



Alectinib Induced SJS/TEN: A Case Report and a Review

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Lung cancer is the second most common type of cancer in the world, adenocarcinoma is one of the most common variants with a rate of 35–40%. [1] Recent years, in NSCLC with relation to genetic alterations, biomolecular markers have emerged as a cornerstone of the advanced NSCLC treatment that overtook the standard chemotherapy.

EGFR, ALK, ROS1, MET and BRAF are the most common driver mutations investigating in adenocarcinomas. Patients who had this rearrangements have been showed improved response rates and progression-free survival compared with chemotherapy. [2] The response rate range is 50 to 80% in targeted therapy. Overall survival was increased to between 18 and 38.6 months. [3,4]

ALK mutation has seen approximately in %3–5 of the patients especially young age, nonsmoker female. [5] There are several types of ALK-TKI including first generation crizotinib; second generation alectinib, Ceritinib, Brigatinib and third generation, Lorlatinib. [6]

Alectinib - an highly selective, oral second generation ALK-TKI has been currently preferred first-line therapy in ALK positive NSCLC based on ALEX, J-ALEX and ALESIA study. [7,8] Patients who had received Alectinib patients had significantly higher PFS rates (34.8 months vs. 10.9 months, HR: 0.43, 95% CI: 0.32–0.58) than Crizotinib. [9] Similarly, Peters et al. [10] demonstrated Crizotinib and alectinib PFS rates of 48.7% vs. 68.4%, respectively.

At the updated ALEX study, median treatment duration of 28.1 months, among 152 patients, any-grade

AEs were seen in 147 patients (97%), grade 3–5 AEs of 79 (52%). Furthermore, alectinib discontinuation, dose reduction and interruption were done due to AEs, 22 (15%), 31(20%), 40 (26%), respectively. [11] Rash was observed in 21 (13.8%) of patients in which grade-1 of 16 (10.5%); grade-2, 2 (1.3%), grade-3 2 (1.3%) and grade-4 1 (0.7%). [12]

Herein we presented a patient with lung adenocarcinoma received Alectinib 1200 mg po for 90 days with a complete radiological response presented with skin rash which was consistent with SJS/TEN and controlled with high dose of steroid. With maintenance dose of steroid Alectinib desensitization was performed and after 2 weeks full dosage of alectinib could be achieved. In the literature, there were no reports that demonstrate the relation between toxicity and response. While the efficacy of targeted therapy has been well-established, the relationship between the severity of treatment-related toxicities and clinical response remains a subject of debate.

Our case is noteworthy because after desensitization with increasing dosage, response achieved maximally without any complication. We also highlight the response-toxicity relation by analyzing 6 cases in terms of approach, treatment and response in which alectinib-induced toxicity is occurred.

Case: A 67 year-old never-smoking female, presented with dry cough and shortness of breath for 3 month symptoms increased progressively. PET/CT revealed primary lung cancer with bone, surrenal

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and pleural metastases, supraclavicular and mediastinal lymphadenopathies. Cranial MRI was compatible also with metastases. Supraclavicular lymph node biopsy confirmed lung adenocarcinoma metastases. Alectinib 600 mg twice a day was commenced following the genetic test which revealed EM4-ALK fusion. After 45 days of treatment, maculopapular rashes started in abdominal region. The patient was followed up with a dermatologist for macular eruptions. Although antihistaminic therapy, itchy white skin that tends to coalesce widely on an erythematous base all over the body after 3 months of Alectinib. Punch biopsy taken from the right leg reported with no eosinophils and the findings were interpreted as a Drug Reaction because of MPO (Myeloperoxidase) positive - PMNLs (Polymorphonuclear neutrophils). Stevens-Johnson Syndrome was conceded and Alectinib was stopped with commencement of 1 mg/kg steroid therapy. There was no mucosal involvement in the patient whose skin involvement was 10–30% of the body surface area and was followed up with the diagnosis of SJS/TEN (Fig. 1). 5 days of iv steroids, antihistamines and topical lotions significant regression was detected in lesions.

