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Case report

Successful osimertinib rechallenge after osimertinib-induced pneumonitis in a patient with lung adenocarcinoma

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ABSTRACT

Pneumonitis is a serious adverse event of EGFR-TKI treatment. Although several cases of EGFR-TKI rechallenge after EGFR-TKI-induced pneumonitis have been reported, little is known about post-pneumonitis osimertinib rechallenge. We describe a 69-year-old never-smoking Japanese woman with postoperative recurrent lung adenocarcinoma retreated with osimertinib after osimertinib-induced pneumonitis. Although osimertinib rechallenge must be carefully chosen based on risk/benefit analysis, osimertinib rechallenge after osimertinib-induced pneumonitis may be an option, with limited alternative therapeutic options.

1. Introduction

Osimertinib has been approved for the treatment of epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer resistant to first- or second-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs). As with other EGFR-TKIs, osimertinib can cause pneumonitis; the incidence of osimertinib-induced pneumonitis is reportedly approximately 2–4%, with a mortality rate < 1.0% [1,2]. Although permanent discontinuation of the drug after developing pneumonitis is preferable, several cases of drug rechallenge after EGFR-TKI-induced pneumonitis have been reported. However, little is known about osimertinib rechallenge after developing pneumonitis. Here, we report a case of successful osimertinib rechallenge after osimertinib-induced pneumonitis in a patient with lung adenocarcinoma.

2. Case

A 69-year-old never-smoking Japanese woman with postoperative recurrent lung adenocarcinoma harboring EGFR L858R mutation had disease progression of multiple pulmonary and brain metastases. She had received five regimens of chemotherapy, including gefitinib, afatinib, erlotinib, carboplatin plus pemetrexed, and gefitinib-rechallenge, and treatment with γ knife for brain metastases. We performed bronchoscopic rebiopsy to evaluate the resistance mechanisms, which revealed the emergence of the EGFR T790M mutation with L858R mutation using cobas® EGFR Mutation Test ver.2 (Roche Molecular Systems). Based on these findings, we initiated 80 mg osimertinib once daily. Fourteen days later, a rapid improvement in the multiple pulmonary metastases was observed (Fig. 1A and B).

However, on day 55 of osimertinib treatment, follow-up chest computed tomography (CT) showed patchy ground-glass opacity (GGO) (Fig. 1C). Because the possibility of osimertinib-induced pneumonitis was considered, osimertinib was immediately discontinued. She was also receiving 10 mg/day oral prednisolone to treat the brain metastases-related symptomatic epilepsy, however, there was no clear evidence of infection from the results of the physical and laboratory examinations, such as beta D-glucan. Although other diseases cannot be completely excluded, the most likely diagnosis was osimertinib-induced pneumonitis. Since her symptoms and general condition had not worsened, we only discontinued osimertinib and continued the prednisolone dosage of 10 mg/day. Chest CT 15 days after the discontinuation of osimertinib demonstrated that the radiologic findings of osimertinib-induced pneumonitis had improved, while the known pulmonary metastases had rapidly progressed; she had also developed progressive general fatigue, cough, and bloody sputum. Her condition became life-threatening, and she was intolerant to further cytotoxic chemotherapy because of her poor performance status (score of 3); therefore, osimertinib was readministered at a reduced dose of 40 mg once daily after receiving full informed consent regarding the risk of recurrent pneumonitis and its high mortality rate. Her symptoms rapidly improved one week after the readministration of osimertinib. One month after the readministration of osimertinib, chest CT revealed no

Abbreviations: EGFR, epidermal growth factor receptor; CT, computed tomography; GGO, ground-glass opacity

