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# Exploring the educational needs for severe immune-related adverse events of PD-1/PD-L1 inhibitors in advanced lung cancer: A single-center observational study

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## ARTICLE INFO

## ABSTRACT

*Objective:* With the expanded use of immunotherapy in medical oncology, effective patient education regarding immune-related adverse events (irAEs) is crucial for oncology nursing. Therefore, this study aimed to identify educational needs for preventing unscheduled hospitalizations due to severe irAEs.

*Methods:* We retrospectively reviewed the medical records of 159 consecutive patients with lung cancer who received programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors in 2020. We evaluated the frequency, severity, and unscheduled hospitalization due to irAEs based on the PD-1/PD-L1 inhibitor use. Educational needs were assessed based on initial symptoms, reporters, telephone consultation, and the time lag between symptom onset and hospital visit.

*Results:* Among 159 patients evaluable for irAEs, 73 (45.9%) experienced 91 irAEs during the study period. Seventeen patients (10.7%) required unscheduled hospitalization due to severe irAEs after a median duration of 4.1 days from symptom onset, and 52.9% visited hospitals after telephone consultations from caregivers. Pneumonitis (10 events) was the most frequent irAE requiring hospitalization, followed by adrenal insufficiency (three events). The type and severity of irAEs varied based on PD-1/PD-L1 inhibitor use.

*Conclusions:* The frequency of severe irAEs requiring hospitalization was high in patients who received PD-1/PD-L1 inhibitors for advanced lung cancer. The early detection of severe irAEs may be possible through education focusing on common irAEs that are potentially severe. Patients and caregivers should be aware of the importance of reporting slight changes in symptoms after PD-1/PD-L1 therapy initiation in a timely manner. Healthcare professionals need to acknowledge common irAEs and be qualified to implement systematic telephone triage of irAEs.

## Introduction

Newly emerged immune checkpoint inhibitors (ICIs) improved the progression-free and overall survival of patients with various cancer[1–4] and have been incorporated into the current standard of oncologic care. Among several ICIs, programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors are widely used to treat advanced lung cancer in Japan. Long-term survival has been achieved in patients who respond well to PD-1/PD-L1 inhibitors.[2,5] However, healthcare professionals (HCPs) need to focus their attention on immune-related adverse events (irAEs) because they require a screening and management strategy that is completely different from conventional chemotherapy.[6–8] IrAEs potentially occur in multiple organs, and onset timing varies extensively.[7,9] Most irAEs are mild in severity and are managed by close monitoring and symptomatic treatment. However, when some irAEs progress to severity, they may require intensive immunosuppressive therapy and lead to the discontinuation of treatment[9–12] or even life-threatening consequences.[13–16] Thus, the early detection of irAEs is key to appropriate management.[7,17–20] Moreover, since the presence of irAEs indicates enhanced efficacy,[21,22] the appropriate management of

irAEs potentially maximizes therapeutic outcomes. Based on these features of irAEs, HCPs must shift their mindset toward strategies against adverse drug reactions.

Guidelines and other literature emphasize the importance of patient education because irAE onset is unpredictable, and patient education is critical for maximizing the early recognition and reporting of irAEs.[10,17–19,23–26] Patients need to receive timely and up-to-date education on the mechanism of action underlying immunotherapy and the possible clinical manifestations of irAEs. However, effective patient education and the ideal duration for monitoring irAEs are not clear. In addition, appropriate educational tools and outcome measures have not yet been established. Hence, developing effective patient education and establishing standard outcome measures is important to ensure the quality of patient care in oncology nursing.

Accordingly, we aimed to explore the educational needs of patients with advanced lung cancer who received PD-1/PD-L1 inhibitors. We collected detailed clinical data on the onset of severe irAEs to obtain implications for strategic patient education.

## Methods

### Participants and procedures

We retrospectively reviewed patients with advanced lung cancer who started treatment with PD-1/PD-L1 inhibitors at Shizuka Cancer Center between January and December 2020. Patients were excluded if they received PD-1/PD-L1 inhibitors in clinical trials or transferred to other hospitals during PD-1/PD-L1 therapy. IrAEs were defined as adverse events confirmed to be related to PD-1/PD-L1 inhibitors by the attending physicians based on onset timing, symptoms, laboratory data, imaging studies, and responsiveness to immunosuppressive treatment. Severe irAEs were defined as irAEs that required unscheduled hospitalization for management.

