Original Article

Efficacy and safety of crizotinib in patients with *ROS1* rearranged non-small cell lung cancer: a retrospective analysis

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Background: Tyrosine kinase inhibitors (TKIs) are remarkably effective in patients with non-small cell lung carcinoma (NSCLC) harboring driver gene mutations and rearrangements. Crizotinib, a small-molecule TKI, has been demonstrated to be an efficacious drug against c-ros oncogene 1-rearranged NSCLC (*ROS1*-NSCLC) in clinical trials. However, information regarding the use of crizotinib in clinical practice in Japan is limited.

Methods: Subjects with a definite diagnosis of advanced/relapsed *ROS1*-NSCLC were selected from consecutive NSCLC patients treated at the National Cancer Center Hospital between December 2014 and May 2018. We retrospectively assessed the efficacy and safety of crizotinib in clinical practice.

Results: Among 24 patients with *ROS1*-NSCLC, the *ROS1* rearrangement status was assessed using reverse transcription polymerase chain reaction (RT-PCR) (n=17), fluorescence in situ hybridization (FISH) (n=8), or next-generation sequencing (n=5) (some overlap occurred). Thirteen patients were treated with crizotinib in clinical practice. Among the 10 patients in whom clinical efficacy could be evaluated, the objective response rate (ORR) was 80.0% [95% confidence interval (CI), 49.0 to 94.3]. The median follow-up time was 35.5 months (95% CI, 8.9 to 44.6), the median progression-free survival (PFS) time was 10.0 months (95% CI, 5.1 to 27.0), and the median overall survival (OS) time was 28.7 months (95% CI, 6.7 to not reached). The most common adverse events were an aspartate/alanine aminotransferase (AST/ALT) increased and vision disorder. No severe adverse events related to crizotinib occurred.

Conclusions: The use of crizotinib in patients with *ROS1*-NSCLC was effective and well tolerated in clinical practice in Japan without severe adverse events.

Keywords: C-ros oncogene 1 (*ROS1*); crizotinib; non-small cell lung carcinoma (NSCLC); tyrosine kinase inhibitors (TKIs)

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Introduction

Protein kinase activation induced by somatic mutation or chromosomal alteration is one of the mechanisms of tumorigenesis and has led to targeted therapies with specific inhibitor drugs (1). For patients with non-small cell lung carcinoma (NSCLC) harboring driver gene mutations and rearrangements, the use of small-molecule tyrosine kinase inhibitors (TKIs) has been a standard therapy (2,3). Oncogenic c-ros oncogene 1 (*ROS1*) is one of the rearrangements found in NSCLC. The *ROS1* gene-fuses to

several partner genes, and the activated *ROS1* fusion kinases drive cellular transformation (4-6). *ROS1* fusion is generally known to be present in approximately 1–3% of NSCLC cases, and an effective TKI is available (7-9).

For *ROS1* rearranged NSCLC *(ROS1*-NSCLC), crizotinib, a small-molecule TKI, has been used. Crizotinib was initially approved for *ALK*-rearranged NSCLC. In 2012, the possibility that crizotinib might be exquisitely effective against *ROS1*-NSCLC *in vitro* was reported (7). In addition, several reports showed its efficacy in patients with *ROS1*-NSCLC. Thereafter, two prospective cohort studies were conducted: PROFILE 1001 and OO12-01. PROFILE 1001 was a phase 1 expansion study evaluating the efficacy and safety of crizotinib in 50 patients with *ROS1*-NSCLC (10). The objective response rate (ORR) was 72.0% [95% confidence interval (CI), 58.0 to 84.0], and the median progression-free survival (PFS) was 19.2 months (95% CI, 14.4 to not reached). OO12-01 was a large phase 2 study that enrolled 127 patients with *ROS1*-NSCLC. It demonstrated a clinically meaningful benefit and durable responses with crizotinib in East-Asian patients (11). The ORR was 71.7% (95% CI, 63.0 to 79.3), and the median PFS was 15.9 months (95% CI, 12.9 to 24.0). Based on these two studies, crizotinib was approved for the treatment of *ROS1*-NSCLC in Japan in May 2017. However, because of the small number of patients with *ROS1*-NSCLC, the efficacy and safety of crizotinib in clinical practice has been poorly documented in Japan.