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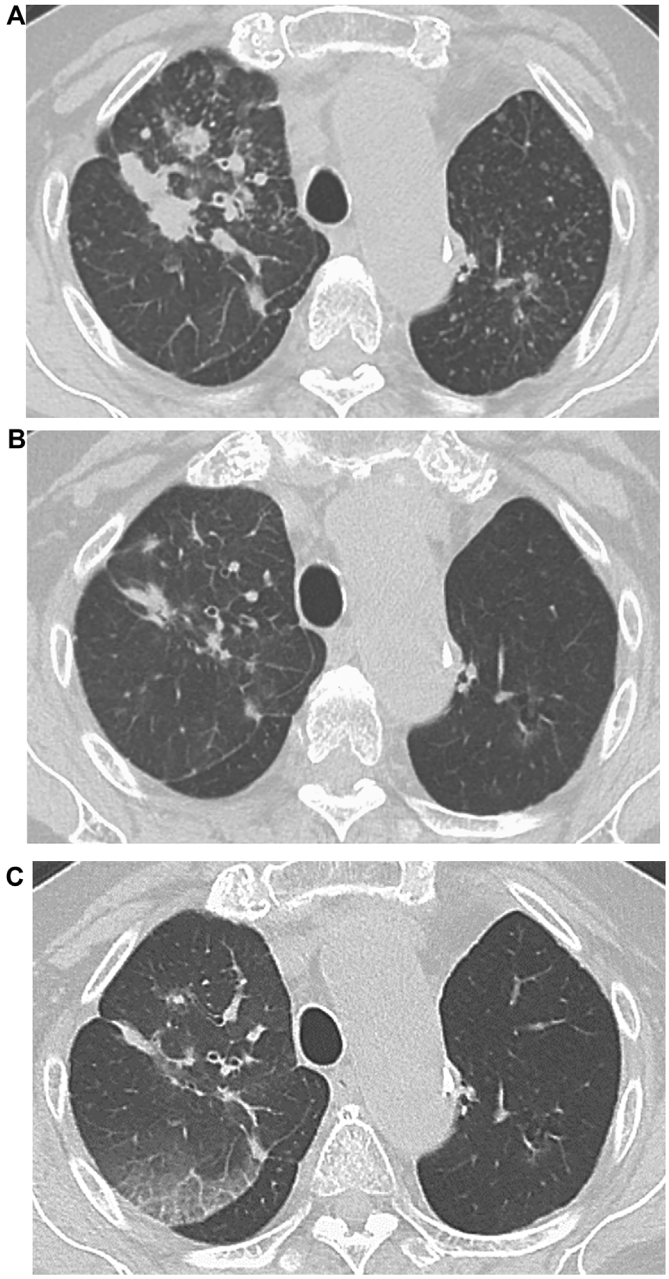

Fig. 1. Chest computed tomography scan. (A) Before treatment with osimertinib, the scan showed the multiple nodules in the right upper lobe of the lung. (B) Two weeks after initiation of osimertinib, the scan showed remarkable remission of the tumor. (C) Two months after initiation of osimertinib, the scan showed visible ground-glass opacities in the right lung.

evidence of recurrent pneumonitis and a remarkable reduction in the size of the multiple pulmonary metastatic nodules. At the time of this report, she was being treated with osimertinib over a period of 6 months without major adverse events.

3. Discussion

In this report, we presented a case of successful osimertinib rechallenge after osimertinib-induced pneumonitis and have summarized previous similar reports (Table 1). If alternative cytotoxic chemotherapy is not available because of poor performance status, especially with life-threatening flares of tumor growth such as in the present case, the prognosis will become extremely poor. Since EGFR-TKIs are key drugs for patients with an EGFR-sensitizing mutation or EGFR T790M mutation, it is important to continue treatment with this essential drug and manage the adverse events. Although the precise mechanism for EGFR-TKI-induced pneumonitis remains unknown, previous findings suggest that both a direct, dose-dependent cytotoxic mechanism and immune-mediated mechanism generally exist, which are probably interdependent [3]. Previous reports have suggested that EGFR-TKI rechallenge in combination with a corticosteroid can prevent the recurrence of pneumonitis because of the anti-inflammatory action [4–7]. There is no clear evidence to guide the osimertinib rechallenge dose after osimertinib-induced pneumonitis; however, considering those factors, we retreated the present case with osimertinib by reducing the dosage to 40 mg once daily in combination with prednisolone. A recent report has described the safety and efficacy of osimertinib rechallenge after osimertinib-induced acute pulmonary embolism,

Table 1
Literature Review of EGFR-TKI Rechallenges.

