（肺癌．2023;63:33-39）

CASE REPORT

Efficacy of Osimertinib for EGFR Exon 20 Insertion Mutation-positive Non-small Cell Lung Cancer with Brain Metastases in a Very Elderly Man

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ABSTRACT —— ***Background.*** Epidermal growth factor receptor (EGFR) exon 20 insertion mutations represent the third most common EGFR mutation in non-small cell lung cancer (NSCLC). EGFR tyrosine kinase inhibitors (TKIs) are highly effective for EGFR-positive NSCLC but not for EGFR exon 20 insertion mutations, which carry a poor prognosis. ***Case.*** A 90-year-old man was referred to our hospital because of an infiltrative shadow and a small nodule in the right lung on chest X-ray. Chest computed tomography revealed a mass in the right lung apex, a small nodule in the right upper lobe, a hypoattenuated area in the left lobe of the liver, bilateral pleural effusion, and enlarged mediastinal lymph nodes. Thoracentesis on the right and transbronchial lung biopsy of the mass were performed. Magnetic resonance imaging of the brain revealed contrast-enhanced nodules. We finally diagnosed the patient with lung adenocarcinoma, cT3N3M1c stage IVB. Genetic testing detected EGFR exon 20 insertion mutations. Considering the patient's age, renal function and performance status (PS), we administered osimertinib, which led to the resolution of the bilateral pleural effusion and a reduction in the size of the primary lesion, as well as the intrapulmonary and brain metastases. The progression-free survival was 5.9 months. ***Conclusion.*** In EGFR exon 20 insertion mutation-positive NSCLC, platinum-based chemotherapy has been shown to be more effective than EGFR-TKIs, including osimertinib, and has been the recommended by guidelines. EGFR exon 20 insertion mutations are generally unresponsive to EGFR-TKIs, but some case reports have demonstrated the efficacy of osimertinib. In our case, osimertinib was effective in a very old patient with EGFR exon 20 insertion mutation-positive NSCLC with brain metastases. Osimertinib may be a treatment option in the elderly for whom chemotherapy and late-line treatment options are limited.

(*JJLC.* 2023;63:33-39)

KEY WORDS —— EGFR exon 20 insertion mutations, Osimertinib, Non-small cell lung cancer

INTRODUCTION

Activating mutations in the epidermal growth factor receptor (EGFR) gene are particularly common among patients with non-small cell lung cancer (NSCLC), with a reported incidence of approximately 40% among Asians and 10-30% among Caucasians.[1] Exon 19 deletion and L858R point mutations in exon 21 account for approximately 85% of EGFR mutations,[2] while uncommon mutations, including EGFR exon 20 insertion mutations, account for the remaining 10-15%. EGFR exon 20 insertion mutations, the third most common type of EGFR mutation, which account for 4-10% of EGFR mutations,[3] generally carry a worse prognosis in comparison to the two most common types of mutation (i.e., exon 19 deletion and L858R point mutation in exon 21).[4] To date, EGFR mutations in NSCLC represent the most prevalent treatment target of highly effective drugs, such as EGFR tyrosine kinase inhibitors (TKIs). However, tumors with EGFR exon 20 insertion mutations are generally poorly responsive to EGFR-TKIs, including the third-generation EGFR-TKI, osimertinib, with a reported overall response rate (ORR) of 0-20% and progression-free survival (PFS) of 1.4-3.0 months.[5] In a nationwide

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Received May 20, 2022; accepted September 5, 2022.

Table 1. Blood Test Findings at the Diagnosis

Hematology		Blood chemistry	
WBC	5170/μl	TP	6.9 g/dl
Neu	75.6%	Alb	3.8 g/dl
Lym	14.9%	T-bil	0.4 mg/dl
Eos	2.3%	AST	27 U/*l*
Baso	0.2%	ALT	20 U/*l*
Mono	7.0%	LDH	292 U/*l*
Hb	10.5 g/dl	BUN	19.1 mg/dl
Plt	18.5×10^4/μl	Cre	1.23 mg/dl
Serology		Ccr	27.6 ml/min
CRP	1.30 mg/dl	Na	141 mEq/*l*
BNP	39.0 pg/ml	K	4.1 mEq/*l*
		Cl	107 mEq/*l*
		CEA	23.9 ng/ml
		CYFRA	2.4 ng/ml
		ProGRP	89.6 pg/ml
		KL-6	2290 U/ml

WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; Eos, eosinophil; Baso, basophil; Mono, monocyte; Hb, hemoglobin; Plt, platelet; CRP, C-reactive protein; BNP, brain natriuretic peptide; TP, total protein; Alb, albumin; T-bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; Cre, creatinine; Ccr, creatinine clearance; Na, sodium; K, potassium; Cl, chlorine; CEA, carcinoembryonic antigen; CYFRA, cytokeratin fragment; ProGRP, progastrin-releasing peptide; KL-6, Krebs von den Lungen-6.

real-world study,[4] conventional platinum-based chemotherapy was reported to be superior to the currently available EGFR-TKIs (ORR, 19.2% vs. 8.7%; median PFS, 6.4 months vs. 2.9 months; $P<0.001$). Platinum-based chemotherapy has been demonstrated to be more effective than EGFR-TKIs, including osimertinib, in patients with EGFR exon 20 insertion mutation-positive NSCLC, and it has been recommended by guidelines. Besides, the guidelines recommended that EGFR-TKIs should not be used in such cases. Therefore, conventional cytotoxic chemotherapy is the standard treatment for patients with NSCLC with EGFR exon 20 insertion mutations. However, in the clinical setting, EGFR-TKIs are the treatment of choice for some patients when chemotherapy cannot be given due to old age, a poor performance status (PS), or other reasons.

In this report, we presented our case of therapeutic response to the EGFR-TKI osimertinib in an elderly patient with NSCLC with EGFR exon 20 insertion mutations and brain metastases. To the best of our knowledge, this is the oldest patient for whom osimertinib was effective against EGFR exon 20 insertion-positive NSCLC.

CASE

A 90-year-old man was referred to our hospital after an infiltrative shadow and small nodule were detected in the right lung on a chest X-ray. No subjective symptoms were observed. He had smoked 20 cigarettes per day for 45 years, and had quit smoking 25 years previously. No pertinent medical history was found, other than an elbow fracture. His PS was 0, and he was able to do farm work. His peripheral oxygen saturation in room air was 98%.

Blood tests revealed that the of the tumor marker carcinoembryonic antigen (CEA) was elevated, at 23.9 ng/ml, a decreased renal function, and a creatinine clearance (Ccr) rate of 27.6 ml/min (Table 1). Chest computed tomography (CT) revealed a 44×42 mm mass in the right lung apex, a small (11×10 mm) nodule in the right upper lobe, a hypoattenuated area in the left lobe of the liver, bilateral pleural effusion, and enlarged mediastinal lymph nodes (Figure 1A).

Based on the suspicion of malignancy, we performed thoracentesis on the right and transbronchial lung biopsy. The pleural fluid was lymphocyte-predominant, exudative in character, and had an elevated CEA level of 151.6 ng/ml. Pleural effusion cytology showed malignant cells. A histological examination of the transbronchial lung biopsy specimen revealed the infiltration of atypical epithelial cells with papillary or acinar-predominant structure. Based on these findings, we diagnosed the patient with adenocarcinoma of the lung. Further staging with ^{18}F-fluorodeoxyglucose positron emission tomography-CT (^{18}F-FDG PET-CT) revealed the accumulation of ^{18}F-FDG in the right lung apex mass, right upper lobe nodule, mediastinal lymph nodes, right supraclavicular lymph nodes, the eighth thoracic vertebra, and left lobe of the liver (Figure 2). Magnetic resonance imaging (MRI) of the brain showed contrast-enhanced nodules (Figure 3A), and brain metastases was observed. The patient was finally diagnosed with lung adenocarcinoma, cT3N3M1c stage IVB, based on the eighth edition of the TNM staging of lung cancer.

