Original Article

Herpes zoster in lung cancer patients treated with PD-1/PD-L1 inhibitors

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Background: Herpes zoster (HZ) occurs mostly in elderly and immunocompromised individuals. Immune reconstitution may be associated with the pathogenesis of HZ. As immune checkpoint inhibitor (ICI) treatment amplifies the immune response, use of ICI may increase the incidence of HZ. There have been few studies of HZ in lung cancer patients treated with ICI. This study was performed to investigate the frequency of HZ in lung cancer patients who received ICI or cytotoxic chemotherapeutic agents.

Methods: We searched the electronic medical records for lung cancer patients receiving anticancer drug therapy at our hospital, who developed HZ between April 2011 and June 2020.

Results: The review identified 80 patients with a history of ICI treatment (ICI group) and 356 who had been treated with cytotoxic chemotherapeutic agents alone (non-ICI group). Among the 20 patients who developed HZ, 4 (5.0%) belonged to the ICI group and 16 (4.5%) to the non-ICI group (P=0.782). After exclusion of patients aged 65 years and older, to avoid effects of advanced age on the results, the ICI and non-ICI groups consisted of 24 and 81 patients, respectively. In total, 3 of the 24 patients (12.5%) in the ICI group and 1 of the 81 (1.2%) patients in the non-ICI group developed HZ (P=0.0365).

Conclusions: There was no significant difference in the rate of HZ between lung cancer patients treated with ICI and those treated with cytotoxic chemotherapy alone. However, patients younger than 65 years treated with ICI might be at increased risk of HZ. Because this is a retrospective small study, further prospective observational studies are needed.

Keywords: Herpes zoster (HZ); immune checkpoint inhibitor (ICI); lung cancer

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Introduction

Cancer immunotherapy with immune checkpoint inhibitors (ICIs) is an important cancer treatment strategy. ICI strengthens the immune system by activating and proliferating effector T cells suppressed by antitumor lymphocytes or signals from cancer cells (1). ICI is unlikely to cause immunosuppression, and the risk of infectious diseases related to ICI has not attracted a great deal of

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attention from physicians. However, approximately 7% of patients with malignant melanoma in the US who received ICIs were reported to develop serious infectious complications (2). In addition, cases of tuberculosis have been reported in patients receiving nivolumab (3).

Herpes zoster (HZ) is a viral infection that occurs along with reactivation of the varicella-zoster virus (VZV). The incidence of HZ has increased from 2.5 per 1,000 person-years in 1993 to 7.2 per 1,000 person-years in 2016 (4). The reactivation of suppression of cellular immunity has been implicated in the pathogenesis of VZV reactivation, because recurrent HZ occurs mostly in elderly or immunocompromised individuals (5).

Immune reconstitution inflammatory syndrome (IRIS) was originally described in human immunodeficiency virus (HIV) patients receiving highly active antiretroviral therapy (HAART) (6). Recently, drug-induced hypersensitivity syndrome (DIHS) and drug reaction with eosinophilia and systemic symptoms (DRESS) were reported as characteristic forms of non-HIV IRIS (7). HZ is likely to be one of the manifestations of IRIS in the setting of DIHS/DRESS (8,9). Therefore, we hypothesized that immune reconstitution due to ICI may increase the incidence of HZ. There have been few reports on HZ in lung cancer patients treated with ICI. We investigated whether the incidence of HZ is increased in patients receiving ICI consisting of anti-programmed cell death 1 (PD-1) antibody, including nivolumab and pembrolizumab, or anti-programmed cell death-ligand 1 (PD-L1) antibody, including atezolizumab and durvalumab (ICI group), in comparison with those receiving cytotoxic chemotherapeutic agents alone (non-ICI group). We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2764/rc).

Methods

Patients

We searched for lung cancer patients who received anticancer drug therapy and developed HZ between April 2011 and June 2020 at the General Medical Center, Kawasaki Medical School. Patients were retrospectively selected according to the following criteria: histologically or cytologically diagnosed lung cancer; diagnosis of HZ by a dermatologist based on Tzanck smear; and development of HZ during anticancer drug therapy or within 1 year of the last treatment.