We collected patient demographic data, such as age, gender, tumor histology, stage, and mode of PD-1/PD-L1 therapy (single-use, combination with other cytotoxic chemotherapy, or maintenance therapy after chemoradiation). IrAE severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE, Ver 5.0). To explore the educational need of patients and family caregivers, we reviewed the exact situation at the time of onset using electronic medical records, including initial symptoms, reporters, telephone consultations, and the time lag between symptom onset and hospital visit for patients with severe irAEs. Herein, we describe the initial hospitalization of patients who were hospitalized on multiple occasions for recurrence of the same irAEs. The institutional ethical review board approved the study protocol (Approval No. J2021-40-2021-1-2).

### Data analysis

Patients with irAEs were divided into two groups according to whether they were hospitalized due to irAEs, and the chi-square or Fisher's exact test was applied to categorical variables to compare the characteristics of patients in the two groups. For continuous variables, the Mann–Whitney U test was performed. Statistical significance was set at $P < 0.05$, and IBM SPSS Statistics for Windows (version 27.0; IBM, Tokyo, Japan) was used for statistical analyses. Descriptive statistics were generated for the incidence and severity of irAEs, hospitalizations due to severe irAEs, duration from PD-1/PD-L1 initiation to irAE onset, and the time lag between symptom onset and hospital visit. In addition, the situation at the time of irAE onset was described narratively.

## Results

### Patient backgrounds and irAE incidence

A total of 171 patients with advanced lung cancer started PD-1/PD-L1 inhibitors between January and December 2020 (Fig. 1). One hundred and fifty-nine patients were evaluated in this study. The median follow-up period after the initiation of PD-1/PD-L1 inhibitors was 214 days (range: 37–391). Seventy-three patients (45.9%) who developed any irAE during the observation period were included in this analysis.

The median age was 71 (46–86) years. Most patients were men with stage IV disease or postoperative recurrence. The most commonly used PD-1/PD-L1 inhibitor was durvalumab, followed by pembrolizumab, atezolizumab, and nivolumab. Seventeen (10.7%) patients with irAEs required irAE-related hospitalization. There were no significant differences in age, sex, and tumor histology between hospitalized and non-hospitalized patients (Table 1).

### Distribution of irAEs and differences according to the mode of PD-1/PD-L1 usage

A total of 91 various grades of irAEs were observed in 73 (45.9%) of 160 evaluable patients during the observation period (Table 2). Fifty-six patients developed one irAE, 16 developed two, and one patient developed three. The most common irAE was dermatitis (31 patients, 19.5%), followed by pneumonitis (22 patients, 13.8%), hypothyroidism (18 patients, 11.3%), adrenal insufficiency (six patients, 3.6%), and hepatitis (six patients, 3.8%). Colitis occurred in one patient. Seventeen patients (10.7%) required hospitalization owing to irAEs. The most common cause of severe irAEs was pneumonitis (10 patients, 6.3%), followed by adrenal insufficiency (three patients, 1.9%). Dermatitis and other irAEs occurred at a rate of <1% each.

The frequency, types, and severity of irAEs varied according to the three modes of PD-1/PD-L1 usage, as follows: Regarding single-use PD-1/PD-L1 inhibitors, 23 of 46 evaluable patients (50.0%) developed any-grade irAEs, and eight (17.4%) patients required hospitalization for pneumonitis (five patients, 10.9%), adrenal insufficiency (three patients, 6.5%), and hepatitis (one patient, 2.2%). As regards the combined use of PD-1/PD-L1 inhibitors with cytotoxic chemotherapy, 22 of 68 evaluable patients (32.4%) developed any-grade irAEs, and seven (10.3%) required hospitalization for pneumonitis (five patients, 7.4%), dermatitis (one patient, 1.5%), and autoimmune hemolytic anemia (one patient, 1.5%). In terms of the maintenance use of durvalumab, 28 of 45 evaluable patients (62.2%) developed any-grade irAEs, and two (4.4%) required hospitalization for colitis and posterior reversible encephalopathy syndrome (one patient, 2.2% each). The frequency of dermatitis with durvalumab (16 patients, 35.6%) was higher than that with the other two modes of PD-1/PD-L1 usage; however, no patient required hospitalization. The frequency of pneumonitis (five patients, 11.1%) was similar to that with the other two modes of PD-1/PD-L1 usage; nevertheless, no patient required hospitalization.

