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ORIGINAL ARTICLE

Mixed response to osimertinib and the beneficial effects of additional local therapy

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Abstract

Background: Although non-small cell lung cancers (NSCLCs) harboring *EGFR* mutations initially respond well to EGFR-tyrosine kinase inhibitors (TKIs), they typically progress after approximately one year. The *EGFR* T790M mutation is the most common resistance mechanism. NSCLCs with T790M respond well to osimertinib; however, the heterogeneity of NSCLCs may limit the efficacy. Some patients exhibit a mixed response (MR), in which some lesions shrink and others progress, but little is known of the incidence and characteristics of such a response. We sought to determine the frequency and clinical course in MR patients.

Methods: We retrospectively reviewed the records of patients who had received osimertinib for NSCLC with *EGFR* T790M.

Results: Between April and December 2016, 48 patients were administered osimertinib. Seven patients (15%) exhibited one of two MR types: (i) progressive lesions that did not include the re-biopsy site (5 patients), and (ii) progressive lesions that included the re-biopsy site (2 patients). The most frequent progressive sites were liver and lung metastases (4 patients). Three patients continued osimertinib following an MR, one of whom had received local therapy for liver metastasis and achieved disease control on osimertinib for an additional four months.

Conclusion: An MR was detected in 15% of NSCLC patients with T790M. This finding suggests that several different resistance mechanisms are active within a single patient who develops resistance to EGFR-TKIs. Osimertinib is basically effective for tumors that acquire resistance to EGFR-TKIs as a result of T790M mutation. Therefore, additional local therapy may be beneficial for patients who develop an MR to osimertinib.

Introduction

Lung cancer is the most common cause of cancer-related death worldwide,[1] and non-small cell lung cancer (NSCLC) accounts for almost 85% of lung cancers. *EGFR* is among the most prevalent oncogenic drivers of NSCLC. Somatic *EGFR* mutations are detected in about 30–40% of Asian NSCLC patients, and in approximately 10–20% of European or American patients.[2] Patients with NSCLC harboring *EGFR*-activating mutations (*EGFR*-mutated NSCLC) respond well to first and second-generation EGFR-tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, or afatinib. However, in most patients, NSCLC progresses within one to two years after the initiation of such treatment.[3–5] At the time of progression, *EGFR* T790M mutation is the most common resistance mechanism, accounting for acquired resistance in more than half of cases.[6] Osimertinib is an irreversible EGFR-TKI that is selective for *EGFR*-activating mutations and T790M. It has a reported response rate of 61% and median progression-free survival of 9.6 months in patients with NSCLC harboring the *EGFR* T790M mutation that experienced disease progression following previous EGFR-TKI treatment.[7]

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As a first-line treatment for *EGFR*-mutated NSCLC, osimertinib has recently shown longer progression-free survival times than first generation EGFR-TKIs.[8]

A mixed response (MR) is a phenomenon in which some lesions shrink during treatment while others progress. When the number of progressing lesions is limited, the phenomenon is called oligoprogressive disease (OPD).[9] Although OPD is not strictly defined, the most common definition is progression in up to five lesions during treatment.[10] The incidence of an MR in NSCLC patients administered EGFR-TKI treatment differs among reports, ranging from 14.7 to 47.2%.[11,12] This inconsistent response to EGFR-TKI treatment could be explained by heterogeneity within individual patients.[13] Apart from T790M acquisition, several different mechanisms for EGFR-TKI resistance have been reported. In a previous study, multiple biopsies revealed multiple resistance mechanisms to EGFR-TKI treatment in a single patient.[14] Nevertheless, clinical patients receive osimertinib on the basis of a single tissue biopsy, which may not appropriately reflect intratumoral or intertumoral heterogeneity. A subset of patients exhibits an MR to osimertinib; however, little is known of the incidence and characteristics of this response, and the optimal management approach following an MR has yet to be determined.