Data collection process and data items

To avoid bias, two medical oncologists (MT and NO) independently extracted data from electronic medical records. The following information was obtained from each report: patient characteristics [age, sex, smoking history, Eastern Cooperative Oncology Group performance status (PS), histological features, clinical stage, comorbidities, and steroid use], date of starting cancer treatment, regimen of cancer medication, date of diagnosis of HZ, and survival time from diagnosis of HZ. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Kawasaki Medical School (No. 5160-00) and individual consent for this retrospective analysis was waived.

Statistical analysis

Parametric data were compared between the two groups using Student's *t*-test and Fisher's exact test was used to compare nonparametric data. All P values were two-sided, and the significance level was set at $P<0.05$.

Results

Clinical characteristics

The ICI group consisted of 80 patients and the non-ICI group included 356 patients (*Table 1*). The proportions of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) were higher in the ICI than non-ICI group (87.5% *vs.* 76.1%, respectively, P=0.026; 22.5% *vs.* 10.0%, respectively, P=0.012) because anti-PD-1 antibodies had not been approved for treatment of SCLC until August 2019 (atezolizumab) and August 2020 (durvalumab) in Japan. The proportion of patients with advanced stage disease (IIIB–IV) was higher in the ICI than non-ICI group (82.5% *vs.* 62.4%, respectively, P=0.0006).

Patients with HZ

The 20 patients who developed HZ included 4 (5%) in the ICI group and 16 (4.5%) in the non-ICI group developed HZ (P=0.782). The characteristics of patients with HZ are shown in *Table 2*. The mean age at onset of HZ was 62.5 (range, 46–77) years in the ICI group and 73.7 (range, 61–91) years in the non-ICI group (P=0.142). The proportion of patients aged <65 years was markedly higher in the ICI than non-ICI group (75.0% *vs.* 6.3%, respectively, P=0.013).

Table 1 Patient characteristics

	ICI group	Non-ICI group	P value
No.	80	356	
Mean age, years (range)	67.0 (29–89)	70.5 (37–88)	0.142
Sex			
Male	59	264	0.940
Female	21	92	
Performance status			
0	21	65	0.104
1	50	213	0.659
2	6	50	0.114
3/4	3	28	0.196
Histological type			
NSCLC	70	271	0.026
Ad	52	186	0.047
Sq	16	72	0.964
LCNEC	2	13	1.000
SCLC	8	80	0.012
Other	2	5	0.617
Stage			
I-IIIA	14	134	0.0006
IIIB-IV	66	222	

Ad, adenocarcinoma; ICI, immune checkpoint inhibitor; LCNEC, large cell neuroendocrine carcinoma, NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; Sq, squamous cell carcinoma.

Table 2 Patient characteristics at the onset of herpes zoster

	ICI group	Non-ICI group	P value
No.	4	16	
Mean age, years (range)	62.5 (46–77)	73.7 (61–91)	0.142
Sex			
Male	4	11	0.530
Female	0	5	
Smoker (Brinkman Index ≥400)	4	14	1.000
Performance status			
0	1	5	1.000
1	1	9	0.582
2	0	1	1.000
3/4	2	1	0.088
Histological type			
NSCLC	4	12	0.540
Ad	1	8	0.591
Sq	3	3	0.061
LCNEC	0	1	1.000
SCLC	0	4	0.538
Other	2	5	0.587
Stage			
I-IIIA	1	6	1.000
IIIB-IV	3	10	
Use of systemic steroids			
Yes	0	2	1.000

Ad, adenocarcinoma; ICI, immune checkpoint inhibitor; LCNEC, large cell neuroendocrine carcinoma, NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; Sq, squamous cell carcinoma.