Case	Age	Sex	Histology	Time to onset	Cause of pneumonitis	Rechallenge	Corticosteroid during rechallenge	Recurrence of pneumonitis	References
1	62	F	Ad	13 months	Gefitinib (250mg[a])	Gefitinib (250mg[a])	NA	No	[8]
2	56	M	Ad	45 days	Gefitinib (250mg)	Gefitinib (250mg[a])	No	No	[9]
3	59	M	Ad	23 days	Gefitinib (250mg)	Gefitinib (250mg)	No	Yes	[10]
4	28	F	Ad	28 days	Gefitinib (250mg)	Erlotinib (50mg)	Yes	No	[11]
5	62	M	Ad	24 days	Gefitinib (250mg)	Erlotinib (150mg)	NA	No	[12]
6	62	M	Ad	6 weeks	Gefitinib (250mg)	Erlotinib (150mg)	Yes	No	[13]
7	77	F	Ad	7 weeks	Gefitinib (250mg)	Erlotinib (100mg)	Yes	No	[13]
8	41	F	Ad	20 days	Gefitinib (250mg)	Erlotinib (75mg)	Yes	No	[14]
9	77	F	Ad	5 weeks	Erlotinib (150mg)	Erlotinib (100mg)	Yes	No	[15]
10	68	M	Ad	8 weeks	Erlotinib (150mg)	Erlotinib (150mg)	Yes	No	[4]
11	62	F	Ad	29 days	Gefitinib (250mg)	Erlotinib (25mg)	No	Yes	[16]
12	49	F	Ad	2 days	Gefitinib (250mg)	Erlotinib (150mg)	No	No	[17]
13	41	F	Ad	5 months	Erlotinib (25mg)	Afatinib (20mg)	Yes	No	[5]
14	62	M	Ad	NA	Gefitinib (250mg)	Gefitinib (250mg)	Yes	No	[18]
15	64	M	Ad	NA	Gefitinib (250mg)	Gefitinib (250mg)	Yes	Yes	[18]
16	74	F	Ad	NA	Gefitinib (250mg)	Erlotinib (150mg)	Yes	No	[18]
17	71	F	Ad	NA	Gefitinib (250mg)	Erlotinib (150mg)	Yes	No	[18]
18	39	F	Ad	NA	Erlotinib (150mg) + BEV	Gefitinib (250mg) + BEV	Yes	No	[18]
19	82	M	Adsq	8 months	Osimertinib (80mg)	Osimertinib (80mg[a])	Yes	No	[7]
20	60	M	Ad	6 weeks	Osimertinib (NA)	Osimertinib (NA)	Yes	No	[7]
21	38	F	Ad	31 days	Osimertinib (80mg)	Osimertinib (80mg)	No	No	[19]
22	75	F	Ad	64 days	Osimertinib (80mg)	Osimertinib (40mg)	Yes	No	[6]
23	62	M	Ad	82 days	Osimertinib (80mg)	Osimertinib (40mg)	Yes	No	[20]
24	69	F	Ad	55 days	Osimertinib (80mg)	Osimertinib (40mg)	Yes	No	Present case

NA, not available; Adsq, adenosquamous; BEV, bevacizumab.
[a] Administered every other day.

suggesting that physicians should be aware of the possibility of venous thromboembolism as well as pneumonitis for the differential diagnosis of GGO that develops during osimertinib treatment [21].

Although osimertinib rechallenge must be carefully chosen based on the balance the risks and benefits for the patient, this case suggests that osimertinib rechallenge after osimertinib-induced pneumonitis may be a treatment option when alternative therapeutic options are limited.

Conflict of interest statement

None declared.

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None.

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