best practice guidelines for immunization. Best practices guidance of the Advisory Committee on Immunization Practices (ACIP). Atlanta, GA: US Department of Health and Human Services, CDC. Available at <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf>. Accessed May 24, 2022.
40. Schwarz TF, Aggarwal N, Moeckesch B, et al. Immunogenicity and safety of an adjuvanted herpes zoster subunit vaccine coadministered with seasonal influenza vaccine in adults aged 50 years or older. *J Infect Dis*. 2017;216(11):1352-1361.
41. Dooling KL, Guo A, Patel M, et al. Recommendations of the advisory committee on immunization practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67(3):103-108.
42. Maia CMF, Marques NP, de Lucena EH, de Rezende LF, Martelli D, Martelli-Júnior H. Increased number of herpes zoster cases in Brazil related to the COVID-19 pandemic. *Int J Infect Dis*. 2021;104:732-733.
43. Eid E, Abdullah L, Kurban M, Abbas O. Herpes zoster emergence following mRNA COVID-19 vaccine. *J Med Virol*. 2021;93(9):5231-5232.
44. Toscani I, Troiani A, Citterio C, Rocca G, Cavanna L. Herpes zoster following COVID-19 vaccination in long-term breast cancer survivors. *Cureus*. 2021;13(10):e18418.
45. Palanivel JA. Herpes zoster after COVID-19 vaccination-Can the vaccine reactivate latent zoster virus? *J Cosmet Dermatol*. 2021;20(11):3376-3377.
46. Marra F, Parhar K, Huang B, Vadlamudi N. Risk factors for herpes zoster infection: a meta-analysis. *Open Forum Infect Dis*. 2020;7(1):ofaa005.
47. Qian J, Heywood AE, Karki S, et al. Risk of herpes zoster prior to and following cancer diagnosis and treatment: a population-based prospective cohort study. *J Infect Dis*. 2019;220(1):3-11.
48. Lai SW, Kuo YH, Liao KF. Herpes zoster and subsequent cancer risk. *Dermatology*. 2020;236(6):603-604.
49. Hansson E, Forbes HJ, Langan SM, Smeeth L, Bhaskaran K. Herpes zoster risk after 21 specific cancers: population-based case-control study. *Br J Cancer*. 2017;116(12):1643-1651.
50. Vink P, Mingorance ID, Alonso CM, et al. Immunogenicity and safety of the adjuvanted recombinant zoster vaccine in patients with solid tumors, vaccinated before or during chemotherapy: a randomized trial. *Cancer*. 2019;125(8):1301-1312.
51. Snowden JN, Sanchez-Ortega I, Corbacioglu S, et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. *Bone Marrow Transplant*. 2022;1-23.
52. Stadtmayer EA, Sullivan KM, El Idrissi M, et al. Adjuvanted recombinant zoster vaccine in adult autologous stem cell transplant recipients: polyfunctional immune responses and lessons for clinical practice. *Hum Vaccin Immunother*. 2021;17:1-11.
53. Kawamura K, Hayakawa J, Akahoshi Y, et al. Low-dose acyclovir prophylaxis for the prevention of herpes simplex virus and varicella zoster virus diseases after autologous hematopoietic stem cell transplantation. *Int J Hematol*. 2015;102(2):230-237.
54. Zhang D, Weiss T, Feng Y, Finelli L. Duration of antiviral prophylaxis and risk of herpes zoster among patients receiving autologous hematopoietic stem cell transplants: a retrospective, observational study. *Adv Ther*. 2017;34(7):1610-1621.
55. Bastidas A, de la Serna J, El Idrissi M, et al. Effect of recombinant zoster vaccine on incidence of herpes zoster after autologous stem cell transplantation: a randomized clinical trial. *JAMA*. 2019;322(2):123-133.
56. Serra F, Cassaniti I, Lilleri D, Pedrazzoli P, Baldanti F, Lasagna A. Herpes zoster in patients with solid tumors treated with immune checkpoint inhibitors. *Immunotherapy*. 2022;14(6):389-393.
57. Watanabe Y, Kikuchi R, Iwai Y, et al. Varicella zoster virus encephalitis mimicking nivolumab-induced autoimmune neuropathy in a patient with lung cancer. *J Thorac Oncol*. 2019;14(8):e163-e165.
58. Gozzi E, Rossi L, Angelini F, et al. Herpes zoster granulomatous dermatitis in metastatic lung cancer treated with nivolumab: a case report. *Thorac Cancer*. 2020;11(5):1330-1333.
59. Chakravarty EF, Michaud K, Katz R, Wolfe F. Incidence of herpes zoster among patients with systemic lupus erythematosus. *Lupus*. 2013;22:238-244.
60. Lasagna A, Cassaniti I, Sacchi P, Baldanti F, Bruno R, Pedrazzoli P. Infectious complications and immunotherapy: old pitfalls and new horizons. *Future Oncol*. 2022;18:2377-2381.
61. Dunst J, Steil B, Furch S, Fach A, Bormann G, Marsch W. Herpes zoster in breast cancer patients after radiotherapy. *Strahlenther Onkol*. 2000;176:513-516.
62. Lai YL, Su YC, Kao CH, Liang JA. Increased risk of varicella-zoster virus infection in patients with breast cancer after adjuvant radiotherapy: a population-based cohort study. *PLoS One*. 2019;14:e0209365.
63. Shimizuguchi T, Sekiya N, Hara K, et al. Radiation therapy and the risk of herpes zoster in patients with cancer. *Cancer*. 2020;126(15):3552-3559.
64. Ramirez-Fort MK, Zeng J, Feily A, et al. Radiotherapy-induced reactivation of neurotrophic human herpes viruses: overview and management. *J Clin Virol*. 2018;98:18-27.
65. Lee PY, Lai JN, Chen SW, Lin YC, Chiu LT, Wei YT. Radiotherapy combined with chemotherapy increases the risk of herpes zoster in patients with gynecological cancers: a nationwide cohort study. *J Gynecol Oncol*. 2021;32(2):e13.
66. Lee PY, Lai JN, Chiu LT, Wei YT. Incidence and time trends of herpes zoster among patients with head and neck cancer who did and did not undergo radiotherapy: a population-based cohort study. *PLoS One*. 2021;16(5):e0250724.
67. Andreoni M, Sticchi L, Nozza S, Sarmati L, Gori A, Tavio M, Society for Infectious and Tropical Diseases (SIMIT). Recommendations of the Italian society for infectious and tropical diseases (SIMIT) for adult vaccinations. *Hum Vaccin Immunother*. 2021;17(11):4265-4282.
68. CDC. Shingles (Herpes Zoster). 2022. Available at www.cdc.gov/shingles/surveillance.html. Accessed May 14, 2022.
69. Jorga A, Friedland LR, Lecrenier N, Safonova E, Vink P, Widenmaier R. BPI22-019: guidelines and recommendations for the adjuvanted recombinant zoster vaccine in immunocompromised cancer patients. *JNCCN*.