### Timing of irAE onset

The median duration between irAE onset and PD-1/PD-L1 initiation among the 91 events was (interquartile range [IQR], 27–126) days (Fig. 2). Regarding the 18 hospitalized events, the median duration between irAE onset and PD-1/PD-L1 initiation was 7 (IQR, 21–97.8) days. Dermatitis, the most frequently observed irAE, tended to occur early; the median duration between irAE onset and PD-1/PD-L1 initiation was 41.0 (IQR, 14–102.5) days. Only one event required hospitalization: Stevens–Johnson syndrome which occurred 13 days after the PD-1/PD-L1 initiation. Pneumonitis, the next most frequent irAE, occurred at a median of 70.0 (IQR, 28–141.3) days after the PD-1/PD-L1 initiation. The distribution of onset time was bimodal, with over half of the events occurring within the first 90 days. The median onset time for patients who required hospitalization was 60 (IQR, 19–154) days, and four of seven hospitalizations occurred after 180 days. In terms of endocrine disorders, hypothyroidism was predominantly observed within 90 days of PD-1/PD-L1 initiation (median, 87.5 [IQR, 59.5–136.3] days), and no patient required hospitalization. In contrast, adrenal insufficiency was predominantly observed after 90 days (median, 119.5 [IQR,
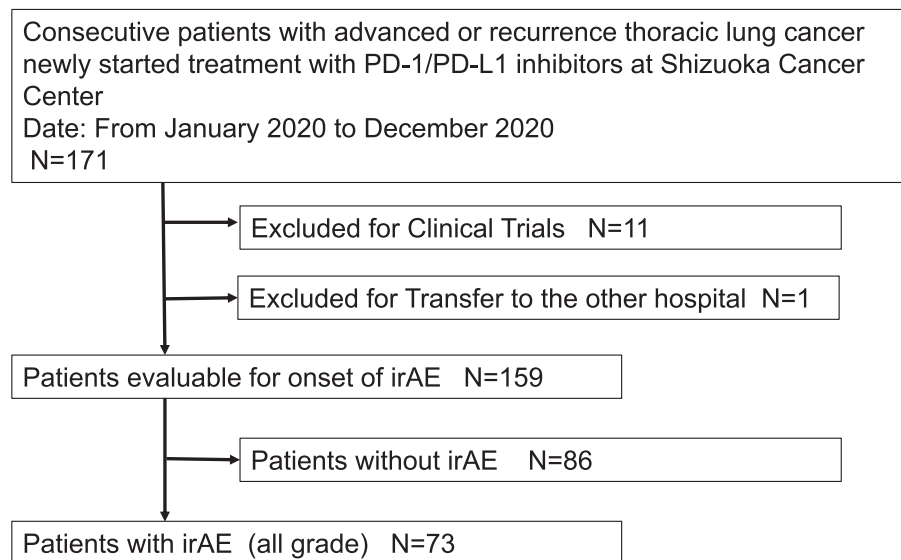
**Fig. 1.** Patient flow diagram. irAE, immune-related adverse event; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

**Table 1**
Patient characteristics.

| Characteristics | All patients with irAEs | Patients with irAEs who did not require hospitalization | Patients with irAEs who required hospitalization | P-value |
|---|---|---|---|---|
| No. of patients | 73 | 56 | 17 | |
| Median age (range) | 71 | 70 (46–86) | 72 (56–82) | 0.23 |
| Gender | | | | |
| Male | 51 | 38 (74.5) | 13 (25.5) | 0.50 |
| Female | 22 | 18 (81.8) | 4 (18.2) | |
| Histology | | | | |
| Non-small-cell lung cancer | 63 | 50 (79.4) | 13 (20.6) | 0.23 |
| Small-cell lung cancer | 10 | 6 (60.0) | 4 (40.0) | |
| Stage | | | | |
| III | 34 | 30 (88.2) | 4 (11.8) | 0.03 |
| IV or postoperative recurrence | 39 | 26 (46.4) | 13 (72.2) | |
| Type of immunotherapy | | | | |
| Durvalumab | 29 | 27 (93.1) | 2 (6.9) | 0.02 |
| Pembrolizumab | 28 | 19 (67.9) | 9 (32.1) | |
| Atezolizumab | 13 | 7 (53.8) | 6 (46.2) | |
| Nivolumab | 3 | 3 (100.0) | 0 (0.0) | |
| Modes of PD-1/PD-L1 usage | | | | |
| Single-use | 23 | 15 (65.2) | 8 (34.8) | 0.04 |
| Combination with cytotoxic chemotherapy | 22 | 15 (68.2) | 7 (31.8) | |
| Maintenance therapy after chemoradiation | 28 | 26 (92.9) | 2 (7.1) | |

