Successful erlotinib rechallenge for leptomeningeal metastases of lung adenocarcinoma after erlotinib-induced interstitial lung disease. A case report and review of the literature

Authors:

Yosuke Togashi *, Katsuhiro Masago, Yasuhiro Hamatani, Yuichi Sakamori, Hiroki Nagai, Young Hak Kim, Michiaki Mishima

Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507 Japan

Grant support: none

*** Corresponding author:**

Yosuke Togashi, M.D.

Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507 Japan.

Tel: +81-75-751-3830; Fax: +81-75-751-4643

18 E-mail: ytogashi@kuhp.kyoto-u.ac.jp

19

Abstract

The most serious adverse reaction associated with treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) is drug-induced interstitial lung disease (ILD). Because EGFR-TKIs are key drugs for patients with non-small cell lung cancer who have somatic activating mutations of the epidermal growth factor receptor gene (*EGFR* mutations), several cases of retreatment with EGFR-TKIs after ILD induced by these drugs have been reported. Here, we present a 68-year-old man with lung adenocarcinoma and leptomeningeal metastases having an *EGFR* mutation who was retreated with erlotinib after erlotinib-induced ILD. He suffered no ILD recurrence and his leptomeningeal metastases dramatically improved. In addition to the present case, reports of nine patients who were retreated with EGFR-TKIs after ILD were found in the literature. Only one patient had recurrence of ILD (although seven were retreated at a reduced dose of EGFR-TKIs, including the patient with recurrence). In contrast, three patients had no recurrence of ILD even without dose-reduction. These reports suggest that dose-reduction plays a limited role in preventing recurrence. Many patients received corticosteroids during retreatment, but not the one with recurrence of ILD. This may suggest that corticosteroids can prevent recurrence due to their

antiinflammatory properties.

Key words: epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib, erlotinib, interstitial lung disease, rechallenge, epidermal growth factor receptor gene mutation, leptomeningeal metastases

1. Introduction

Because patients with non-small cell lung cancer (NSCLC) who have somatic activating mutations of the epidermal growth factor receptor (EGFR) gene (*EGFR* mutations) generally respond to EGFR-tyrosine kinase inhibitors (EGFR-TKIs; gefitinib or erlotinib) and can achieve long-term progression-free survival, the presence of *EGFR* mutations is a very useful marker for facilitating the choice of treatment for NSCLC [1-7]. Although systemic chemotherapy for leptomeningeal metastasis (LM) has been thought to play a limited role because of the belief that the brain is a pharmacologic sanctuary site, several studies have documented the effectiveness of EGFR-TKIs in the treatment of LM of NSCLC with *EGFR* mutations [8-10].

The most common adverse events associated with treatment with EGFR-TKIs are rash and diarrhea [11, 12]. Although not too frequent, the most serious adverse reaction is drug-induced interstitial lung disease (ILD) [13-16]. Because EGFR-TKIs are key drugs for patients with NSCLC having *EGFR* mutations, several cases of drug rechallenge after ILD induced by EGFR-TKIs have been reported. Here, we present a case report of a 68-year-old man with lung adenocarcinoma and LM having an *EGFR*

mutation who received erlotinib retreatment after erlotinib-induced ILD. No evidence of ILD recurrence was seen, and his LM dramatically improved. We also review the relevant published literature in this topic.

2. Case presentation

A 68-year-old Japanese man with a 40 pack-year history of smoking was diagnosed with stage IV lung adenocarcinoma (bone metastases). After one cycle of ~~carboplatin plus pemetrexed as~~ first-line cytotoxic chemotherapy, he suffered fatigue and electrolyte abnormality (both grade 3) as complications and elected to discontinue the~~se drugs~~ chemotherapy. *EGFR* mutational analysis revealed an exon 20 point mutation (L858R), and he therefore started erlotinib at 150 mg daily. Although he achieved a partial response (Fig 1A and 1B), he had cough and dyspnea on effort 8 weeks after initiation of erlotinib therapy. Chest computed tomography (CT) showed bilateral air space consolidations (Fig. 1C). Bronchoalveolar lavage (BAL) fluid contained no malignant cells and no pulmonary pathogens including bacteria, fungi, and Pneumocystis were identified. The fraction of lymphocytes in BAL fluid was

increased to 60%. Therefore, erlotinib-induced ILD (organized pneumonia [OP] pattern) was strongly suspected. Erlotinib was discontinued and 30 mg daily prednisolone (PSL) was initiated. Symptoms and bilateral consolidations in the CT improved, and PSL was gradually tapered to 5 mg (Fig. 1D).