Four patients in the ICI group had advanced stage NSCLC (PS 0, n=1; PS 1, n=1; PS 3, n=1; and PS 4, n=1). All of these patients died of lung cancer, and their survival times from onset of HZ were 4, 4, 1, and 1 month, respectively. The median time from ICI administration to the onset of HZ was 8.5 (range, 7–10) months.

Non-elderly patients

The lifetime risk of contracting HZ increases markedly in elderly patients due to an age-related decline in VZV-specific cell-mediated immunity (5). Therefore, we further analyzed the frequency of HZ in lung cancer patients aged under 65 years (*Table 3*). Our population included 105 patients aged <65 years, including 24 in the ICI group and 81 in the non-ICI group. A total of four patients developed HZ, including three (12.5%) in the ICI group and one (1.2%) in the non-ICI group (P=0.0365). The ages of onset of HZ were 46, 63, and 64 years in patients in the ICI group with a PS of 0, 3, and 4, respectively, and 61 years in patients in the non-ICI group with a PS of 0. There were more patients with stage IIIB–IV than stage I–IIIA (P=0.008) in the ICI group, which may suppress cellular immunity for VZV. None of the patients used steroids. Survival time after HZ onset was short (1–4 months) in the ICI group.

Table 3 Characteristics of patients <65 years old

	ICI group	Non-ICI group	P value
No.	24	81	
Mean age, years (range)	54.6 (29–64)	57.1 (37–64)	0.111
Smoker (Brinkman Index ≥400)	14	66	1.000
Performance status			
0	10	38	0.650
1	14	33	0.130
2	0	8	0.190
3/4	0	2	1.000
Histological type			
NSCLC	23	72	0.310
Ad	16	52	1.000
Sq	6	14	0.390
LCNEC	1	5	1.000
SCLC	1	9	0.448
Stage			
I-IIIA	3	34	0.008
IIIB-IV	21	47	

Ad, adenocarcinoma; ICI, immune checkpoint inhibitor; LCNEC, large cell neuroendocrine carcinoma: NSCLC, non-small cell lung cancer; SCLC: small cell lung cancer; Sq, squamous cell carcinoma.

Details of the four patients under the age of 65 years who developed HZ are shown in *Table 4*.

Discussion

There was no difference in the frequency of HZ between lung cancer patients who received ICI and those who received cytotoxic chemotherapy alone. However, patients under 65 years of age treated with ICI had a higher likelihood of HZ than those treated with chemotherapy alone (12.5% *vs.* 1.2%, respectively, P=0.0365).

Association of infection and treatment with ICI

Preclinical and clinical data support the use of ICI in a rapidly expanding spectrum of malignancies. The use of ICI seems to be less likely to cause infection because it upregulates the immune system. In a previous study, serious infectious complications developed in 54 of 740 patients with malignant melanoma treated with ICI over a 4-year period (2). The average time from administration of ICI to the onset of infection was 135 days. In the first 6 months after the start of ICI, 43 of 54 patients (79.6%) with a mean age of 61.6 years developed infection, and it was estimated that nine patients (17%) died as a result of the infection. The causative microorganisms were bacteria (79.3%), fungi (10.3%), and viruses (8.6%). HZ develops in association with the immunocompromised state associated with aging, underlying illness, and treatment with immunosuppressive agents (5).

Hypothesis of HZ onset during recovery of immune function

A unique set of complications emerged after the start of HAART despite confirmed virological control and immunological recovery (7). The opportunistic infections that should have subsided worsened again, and new infections were triggered within weeks to months of the onset of HAART, despite increased $CD4^+$ T cell counts and decreased viral load. The pathophysiology underlying IRIS is not completely understood, but it is assumed that the clinical symptoms are not a reflection of the virus growth itself, but rather of the immune response to the viral antigen (10). The concept of IRIS is expanding beyond HAART therapy for HIV infection, and IRIS is thought to occur with recovery or enhancement of immune function. Non-HIV IRIS is broadly defined as an inflammatory event in various organs against antigens or pathogenic microorganisms assumed to have been present before recovery from immunodegradation in HIV-negative patients. Potential triggers for recovery from immunocompromised conditions include discontinuation or sudden tapering of systemic steroids or immunosuppressants, diminished efficacy of biologics containing antitumor necrosis factor (TNF)-α antibodies, and possibly the use of ICI for advanced malignancies (*Figure 1*). Discontinuation of systemic steroids, immunosuppressants, and TNF-α inhibitors may be associated with paradoxical exacerbation of tuberculosis (11-13). A case of tuberculosis in a patient receiving nivolumab was considered to involve IRIS (3). IRIS due to immune recovery is assumed to be a factor in HZ (14), and there is concern about increases in the rate of HZ caused by non-HIV IRIS, especially with ICI treatment (15). As elderly patients are often treated with ICI (16), attention should be

