Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7472-21
Intern Med 61: 1735-1738, 2022
http://internmed.jp

【 CASE REPORT 】

Severe Skin Toxicity Caused by Sequential Anti-PD-1 Antibody and Alectinib in Non-small-cell Lung Cancer: A Report of Two Cases and a Literature Review

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Abstract:
Immune checkpoint inhibitors (ICIs) have demonstrated marked efficacy in some cancer patients, but they may cause various severe immune-related adverse events. Alectinib is a second-generation anaplastic lymphoma kinase (ALK)-tyrosine kinase inhibitor (TKI) approved for ALK-rearranged non-small-cell lung cancer (NSCLC). Alectinib is said to be safer than other TKIs. We conducted an investigator-initiated trial of alectinib, which also has RET kinase-inhibitory activity, against RET-rearranged NSCLC. Two RET-rearranged NSCLC patients experienced severe skin toxicity with alectinib after first undergoing anti-PD-1 antibody treatment with an ICI. These findings suggest that we should carefully follow patients for adverse effects of targeted drugs following ICI treatment.

Key words: severe skin toxicity, anti-PD-1 antibody, alectinib, ICIs

(Intern Med 61: 1735-1738, 2022)
(DOI: 10.2169/internalmedicine.7472-21)

Introduction

Immune checkpoint inhibitors (ICIs), such as anti-programmed death-1 (PD-1) antibody and anti-PD-ligand 1 (PD-L1) antibody, show anti-tumor efficacy by activating the immune system. ICIs have been approved for various types of tumors, including small-cell lung cancer (SCLC) and non-SCLC (NSCLC). While ICIs demonstrate marked efficacy in some patients, they may cause various severe immune-related adverse events (irAEs), including drug-induced skin toxicity and interstitial lung disease (ILD), presumably by activating the autoimmune system. Previous studies have reported that severe irAEs, including ILD (1), were induced by a concurrent combination of ICIs and osimertinib, a third-generation epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) (2). However, severe adverse events associated with concurrent or sequential treatment with ICIs and other TKIs are not well reported.

Alectinib is a second-generation anaplastic lymphoma kinase (ALK)-TKI approved for ALK-rearranged NSCLC (3). Although several severe adverse events of alectinib, including dysgeusia, increased AST levels, increased bilirubin levels, rashes, and constipation, have been reported, their incidence is generally lower than those of other TKIs, such as crizotinib, an FDA-approved inhibitor for ALK and ROS1 kinases, and EGFR-TKIs (4-6).

We conducted an investigator-initiated trial of alectinib, which also has RET kinase-inhibitory activity, against RET-rearranged NSCLC (UMIN000020628) (7). In the trial, two NSCLC patients with RET rearrangements experienced severe skin toxicity with alectinib administration after first having undergone anti-PD-1 antibody treatment. These findings suggest that we should carefully follow the patients for the adverse effects of targeted drugs following ICIs.

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Received: March 3, 2021; Accepted: September 1, 2021; Advance Publication by J-STAGE: November 20, 2021
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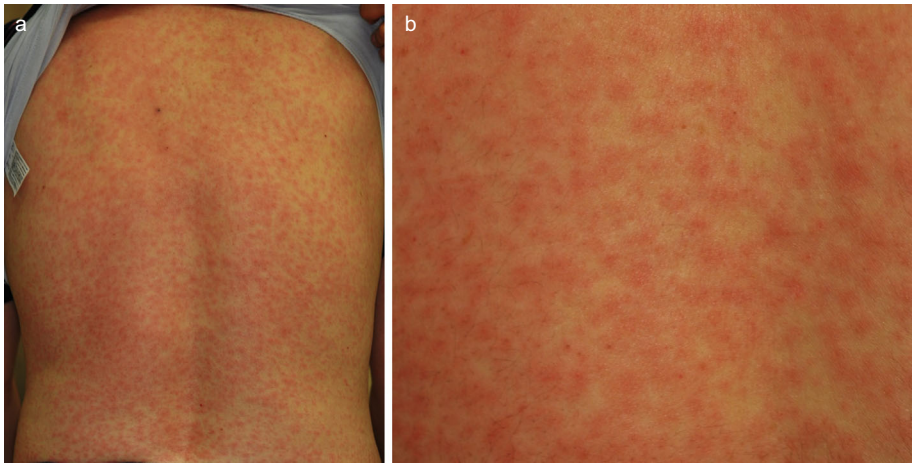