After ~~cessation of erlotinib, he had received no treatment for 6 months because his lung cancer did not progress and he refused any further treatment. However; after~~ 6 months without treatment, he had headache and impaired consciousness, and his Eastern Cooperative Oncology Group performance status (ECOG PS) deteriorated to 2. Cerebrospinal fluid (CSF) testing revealed the presence of malignant cells and he was diagnosed with LM. He refused any cytotoxic chemotherapy; instead administration of 250 mg daily gefitinib and 4 mg daily betamethasone in addition to whole brain radiotherapy was initiated. His symptoms and CSF test, however, worsened, and his ECOG PS deteriorated to 4. The patient requested erlotinib retreatment despite the risk of ILD, so we initiated administration of 150 mg daily erlotinib together with 4 mg betamethasone. Soon after initiation of erlotinib, his symptoms dramatically improved and ECOG PS improved to 1. Both his CSF test and brain magnetic resonance imaging also improved (Fig. 2). His LM has not worsened for 8 months of erlotinib rechallenge.

During the period, betamethasone was gradually tapered to zero and ILD recurrence has not been observed.

3. Literature review

In addition to the present case, a literature search identified a total of nine cases who received EGFR-TKI retreatment after ILD induced by these drugs (Table 1) [17-24]. Three received gefitinib after gefitinib-induced ILD [17, 18, 24], 5 were treated with erlotinib after gefitinib-induced ILD [19-22], and the remaining one (two including the present case) received erlotinib after erlotinib-induced ILD [23]. Two patients were Asians and the other reports were also from Asia, but the ethnicity of the patients was not stated. Six patients were never-smokers and m~~M~~any had severe ILD as revealed by bilateral diffuse ground glass opacities (GGO) on CT. ILD of all patients went into remission on cessation of EGFR-TKIs and initiation of corticosteroid therapy. Two patients (cases 2 and 10 in Table 1) could not be given any chemotherapy other than EGFR-TKIs due to their poor PS. Although the others were fit enough to receive chemotherapy, they requested EGFR-TKIs again instead. During the EGFR-TKI

rechallenge, only case 3 suffered recurrence of ILD. Seven patients were retreated with a lower dose of EGFR-TKIs including case 3 who nonetheless recurred. In contrast, cases 5, 6, and 10 had no recurrence in spite of receiving 150 mg daily erlotinib. Many patients were given corticosteroids during EGFR-TKI rechallenge, but not case 3. However; case 2 also received no corticosteroids but did not recur.

4. Discussion

In this article, we presented a case of successful erlotinib rechallenge for LM after erlotinib-induced ILD and have summarized previous similar reports (Table 1). Although nine of these ten cases successfully rechallenged with EGFR-TKIs without the recurrence of ILD, most of the cases that do suffer recurrence might simply not be reported. Therefore, the risk of ILD should be considered whenever reinitiating EGFR-TKI treatment after ILD induced by these drugs. Eight of these ten cases could have received other chemotherapies, but the patients requested EGFR-TKI therapy again despite their awareness of the risk of ILD. This was permissible because the efficacy of EGFR-TKIs was predicted from *EGFR* mutations or previous tumor

response. Our case (case 10 in Table 1) was not eligible for other chemotherapy due to his poor PS, and the treatment of choice remained erlotinib or best supportive care. Several cases in which LM resistant to gefitinib were improved by erlotinib due to its higher CSF concentration have been reported [25-27] and ILD with an OP pattern on CT seems to be associated with good prognosis [28]. Therefore, we used 150 mg daily erlotinib because of its expected clinical benefit and efficacy despite the risk of ILD.

