Trends in Immunotherapy (2022) Volume 6 Issue 1
doi:10.24294/ti.v6.i1.1386

CASE REPORT

Immune-related adverse events caused by combined immune checkpoint inhibitor therapy with nivolumab and ipilimumab for lung cancer

Takashi Nomizo[1*], Haruka Yamamoto[1], Tsunetaka Murayama[1], Hiroko Fukata[1], Yasukiyo Nakamura[1], Mami Sonomura[2], Aika Okuno[2], Naoki Kanda[3], Chihiro Watanabe[4], Hideo Kita[1]

[1] Department of Respiratory Medicine, Takatsuki Red Cross Hospital, 1-1-1 Abuno, Takatsuki, Osaka 569-1096, Japan. E-mail: hideok@takatsuki.jrc.or.jp*

[2] Department of Dermatology, Takatsuki Red Cross Hospital, 1-1-1 Abuno, Takatsuki, Osaka 569-1096, Japan.

[3] Department of Gastroenterology, Takatsuki Red Cross Hospital, 1-1-1 Abuno, Takatsuki, Osaka 569-1096, Japan.

[4] Department of Pathology, Takatsuki Red Cross Hospital, 1-1-1 Abuno, Takatsuki, Osaka 569-1096, Japan.

ABSTRACT

It has been less than a decade since immune checkpoint inhibitors became the mainstay of lung cancer treatment, and 2020 saw the advent of the era of complex immune checkpoint inhibitors. Although clinical trials have shown that the therapeutic effects of complex immune checkpoint inhibitors are favorable, they are associated with an increase in adverse events. The use of combined immune checkpoint inhibitors in clinical practice has progressed slowly, and the frequency and types of adverse events they cause remain unclear. Here we report the adverse events of six patients with lung cancer treated with regimens containing nivolumab and ipilimumab in 2021. Four of the six patients had grade 3 or higher adverse events, including one patient with lung injury and one patient with skin injury, both of whom died. The timing and nature of the adverse events were difficult to predict.

Keywords: Lung Cancer; Immune Checkpoint Inhibitors; Nivolumab; Ipilimumab; 9LA; Immune-related Adverse Events

ARTICLE INFO

Received 11 November 2021
Accepted 2 December 2021
Available online 14 January 2022

1. Introduction

According to statistics from The American Cancer Society, lung cancer is the second most common malignant disease of both sexes in the United States, affecting 230,000 people and killing more than 130,000 people annually, accounting for 25% of all cancer deaths[1]. In Japan, more than 70,000 people die of lung cancer annually, making it the leading cause of death among men and the second leading cause of death among women[2]. As such, lung cancer represents a profoundly serious disease, and treatment options are constantly advancing. Historically, tyrosine kinase inhibitors, which were introduced in the 2000s, have shown dramatic therapeutic effects on some lung cancers. Nivolumab (NIVO) and other immune checkpoint inhibitors (ICIs) were first used in clinical practice in the 2010s, leading to a dramatic improvement in lung cancer treatment. In 2015, the focus of lung cancer treatment shifted to ICIs, such as NIVO or pembrolizumab, and in 2021, the combination of two ICIs was incorporated into clinical practice. The Checkmate 9LA regimen is a combination of NIVO 360 mg (Q3W) and ipilimumab (IPI) 1 mg/kg (Q6W) plus chemothera-

py (two cycles) for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC), regardless of PD-L1 expression level or tumor histology[3]. This is an innovative regimen that adds two courses of chemotherapy in the early phase of treatment to overcome early disease progression, which is a weakness of ICIs. The Checkmate 9LA regimen, which is indicated for lung cancer, is one-third the dose of ipilimumab used for melanoma, although this is not always beneficial. Because the combination of ipilimumab-nivolumab is new, in lung cancer, the frequency and severity of adverse events in clinical practice remain unknown.

Here we report on the clinical efficacy and adverse events of six patients with lung cancer who received ipilimumab and nivolumab in clinical practice.

2. Case presentation

Six patients were treated for stage IV or postoperative recurrence of NSCLC with an ipilimumab and nivolumab regimen at the Takatsuki Red Cross Hospital from March to June 2021.