Methods

Patients

We performed a retrospective review of the records of patients treated with osimertinib for NSCLC harboring the *EGFR* T790M mutation at the National Cancer Center Hospital in Tokyo, Japan, from April to December 2016. We collected the following information: tumor histological subtype; patient age, gender, and smoking status (light smoker, Brinkman index [BI] < 400; heavy smoker, BI ≥ 400); tumor *EGFR* mutation status; response to prior EGFR-TKIs; re-biopsy procedure; and outcome. We obtained ethical approval from the National Cancer Center Hospital, and patient confidentiality was maintained.

Response evaluation

We evaluated the response to osimertinib by computed tomography (CT), and compared CT images taken immediately before (baseline CT) and during osimertinib treatment. We defined progressive lesions as those having increased in diameter or new lesions that were absent in the baseline CT, and responsive lesions as those having decreased in diameter or disappeared. The responses of patients who had both progressive and responsive lesions were documented as an MR. Because our focus was resistance mechanism heterogeneity at the time of T790M detection and not secondary resistance mechanisms to osimertinib, we used the first CT evaluation to define the MR and initial osimertinib response. Patients were divided into three groups: those in whom all tumors responded (responsive group), those in whom all tumors progressed (progressive group), and those who exhibited an MR (MR group).

Data analysis

We conducted analyses using the Fisher's exact test for categorical variables, and the Kruskal–Wallis test for continuous variables. We performed Kaplan–Meier analysis to compare overall survival (OS) among the three groups, which was defined as the interval from the initiation of osimertinib to the date of death from any cause. Log-rank tests are reported as two-group tests. For pairwise comparisons, a Bonferroni-adjusted criterion was used. All statistical analyses were performed using JMP Pro version 13.0 software (SAS Institute, Cary, NC, USA).

Results

Patients

Between April and December 2016, 48 patients with NSCLC harboring a T790M mutation received osimertinib. All tumors were adenocarcinomas. The median interval between the initiation of osimertinib treatment and the first CT evaluation was 65 (range: 27–181) days. Seven patients (15%) exhibited an MR; the remaining patients exhibited a concordant response: 38 patients (79%) responded, and all tumor lesions progressed in 3 patients (6%). Patient characteristics are listed in Table 1. There was no significant difference between any of the variables.

Patients exhibiting a mixed response (MR)

We obtained detailed characteristics and clinical courses following the MR in the seven patients in the MR group (Table 2). Re-biopsy specimens in which T790M was detected were derived from the primary tumor lesion in six patients and from a metastatic lymph node in one patient. Among these seven patients, two MR types were observed: progressive lesions that did not include the re-biopsy site (5 patients),[1] and progressive lesions that included the re-biopsy site (2 patients).[2] The most frequent progressive sites were liver and lung metastases (4 patients). Three patients continued to receive osimertinib after the MR; of these, one patient received additional local treatment (No. 2, Table 2). This patient had multiple lung tumors, metastatic lymph nodes, and multiple liver metastases.

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Table 1 Characteristics of the included patients

Characteristics	Responded† (*n* = 38)	Mixed response (*n* = 7)	Progressed‡ (*n* = 3)
Age, median (range)	66 (45–82)	58 (36–69)	72 (67–79)
Gender, N (%)			
Male	16 (42%)	5 (71%)	1 (33%)
Female	22 (58%)	2 (29%)	2 (67%)
Smoking status, N (%)			
Never	17 (45%)	3 (43%)	2 (67%)
Light	16 (42%)	3 (43%)	1 (33%)
Heavy	5 (13%)	1 (14%)	0
Performance status, N (%)			
0	12 (32%)	2 (29%)	2 (67%)
1	21 (55%)	5 (71%)	1 (33%)
≥ 2	5 (13%)	0	0
Primary mutation status, N (%)			
Exon19 deletion	25 (66%)	3 (43%)	3 (100%)
L858R	11 (29%)	4 (57%)	0
Positive (NOS)	2 (5%)	0	0
No. of prior EGFR-TKIs			
1	18 (47%)	3 (43%)	2 (67%)
≥ 2	20 (53%)	4 (57%)	1 (33%)
Administration of second-generation EGFR-TKIs			
Yes	8 (21%)	3 (43%)	0
No	30 (79%)	4 (57%)	3 (100%)
Best response to prior TKIs, N (%)			
PR	28 (74%)	6 (86%)	3 (100%)
SD	10 (26%)	1 (14%)	0
Re-biopsy procedure, N (%)			
TBB	12 (32%)	4 (57%)	2 (67%)
CNB	9 (24%)	1 (14%)	0
Pleural effusion (cell block)	5 (13%)	1 (14%)	1 (33%)
TBNA	5 (13%)	1 (14%)	0
Surgery/VATS	3 (8%)	0	0
Cytology	2 (5%)	0	0
Plasma	2 (5%)	0	0