Seven patients were retreated with lower doses of EGFR-TKIs. Three received a lower dose of erlotinib after gefitinib-induced ILD. However, the area under the curve (AUC) of serum concentration of erlotinib at the approved dose (150 mg daily) is 7 times larger than gefitiinib at the approved dose (250 mg daily) [29]. Therefore, in spite of dose-reduction, higher AUC could be achieved by erlotinib than gefitinib in these patients. In addition, case 3 had recurrence of ILD despite dose-reduction, and three cases (cases 4, 5, and 10) had no recurrence of ILD although they received 150 mg daily erlotinib. From these findings, we speculate that blockade of the EGFR signaling pathway by EGFR-TKIs is not necessarily associated with the occurence of ILD and that EGFR-TKI dose-reduction plays only a limited role in preventing recurrence.

Dallas et al. have reported a similar case of successful erlotinib rechallenge after erlotinib-induced ILD (case 9). As with the case reported here, that patient had also received erlotinib retreatment together with corticosteroid after erlotinib-induced ILD. Many cases were also given corticosteroids together with the EGFR-TKIs, resulting in clinical benefit. In contrast, case 3 had recurrence of ILD without administration of corticosteroid. This is consistent with the general use of corticosteroids for treating drug-induced ILD [30, 31]. Thus, corticosteroid can prevent the recurrence of ILD, probably because of its antiinflammatory action.

Six patients were never-smokers and CT finding of many patients revealed bilateral diffuse GGO. We can predict the recurrence of ILD from these factors. In fact, a previous report has shown that smoking status is one of the risk factors for ILD [14]. In contrast, another report has shown that the incidence of the bilateral GGO pattern on CT was relatively high and that such patients have high mortality rate [28]. Therefore, great caution is required when undertaking rechallenge in these patients.

The mechanism responsible for ILD induced by EGFR-TKIs remains unclear and several instances of successful EGFR-TKI rechallenge after ILD have been reported, as described above. EGFR-TKIs are key drugs for patients with NSCLC having *EGFR*

mutations. Therefore, rechallenge after ILD should be undertaken considering the balance between risk and benefit. This present case had an *EGFR* mutation and was not eligible for other chemotherapy due to his poor PS. Therefore, the treatment of choice remained erlotinib or best supportive care. Although he recognized the risk of ILD, he requested erlotinib retreatment, and this was successful. From these findings, we suggest 3 criteria before deciding on EGFR-TKI rechallenge after ILD; a) The patient has an *EGFR* mutation. b) Few other treatment options except EGFR-TKI remain. c) The patient recognizes the risk of ILD and makes an informed decision to go ahead with the rechallenge. In order to assess the safety and the risk of this approach, more similar cases including other ethnicities need to be accumulated and, if ethically possible, prospective studies in patients who meet these criteria should be performed~~are required~~.

Conflict of interest statement

None declared.

References

1. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE, Meyerson M. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304: 1497-1500.

2. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004; 350: 2129-2139.

3. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361: 947-957.

4. Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS,

Sriuranpong V, Chao TY, Nakagawa K, Chu DT, Saijo N, Duffield EL, Rukazenkov Y, Speake G, Jiang H, Armour AA, To KF, Yang JC, Mok TS. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol 2011; 29: 2866-2874.

5. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K, Fukuoka M, West Japan Oncology G. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010; 11: 121-128.

6. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y,

Hagiwara K, Morita S, Nukiwa T, North-East Japan Study G. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362: 2380-2388.

7. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, You C. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011; 12: 735-742.

8. Gleissner B, Chamberlain MC. Neoplastic meningitis. Lancet Neurol 2006; 5: 443-452.

9. Lombardi G, Zustovich F, Farina P, Della Puppa A, Manara R, Cecchin D, Brunello A, Cappetta A, Zagonel V. Neoplastic meningitis from solid tumors: new diagnostic and therapeutic approaches. Oncologist 2011; 16: 1175-1188.