Case 1

A 72-year-old man was diagnosed with a stage IV squamous cell carcinoma (SCC) and was started on ICI treatment, with IPI (1 mg/kg), NIVO (360 mg), Paclitaxel (PTX) (5 mg/kg 200 mg/m^2), and carboplatin (CBDCA) (AUC 5) (**Table 1**). At the time of diagnosis, the patient had multiple brain metastases, multiple bone metastases, multiple skin metastases, and multiple lymph node metastases, and the Oncomine Dx Target Test showed the presence of a Met ex14 skipping mutation. Ideally, tepotinib, a tyrosine kinase inhibitor to the Met ex14 skipping mutation, should be administered immediately; however, in Japan, diagnosis by the Archer-MET companion diagnostic system, a companion diagnostic agent, is required, and an additional 3 weeks of turnaround time are needed. The patient was showing a daily decline in strength, and we felt that he needed immediate treatment, so we started treatment with the 9LA regimen.

Although there were no obvious adverse events, the rapid progression of the disease could not be stopped, and the patient died on the 23rd day of the day of administration.

Case 2

A 67-year-old female was diagnosed with postoperative recurrence of Met ex14 skipping mutation-positive SCC and was started on tepotinib followed by ICI treatment with IPI (1 mg/kg) (Q6W), NIVO (360 mg) (Q3W), PTX (200 mg/m^2) and CBDCA (AUC 5) (**Table 1**).

The patient received two courses of chemotherapy followed by four courses of ICI, but the treatment was changed due to tumor growth after 3 months. Grade 2 rash was observed on day 10 as an adverse event. Prednisolone 15 mg was started to treat the rash, and the rash disappeared quickly, so the treatment was terminated after 7 days. After that, no new immune-related adverse events (irAE) were observed.

Case 3

A 77-year-old female was diagnosed with postoperative recurrence of adenocarcinoma and was started on ICI treatment with IPI (1 mg/kg), NIVO (360 mg), Pemetrexed (PEM) (500 mg/m^2), and CBDCA (AUC 5) (**Table 1**).

After two courses of ICI with chemotherapy, followed by two courses of ICI and pemetrexed, grade 2 drug-induced lung injury was observed on day 105, and steroids were tapered off over 3 weeks after 3 days of methylprednisolone treatment at 2 mg/kg.

The patient was admitted to the hospital on day 140 for dehydration and grade 4 elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). On the fifth day after admission, the AST/ALT was elevated to 986/565 IU/L, and methylprednisolone 1 g/day was started. On the seventh day after admission, the AST/ALT increased to 987/966 IU/L, and mycophenolate mofetil (MMF) was started, resulting in a gradual improvement in liver enzymes[3,4]. Over the next 2 months, steroids and MMF were gradually reduced. Treatment led to shrinkage of recurrent foci, but when the treatment of liver damage by irAE was completed, a chest computed tomography scan showed that the tumor size had increased.

Case 4

A 72-year-old female was diagnosed with stage IV SCC and was started on ICI treatment with IPI (1 mg/kg), NIVO (360 mg), PTX (200 mg/m^2), and CBDCA (AUC 5) (**Table 1**). A grade 2 rush was observed on day 7, and the patient was started on 25 mg (0.5 mg/kg of prednisolone), following which, the rash disappeared. From day 48 to 75, AST/ALT was in the normal range, but grade 3 elevation of alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γGTP) was observed. However, autoimmune hepatitis and primary biliary cholangitis were ruled out, and the patient recovered during follow-up. The treatment course was favorable after that. On the 188th day, the patient visited the hospital with the chief complaint of frequent diarrhea. A diagnosis of grade 3 irAE enteritis was made by lower gastrointestinal endoscopy (**Figure 1**).

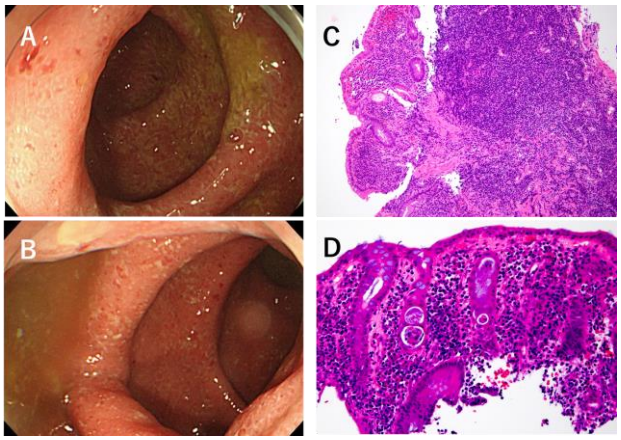

Figure 1. (**A**, **B**) Colonoscopy findings showed erythematous erosive lesions all around. (**C**, **D**) Hematoxylin-eosin-stained sections demonstrating diffuse and dense infiltration throughout the mucosal layer. (**D**) Scatters crypt abscesses indistinguishable from active stage of ulcer colitis.