irAE, immune-related adverse event; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.

97.8–150.5]), and three of six patients required hospitalization. Hospitalization events for hepatitis, colitis, and autoimmune hemolytic anemia were observed within 90 days.

*IrAEs requiring hospitalization and the situation at onset*

Table 3 summarizes the clinical data of the 16 patients (17 events) at the onset of severe irAEs requiring hospitalization. We excluded one patient with posterior reversible encephalopathy syndrome, who was initially hospitalized at another hospital at irAE onset and subsequently transferred to our hospital because detailed clinical information at the onset was unavailable. The median number of days from irAE-symptom onset to hospital visit was four days (range, 0–14), with five events (29.4%) taking more than seven days. Thirteen hospitalizations (76.5%) were found in unscheduled hospital visits. Regarding telephone consultation, most reporters were caregivers (nine hospitalizations, 52.9%), patients themselves (three hospitalizations, 17.6%), and home-visit nurses (one hospitalization, 5.9%).

Dyspnea was the initial symptom in eight of the 10 cases of pneumonitis, followed by fatigue and anorexia. The median number of days from irAE-symptom onset to hospital visit was four days (range, 0–14). Two of the 10 patients did not consult HCPs despite their awareness of dyspnea. Furthermore, after more than a one-week time lag, the patients were diagnosed with severe pneumonitis at scheduled hospital visits. The remaining eight events were all unscheduled visits triggered by reports made by individuals other than patients. The median CTCAE grade was 3 (range, 2–4), and there was no clear association between the onset of PD-1/PD-L1 initiation and severity.

In terms of adrenal insufficiency, fatigue was the initial symptom in all three events. Nausea, dyspnea, and fever were also observed. The median number of days from symptom onset to hospital visit was four days (range, 2–8). Two severe (CTCAE grade 3) events were observed at scheduled hospital visits, and the remaining one was grade 2, identified at an unscheduled hospital visit triggered by a report from a family caregiver. One patient was re-hospitalized for the recurrence of adrenal insufficiency caused by the discontinuation of oral steroids.

The other four hospitalized events were all observed during unscheduled hospital visits, and all were grade 3 or 4. The median number of days from symptom onset to hospital visit was one day (range, 0–11). Two severe-irAE events required hospitalization after the discontinuation of PD-1/PD-L1 therapy: one patient had pneumonia, and the other had adrenal insufficiency.

## Discussion

To the best of our knowledge, this is the first study to uncover the detailed clinical course of severe irAEs, including symptom onset, reporters, and delays, among patients with lung cancer receiving PD-1/PD-L1 inhibitors. First, we found that 11% of patients with advanced lung cancer receiving PD-1/PD-L1 inhibitors required hospitalization because of severe irAEs, with pneumonitis being the most frequent, followed by adrenal insufficiency. Second, severe irAEs were often detected during unscheduled hospital visits triggered by reports from caregivers after a

**Table 2**
Frequency of irAE and associated hospitalizations by the modes of PD-1/PD-L1 usage. $N = 91$ (Include overlapping).