10. Yi HG, Kim HJ, Kim YJ, Han SW, Oh DY, Lee SH, Kim DW, Im SA, Kim TY, Kim CS, Heo DS, Bang YJ. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective for leptomeningeal metastasis

229 from non-small cell lung cancer patients with sensitive EGFR mutation or
230 other predictive factors of good response for EGFR TKI. Lung Cancer 2009;
231 65: 80-84.
232 11. Cohen MH, Williams GA, Sridhara R, Chen G, Pazdur R. FDA drug approval
233 summary: gefitinib (ZD1839) (Iressa) tablets. Oncologist 2003; 8: 303-306.
234 12. Cohen MH, Johnson JR, Chen YF, Sridhara R, Pazdur R. FDA drug approval
235 summary: erlotinib (Tarceva) tablets. Oncologist 2005; 10: 461-466.
236 13. Inoue A, Saijo Y, Maemondo M, Gomi K, Tokue Y, Kimura Y, Ebina M,
237 Kikuchi T, Moriya T, Nukiwa T. Severe acute interstitial pneumonia and
238 gefitinib. Lancet 2003; 361: 137-139.
239 14. Kudoh S, Kato H, Nishiwaki Y, Fukuoka M, Nakata K, Ichinose Y, Tsuboi M,
240 Yokota S, Nakagawa K, Suga M, Japan Thoracic Radiology G, Jiang H, Itoh Y,
241 Armour A, Watkins C, Higenbottam T, Nyberg F. Interstitial lung disease in
242 Japanese patients with lung cancer: a cohort and nested case-control study. Am
243 J Respir Crit Care Med 2008; 177: 1348-1357.
244 15. Hotta K, Kiura K, Takigawa N, Yoshioka H, Harita S, Kuyama S, Yonei T,
245 Fujiwara K, Maeda T, Aoe K, Ueoka H, Kamei H, Umemura S, Moritaka T,

Segawa Y, Kawai H, Bessho A, Kato K, Tabata M, Tanimoto M. Comparison of the incidence and pattern of interstitial lung disease during erlotinib and gefitinib treatment in Japanese Patients with non-small cell lung cancer: the Okayama Lung Cancer Study Group experience. In: J Thorac Oncol. United States, 2010: 179-184.

16. Ter Heine R, van den Bosch RT, Schaefer-Prokop CM, Lankheet NA, Beijnen JH, Staaks GH, van der Westerlaken MM, Malingre MM, van den Brand JJ. Fatal interstitial lung disease associated with high erlotinib and metabolite levels. A case report and a review of the literature. In: Lung Cancer: 2011 Elsevier Ireland Ltd, 2011.

17. Takamochi K, Suzuki K, Bashar AH, Yajima K, Mochizuki T, Itaya T, Funai K. Readministration of gefitinib in a responder after treatment discontinuation due to gefinitib-related interstitial lung disease: a case report. J Med Case Reports 2007; 1: 138.

18. Suzuki M, Asahina H, Konishi J, Yamazaki K, Nishimura M. Recurrent gefitinib-induced interstitial lung disease. In: Intern Med. Japan, 2008: 533-536.

19. Fukui T, Otani S, Hataishi R, Jiang SX, Nishii Y, Igawa S, Mitsufuji H, Kubota M, Katagiri M, Masuda N. Successful rechallenge with erlotinib in a patient with EGFR-mutant lung adenocarcinoma who developed gefitinib-related interstitial lung disease. Cancer Chemother Pharmacol 2010; 65: 803-806.

20. Chang SC, Chang CY, Chen CY, Yu CJ. Successful erlotinib rechallenge after gefitinib-induced acute interstitial pneumonia. In: J Thorac Oncol. United States, 2010: 1105-1106.

21. Takeda M, Okamoto I, Makimura C, Fukuoka M, Nakagawa K. Successful treatment with erlotinib after gefitinib-induced severe interstitial lung disease. In: J Thorac Oncol. United States, 2010: 1103-1104.