†All lesions responded. ‡All lesions progressed. CNB, core needle biopsy; CR, complete response; NOS, not otherwise specified; PR, partial response; TBB, transbronchial biopsy; TBNA, transbronchial needle aspiration; TKIs, tyrosine kinase inhibitors; VATS, video assisted thoracic surgery.

The first CT scan revealed that multiple liver metastases had progressed, while all other lesions responded. The patient underwent transcatheter arterial chemoembolization for liver metastases and continued osimertinib for 168 days after the MR. The other two patients continued osimertinib without any additional treatment for 154 and 453 days, respectively.

Survival analysis

Figure 1 shows the OS of patients in each group. The median follow-up duration was 20.2 (range: 1.8–28.8) months. The median OS were: responsive group, not reached (95% confidence interval [CI] 21.7–not reached); MR group, 12.3 months (95% CI 3.1–not reached); and progressive group, 5.3 months (95% CI 2.5–not reached). Although the results showed no statistical significance, the MR group tended to have poorer OS than the responsive group ($P = 0.04$). No significant difference in OS was observed between the MR and progressive groups ($P = 0.68$), or between the responsive and progressive groups ($P = 0.09$).

Discussion

An MR to osimertinib was observed in 15% of patients with NSCLC harboring the *EGFR* T790M mutation. The prognosis of patients who exhibited an MR was poorer than that of patients whose tumors responded, at all sites. The continuation of osimertinib after an MR with appropriate local therapy may be beneficial for a subset of patients.

Heterogeneous resistance mechanisms may play a role in an MR to osimertinib. In a previous report, multiple re-biopsies revealed intertumoral heterogeneous resistant mechanisms to erlotinib.[14] However, multiple re-biopsies are usually difficult to conduct in clinical settings because of invasiveness or the anatomical site of progressive lesions, which can include the central nervous system or bones. Liquid biopsy, an evaluation of circulating tumor DNA (ctDNA) in plasma, was recently approved for the detection of *EGFR* mutations in lung cancer. Because ctDNA is extracted from plasma samples, a liquid biopsy is much less invasive than a tissue biopsy, thus enabling serial evaluation. In addition, ctDNA evaluation promotes a comprehensive understanding of mutation status from several tumor sites. Indeed, ctDNA evaluation has been used to detect higher frequencies of the co-occurrence of T790M and other resistance mechanisms than were observed in the present study.[15] Moreover, quantitative analysis of ctDNA can track temporal changes in ctDNA levels[16] and may be suitable to evaluate tumor burden.[17] Therefore, serial analysis of ctDNA may prove useful for identifying the dominant tumor phenotype at the time of progression. Liquid biopsy was approved in June 2017, thus only two patients (5%) in our study received osimertinib based on the results of liquid biopsy as it was covered by Japanese health insurance during the period. Further information about liquid biopsy is expected. However, a liquid biopsy may be unable to detect several resistance mechanisms, such as transformation to small cell lung cancer, which is reported to exist concomitantly with T790M mutations.[6] In one case series, five patients were tested by liquid biopsy and found to be positive for T790M; these patients received osimertinib but exhibited tumor

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Table 2 Characteristics of the patients who exhibited an MR to osimertinib