| | Any use | | Single-use | | Combination with cytotoxic chemotherapy | | Maintenance therapy after chemoradiotherapy | |
|---|---|---|---|---|---|---|---|---|
| No. of evaluable patients for onset of irAEs | 159 | | 46 | | 68 | | 45 | |
| irAEs, n (%)[a] | All | Hospitalization required | All | Hospitalization required | All | Hospitalization required | All | Hospitalization required |
| Any irAEs | 73 (45.9) | 17 (10.7) | 23 (50.0) | 8 (17.4) | 22 (32.4) | 7 (10.3) | 28 (62.2) | 2 (4.4) |
| Dermatitis | 31 (19.5) | 1 (0.6) | 6 (13.0) | 0 | 9 (13.2) | 1 (1.5) | 16 (35.6) | 0 |
| Pneumonitis | 22 (13.8) | 10 (6.3) | 9 (19.6) | 5 (10.9) | 8 (11.8) | 5 (7.4) | 5 (11.1) | 0 |
| Hypothyroidism | 18 (11.3) | 0 | 5 (10.9) | 0 | 5 (7.4) | 0 | 8 (17.8) | 0 |
| Adrenal insufficiency | 6 (3.8) | 3 (1.9) | 4 (8.7) | 3 (6.5) | 2 (2.9) | 0 | 0 | 0 |
| Hepatitis | 6 (3.8) | 1 (0.6) | 2 (4.3) | 1 (2.2) | 1 (1.5) | 0 | 3 (6.7) | 0 |
| Colitis | 1 (0.6) | 1 (0.6) | 0 | 0 | 0 | 0 | 1 (2.2) | 1 (2.2) |
| Others[b] | 7 (4.4) | 2 (1.3) | 2 (4.3) | 0 | 4 (5.9) | 1 (1.5) | 1 (2.2) | 1 (2.2) |

irAE, immune-related adverse event; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.
[a] Proportion of patients evaluable for irAEs.
[b] Infusion reaction; 2: Dry mouth; 1: Autoimmune hemolytic anemia; 1: Hyperamillasemia; 2: Posterior reversible encephalopathy syndrome; 1.
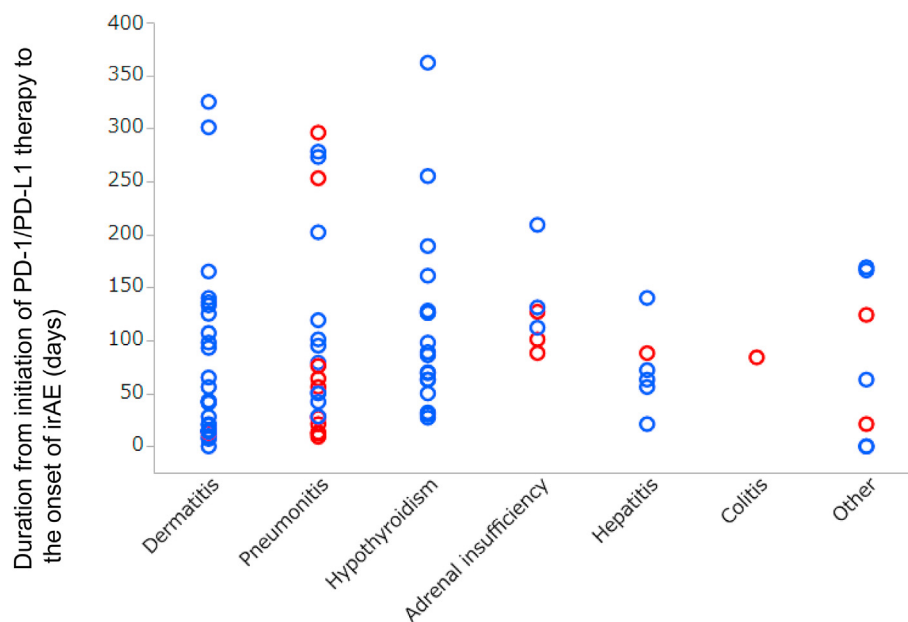


**Fig. 2.** Duration from initiation of PD-1/PD-L1 therapy to irAE onset. Red circle: irAE with hospitalization; Blue circle: irAE without hospitalization. irAE, immune-related adverse event; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

several-day time lag from symptom onset. Third, frequent irAEs and their severities varied depending on the mode of PD-1/PD-L1 usage, that is, single-use, combination with cytotoxic chemotherapy, or maintenance use after chemoradiotherapy.