22. Tian Q, Chen LA. Erlotinib achieved partial response in a non-small cell lung cancer patient with gefitinib-induced interstitial lung disease. Case Rep Oncol 2011; 4: 464-466.

23. Dallas JL, Jantz MA, Lightsey JL, Sonntag C, Kaye FJ. Successful erlotinib rechallenge after erlotinib-induced interstitial lung disease. In: J Thorac Oncol. United States, 2011: 1142-1143.

24. Yano S, Nakataki E, Ohtsuka S, Inayama M, Tomimoto H, Edakuni N,

Kakiuchi S, Nishikubo N, Muguruma H, Sone S. Retreatment of lung adenocarcinoma patients with gefitinib who had experienced favorable results from their initial treatment with this selective epidermal growth factor receptor inhibitor: a report of three cases. Oncol Res 2005; 15: 107-111.

25. Katayama T, Shimizu J, Suda K, Onozato R, Fukui T, Ito S, Hatooka S, Sueda T, Hida T, Yatabe Y, Mitsudomi T. Efficacy of erlotinib for brain and leptomeningeal metastases in patients with lung adenocarcinoma who showed initial good response to gefitinib. J Thorac Oncol 2009; 4: 1415-1419.

26. Masuda T, Hattori N, Hamada A, Iwamoto H, Ohshimo S, Kanehara M, Ishikawa N, Fujitaka K, Haruta Y, Murai H, Kohno N. Erlotinib efficacy and cerebrospinal fluid concentration in patients with lung adenocarcinoma developing leptomeningeal metastases during gefitinib therapy. Cancer Chemother Pharmacol 2011; 67: 1465-1469.

27. Tetsumoto S, Osa A, Kijima T, Minami T, Hirata H, Takahashi R, Kuhara H, Nagatomo I, Takeda Y, Kida H, Goya S, Tachibana I, Kawase I. Two cases of leptomeningeal metastases from lung adenocarcinoma which progressed during gefitinib therapy but responded to erlotinib. Int J Clin Oncol 2011.

28. Endo M, Johkoh T, Kimura K, Yamamoto N. Imaging of gefitinib-related interstitial lung disease: multi-institutional analysis by the West Japan Thoracic Oncology Group. Lung Cancer 2006; 52: 135-140.

29. Mitsudomi T. Erlotinib, gefitinib, or chemotherapy for EGFR mutation-positive lung cancer? Lancet Oncol 2011; 12: 710-711.

30. Tsuboi M, Le Chevalier T. Interstitial lung disease in patients with non-small-cell lung cancer treated with epidermal growth factor receptor inhibitors. Med Oncol 2006; 23: 161-170.

31. Kuo LC, Lin PC, Wang KF, Yuan MK, Chang SC. Successful treatment of gefitinib-induced acute interstitial pneumonitis with high-dose corticosteroid: a case report and literature review. Med Oncol 2011; 28: 79-82.

Figure Legends

Figure 1. Chest computed tomography (CT) in a 68-year-old man. A: CT scan before erlotinib treatment showing a mass in the left upper lobe. B, C: CT scan 10 weeks after initiation of erlotinib treatment showing a decreased mass (B), but visible bilateral air space consolidations (C). D: Eight weeks after cessation of erlotinib and initiation of corticosteroid, showing improvement of the bilateral air space consolidations.

Figure 2. Brain magnetic resonance imaging (MRI). A: Contrast (gadolinium)-enhanced T1-weighted MRI during gefitinib treatment before erlotinib rechallenge, revealing leptomeningeal metastases (arrowheads). Patient performance status (PS) had deteriorated to 4. B: Two weeks after the initiation of erlotinib, showing improvement of the leptomeningeal metastases. PS also improved to 1.