In this report, we retrospectively reviewed the clinical characteristics of patients with *ROS1*-NSCLC and sought to assess the efficacy and safety of crizotinib in Japanese patients in actual clinical practice.

Methods

Subjects

Between December 2014 and May 2018, patients with a definite diagnosis of advanced/relapsed *ROS1*-NSCLC were selected from consecutive NSCLC cases treated at the National Cancer Center Hospital. The diagnosis of *ROS1*-NSCLC was primarily based upon reverse transcription polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), or next generation sequencing (NGS). We reviewed the patients' medical records and collected the following information: patient characteristics, histology, treatment history, and methods of *ROS1* detection. Especially, we assessed the efficacy of the most commonly used previous treatment regimens.

Treatment and assessment

We extracted patients with *ROS1*-NSCLC who had been treated with crizotinib in actual clinical practice. We excluded patients in whom the efficacy of the treatment could not be evaluated or who had participated in clinical trials for *ROS1*-NSCLC. For the efficacy analysis, we included patients who had at least one measurable lesion and had undergone a computed tomography evaluation 6 to 8 weeks after the start of crizotinib therapy. We evaluated the efficacy of the treatment based on the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). PFS was defined as the time from the beginning of treatment until disease progression or death, and overall survival (OS) was measured from the initiation of treatment until the date of death. PFS was censored as of the last date on which the patient was known to be progression-free, and OS was censored as of the date of the last follow-up. If a patient changed to another treatment because of toxicity, we handled them as censored cases as of the beginning of the next treatment. In the safety analysis, we assessed all the patients with *ROS1*-NSCLC who were treated with crizotinib in clinical practice. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, ver. 4.03. The survival rates were estimated using the Kaplan-Meier method. All the statistical analyses were performed using JMP version 14.0 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

During the study period, 24 patients (1.9%) were diagnosed as having *ROS1*-NSCLC. The baseline characteristics of the patients are shown in *Table 1*. The *ROS1* rearrangement status was assessed using RT-PCR (n=17), FISH (n=8), or NGS (n=5). Among the 24 patients who were diagnosed as having *ROS1*-NSCLC, the 13 patients who were treated with crizotinib in actual clinical practice (female, n=8; male, n=5) had a median age of 56 years (range, 36–78 years). Twelve patients had adenocarcinoma, and 8 were never-smokers. The median number of prior chemotherapy treatments before crizotinib was 2 (range, 0–7). Two and three patients received crizotinib as first and second line, respectively. Among the 11 patients who did not receive

Table 1 Characteristics of patients with ROS1-NSCLC

Characteristics	All patients (N=24)	Patients treated with crizotinib (N=13)
Median age, years (range)	55.5 (32.0–78.0)	56.0 (36.0–78.0)
Sex		
Male	9 (37.5)	5 (38.5)
Female	15 (62.5)	8 (61.5)
Smoking history		
No	15 (62.5)	8 (61.5)
Yes	9 (37.5)	5 (38.5)
ECOG PS at the treatment	–	
0		5 (38.5)
1		6 (46.2)
2		2 (15.4)
Histologic classification		
Adenocarcinoma	23 (95.8)	12 (92.3)
Pleomorphic	1 (4.2)	1 (7.7)
Brain metastasis	4 (16.7)	4 (30.8)
Diagnostic methods of ROS1		
RT-PCR	17 (70.8)	11 (84.6)
FISH	8 (33.3)	4 (30.8)
NGS	5 (20.8)	1 (7.7)
Previous regimens for advanced disease (range)	–	2 (0–7)
Previous regimens*	–	
Platinum plus pemetrexed		5 (38.5)
Immune checkpoint inhibitor		3 (23.1)
Erlotinib		2 (15.4)
Docetaxel		2 (15.4)
Other ROS1 inhibitor		2 (15.4)