An overview of the incidence of severe irAEs shows that one in every 10 patients required irAE-related hospitalization. A previous study reported a lower proportion of severe irAEs than this study in patients with lung cancer receiving PD-1/PD-L1 inhibitors in clinical trials.[27] As for hospitalization due to irAE, there are some studies reporting a similar rate to our study.[28,29]

*Educational needs of patients and family caregivers*

The importance of early identification in the management of irAEs cannot be overemphasized. Patient education is even more important than conventional chemotherapy or targeted therapy.[18,26,30] In the

present study, severe irAEs were often detected during an unscheduled hospital visit, triggered by reports from caregivers via phone. Most patients experienced a time lag of several days from symptom onset before reporting to the HCPs. Four of the 17 patients did not report symptoms to the HCPs and waited until scheduled visits. First, this result supports the importance of educating patients and caregivers. Caregivers play an important role in managing irAEs to detect abnormalities in patients or report them on their behalf. Second, non-specific symptoms potentially contribute to the time lag, especially pneumonitis and adrenal insufficiency, which are common in hospitalized patients. Non-specific symptoms, such as fatigue and anorexia, render it difficult for patients and caregivers to recognize irAEs, and they tend to disregard these symptoms.[31] Although patients need to understand the mechanisms underlying irAEs and differences in the side effects of cytotoxic chemotherapy, older patients, who commonly develop lung cancer, may find them difficult to understand. Therefore, the amount of knowledge provided

**Table 3**

Situation at the onset of irAE for patients who required hospitalization.

| Type of irAE | Age/Gender | Days from the onset of irAE to the hospital visit | Type of hospital visit | Person who consulted health care professionals via phone | Trigger symptoms | Grade for irAE | Days from initiation of PD-1/PD-L1 to the onset of irAE |
|---|---|---|---|---|---|---|---|
| Pneumonitis | | | | | | | |
| | 63/M[a] | 14 | Planned | none | Dyspnea, fatigue, anorexia | 2 | 21 |
| | 81/M | 7 | Planned | none | Dyspnea, anorexia, sputum | 2 | 64 |
| | 71/M[b] | 7 | Unplanned | Caregiver | Fatigue, fever, headache | 3 | 76 |
| | 76/M[b] | 5 | Unplanned | Caregiver | Dyspnea, cough | 3 | 296 |
| | 76/M | 4 | Unplanned | Caregiver | Dyspnea | 3 | 12 |
| | 72/M | 4 | Unplanned | Caregiver | Dyspnea, chest pain | 3 | 27 |
| | 72/M | 2 | Unplanned | Home-visit nurse | Dyspnea, anorexia | 3 | 56 |
| | 67/M | 0 | Unplanned | Patient | Dyspnea | 3 | 253 |
| | 82/M | 0 | Unplanned | Caregiver | Fatigue, immobility, abnormal behavior | 4 | 9 |
| | 80/M | 0 | Unplanned | Caregiver | Dyspnea, vomiting | 2 | 13 |
| Adrenal insufficiency | | | | | | | |
| | 77/F | 8 | Planned | none | Fatigue, anorexia, nausea, vomiting | 3 | 101 |
| | 63/M[a,c] | 4 | Planned | none | Fatigue, anorexia, fever | 3 | 127 |
| | 56/M | 2 | Unplanned | Caregiver | Fatigue, fever, dyspnea, hypotension | 2 | 88 |
| Dermatitis | | | | | | | |
| | 64/F | 1 | Unplanned | Patient | Skin rash, hot flash, fever | 4 | 13 |
| Hepatitis | | | | | | | |
| | 76/M | 11 | Unplanned | Patient | Abdominal pain | 4 | 88 |
| Colitis | | | | | | | |
| | 71/F | 1 | Unplanned | Caregiver | Diarrhea | 3 | 84 |
| Autoimmune hemolytic anemia | | | | | | | |
| | 71/F | 0 | Unplanned | Caregiver | Fatigue, nausea, anorexia | 3 | 21 |

irAE, immune-related adverse event; PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1M: male; F: female.

A patient with posterior reversible encephalopathy syndrome was excluded from this analysis because of hospitalization at another hospital at the onset of irAE and later transfer.

[a] Patient onset of another irAE at different times.

[b] Patients hospitalized twice or thrice with pneumonitis recurrence. This table describes the first hospitalization.