Table 1. Patient characteristics

Case	Age (yr)	Sex	Ethnicity [a]	Histology	*EGFR* status	Smoking status	Onset of ILD	Cause of ILD (dose)	CT of ILD	Respiratory condition [d]	Treatment for ILD
1	62	F	NA	Ad	NA	Never	13 months	Gefitinib (125 mg/day [b])	NA [c]	NA	Cessation and corticosteroid
2	56	M	NA	Ad	Exon 21; L858R	15 pack-year	45 days	Gefitinib (250 mg/day)	Diffuse GGO	Severe	Cessation and corticosteroid
3	59	M	NA	Ad	Wild type	60 pack-year	23 days	Gefitinib (250 mg/day)	Diffuse GGO	PaO_2, 46.9 mmHg	Cessation and corticosteroid
4	28	F	NA	Ad	Exon 19 deletion	Never	28 days	Gefitinib (250 mg/day)	Diffuse GGO	Need nasal oxygen	Cessation and corticosteroid
5	62	M	NA	Ad	Exon 19 deletion	18 pack-year	24 days	Gefitinib (250 mg/day)	Diffuse GGO	Severe	Cessation and corticosteroid
6	62	M	NA	Ad	NA	Never	6 weeks	Gefitinib (250 mg/day)	Diffuse GGO	Oxygen saturation, 84%	Cessation and corticosteroid
7	77	F	NA	Ad	NA	Never	7 weeks	Gefitinib (250 mg/day)	Diffuse GGO	Oxygen saturation, 93%	Cessation and corticosteroid
8	41	F	NA	Ad	NE	Never	20 days	Gefitinib (250 mg/day)	Patchy air space consolidation	PaO_2 <45 mmHg	Cessation and corticosteroid
9	77	F	Asian	Ad	Exon 19 deletion	Never	5 weeks	Erlotinib (150 mg/day)	Diffuse GGO	Oxygen saturation, 92%	Cessation and corticosteroid
10	68	M	Asian	Ad	Exon 21; L858R	40 pack-year	8 weeks	Erlotinib (150 mg/day)	OP pattern	PaO_2, 78.6 mmHg	Cessation and corticosteroid

F, female; M, male; *EGFR*, epidermal growth factor receptor gene; ILD, interstitial lung disease; CT, computed tomography; GGO, ground glass opacity; OP, organized pneumonia; PaO_2, arterial oxygen pressure; NA, not available; NE, not evaluated.

[a] The ethnicity of eight cases was not available, but all reports were from Asia.

[b] Gefitinib was administered every other day due to blepharitis.

[c] Case 1 had alveolar hemorrhage.

[d] There was no description of actual PaO_2 or oxygen saturation in Cases 2, 4 and 5. But Cases 2 and 5 had severe ILD and Case 4 needed nasal oxygen supplementation (1 L/minute). Case 9 was supported by mechanical ventilation.

Table 1. Continued

Case	ECOG PS (symptoms)	Period between EGFR-TKIs	Rechallenge (dose)	Corticosteroid during rechallenge	Recurrence of ILD	Response of initial/rechallenge	References
1	1	12 months	Gefitinib (125 mg/day [e])	NA	No	SD/SD	[17]
2	NA (Severe dyspnea and confined to bed)	5 months	Gefitinib (125 mg/day)	No	No	PR/PR	[18]
3	NA (General fatigue)	3 months	Gefitinib (Intermittent [f])	No	Yes	NA	[19]
4	NA (Dyspnea)	4 months	Erlotinib (50 mg/day)	Yes → tapered	No	PR/PR	[20]
5	NA (Neurological symptoms)	3 months	Erlotinib (150 mg/day)	NA	No	NA/PR	[21]
6	NA	6 days	Erlotinib (150 mg/day)	Yes	No	PR/PR	[22]
7	NA	6 weeks	Erlotinib (100 mg/day)	Yes	No	PR/PR	[22]
8	NA	NA (about 6 months)	Erlotinib (75 mg/day)	Yes → off	No	PR/PR	[23]
9	NA	10 days	Erlotinib (100 mg/day)	Yes → off	No	PR/NA	[24]
10	4 (Impaired conscious)	7 months	Erlotinib (150 mg/day)	Yes → off	No	PR/PR	Present case

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; SD; stable disease; PR, partial response.

[e] Gefitinib was administered every other day.