*, previous chemotherapy regimen in patients treated with crizotinib. ROS1, c-ros oncogene 1; NSCLC, non-small cell lung carcinoma.

crizotinib in clinical practice, 5 received crizotinib as part of investigator sponsored trials for *ROS1*-NSCLC. We identified the following fusion partners of *ROS1*: CD74 molecule gene (*CD74*; n=3), syndecan 4 gene (*SDC4*; n=1), and solute carrier family 34 member 2 (*SLC34A2*; n=1).

Treatment efficacy and toxicity

Patients received the standard crizotinib dose of 250 mg twice a day until one of the following events occurred; disease progression, clinical deterioration, or unacceptable toxicity. When AEs were related to crizotinib, the dose of crizotinib was modified depending on the grade of the adverse events. Among 13 patients, three patients were excluded because they were not fully performed imaging evaluations. In the 10 evaluable patients, the median follow-up time was 35.5 months (95% CI, 8.9 to 44.6 months), the median PFS was 10.0 months (95% CI, 5.1 to 27.0 months), and the OS was 28.7 months (95% CI, 6.7 to not reached) (*Figure 1*). A waterfall plot of the patients in whom the

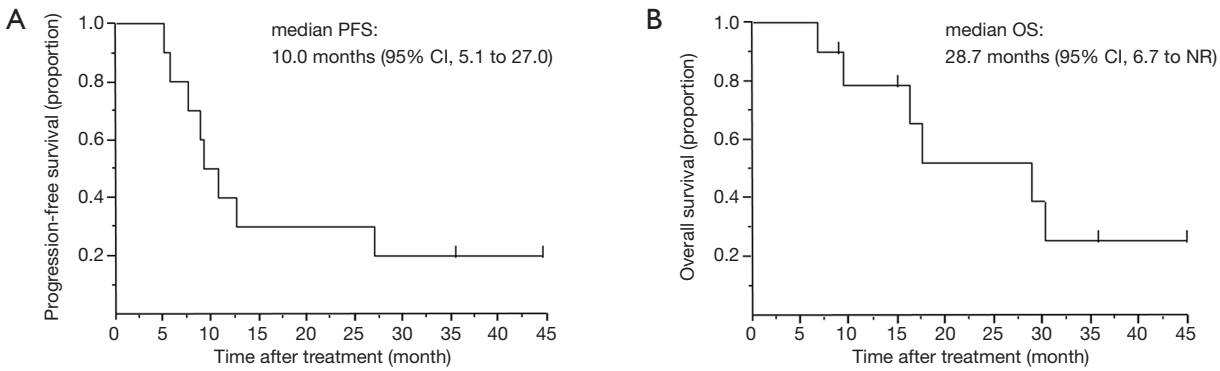

Figure 1 Progression-free survival (A) and overall survival (B) in patients with ROS1-NSCLC who were treated with crizotinib (N=10). ROS1, c-ros oncogene 1; NSCLC, non-small cell lung carcinoma.

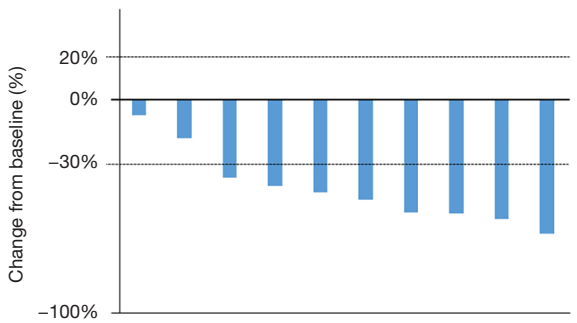

Figure 2 Best response to crizotinib, based on the maximal percentage of tumor reduction (N=10).