[c] A patient was re-hospitalized due to recurrence of adrenal insufficiency caused by discontinuation of oral steroids. This table describes the first hospitalization.

and timing of education must be determined. The bottom line of patient education is that patients can consult HCPs in a timely manner and report that they have been exposed to PD-1/PD-L1 inhibitors and their subjective symptoms. McGettigan et al highlighted that any change from baseline health, whether subtle or seemingly insignificant, may be a sign of an irAE and should thus be reported immediately to HCPs.[25]

Differences in irAE frequency and severity according to the mode of PD-1/PD-L1 usage are another point to be considered in patient education. In this study, patients who received PD-1/PD-L1 inhibitors as maintenance therapy after chemoradiation were characterized by a high frequency and low severity of irAEs. Most of the patients experienced mild dermatitis or hyperthyroidism. The purpose of chemoradiation followed by PD-1/PD-L1 therapy for stage III lung cancer is to achieve a radical cure[32]; therefore, it would be beneficial for patients to avoid treatment interruption or discontinuation by appropriately educating them.

It is important to educate patients and caregivers that even slight changes in symptoms after initiating ICI therapy should be reported and encourage them not to hesitate to consult HCPs by phone. In addition, education and follow-up of symptoms should be provided regularly and repeatedly, even after the completion or discontinuation of ICI therapy.

*Importance of telephone triage*

Twelve patients were found to have severe irAEs during unscheduled hospital visits, and they consulted HCPs via phone regarding their symptoms before hospital visits. The importance of telephone triage in managing the side effects of anticancer treatment is significant.[33,34] The purpose of telephone triage is to identify patients requiring an immediate

hospital visit, those requiring follow-up at shorter intervals, and those able to wait until the next scheduled visit.[35] Reducing unnecessary emergency room visits and medical costs is also important.[36] For the management of irAEs, telephone triage is often the initial step to detecting irAEs.[19] In response to telephone consultations from patients and caregivers, quick and in-depth assessments using professional irAE knowledge are required in HCPs. In addition to the triage itself, HCPs also need to inform patients and caregivers of how their symptoms can change in the future and signs of deterioration that require further contact. Thus, phone communication is an opportunity for patient education. Jamieson et al reported that patients and caregivers hesitated to consult HCPs for the following reasons: they thought that they might be very busy; past experiences of not being treated properly, such as being told to call back again during business hours; or fear of disease progression or treatment discontinuation.[31] HCPs need to respond carefully to patients and caregivers through open communication and pay attention to the psychological aspects of patients and caregivers.

In addition to education for HCPs, a systematic approach is required to improve telephone triage quality because not all HCPs specialize in irAEs. Developing evidence-based triage and care protocols based on institutional requirements is warranted.[35] As Cole et al highlighted, interventions are necessary at three levels (patients, HCPs, and institutions) to improve irAE management.[30] Optimizing telephone triage by both HCP education and organizational interventions is valid.

*IrAEs that frequently required hospitalization*

In this study, one in every 10 patients required irAE-related hospitalization. The most frequent complication was pneumonitis, followed by

adrenal insufficiency. These results are consistent with those of the previous study focusing on irAE-related hospitalizations.[28]

Pneumonitis is an irAE with many severe cases.[13] In this study, ten patients (6.3% of evaluable patients) required hospitalization because of pneumonitis, a slightly higher figure than in previous reports.[37,38] Two patients were diagnosed with severe pneumonitis at scheduled visits after more than a one-week time lag after dyspnea onset. Fifty to 87% of patients with lung cancer have dyspnea at baseline,[39,40] and difficulty recognizing increased dyspnea might have contributed to the delay in consultation and diagnosis. The self-monitoring of oxygen saturation using pulse oximetry may contribute to early detection.

The timing of pneumonitis onset varies widely. However, severe pneumonitis is often reported to develop early during treatment.[13] In the present study, all but two events occurred within 90 days of PD-1/PD-L1 therapy initiation. This result demonstrates the importance of recognizing that severe pneumonitis tends to occur relatively early after initiating PD-1/PD-L1 therapy, and pneumonitis is an irAE that tends to be severe.