When starting with PSL 1 mg/day, the diarrhea and symptoms tended to improve, and gradually decreased over 90 days. Regarding the therapeutic effect, an excellent partial response was obtained.

Case 5

A 78-year-old male was diagnosed with a postoperative recurrence of SCC and was started on ICI treatment with IPI (1 mg/kg), NIVO (360 mg), PTX (200 mg/m^2), and CBDCA (AUC 5) (**Table 1**). On day 7, a grade 2 rash was observed, and a dose of 50 mg prednisolone (equivalent to 1 mg/kg) was started. After two courses of ICI with chemotherapy, fever due to irAE was observed. After the interruption of chemotherapy due to persistent malaise, the patient was admitted to hospital on day 85 with elevated liver enzymes. After admission, treatment with steroids was started, and the liver enzymes started to improve. However, on day 97, erosions on the lips appeared (which were treated with topical steroids), followed by a rash over the entire chest, and systemic steroid administration was started at 2 mg/kg. After 3 days of treatment, the symptoms worsened and 1 g of methylprednisolone was administered for 3 days, followed by intravenous gamma globulin (IVIG) for 5 days. However, the patient's condition did not improve, and the disease shifted to toxic epidermal necrolysis (**Figure 2**). The patient's respiratory condition subsequently worsened, and infliximab (5 mg/kg) was administered. The progression of the rash appeared to have stopped, but ground glass opacity in the lung fields appeared and the patient ultimately died on day 114.

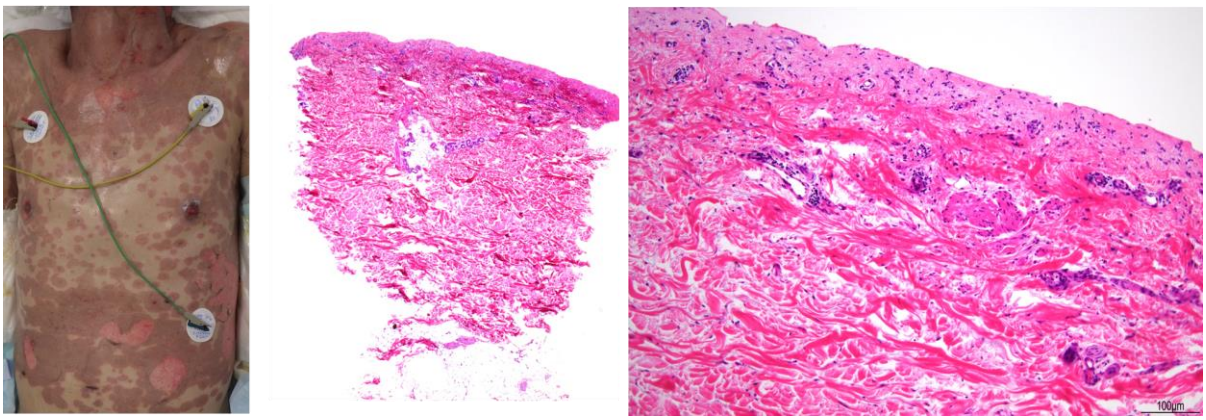

Figure 2. (**A**) Nikolsky phenomenon, in which the epidermis easily detached when external force was applied, was observed throughout the body. (**B**, **C**) Completely loss of epidermis, and the mild inflammatory cells are infiltrated around the blood vessels in the upper dermis.

Case 6

A 75-year-old male was diagnosed with stage IV SCC along with invasion to vertebral (Th9). The patient was started on radiotherapy, followed by ICI treatment with IPI (1 mg/kg), NIVO (360 mg), PTX (200 mg/m^2), and CBDCA (AUC 5) (**Table 1**).

On day 3 after the administration of the ICI with chemotherapy, lung injury was observed and hypoxemia occurred. As a result, the patient was placed on a ventilator, and methylprednisolone (1 g) and intensive care were started. However, lung injury did not improve, and the patient died on day 21.