response could be evaluated is shown in *Figure 2*. The best overall responses were a partial response (PR) in 8 patients and stable disease (SD) in 2 patients. The ORR was 80.0% (95% CI, 49.0 to 94.3). In terms of the efficacy of the previous treatments that had been performed in 18 patients, 11 patients received pemetrexed/platinum and 7 patients received ICIs. The ORRs for treatment with pemetrexed/platinum and immune checkpoint inhibitors (ICIs) were 45.5% (95% CI, 21.3 to 72.0) and 14.3% (95% CI, 2.6 to 51.3), respectively. A swimmer's plot of the duration of the previous chemotherapies in the 13 patients who received crizotinib in clinical practice is shown in *Figure 3*.

Table 2 shows the details of the adverse events in the 13 patients who received at least one dose of crizotinib in clinical practice. The most frequent adverse events were aspartate aminotransferase (AST) increased and alanine aminotransferase (ALT) increased (69.2%). Overall, the number of grade 3 adverse events was 8: electrocardiogram QT corrected (QTc) interval prolonged (n=2), anemia, AST increased, weight loss, pleural effusion, pneumonitis and thromboembolic event (all n=1). Regarding the patient with grade 3 pneumonitis, the physician suspected interstitial lung disease (ILD) related to crizotinib treatment and discontinued the treatment. In contrast, the other patients with grade 3 adverse events continued crizotinib treatment after a treatment interruption or dose reduction. No grade 4 or 5 adverse events related to crizotinib were reported.

Discussion

Since crizotinib was first approved for the treatment of *ROS1*-NSCLC in Japan in May 2017, we have only been able to treat a few *ROS1*-NSCLC patients with crizotinib in clinical practice in Japan. In addition, *ROS1*-NSCLC itself is a rare lung cancer, and an even smaller number of patients are treated with crizotinib at individual hospitals in Japan (12). For this reason, we reviewed the efficacy and safety of crizotinib in clinical practice at our hospital.

In addition to PROFILE 1001 and OO12-01, several studies have reported the efficacy and safety of crizotinib for the treatment of *ROS1*-NSCLC. The EUROS1 cohort was assembled from six European countries (13). The investigators retrospectively identified 32 patients who had received crizotinib for the treatment of *ROS1*-NSCLC. The median PFS was 9.1 months, the response rate was 80%, and no unexpected adverse effects were observed in their study. Park *et al.* reported the characteristics and outcomes of *ROS1*-NSCLC patients in clinical practice in Korea (14). Within their cohort, 15 patients received crizotinib. The median PFS was 13.1 months, and the response rate was 73.3%. Noronha *et al.* reported that crizotinib resulted in durable disease control and prolonged PFS in 5 ROS1-

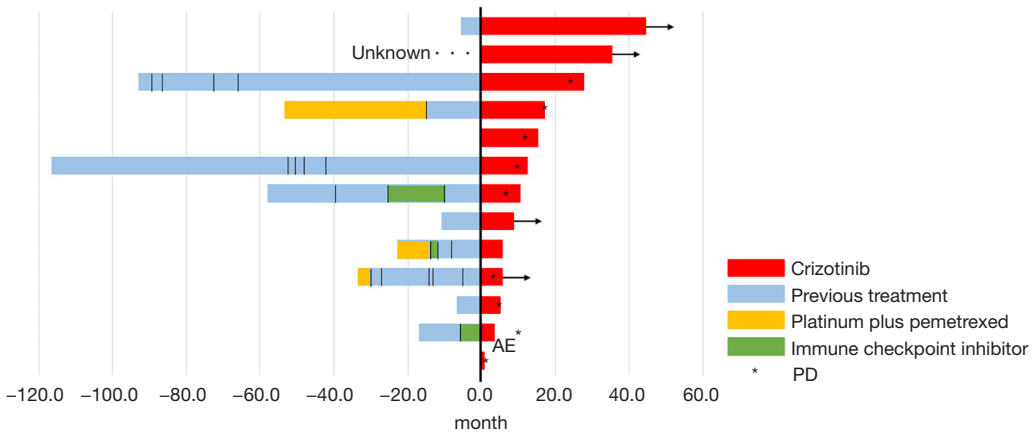

Figure 3 Swimmer's plot showing the duration of the treatment with ROS1-NSCLC (N=13). ROS1, c-ros oncogene 1; NSCLC, non-small cell lung carcinoma; AE, adverse event; PD, progressive disease.

