Pharmacokinetic profiles of significant adverse events with crizotinib in Japanese patients with \textit{ABCB1} polymorphism

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Crizotinib is a standard treatment for advanced ALK-positive non-small-cell lung cancer (NSCLC). We undertook this study to investigate the pharmacokinetics of crizotinib and clinical and pharmacogenomic factors that may increase the risk of adverse events (AEs). We defined clinically significant AEs as grade 4 hematological toxicity, grade ≥3 non-hematological toxicity, and any grade of interstitial lung disease. Eight subjects with ALK-positive NSCLC scheduled to receive crizotinib 250 mg twice daily were studied. Six patients were female and two were male, and most of the patients had low body weight with a median body weight of 46.8 kg (range, 42.4–61.0 kg). All patients developed AEs, five developing six clinically significant AEs. Six patients required dose reduction. In pharmacokinetic analysis, blood samples were obtained on days 1 and 15. The mean area under the plasma concentration–time curve from 0–12 h (AUC\textsubscript{0–12}) on day 15 was significantly increased in patients with clinically significant AEs (\(n=5\)) compared with those without (\(n=3\)) (\(P=0.04\)). Genetic polymorphisms of \textit{ABCB1} were analyzed. One patient with the \textit{ABCB1} 1236TT-2677TT-3435TT genotype was an outlier, with an AUC\textsubscript{0–12} and peak concentrations on day 15 of 2.84\textsuperscript{x} and 2.61\textsuperscript{x} the mean, respectively, compared with those with other genotypes. Our results suggest that some Japanese NSCLC patients treated with crizotinib developed clinically significant toxicities that were related to altered pharmacokinetics parameters due to genotype and body weight factors.
The most common adverse events (AEs) in these crizotinib studies have been vision abnormalities (most frequently visual impairment, photophobia, or blurred vision), diarrhea, nausea, vomiting, constipation, elevated transaminase levels, edema, upper respiratory infection, dysgeusia, and dizziness. Grade 3 or higher AEs including neutropenia, elevated transaminase levels, fatigue, interstitial lung disease, pneumonia, and electrocardiogram QTc prolongation occasionally occurred.

Here, we investigated possible clinical and pharmacogenomic factors in the PK, PD, or pharmacogenomics (PGx) of crizotinib in Japanese patients with ALK-positive NSCLC.

Patients and Methods

Patient selection criteria. Inclusion criteria were advanced ALK-positive NSCLC scheduled for treatment with crizotinib therapy, age ≥20 years, and adequate organ function (serum total bilirubin ≤2.0 mg/dL, aspartate aminotransferase ≤150 IU/L, alanine aminotransferase ≤150 IU/L, serum creatinine ≤2.0 mg/dL, and SpO2 ≥90%). Exclusion criteria included: concomitant treatment with other anticancer agents, radiotherapy, or surgery; the inability to swallow tablets; gastrointestinal disorders that could affect the ingestion or absorption of crizotinib, such as watery diarrhea, intestinal paresis, ileus, or a history of gastrectomy or intestinal resection; intake of drugs or food that could act as potent cytochrome P450 inhibitors or inducers; and women of childbearing age unless using effective contraception.

Study design and outcome. The study was carried out under an open-label observational design to evaluate the PK/PD/PGx of crizotinib in Japanese patients with ALK-positive NSCLC. The primary objective was to characterize PK parameters of crizotinib in these patients. Secondary objectives were to investigate the relationship between PK parameters and PD, including toxicities and anticancer effects, and to explore any genetic factors, including ABCB1 SNPs.

This study (UMIN000009867) was designed and carried out at the National Cancer Center Hospital (Tokyo, Japan). The protocol was approved by the review board of the National Cancer Center Hospital on January 31, 2013, and the study was carried out in accordance with the ethical principles stated in the Declaration of Helsinki. All patients provided written informed consent.