No.	Age	Gender	*EGFR* mutation	Tumor lesions and response		Treatment after MR	Duration of treatment after MR (months)
				Responded	Progressed		
1	36	F	19 del	Primary† Bone	Lung‡	Continued osimertinib	5.1
2	58	M	L858R	Primary† Pleural effusion Ascites	Liver	Continued osimertinib TACE to liver metastasis	5.5
3	60	M	19 del	Primary† Lymph nodes Brain	Bone	Continued osimertinib	14.9
4	42	M	L858R	Primary† Adrenal gland	Lung‡ Liver Pleural effusion	Docetaxel	0
5	69	M	19 del	Primary† Lymph nodes Brain	Lung‡ Liver Bone	Nivolumab	0
6	45	M	L858R	Primary Lung‡	Lymph nodes† Pleural effusion	Pemetrexed	0
7	64	F	L858R	Lymph nodes	Primary‡ Lung‡ Liver	S-1	0

†Re-biopsy tissue was obtained. ‡Intrapulmonary metastasis.MR, mixed response; TACE, transcatheter arterial chemoembolization.

progression by the first evaluation. Tissue samples that were obtained at the time of the liquid biopsy revealed transformation to small cell lung cancer.[18] Thus, the clinical significance of liquid biopsy results should be interpreted with caution.

Patients who exhibited an MR tended to have poorer prognoses than patients who achieved a tumor response. A previous study concluded that an MR was an unfavorable prognostic factor.[12] Optimal management after an MR remains unclear. In this study, three patients continued osimertinib after an MR for more than 150 days. The continuation of EGFR-TKIs after radiological progression remains controversial.[19,20] However, a subset of patients can benefit from the continuation of EGFR-TKIs.[20,21] Patients who exhibited an MR to osimertinib had several tumor lesions that remained sensitive to osimertinib. Therefore, particularly when the number of progressing lesions is limited (i.e. in OPD), the continuation of osimertinib with additional local therapy is an attractive strategy. The addition of stereotactic body radiation to TKI treatment in NSCLC patients with oncogenic driver mutations has also shown promising results.[22] In the present study, one patient who exhibited an MR underwent transcatheter arterial chemoembolization for liver metastasis and continued

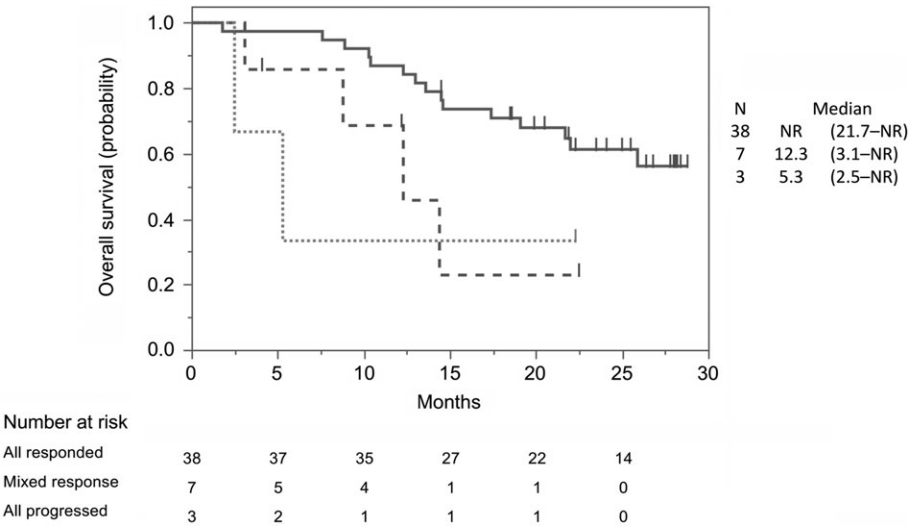

Figure 1 Kaplan–Meier curves. The median overall survival (OS) of responsive, mixed response (MR), and progressive groups were as follows: not reached [(95% confidence interval [CI] 21.7–not reached), 12.3 months (95% CI 3.1–not reached), and 5.3 months (95% CI 2.5–not reached), respectively. The MR group had relatively poorer OS than the responsive group ($P = 0.04$). No significant difference was observed between the MR and progressive groups ($P = 0.68$), or between the responsive and progressive groups ($P = 0.09$). —— all responded, ------ mixed response, ····· All progressed. NR, not reached.