Table 4 Characteristics of patients <65 years old at the onset of herpes zoster

No.	Age	PS	Metastatic sites	ICI	Survival from HZ onset (months)
1	46	0	Non-regional lymph nodes	Nivolumab	4
2	63	3	Bone, liver, non-regional lymph nodes	Pembrolizumab	1
3	64	4	None	Nivolumab	1
4	61	0	Bone, liver, non-regional lymph nodes	None	61

ICI, immune checkpoint inhibitor; HZ, herpes zoster; PS, performance status.

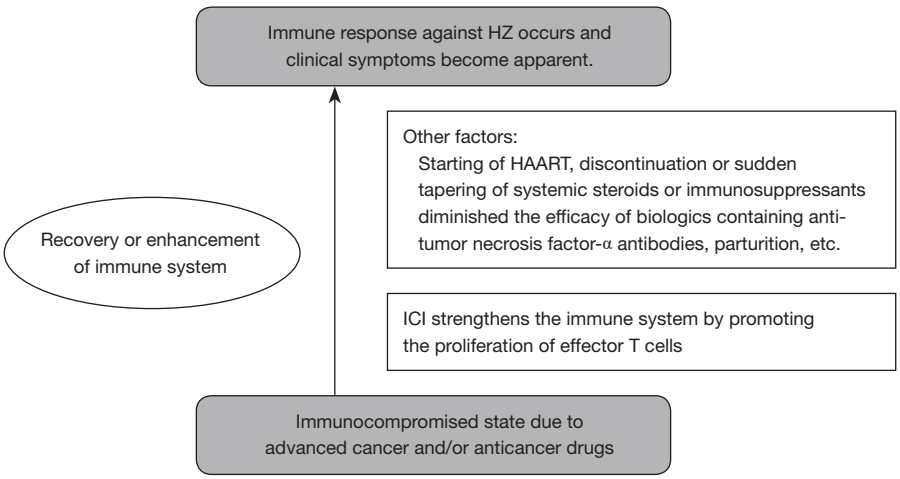

Figure 1 Schematic representation of the concept of immune reconstitution inflammatory syndrome. HAART, highly active antiretroviral therapy; HZ, herpes zoster; ICI, immune checkpoint inhibitor.

paid to the emergence of HZ.

Although the pathogenesis of HZ as HIV-associated IRIS remains unknown (17), increase in $CD8^+$ T cells were associated with the risk of HZ (18). When HIV patients with IRIS were divided into those developing HZ and those developing any other manifestations, there were no differences in baseline $CD4^+$ and $CD8^+$ T cell counts (19). In HIV patients who experienced tuberculosis-associated IRIS (TB-IRIS), a significantly lower proportion of regulatory T cells in TB-IRIS patients as compared to non-TB-IRIS patients at week 34 post-tuberculosis therapy initiation (20). The analysis of T cell subsets at baseline and at the onset of HZ may be useful for clarifying the mechanism.