Treatment and assessments. Patients received the standard crizotinib dose of 250 mg twice daily. Patients continued to receive therapy until disease progression, clinical deterioration, or intolerable AEs that did not improve with dose adjustment. The ALK fusion gene was confirmed by real-time RT-PCR, immunohistochemistry staining with D5F3 antibody (Cell Signaling Technology, Danvers, MA, USA) or FISH. The ALK FISH testing was carried out using a Vysis ALK break-apart probe set (Abbott Molecular, Abbott Park, IL, USA). The specimen was considered positive if more than 15% of scored tumor cells had split ALK 5' and 3' probe signals or had isolated 3' signals.

Blood samples for PK analysis were collected immediately before and 0.5, 1, 2, 4, 6, 8, and 12 h after administration of crizotinib on days 1 and 15. Serial electrocardiography (ECG) was carried out in triplicate immediately before and 4 and 12 h after treatment with crizotinib on days 1 and 15 to assess for QTc prolongation.

Adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. Objective tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) was evaluated in all eligible patients before treatment, 8 weeks after the start of treatment, and then every 3–4 months.

Pharmacokinetic analysis. After blood was collected in EDTA-containing tubes, plasma was separated within 30 min by centrifugation at 1500g for 10 min at 4°C and stored at –80°C until analysis. Plasma concentrations of crizotinib were measured by liquid chromatography–tandem mass spectrometry. Chromatographic separation of crizotinib and the internal standard, erlotinib-d6, was carried out using an XBridge C18 HPLC column (2.1 × 5.0 mm, 3.5 μm) (Waters Corp., Milford, MA, USA) maintained at 40°C. Mobile phases A and B consisted of 0.1% formic acid aqueous solution and acetonitrile containing 0.1% formic acid, respectively. Separation was carried out using a gradient elution (from B of 15–90% over 5 min, B of 99% for 2.5 min, B of 15% for 3 min) at a flow rate of 0.3 mL/min with XeXEN X2 ultra-HPLC (Shimadzu Co., Kyoto, Japan). Quantitation was undertaken by selected reaction monitoring on a QTRAP5500 mass spectrometer (AB SCIEX, Framingham, MA, USA) with electrospray ionization in the positive mode. The selected reaction monitoring transitions were m/z 451.1–261.1 for crizotinib and m/z 400.2–278.0 for erlotinib-d6. All data were acquired and analyzed using Analyst version 1.6.1 software (AB SCIEX). All sample analyses were carried out according to the internal assay quality guidelines. The lower limit of quantification was 5 ng/mL.

Pharmacokinetic variables of crizotinib and its metabolites were determined using the Phoenix WinNonlin PK program (Pharsight, Mountain View, CA, USA). The Cmax and time to maximum concentration were recorded directly from the data. The AUC with extrapolation to 12 h (AUC0–12h) was calculated by the trapezoidal rule. The linear trapezoidal rule was used for successively increasing concentration values, and the logarithmic trapezoidal rule for decreasing concentration values.