Table 1. Clinical and biochemical findings

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age/sex	72/M	67/F	77/F	72/F	78/M	75/M
Histology	Squamous	Squamous	Adenocarcinoma	Squamous	Squamous	Squamous
Stage	Stage 4	Postoperative recurrence	Postoperative recurrence	Stage 4	Postoperative recurrence	Stage 4
PD-L1 status (TPS)	75%	10%	>1%	100%	>1%	40%
Driver mutation	Met ex14 skipping	Met ex14 skipping	Wild	Wild	Wild	Wild
ICI regimen	IPI NIVO	IPI NIVO	IPI NIVO	IPI NIVO	IPI NIVO	IPI NIVO
Chemotherapy regimen	CBDCA PTX	CBDCA PTX	CBDCA PEM	CBDCA PTX	CBDCA PTX	CBDCA PTX
Best response	PD	SD	SD	PR	PR	PD
Immune-related toxicities						
Dermatologic toxicity	None	G2	None	G2	G5	None
Gastrointestinal toxicity	None	None	None	G3	None	None
Pulmonary toxicity	None	None	None	None	None	G5
Immune-related hepatitis	None	None	G3	G2	G2	None

Abbreviation: ICI: Immune checkpoint inhibitor, PD: Progression of disease, SD: Stable disease, PR: Partial response, IPI: Ipilimumab, NIVO: Nivolumab, CBDCA: Carboplatine, PTX: Paclitaxel, PEM: Pemetrexed, G: Grade.

3. Discussion

The anti-CTLA-4 antibody IPI is an anticancer drug that inhibits CTLA-4, a signal transducer and activator of immune system suppression, which was approved by the Food and Drug Administration (FDA) in 2011 for treating malignant melanoma. In 2018, it was approved by the FDA for treating renal cell carcinoma along with NIVO, and was also approved in Japan in 2018. For lung cancer, the indication was expanded in 2020 based on the Checkmate 9LA[3] and Checkmate 227 trials[4]. The efficacy of IPI has been proven, with satisfactory results against standard chemotherapy. However, the irAE associated with the use of two ICIs in combination remain unclear in clinical practice. At the very least, it is clear that combination therapy is effective; however, in the Checkmate 227 trial, treatment-related serious adverse events occurred approximately 2-fold more than with standard chemotherapy[4].

In the Checkmate 9LA study, grade 3 or higher skin disorders were reported in 3% of subjects, grade 3 or higher diarrhea in 4%, and any grade 3–4 adverse events in 47%, of which neutropenia was the most frequent (7%). Treatment-related deaths were observed at a frequency of 2%, and were due to renal failure, diarrhea, liver damage, pneumonia, and sepsis. Based on these data, the irAE were considered acceptable[5].

In terms of irAE with the Checkmate 9LA regimen in actual clinical practice at our hospital, the frequency of grade 2 rash was high in 4 of 6 patients, but the response to corticosteroids was favorable and manageable. Hepatic dysfunction appeared in three of the six patients, but two could be treated with steroids alone and one improved with the addition of MMF. Additionally, one of the six patients had irAE enteritis, which improved with steroids.

Toxic epidermal necrolysis was observed in one of six patients and was fatal. However, this is

considered rare, with an incidence of less than 1% in clinical trials[6] (reported in Logan, *et al*.[7] and Gopee, *et al*.[8] with IPI and NIVO for malignant melanoma in 2020, respectively). The mechanism of ICI-induced toxic epidermal necrolysis (TEN) is not fully understood[9], but may be associated with the activation of cytotoxic CD4+/CD8+ T cells against unidentified dermal and epidermal antigens[10]. There is currently no established treatment for stevens-johnson syndrome (SJS) and TEN occurring as a result of ICI use, and the prognosis appears to be poor. Although treatments such as steroids, IVIG, tocilizumab, and infliximab have been tried, they are probably not sufficient, and it is hoped that further treatment methods will be established in the future[11].

In this article, we report on irAE in consecutive patients treated with Checkmate 9LA, including ICI combinations. The frequency and severity of adverse events in the Checkmate 9LA and Checkmate 227 trials were not significantly different to those of the IMpower150[12] and KEYNOTE-189[13] trials, which combined chemotherapy with a single-agent ICI. A simple comparison of clinical trial reports would suggest that the addition of ipilimumab does not increase adverse events. However, adverse events associated with the addition of IPI to NIVO were compared in the Checkmate 227 trial, where grade 3 or 4 treatment-related adverse events occurred in 35.5%, and 19.4% of the patients in the NIVO+IPI group, respectively. In particular, there was an increase in skin disorders, endocrine dysfunction, gastrointestinal disorders, hepatic dysfunction, and pulmonary disease[4]. Additionally, in a clinical trial of malignant melanoma, the Checkmate 067 trial, grade 3 or 4 treatment-related adverse events occurred in 59%, 23%, and 28% of the patients in the NIVO+IPI, NIVO, and IPI groups, respectively[14]; thus, the irAE profile was similar to that of the Checkmate 227 trial. Therefore, it is conceivable that the addition of IPI to NIVO increases the number of serious irAEs. Although the dose of IPI has been reduced for treating lung cancer compared to that used for malignant melanoma, it is thought that the increase in irAEs may be due to IPI. In actual clinical practice, there may be more irAEs than reported in clinical trials; this is because patients with poorer performance status or comorbidities are treated more often than in clinical trials. Adding two cycles of chemotherapy to NIVO+IPI resulted in earlier disease control and improved response compared with immunotherapy-only regimens and chemotherapy[5], but it is more difficult to predict how many adverse events will occur in which organs with the addition of IPI. Dealing with irAEs from all directions will be essential in future treatment.