Table 2 Treatment-related adverse events in patients treated with crizotinib (N=13)

Adverse event	All grades, N (%)	Grade 3, N (%)
AST increased	9 (69.2)	1 (7.7)
ALT increased	9 (69.2)	0 (0.0)
Vision disorder	8 (61.5)	0 (0.0)
Edema limbs	4 (30.8)	0 (0.0)
Nausea	4 (30.8)	0 (0.0)
Constipation	3 (23.1)	0 (0.0)
Electrocardiogram QTc interval prolonged	2 (15.4)	2 (15.4)
Pneumonitis	2 (15.4)	1 (7.7)
Anorexia	2 (15.4)	0 (0.0)
Diarrhea	2 (15.4)	0 (0.0)
Dysgeusia	2 (15.4)	0 (0.0)
Anemia	1 (7.7)	1 (7.7)
Pleural effusion	1 (7.7)	1 (7.7)
Thromboembolic event	1 (7.7)	1 (7.7)
Weight loss	1 (7.7)	1 (7.7)
Cough	1 (7.7)	0 (0.0)
Creatinine increased	1 (7.7)	0 (0.0)
Dyspnea	1 (7.7)	0 (0.0)
Epistaxis	1 (7.7)	0 (0.0)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; QTc, QT corrected.

NSCLC patients of India (15). In our study, the median PFS was 10.0 months, the OS was 28.7 months, and the response rate was 80%. Our results are similar to those of previous studies and thus support the efficacy and safety of crizotinib for clinical use in Japan. Some previous studies have indicated that pemetrexed-based therapies and ICIs are effective in patients with *ROS1*-NSCLC (16-19). In our study, 11 patients received pemetrexed-based therapies and 7 patients received ICIs. The ORR of pemetrexed/platinum and ICIs were 45.5% (95% CI, 21.3 to 72.0) and 14.3% (95% CI, 2.6 to 51.3), respectively. The efficacy was relatively the same as that of previous reports. Although our results were for a relatively small sample size, pemetrexed-based therapies and ICIs might be effective in patients with *ROS1*-NSCLC in clinical settings.

Similar to previous clinical trials, we were able to continue to treat patients with *ROS1*-NSCLC using crizotinib safely. A QTc interval prolonged which 2 patients experienced, was the most common grade 3 adverse event (15.4%) in our study. We previously reported that patients with an ATP-binding cassette sub-family B member 1 (*ABCB1*) genotype and a lower body weight were more likely to develop severe adverse events among Japanese NSCLC patients harboring *ALK* fusion gene treated with crizotinib (20). We were aware of the potential cardiotoxicity of crizotinib and were able to avoid fatal adverse events through frequent electrocardiogram examinations. After stopping crizotinib treatment and confirming recovery, we were able to continue treatment after a dose reduction of crizotinib

before the AE became lethal. We suggest that physicians should be cautious of QTc interval prolonged results in patients receiving crizotinib.

Recently, several studies discussing the mechanism of resistance to crizotinib in *ROS1*-NSCLC have been published. Most patients with *ROS1*-NSCLC invariably acquire resistance to crizotinib despite its initial efficacy. Gainor *et al.* reported that they identified 16 patients who underwent a total of 17 repeat biopsies following progression while receiving crizotinib, and they identified *ROS1* resistance mutations in 53% of the specimens (21). In their study, *ROS1* mutations included *G2032R* (41%), *D2033N* (6%), and *S1986F* (6%). Other *ROS1* resistance mutations have been described in some studies (22-25). Moreover, activations of *KIT*, *KRAS* and *EGFR* have been identified as mechanisms of resistance to crizotinib in *ROS1*-NSCLC (26-28). These studies are expected to lead to a large step forward in the development of new drugs for the treatment of *ROS1*-NSCLC with acquired crizotinib resistance. Recently, the efficacy of a new generation of ROS1 inhibitors, including lorlatinib and entrectinib, has been shown in early clinical trials for *ROS1*-NSCLC (29-31).