Figure 1. **a: Skin rash observed in case 1. A woman in her 40s. Alectinib 600 mg twice daily was started 24 days after the final administration of nivolumab. Picture shows erythema multiforme on day 13. b: Close-up picture of (a).**

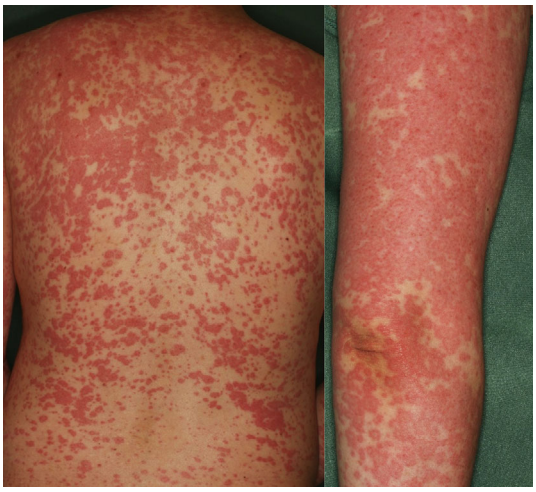

Figure 2. **Skin rash observed in Case 2. A woman in her 30s. Alectinib 600 mg twice daily was started eight weeks after the final administration of nivolumab. Picture shows erythema multiforme on day 12.**

Case Reports

Case 1

A woman in her 40s, a non-smoker, with a history of stage IIIB NSCLC (cT1aN3M0), was initially treated with concurrent chemotherapy (cisplatin and docetaxel) and radiation therapy. She had developed multiple metastases in the brain and bone that were controlled for eight years by multidisciplinary treatment, including stereotactic radiation and brain tumor resection. She showed disease progression with a primary lung tumor in the left upper lobe and was treated with conventional chemotherapy (second-line carboplatin+ pemetrexed, third-line docetaxel, fourth-line vinorelbine). As the fifth-line treatment, she received anti-PD-1 antibody nivolumab for six cycles. Nonetheless, her disease progressed. Genome testing revealed a KIF5B-RET rearrangement, and she entered the Investigator-initiated Trial with alectinib (UMIN000020628).

Alectinib 600 mg twice daily (FDA-approved dose for ALK-rearranged NSCLC) was started 24 days after the final administration of nivolumab. She presented with fever (38.0 °C: Grade 1) on day 10. Skin rash (erythema multiforme, Grade 3; Fig. 1), increase in AST (Grade 3), and increased ALT (Grade 2) appeared on day 13. At that time, she had no mucosal lesion. Thus, alectinib was stopped, and 50 mg prednisolone was administered intravenously for 7 days, followed by decreasing doses of oral prednisolone for 4 weeks. These symptoms, including rash, resolved by day 22.

Case 2

A woman in her 30s, a non-smoker, had a history of stage IV NSCLC (cTaN3M1b, OSS, HEP, PUL). She received seven lines of chemotherapy. As the eighth-line treatment, she received anti-PD-1 antibody nivolumab for four cycles. Nonetheless, her disease progressed. Genome testing revealed KIF5B-RET rearrangement, and she entered the Investigator-initiated Trial with alectinib (UMIN000020628).

Alectinib 600 mg twice daily was started 8 weeks after the final administration of nivolumab. On day 5, she noticed that the right hypochondrial pain due to liver metastases decreased. However, she presented with a skin rash (Grade 2) on day 11, and alectinib was discontinued. On day 12, a severe skin rash and erythema multiforme were observed (Fig. 2), but she had no mucosal lesions. She was administered steroid pulse therapy of 1,000 mg methylprednisolone for 3 days. Her skin rash resolved by day 16.