Conflict of interest

The authors declare no potential conflicts of interest.

Acknowledgements

The authors would like to thank F. Furukawa for useful discussions.

References

1. Cancer Facts & Figures 2020 [Internet]. Atlanta: American Cancer Society; 2020. p. 1–76 [cited 2021 Nov]. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf
2. The editorial board of the Cancer Statistics in Japan (editors). Cancer Statistics in Japan 2021. Tokyo, Japan: Foundation for Promotion of Cancer Research (FPCR); 2021. p. 1–146. Available from: https://ganjoho.jp/public/qa_links/report/statistics/pdf/cancer_statistics_2021.pdf).
3. Reynolds K, Thomas M, Dougan M. Diagnosis and management of hepatitis in patients on checkpoint blockade. The Oncologist 2018; 23(9): 991–997. doi: 10.1634/theoncologist.2018-0174.
4. Hellmann MD, Paz-Ares L, Caro RB, *et al*. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. New England Journal of Medicine 2019; 381(21): 2020–2031. doi: 10.1056/NEJMoa1910231
5. Paz-Ares L, Ciuleanu TE, Cobo M, *et al*. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with

non-small-cell lung cancer (CheckMate 9LA): An international, randomised, open-label, phase 3 trial. The Lancet Oncology 2021; 22(2): 198–211. doi: 10.1016/S1470-2045(20)30641-0

6. Raschi E, Gatti M, Gelsomino F, *et al*. Lessons to be learnt from real-world studies on immune-related adverse events with checkpoint inhibitors: A clinical perspective from Pharmacovigilance. Targeted Oncology 2020; 15(4): 449–466. doi: 10.1007/s11523-020-00738-6.
7. Logan IT, Zaman S, Hussein L, *et al*. Combination therapy of ipilimumab and nivolumab-associated toxic epidermal necrolysis (TEN) in a patient with metastatic melanoma: A case report and literature review. Journal of Immunotherapy 2020; 43(3): 89–92. doi: 10.1097/CJI.0000000000000302
8. Gopee NH, Gourley AM, Oliphant TJ, *et al*. Toxic epidermal necrolysis occurring with immune checkpoint inhibitors. Dermatology Online Journal 2020; 26(8): 1–5. doi: 13030/qt8fc428f6. PMID: 32941713.
9. Thompson JA, Schneider BJ, Brahmer J, *et al*. Management of immunotherapy-related toxicities, version 1.2019, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network 2019; 17(3): 255–289. doi: 10.6004/jnccn.2019.0013
10. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. New England Journal of Medicine 2018; 378(2): 158–168. doi: 10.1056/NEJMra1703481.
11. Woolridge KF, Boler PL, Lee BD. Tumor necrosis factor alpha inhibitors in the treatment of toxic epidermal necrolysis. Cutis 2018; 101(1): E15–E21. PMID: 29529123
12. Socinski MA, Nishio M, Jotte RM, e*t al*. IMpower150 final overall survival analyses for atezolizumab plus bevacizumab and chemotherapy in first-line metastatic nonsquamous NSCLC. Journal of Thoracic Oncology 2021; 16(11): 1909–1924. doi: 10.1016/j.jtho.2021.07.009
13. Gandhi L, Rodríguez-Abreu D, Gadgeel S, *et al*. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. New England Journal of Medicine 2018; 378(22): 2078–2092. doi: 10.1056/NEJMoa1801005
14. Larkin J, Chiarion-Sileni V, Gonzalez R, *et al*. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. New England Journal of Medicine 2019; 381(16): 1535–1546. doi: 10.1056/NEJMoa1910836