Genetic testing revealed an EGFR mutation (exon 20 insertion mutations). The patient was negative for anaplastic lymphoma kinase gene fusion, and the c-ros oncogene 1 gene fusion status was undetermined. A test

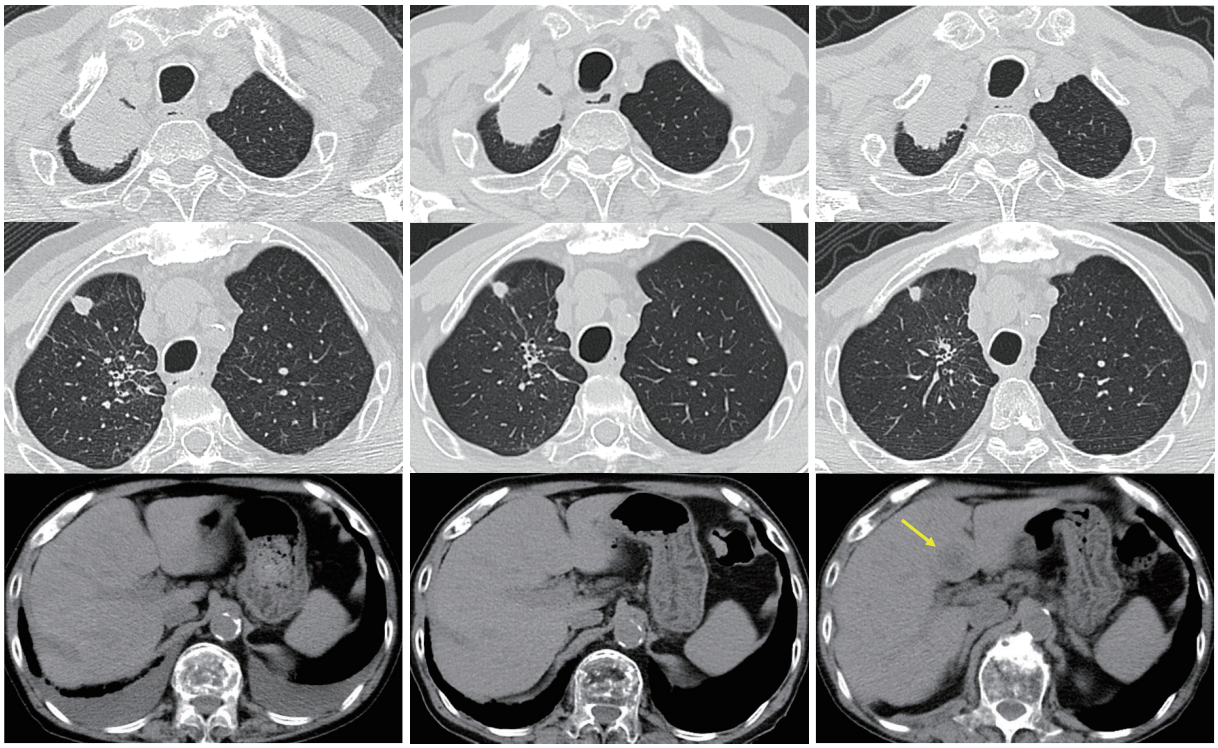

Figure 1. Chest CT findings of NSCLC. **A:** At the diagnosis, the images showed a mass in the right lung apex, a small nodule in the right upper lobe, bilateral pleural effusion. **B:** Three months after the initiation of osimertinib, the images showed a reduction in the size of the primary lesion and lung metastasis and resolution of the bilateral pleural effusion. **C:** Six months after the initiation of osimertinib, the primary lesion and lung metastasis presented at the time of diagnosis continued to decrease in size, but new liver metastases were observed (yellow arrow). CT: computed tomography, NSCLC: non-small cell lung cancer.

for the expression of programmed death-ligand 1 expression was negative. Although the administration of carboplatin-pemetrexed was considered according to the clinical practice guidelines of the Japanese Lung Cancer Society, the administration was not possible due to the deterioration of the patient's renal function. Considering the patient's age—although palliative care was an option—the patient was also eligible for EGFR-TKI treatment. This was determined to be acceptable based on his PS, which was 0. Consequently, the patient and his family requested this treatment, and it was decided that he would be treated with the third-generation EGFR-TKI osimertinib. In a previous report on the use of osimertinib in the elderly, the median age was 80 years (range, 75-90 years); however, the rates of dose reduction and treatment discontinuation because of adverse events of osimertinib (40.9% and 26.5%, retrospectively) were reported to be higher than those reported in the FLAURA study (3.9% and 13.3%, retrospectively).[6] The rate of dose reduction due to adverse events was significantly higher in elderly patients than that in young patients. In our case, the patient was 90 years of age and was included in the elderly category as per the previous report. Based on concerns about adverse events attributable to old age, the dose of osimertinib was initially started at 40 mg but was increased to 80 mg one month later after because no adverse events were observed. At one month after the initiation of treatment, the bilateral pleural effusion resolved on chest CT. Chest CT at three months after the initiation of treatment showed a reduction in the size of the primary lesion from 44×42 mm to 35×34 mm and the metastatic lesion of the lung from 13×10 mm to 8×7 mm; in addition, a reduction of the bilateral pleural effusion was observed (Figure 1B). Contrast-enhanced MRI four months after showed a reduction in the size of the metastatic lesion of the brain (Figure 3B).