Genotyping. Genotyping assays were carried out for eligible patients who had sufficient DNA in their sample. DNA was extracted and the concentration was fixed at 10 ng/μL. Genotyping was undertaken using the i-densy genetic testing platform (ARKRAY, Kyoto, Japan) and the QP-system quenching probe system (J-Bio 21, Tokyo, Japan) based on the principles of mutant detection. To detect the various genotypes, we used QProbe (Nippon Steel Kankyo Engineering, Tokyo, Japan). We analyzed the SNPs ABCB1 1236C>T, 2677G>T/A, and 3435C>T (rs1128503, rs2032582, and rs1045652, respectively). The primers that we used were: ABCB1-1236F, 5'-ctgctgtgaatYgccttagga-3' (Y represents C or T); ABCB1-1236R, 5'-ctgctgccacctgcacctc-3'; ABCB1-2677F, 5'-aaatgttgtctggacagaacctg-3'; ABCB1-2677R, 5'-aattaactaatctatattgattgacctc-3'; ABCB1-3435F, 5'-actgcaagctagtgcaac-3'; and ABCB1-3435R, 5'-cagagagcttcacagctc-3'. The probes that we used were: ABCB1-1236, 5'-ttcgccagcactgccctc-3'; ABCB1-3435, 5'-gaatgacgcttacctaa-3'; and ABCB1-3435R, 5'-gtcgcctcagcttc-3'. The probability of correct genotyping was assessed as the fraction of all genotypes that were observed to be consistent with the expected genotypes. The statistical analysis. Data are expressed as the geometric mean ± SD. The statistical significance of PK parameters was analyzed using a Wilcoxon signed-rank test, with P < 0.05 considered significant. Progression-free survival was defined as the time from the first day of crizotinib therapy to detection of the earliest signs of disease progression or death from any cause. Overall survival (OS) was defined as the time from the first day of crizotinib therapy to the last day on which the patient was confirmed to be alive or dead from any cause.
Median survival was calculated using the Kaplan–Meier method. All statistical analyses were carried out with ssrs Statistics version 23.0 (SPSS, Chicago, IL, USA).

Results

Patient group. From March 2013 to June 2014, a total of eight patients were enrolled (Table 1, Fig. S1). All patients had adenocarcinoma. Six patients were male and two were female, with a median age of 59 years (range, 46–72 years). The median body weight was 66.8 kg (range, 42.4–61.0 kg), and the median body surface area was 1.47 m$^2$ (range, 1.30–1.70 m$^2$).

Treatment efficacy and toxicity. Seven patients were positive for ALK with FISH and one was negative, but positive on immunohistochemistry. Five patients had a partial response, one had stable disease, and two had progressive disease as their best response. The overall response rate by RECIST was 62.5% (95% CI, 24.5–91.5%) (Fig. S2). Of two patients with progressive disease, one developed a brain metastasis on day 47, and after treatment with stereotactic irradiation, she continued crizotinib treatment beyond progression. Another patient, who had a history of previous crizotinib treatment, developed liver metastasis on day 47. Seven patients eventually discontinued crizotinib treatment due to progressive disease, and one due to an AE. Six patients required dose reduction due to AEs. Median PFS was 9.8 (95% CI, 2.3–17.3) months and median OS was not applicable (Figs S3,S4).

Common hematological and non-hematological AEs observed during crizotinib treatment are summarized in Table 2. All patients experienced at least one AE of any grade of toxicity, and five patients experienced clinically significant AEs: grade 3 or 4 alanine aminotransferase increased ($n=2$), grade 3 aspartate aminotransferase increased ($n=1$), grade 3 esophagitis ($n=1$), grade 3 QTc prolongation ($n=1$), and grade 3 interstitial nephritis ($n=1$). We were able to manage these AEs with supportive care and reduced doses in seven patients.

A female patient developed severe esophagitis with dysphagia and odynophagia 4 weeks after starting crizotinib. Gastrointestinal endoscopy revealed diffuse grade 3 esophagitis and the drug was discontinued. When her symptoms resolved 3 weeks after discontinuation, she was restarted at a reduced dose of 200 mg twice daily, but the esophagitis returned.

Another patient developed grade 3 QTc prolongation. Grade 2 nausea and anorexia developed shortly after starting crizotinib. Grade 3 aspartate aminotransferase increased ($n=1$), grade 3 QTc prolongation ($n=1$), and grade 3 interstitial nephritis ($n=1$). We were able to manage these AEs with supportive care and reduced doses in seven patients.

Pharmacokinetic analysis related to toxicity. The PK parameters of crizotinib on days 1 and 15 are presented in Table 3 and Figure S5. The geometric mean of AUC$_{0-12}$ and $C_{\text{max}}$ measured in the Japanese patients in this study were generally similar to those in Asian patients obtained in the previous phase 1 study (Table 4). The geometric mean of AUC$_{0-12}$ on day 15 was significantly increased in patients with clinically significant AEs ($n=5$) compared to those without ($n=3$) (Table 3, Fig. 1a). There was also a significant increase in the geometric mean of $C_{\text{max}}$ and $C_{\text{trough}}$ on day 15 in the patients with significant AEs.