After 3 months of Alectinib, PET/CT was consistent with metabolic complete radiological response. Furthermore, Cranial MRI demonstrated complete radiological response. Skin involvement was 10–30% and the patient followed up with the diagnosis of SJS/TEN evaluated as Grade 4 cutaneous toxicity. The rash of the patient, who was followed up without Alectinib for 2 week, regressed and the prednisolone dose was reduced by 8 mg. Desensitization was started with a daily dose of 150 mg of alectinib for 3 days then increased to 300 mg for 5 days, 600 mg for 7 days finally reached to therapeutic dose which is 1200 mg /day (Table 1). In the meantime the skin lesions resolved from grade 4 to grade 1 (Fig. 2). The patient continues to have a progression-free course with maintenance steroid therapy, and Alectinib is currently being administered at the full dose in the ninth month.

Discussion: Recent years, Alectinib, an highly selective ALK inhibitor, generally well-tolerated oral agent has replaced standard chemotherapy in the treatment of NSCLC. The randomized, global phase-III ALEX study has demonstrated significant improvement in PFS.[12] In Peng et al.'s[13] trial, Alectinib as a first-line treatment demonstrated a substantial increase in overall survival(OS) when compared to standard chemotherapy (HR: 0,61, %95, CI, 0.40–0,94) and



Fig. 1. Patient's initial presentation with maculopapular rashes in bilateral legs.



Fig. 2. Resolving eruptions following three months after the diagnosis of SJS/TEN.

SJS/TEN: Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.

Table 1 The desentization protocole we used in our case

150 mg qd for 3 days
300 mg qd for 5 days
600 mg qd for 7 days
600 mg bid – full standard dose

also to Crizotinib (HR: 0,66, %95, CI, 0,45–0,95). The incidence of the several adverse events is significantly low in alectinib. Peters et al.'s[10] study has showed the grade 3–5 AEs occur in the percentage of 41 vs 50 in Alectinib vs Crizotinib, respectively. According to ALESIA Study among 120 patients that received Alectinib, patients who had grade 3–5 adverse events

Table 2 Summary of the cases on the adverse skin reactions to Alectinib and different management approaches

Reference	Age	Tumor entity	Step	Disease	Time of TKI use (day)	Response	Approach	Outcome
This report	67	NSCLC	1 st	SJS/TEN	45	CR	Desentization 150 mg qd–3 days 300 mg qd–5 days 600 mg qd–7 days 600 mg bid	Recovery
Shirasawa et al.[21]	76	NSCLC	2 nd	Gr-3 MP Rash	10	NM	Desentization 40 mg qd–2 days 80 mg qd–2 days 160 mg qd–2 days 300 mg qd–2 days 300 mg bid	Recovery
Kimura et al.[24]	36	NSCLC	5 th	EM	11	CR	Desentization 20 mg qd–2 days 20 mg bid–2 days 40 mg bid–3 days 80 mg bid–2 days 120 mg bid–2 days 160 mg bid–3 days 200 mg bid	Recovery
Anderson et al.[22]	71	NSCLC	2 nd	Gr-3 MP Rash	14	CR	Desentization 37,5 mg qd–2 days 75 mg qd–2 days 150 mg qd–2 days 150 mg bid–2 days 300 mg bid	Recovery
Seegobin et al.[25]	57	NSCLC	3 rd	Gr-3 MP Rash	12	SD	Desentization 150 mg bid–2 days 300 mg bid–5 days 450 mg bid–8 days 450 mg in the morning with 600 mg in the evening–8 days 600 mg bid	Recovery
Deng et al.[23]	49	NSCLC	2 nd	Type-IV Delayed Hypersensitivity Reaction	10	NM	Rechallenged with brigatinib	Recovery
Farooq et al.[20]	34	NSCLC	1 st	DRESS Syndrome	17	NM	Rechallenged with brigatinib	Recovery

TKI: Tyrosine-kinase inhibitors; SJS/TEN: Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis; CR: Complete remission; MP: Maculopapular; EM: Erythema multiforme; NM: Not mentioned; SD: Stable disease

36 (29%) of 125 or serious adverse events 19 (15%) of 125. AEs lead to alectinib dose reduction, interruption or discontinuation occurred in 24%; 26%; 7% of patients, respectively.[8]

Rash is one of the most common alectinib- induced hypersensitivity reaction. In ALEX trial in 2019, 21 (13,8%) of 152 patients had experienced rash in which 3 (%2) of them were grade 3–5.[12] Skin toxicity of alectinib can range from mild grade-1 rash to severe and highly mortal conditions.[8] While they are usually non-threatening SCAR's may occur including SJS/TEN, DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and AGEP (Acute Generalized Exanthematous Pustulosis).[14] SJS/TEN are rarely seen in ALK-TKIs and there are no reported cases about alectinib induced SJS/TEN.