This study had some limitations. First, the study was performed retrospectively at a single center in Japan. In this regard, it is impossible to compare our results with other global results completely. Second, the numbers and types of previous regimens differed among the patients with *ROS1*-NSCLC. These previous regimens might have influenced the results for the efficacy and toxicity of crizotinib.

Conclusions

Our results demonstrated that the administration of crizotinib to patients with ROS1-NSCLC was effective and safe in clinical practice in Japan.

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None.

Footnote

Conflicts of Interest: Dr. Fujiwara reports grants from Abbvie, grants and personal fees from Astra Zeneca, grants and personal fees from BMS, grants from Chugai, grants from Daiichi-Sankyo, grants from Eisai, grants from Eli Lilly, grants from Incyte, grants from Merck Serono, grants and personal fees from MSD, grants and personal fees from Novartis, personal fees from ONO, personal fees from Sysmex, personal fees from Taiho, outside the submitted work. Dr. Matsumoto reports grants from Hitachi, grants from Hitachi High-Technologies, grants from Boston Scientific, personal fees from Olympus, personal fees from Cook Medical, personal fees from AstraZeneca, outside the submitted work. Dr. Murakami reports grants from Takeda Pharmaceutical, personal fees from Astrazeneca, personal fees from Chugai Pharmaceutical, personal fees from Boehringer Ingelheim, personal fees from Taiho Pharmaceutical, personal fees from Ono Pharmaceutical, outside the submitted work. Dr. Goto reports grants and personal fees from Eli Lilly, personal fees from Chugai, grants and personal fees from Taiho Pharmaceutical, personal fees from Boehringer Ingelheim, personal fees from Pfizer, personal fees from Novartis, personal fees from Glaxo Smith Kline, personal fees from AstraZeneca, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Bristol Myers Squibb, personal fees from Shionogi Pharma, personal fees from Merck Sharp and Dohme, grants from Abbvie, from null, outside the submitted work. Dr. Kanda reports grants and personal fees from AstraZeneca, grants and personal fees from Ono Pharmaceutical, grants from AbbVie, personal fees from Bristol-Myers Squibb, personal fees from Chugai, outside the submitted work. Dr. Horinouchi reports grants and non-financial support from Ono, during the conduct of the study; grants and personal fees from BMS, grants and personal fees from Novartis, grants from Astellas, grants and personal fees from Taiho, grants and personal fees from Chugai, personal fees from Lilly, grants and personal fees from Astra Zeneca, grants and personal fees from MSD, grants from Merck Serono, grants from Genomic Health, outside the submitted work. Dr. Yamamoto reports grants from Chugai, grants from Taiho, grants from Eisai, grants from Lilly, grants from Quintiles, grants from Astellas, grants from BMS, grants from Novartis, grants from Daiichi-Sankyo, grants from Pfizer, grants from Boehringer Ingelheim, grants from Kyowa-Hakko Kirin, grants from Bayer, grants from ONO PHARMACEUTICAL CO., LTD, grants from Takeda, personal fees from ONO PHARMACEUTICAL CO., LTD, personal fees from Chugai, personal fees from AstraZeneca, personal fees from Pfizer, personal fees from Lilly, personal fees from BMS, personal fees from Eisai, personal fees from Otsuka, personal fees from Takeda, personal fees from Boehringer Ingelheim, personal fees from Cimic, grants from Janssen Pharma, grants from MSD, grants from Merck, outside the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Institutional Review Board of the National Cancer Center Hospital (No. 2015-355). Due to the retrospective nature of this study, informed consent was not obtained from each patient.

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