Discussion

Severe skin rashes (Grade 3) because of alectinib treatment are rare events (0-3%) (3, 4). Table summarizes five case reports of severe skin rash caused by alectinib (8-12).

Table. Literature Review of Patients with Severe Skin Rash Caused by Alectinib, Including Our Cases.

Ref.	Age/ Gender	Tumor and gene alteration	Line of alectinib	Previously given ICI	Interval of ICI to alectinib	Onset of rash	Type of rash	Symptomatic treatment	Dat to improvement	Re-challenge of alectinib
9	30/F	NSCLC with EML4-ALK	4th	Anti-PD-1 Ab	Not reported	2weeks	Not reported	Anti-histamine	not reported	Yes
11	76/F	NSCLC with EML4-ALK	2nd	No		10 days	Maculopapular	Anti-histamine, topical steroid	7 days	Yes
8	39/F	NSCLC with EML4-ALK	5th	No		11 days	Erythema multiforme	HT1 antagonist, nadifloxacin, PSL 20-40mg	Not reported PSL 35days	Yes
12	71/F	NSCLC with ALK rearrangement	2nd	Pembrolizumab	3 weeks	2 weeks	Maculopapular	HT1 antagonist, mPSL	1 week	Yes
10	57/ F	NSCLC with EML4-ALK	3rd	Dulvalumab, atezolizumab	4 weeks	12 days	Maculopapular	mPSL	7 days	Yes
Our cases	40s/F	NSCLC with KIF5B-RET	6th	Nivolumab	26 days	13 days	Erythema multiforme	mPSL 50mg	days	No
	30s/F	NSCLC with KIF5B-RET	9th	Nivolumab	8 weels	11 days	Erythema multiforme	mPSL 1000mg	days	No

F: female, NSCLC: non-small cell lung cancer, EML4: echinoderm microtubule-associated protein-like4, ALK: anaplastic lymphoma kinase, KIF5: kinesin family member 5B, RET: rearranged during transfection, ICI; immune checkpoint inhibitor, HT1: hydroxytryptamine1, mPSL: methylprednisolone, PSL: prednisolone

Erythema multiforme caused by alectinib was reported in one case by Kimura et al. (8). In this case, erythema multiforme was observed on day 11 of alectinib treatment and improved by suspension of alectinib and introduction of a histamine-1 receptor antagonist, external preparation of nadifloxacin, and a medium-class steroid.

Severe skin rash (maculopapular) associated with sequential use of alectinib after ICI was reported in two cases (9, 10) (Table). As in the two cases reported here, erythema multiforme was observed after alectinib following treatment with anti-PD-1 antibody. This suggests that anti-PD-1 antibody triggers serious skin toxicity upon alectinib treatment. The details of the mechanism are unknown, but it is possible that PD-1 inhibition activated the immune system and induced an immune response to alectinib. The intervals between nivolumab and alectinib treatments in our Cases 1 and 2 were one and two months, respectively.

Since previous reports showed that the onset of severe skin toxicity by alectinib treatment was 10-14 days with or without an ICI treatment history, particular attention is required during this period. In these case reports, the rash was improved by the suspension of alectinib and the addition of steroids with or without histamine-1 receptor antagonist, and the patients were re-challenged with a gradual increase in the dose of alectinib, which successfully controlled tumor progression. Our two cases with RET-rearrangement received alectinib as the protocol treatment in the Investigator-initiated Trial, so alectinib was terminated at the onset of erythema multiforme, and patients were not re-challenged. Particularly in Case 2, we administered steroid pulse therapy because the severe erythema multiforme worsened, but the state of her lung cancer remained stable during steroid therapy.

The NCCN guidelines recommend TKI treatment for front-line treatment, as ICIs are not sufficiently effective in lung cancer with driver gene alterations. From the perspective of side effects, including serious skin toxicity, TKIs should be used on the front line, rather than ICIs, particularly in cases where TKIs might eventually be used.

The authors state that they have no Conflict of Interest (COI).

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