In our unique case we discussed SJS/TEN 3 months from Alectinib therapy and represented successful desensitization therapy with radiologically complete responsive disease.

SJS/TEN is a potentially life-threatening disease which is a type-IVc immune reaction and present with mucocutaneous blistering reactions with epidermal detachment and extensive necrosis.[15]

The diagnosis of SJS/TEN may be rendered clinically or histopathologically. In skin biopsy, scattered keratinocytes in the basal epidermis and full thickness epidermal necrosis or subepidermal bullae may be seen, accompanied by perivascular lymphohistiocytic infiltrate with eosinophils in the superficial dermis.[16]

We classified dermatological toxicity according to CTCAE (Common terminology criteria for adverse events) as grade 4 because of maculopapular rash covering >10–30% body surface area with severe and life-threatening symptoms.[17] Furthermore, Naranjo score was found to be 8 which is consisted with probable adverse drug reaction.[18]

According to literature there were 6 more reported cases mentioned alectinib-induced skin toxicity in the treatment of NSCLC. (Table 2) All the patients were female and the mean age was 55,7 years ($\pm 16,7$). Including our case, 2 of them had the alectinib treatment in the first-line.[19] 3 of them had in the 2nd line[20–22] and 1 of them in the 5th line.[23] Time of TKIs use was range from 10 to 45 days in which the mean time was 17 days.

Various skin toxicities were seen in 7 cases, including, Erythema Multiforme, Type-4 Hypersensitivity Reaction, Grade – 3 MP Skin Rash, DRESS and SJS/TEN – in our case.[20,22,23–25] Acute man-

agements to these events were similarly in all cases, discontinuing the TKIs following oral antihistamine, corticosteroid replacement and topical agents. Deng et al.[23] and Farooq et al.[20] switched the oral TKI to brigatinib – which is a 3rd generation ALK-TKI and had favourable outcomes.

On the other hand, in 5 cases, including our case, desensitization was performed.[20,21,23,24] There is no major used desensitization protocols, clinicians chose the suitable approach to each patient. In Shri-sawa et al.,[21] Kimura et al.[24] and Anderson et al.'s[22] protocols, the initial dosage has been maintained at a lower level (40 mg; 20 mg; 37,5 mg, respectively), while dose escalation has been conducted at minimal increments reaching a maximum dose of 600 mg; 400 mg and 600 mg, respectively. Seegobin et al.[25] started the desensitization protocols with a dose of 300 mg and gradually increase the dose by 1200 mg- the full standard dose within 23 days. Regarding our case, we commenced with an initial dose of 300 mg and achieved the full standard dosage within a relatively brief period of 15 days, thereby distinguishing our case.

According to our review, 3 cases, including our case had full clinical response to the Alectinib therapy, in which grade-3 and more skin toxicity following treatment and desensitization protocols had done. In Seegobin et al.'s[25] case, stable disease was noted.

The notion that more severe adverse events indicate a stronger therapeutic effect of targeted agents is not universally applicable. While it is true that certain adverse events, such as immune-related toxicities observed with immune checkpoint inhibitors, may be associated with improved clinical response, this relationship cannot be generalized across all targeted therapies.

More researches have to be done to demonstrate the relation between the toxicity and the effectiveness in targeted therapies.

Alectinib-an oral TKI agent- which is currently the approved first-line treatment of NSCLC, has a low toxicity profile however, such as in our case grade-3 and more severe adverse events can be occur. Considering the possible positive correlation between the severity of the adverse events and the clinical response to treatment, we recommend desensitization with a close follow-up. This case report will provide brief summary in the management of skin toxicities due to Alectinib use and also present different successful desensitization protocols in the recent literature.

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