The second most frequently hospitalized irAEs was adrenal insufficiency. Adrenal insufficiency is reportedly a relatively rare irAE. A large meta-analysis reported the incidence to be 0.7% for all grades.[41] Another report found 3.5%[42] of patients receiving single-use PD-1/PD-L1 inhibitors, similar to the population in this study. In this study, two of three patients were diagnosed at a scheduled hospital visit. However, they did not consult HCPs, regardless of their awareness of fatigue, anorexia, or nausea. Regarding adrenal insufficiency, the non-specific presentation of symptoms might have been associated with a consultation delay. Fatigue, fever, and dyspnea have been noted as risk factors for the misdiagnosis of irAEs.[43] Although fatigue is often observed in patients with advanced cancer,[44] an irAE must be suspected when patients undergoing or past PD-1/PD-L1 therapy report new or worsening fatigue. We also need to educate patients and caregivers on the need to pay attention to fatigue after the initiation of PD-1/PD-L1 therapy, and fatigue deserves to be reported.

The median time from the initiation of PD-1/PD-L1 therapy to the onset of adrenal insufficiency was 119.5 days. All events had onset after 90 days. A similar report from Japan revealed a median duration from the initiation to onset of 5.6 months (1.6–12.6 months).[43] Therefore, the duration from PD-1/PD-L1 therapy initiation to the onset of adrenal insufficiency tends to be longer than that of other endocrine disorders, such as hypothyroidism.

The patient was re-hospitalized for the recurrence of adrenal insufficiency caused by discontinuation of oral steroids. Endocrine disorders include adrenal insufficiency, which often requires long-term hormone replacement therapy.[41] Therefore, it is important to provide patient guidance regarding steroid medication. While adrenal insufficiency potentially leads to fatal adrenal crisis, subjective symptoms such as fatigue often improve quickly with steroid administration.[42] Thus, early consultation and diagnosis might have prevented hospitalization.

In summary, pneumonitis and adrenal insufficiency can be considered irAEs that emphasize patient education during the PD-1/PD-L1 therapy for lung cancer. Pneumonitis has a high frequency and high risk of being severe, whereas adrenal insufficiency has a low frequency but a high proportion of severe events. In addition, both are characterized by non-specific symptom presentations that are difficult to recognize and diagnose.

*Limitations*

This study has certain limitations. First, this was a retrospective study with a small sample size in a single Japanese institution. Therefore, there might have been some unmeasured confounders, and it is difficult to generalize the results of this study. Second, we did not use detailed and structured information sheets to collect patients' educational needs. This is one of the major limitations of our retrospective study. Besides, a deeper qualitative analysis of the situations and experiences of patients

and caregivers based on data obtained through interviews is warranted. Third, the lack of objectivity in the diagnostic criteria of "irAEs requiring hospitalization" is another limitation. Fourth, owing to the difficulty in diagnosing irAEs, not all irAEs might have been recognized as irAEs. Finally, since the observation period was brief, some irAEs were likely to develop after that time. A longer follow-up period may help clarify how long irAEs should be focused on after initiating PD-1/PD-L1 therapy.

Recently, a nurse-led randomized controlled trial[45] was conducted to evaluate the efficacy of a patient-reported monitoring system for irAEs based on the patient-reported outcomes version of the CTCAE (PRO-CT-CAE™).[46] However, the effect of reducing severe irAEs, which was the primary outcome, was not observed. It is necessary to accumulate data through practice and research to ensure effective patient education and timing. Moreover, as the frequency of anti-CTLA-4 antibodies in lung cancer increases, severe irAEs are likely to increase, especially gastrointestinal irAEs, such as colitis.[10,47,48] The single or combinatorial use of ICIs will be more prevalent in various cancers at various stages. Therefore, the management of irAEs in nursing is becoming increasingly important.

## Conclusions

For advanced lung cancer, approximately half of the patients treated with PD-1/PD-L1 developed irAEs, and 11.3% required hospitalization. Over half of the hospitalizations were triggered by reports by caregivers via phone, unscheduled hospital visits led to the detection of severe irAEs, and most patients experienced several-day time lags from symptom onset before reporting to HCPs. When educating patients and caregivers, HCPs need to emphasize that even slight changes in symptoms after initiating ICI therapy should be reported and encourage them to not hesitate to consult HCPs. The minimum goal of education should be to ensure that patients or caregivers consult HCPs in a timely manner and report any exposure to PD-1/PD-L1 inhibitors. The issues to be addressed by HCPs are the establishment of a care system to manage irAEs by improving individual knowledge and HCP skills as well as developing an organizational system, such as the telephone triage protocol.

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