HZ in non-elderly patients

There was no significant difference in the occurrence of HZ between the ICI group (5%) and non-ICI group (4.5%) in the present study. Next, we focused on non-elderly patients, because it was difficult to determine whether HZ in elderly patients was due to immune reconstitution or age-related decline of the immune system. Among patients under 65 years of age, 3 of 24 (12.5%) in the ICI group and 1 of 81 (1.2%) in the non-ICI group developed HZ (P=0.0365). Bortezomib, a proteasome inhibitor, interferes with cell-mediated immunity and has been reported to cause a high rate of HZ during the treatment of multiple myeloma. Bortezomib was reported to be associated with a significantly higher incidence of HZ compared with dexamethasone (13% *vs.* 5%, respectively, P=0.0002) (21). In that study, the median age of patients treated with bortezomib was 62 years, and that of patients treated with dexamethasone was 61 years. This incidence rate of HZ was similar to that of the non-elderly ICI group in our study. The NCCN guidelines classify treatment with bortezomib as a high-risk factor for developing HZ; antiviral prophylaxis, such as acyclovir, famciclovir, and valacyclovir, is recommended (22). In addition, live and recombinant vaccine for VZV were approved by the Food and Drug

Administration for the prevention of HZ in adults aged ≥50 years (23). Therefore, it may be necessary to consider the administration of antivirals and vaccines in patients scheduled to receive ICI.

Limitations

This study had some limitations. First, it was a very small retrospective study conducted in a single institution. A larger prospective observation study is needed. Second, the survival period after the onset of HZ was very short in the ICI group, and serious general conditions including poor PS and advanced stage may have affected the development of HZ. Third, there is no evidence supporting the hypothesis that immune activation due to ICI can increase the incidence of HZ. The analysis of T cell subsets ($CD4^+$, $CD8^+$, regulatory T cell, etc.) at the onset of HZ should be investigated.

Conclusions

HZ was observed frequently in non-elderly patients treated with ICI. Because this was a very small retrospective study, large prospective observational studies are needed.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2764/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2764/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2764/coif). NO reports that he received honoraria for lectures from Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer Japan Inc., Boehringer-Ingelheim Japan, and Bristol-Myers Squibb Company Japan. TY reports that he received honoraria for lectures from Eli Lilly Japan K.K., Taiho Pharmaceutical Co., Ltd., Sun Pharma Japan Ltd., Kyorin Pharmaceutical Co., Ltd., Nippon Zoki Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Maruho Co., Ltd., Torii Pharmaceutical Co., Ltd., AbbVie GK, Sanofi K.K., Eisai Co., Ltd. YA reports that she received grants from AbbVie GK, Japan Blood Products Organization, Kaken Pharmaceutical Co., Ltd., Kyowa Kirin Co., Ltd., Maruho Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Nihon Pharmaceutical Co., Ltd., Sun Pharma Japan Ltd., Taiho Pharmaceutical Co., Ltd., Torii Pharmaceutical Co., Ltd., and honoraria for lectures from Asahi Kasei Pharma Corporation, Bayer Yakuhin Ltd., Bristol-Myers Squibb Company Japan, Chugai Pharmaceutical Co., Ltd., Common Achievement Tests Organization, Daiichi Sankyo Company Ltd., Eisai Co., Ltd., Eli Lilly Japan K.K., Janssen Pharmaceutical K.K., Japanese Dermatological Association, Kyorin Pharmaceutical Co., Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co., Ltd., Sanofi K.K., Sumitomo Dainippon Pharma Co., Ltd., Tsumura & Co. NT reports that he received grants from Eli Lilly Japan, AstraZeneca, Daiichi-Sankyo Pharmaceutical, Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer Japan Inc., Boehringer-Ingelheim Japan, Ono Pharmaceutical, Kyowa Hakko Kirin, Nippon Kayaku Co. Ltd., Takeda Pharmaceutical Co. Ltd., and honoraria for lectures from Eli Lilly Japan, AstraZeneca, Daiichi-Sankyo Pharmaceutical, Chugai Pharmaceutical, Taiho Pharmaceutical, Pfizer Japan Inc., Boehringer-Ingelheim Japan, Ono Pharmaceutical, MSD, Bristol-Myers Squibb Company. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Kawasaki Medical School (No. 5160-00) and individual consent for this retrospective analysis was waived.

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