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osimertinib for more than 150 days. The results of ongoing prospective clinical trials evaluating the addition of local therapy to EGFR-TKI treatment are highly anticipated.[23]

The present study had several limitations. First, there is no clear definition of an MR. In the present study we examined resistance mechanism heterogeneity at the time of *EGFR* T790M detection. Thus, we determined MRs based on the first CT taken during osimertinib treatment, which may reflect tumor heterogeneity at the time of osimertinib initiation. Because of the retrospective nature of the study, the intervals between the initiation of osimertinib treatment and the first CT evaluation differed among patients. Longer intervals may lead to higher MR incidence. However, the median interval (65 days) appears to appropriately reflect clinical practice. Second, we did not conduct molecular analysis of tumors that exhibited an MR to osimertinib. There might be concomitant resistant mechanisms, especially when progressive lesions included the re-biopsy site. These analyses may lead to further understanding of the phenomenon. Third, we cannot reach any conclusion about which patients should continue osimertinib treatment following an MR. Patients who exhibit OPD do not necessarily benefit from continued osimertinib because OPD consists of a heterogeneous population. In clinical settings, the continuation of ongoing treatment is determined by comprehensive evaluation. Further investigation of the characteristics that determine which patients can benefit from continued osimertinib treatment after an MR is needed.

An MR to osimertinib was observed in 15% of patients with NSCLC harboring the *EGFR* T790M mutation. This finding suggests that several different resistance mechanisms are active within a single patient when he or she develops resistance to EGFR-TKIs. Among tumors that are resistant to other EGFR-TKIs, osimertinib is basically effective for tumors with the *EGFR* T790M mutation. Therefore, the addition of local therapy may be beneficial for patients who develop an MR to osimertinib. In contrast, MR seemed to be an unfavorable prognostic factor. Further investigation to determine the optimal management of such patients is needed.

Disclosure

YG has had consulting/advisory roles for Eli Lilly, Chugai, Taiho Pharmaceutical, Boehringer Ingelheim, Pfizer, and Novartis; served on speakers' bureaus for AstraZeneca, Eli Lilly, Chugai, Taiho Pharmaceutical, Boehringer Ingelheim, Ono Pharmaceutical, Bristol-Myers Squibb, Pfizer, MSD, Shionogi Pharma, and Novartis; and received research funding from AbbVie, Eli Lilly, Taiho Pharmaceutical, Bristol-Myers Squibb, and Ono Pharmaceutical.

YM has served on the speakers' bureau for Cook Medical, Olympus, and AstraZeneca; and received research funding from Hitachi, Hitachi High-Technologies, and Boston Scientific.

SK has received research funding from AstraZeneca, Ono Pharmaceutical, and AbbVie; and received honoraria from AstraZeneca, Ono Pharmaceutical, Bristol-Myers Squibb, and Chugai.

HH has received research funding from MSD, Bristol-Myers Squibb, Ono Pharmaceutical, Merck Serono, Novartis, Astellas, Chugai, Taiho Pharmaceutical, and Genomic Health; and received honoraria from Eli Lilly.

YF has received research funding from AbbVie, AstraZeneca, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Incyte, Merck Serono, MSD, Novartis, and Bristol-Myers Squibb; and served on speakers' bureaus from AstraZeneca, MSD, Taiho Pharmaceutical, Bristol-Myers Squibb, and Ono Pharmaceutical.

NY has had consulting/advisory roles for Eisai, Takeda, Otsuka, and Boehringer Ingelheim; and received research funding from Eli Lilly, Quintiles, Astellas, Chugai, Eisai, Taiho Pharmaceutical, Bristol-Myers Squibb, Pfizer, Novartis, Daiichi Sankyo, Bayer, Boehringer Ingelheim, Kyowa Hakko Kirin, Takeda, and Ono Pharmaceutical; and served on speakers' bureaus from Bristol-Myers Squibb, Pfizer, AstraZeneca, Eli Lilly, Ono Pharmaceutical, and Chugai.

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All remaining authors report no conflict of interest.

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