The patient continued to receive treatment with no

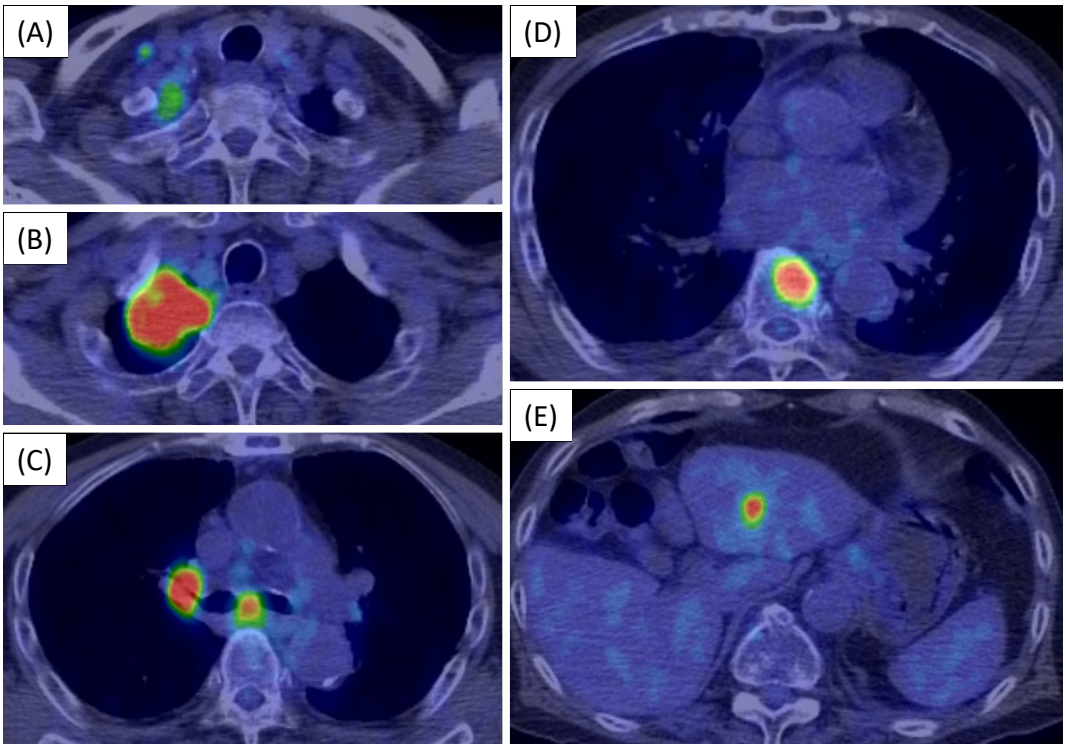

Figure 2. ^{18}F-FDG PET-CT findings. The accumulation of ^{18}F-FDG was observed in the **A:** right supraclavicular lymph nodes, **B:** right lung apex, **C:** mediastinal lymph nodes, **D:** eighth thoracic vertebra, and **E:** left lobe of the liver. ^{18}F-FDG PET-CT: ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography.