[f] Gefitinib (250 mg daily) was administered for 7 days followed by 2 weeks rest.

Figure 1

Click here to download high resolution image

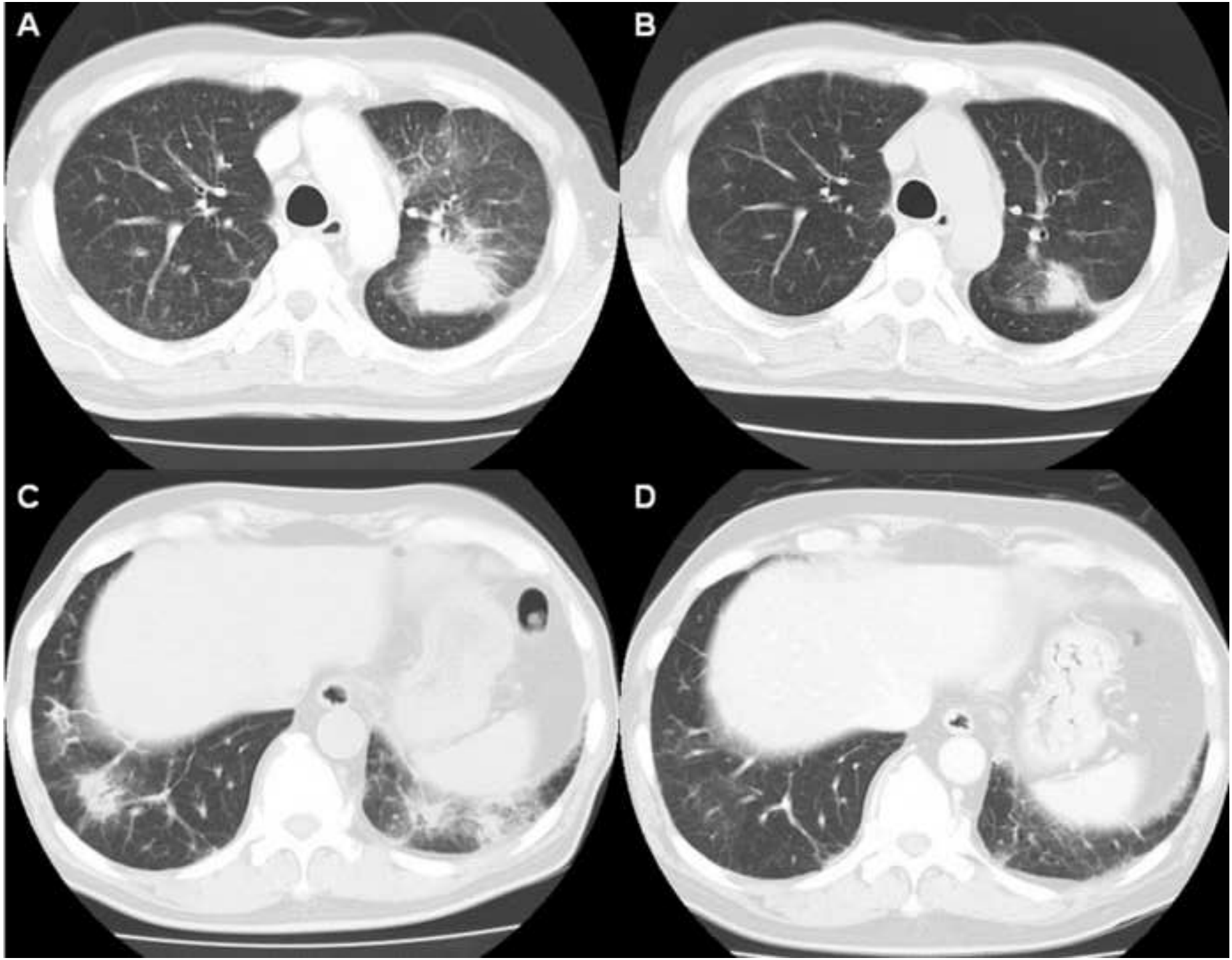

Figure 2

Click here to download high resolution image