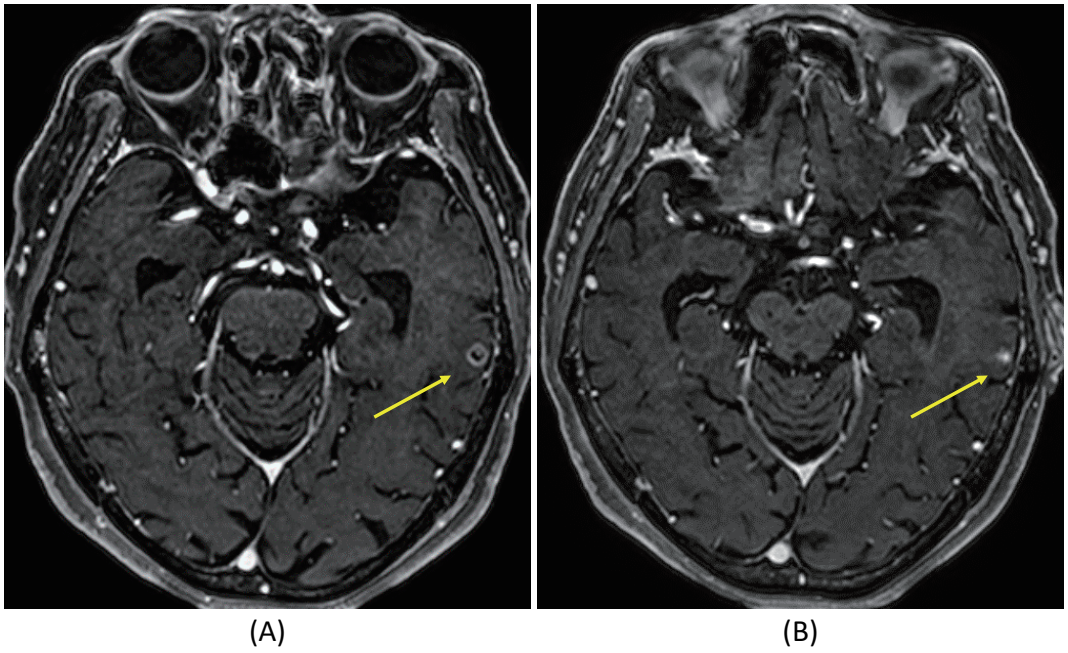

Figure 3. Contrast-enhanced MRI of the brain. **A:** At the diagnosis, a contrast-enhanced nodule was observed in the left temporal lobe (yellow arrow). **B:** Four months after the initiation of osimertinib, MRI showed a reduction in the size of the metastatic lesion of the brain (yellow arrow). MRI: magnetic resonance imaging.

adverse events and was able to perform activities of daily living. On follow-up CT at six months after the start of treatment, the primary lesion and lung metastasis observed at the time of the diagnosis had continued to decrease in size; however, the mediastinal lymph node and liver metastases increased in size. In addition, new intrapulmonary and liver metastases were observed (Figure 1C). At this time, the patient lost his appetite, started to have fatigue, and had a PS of 3. Based on our assessment of progressive disease, we decided to offer the best supportive care. In this case, the reduction rate was 27%, indicating that it was stable disease, as evaluated using the Response Evaluation Criteria in Solid Tumors (version 1.1) ; however, pleural effusion had disappeared, and disease control had been achieved; the PFS was 5.9 months.

DISCUSSION

EGFR-TKIs are highly effective against EGFR-positive NSCLC, but NSCLC with EGFR exon 20 insertion mutations has been generally associated with resistance to EGFR-TKIs.[5] A previous study showed that platinum-based chemotherapy is the most effective first-line treatment for NSCLC with EGFR exon 20 insertion mutations. In particular, the outcomes were more favorable with chemotherapy-based regimens (median PFS, 3.4-6.9 months and ORR, 23-29%) than with EGFR-TKIs (median PFS, 1.8-6.4 months and ORR, 0-8.7%). A similar tendency was observed after second-line treatment with chemotherapy (median PFS, 4.1-4.8 months) and EGFR-TKIs (median PFS, 1.9-3.7 months).[5] Additionally, one study suggested that EGFR-TKI treatment does not affect the median OS of patients with NSCLC and EGFR exon 20 insertion mutations, based on similar outcomes between patients who received any-line EGFR-TKI and those who did not receive any-line EGFR-TKI (median OS, 31.0 months vs. 28.2 months, respectively, $P=0.272$).[7] In the largest nationwide real-world study, with a sample size of 165 patients with NSCLC and EGFR exon 20 insertion mutations reported from China, the PFS of patients who received platinum-based chemotherapy was significantly longer in comparison to those who received all generations of EGFR-TKIs (ORR, 19.2% vs. 8.7%; median PFS, 6.4 months vs. 2.9 months; $P<0.001$).[4] The current standard of treatment for patients with NSCLC and EGFR exon 20 insertion mutations is conventional cytotoxic chemotherapy, and the guidelines recommended that EGFR-TKIs should not be given.

In the JCOG1210 trial, for patients of ≥75 years of age, although carboplatin-pemetrexed was associated with non-inferior overall survival (OS) compared to docetaxel, the PFS was significantly prolonged. Furthermore, among the adverse events, the rates of neutropenia and febrile neutropenia were low.[8] Therefore, we considered that carboplatin-pemetrexed is an effective first-line treatment option for patients of ≥75 years of age. Based on these results, this treatment was also recommended by the clinical practice guidelines of the Japanese Lung Cancer Society for patients of the same age class. We considered using this treatment for the patient in the current case as well; however, his Ccr level was 27.6 ml/min and pemetrexed is contraindicated in patients with Ccr <45 ml/min; thus, it could not be administered.

Several preclinical studies have indicated that osimertinib was active in specific lung cancer cell lines with EGFR exon 20 insertion mutations.[9] Some case reports showed that osimertinib was effective; however, the reported effect of osimertinib in cases with EGFR exon 20 insertion mutations was poor in clinical practice, with reported response rates of 0-6.5% and median PFS of 2.3-3.7 months in retrospective analyses.[3,5,10] The only prospective phase I/II trial that evaluated the efficacy of osimertinib for EGFR exon 20 insertion mutation-positive NSCLC was reported from Japan and revealed an ORR of 0% and a median PFS of 3.8 months.[11]

In our case, the presence of brain metastases made the patient's course worse. EGFR exon 20 insertion mutation-positive NSCLC with central nervous system (CNS) metastasis was reported to be associated with numerically shorter median PFS in comparison to cases without CNS metastasis after first-line chemotherapy (3.6 months vs. 6.5 months; $P=0.645$) or first-line EGFR-TKIs (2.0 months vs. 2.9 months; $P=0.058$).[4] In another report, the median PFS for osimertinib was 2.2 months in patients with EGFR exon 20 insertion mutation-positive NSCLC with brain metastases.[3] Osimertinib shows CNS efficacy in patients with EGFR-positive NSCLC. In addition, previous studies have shown that, in comparison to first- or second-generation EGFR-TKIs, osimertinib reduced the risk of developing CNS metastases.[12]

Although platinum-based chemotherapy has a superior therapeutic effect to osimertinib in EGFR exon 20 insertion mutation-positive NSCLC, it is difficult to ad-

minister to elderly people, and there have been cases in which osimertinib was given as an option in clinical practice. In our case, the patient was very old, but his PS was 0. Based on the previously reported disease control rate with osimertinib (58.3%),[11] a certain therapeutic effect was expected for this patient. Because he had brain metastases, osimertinib was administered with the expectation of a therapeutic effect.

The development of new drugs that target EGFR exon 20 insertion mutations is in progress. Some reports have suggested the efficacy of the following drugs for EGFR exon 20 insertion mutation-positive NSCLC: poziotinib (ORR, 31% and median PFS, 5.5 months) ; mobocertinib (ORR, 43% and median PFS, 7.3 months); and amivantamab (ORR, 40% and median PFS, 8.3 months).[13-15] These drugs are currently in clinical trials and have the potential to improve the prognosis of patients with EGFR exon 20 insertion mutation-positive NSCLC in the future.

Our report was associated with a limitation. We could not determine the exact subtype of EGFR exon 20 insertion mutations variant by polymerase chain reaction (PCR) testing alone. A prior study indicated that the D770delinsGY variant might benefit from second- or third-generation EGFR-TKIs[3]; our patient's subtype may have accounted for the therapeutic response. However, subtypes cannot be measured by PCR alone, and there is much that must be investigated to determine the subtypes that are responsive to EGFR-TKIs.

In the present case, the therapeutic effect of osimertinib was initially assumed to be poor but it led to a PFS of 5.9 months and was also effective for brain metastases. To the best of our knowledge, the oldest patient in previous studies evaluating the efficacy of osimertinib for EGFR exon 20 insertion mutation-positive NSCLC was 84 years of age.[11] Our study is the first to report the long-term efficacy of osimertinib for EGFR exon 20 insertion mutation-positive NSCLC with brain metastases, and our patient is the oldest among the previously reported cases.

CONCLUSIONS

Based on this case, osimertinib may be a treatment option for elderly patients for whom chemotherapy and late-line treatment options are limited. However, the prognosis of patients with EGFR exon 20 insertion mutation-positive NSCLC remains poor, and we look forward to the emergence of new drugs in the future.

本論文内容に関連する著者の利益相反：なし

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