Genotype related to PK and toxicity. Figure 1(b) and Table 5 depict the genotype findings. For the $ABCBI$ 1236C>T SNPs, we identified one CC, three CT, and four TT genotypes among all eight patients. One patient showed all TT alleles (TT-TT, homzygous variant), and three patients had at least one TT allele. Regarding the relationship between $ABCBI$ genotype and PKs, one patient (#7) with all-TT $ABCBI$ alleles was a pronounced outlier in AUC$_{0-12}$ and $C_{\text{max}}$ on day 15 of therapy.
Table 3. Pharmacokinetic parameters of crizotinib in Japanese non-small-cell lung cancer patients with ABCB1 polymorphism

|                     | All patients | Significant AE | No significant AE | P-value |
|---------------------|--------------|----------------|-------------------|---------|
|                     | n = 8        | n = 5          | n = 3             |         |
| AUC0–12h, ng h/mL   |              |                |                   |         |
| Day 1               | 872 ± 379    | 1040 ± 264     | 650 ± 519         | 0.57    |
| Day 15              | 5410 ± 3220  | 6540 ± 3660    | 3940 ± 277        | 0.04    |
| Ratio               | 6.20 ± 3.55  | 6.28 ± 3.75    | 6.06 ± 4.01       |         |
| Cmax, ng/mL         |              |                |                   |         |
| Day 1               | 129 ± 54.0   | 156 ± 49.1     | 94.6 ± 44.4       | 0.14    |
| Day 15              | 525 ± 279    | 631 ± 312      | 387 ± 28.7        | 0.04    |
| Ctrough on day 15   | 422 ± 302    | 512 ± 354      | 305 ± 39.3        | 0.04    |
| Half-life, min      |              |                |                   |         |
| Day 1               | 447 ± 522    | 528 ± 645      | 338 ± 117         | 0.25    |
| Day 15              | 2010 ± 3780  | 1840 ± 1830    | 2310 ± 6190       | 1.00    |
| Tmax, min           |              |                |                   |         |
| Day 1               | 304 ± 86.8   | 323 ± 97.8     | 275 ± 67.0        | 0.57    |
| Day 15              | 268 ± 198    | 245 ± 246      | 310 ± 68.9        | 0.79    |

AE, adverse event; AUC0–12h, area under the plasma concentration–time curve from 0 to 12 h; Cmax, peak concentration; Ctrough, trough concentration; Tmax, time to maximum concentration.

Table 4. Pharmacokinetic parameters (mean [coefficient of variation %]) of crizotinib on day 15 in this study of Japanese non-small-cell lung cancer patients with ABCB1 polymorphism compared with subjects in a global phase I study

|                     | Japanese | Non-Asian | Asian |
|---------------------|----------|-----------|-------|
|                     | n = 8    | n = 11    | n = 13|
| AUC0–12h, ng h/mL   | 5410 (60) | 3137 (55) | 4696 (11) |
| Cmax, ng/mL         | 525 (53) | 322 (67)  | 506 (23) |

AUC0–12h, area under the plasma concentration–time curve from 0 to 12 h; Cmax, peak concentration.

Fig. 1. Mean area under the plasma concentration–time curve from 0–12 h (AUC0–12h) of crizotinib in Japanese patients with non-small-cell lung cancer with ABCB1 polymorphism. (a) Comparison of those with clinically significant adverse events with those without. (b) Comparison of AUC0–12h of crizotinib by ABCB1 genotyping.

Discussion

In this evaluation of the PKs of crizotinib in Japanese patients with ALK-positive NSCLC, we found that patients appeared to develop toxicities of any grade, especially clinically significant toxicities, more frequently than in previous trials. Nevertheless, all AEs could be managed with appropriate supportive care and dose reduction, and only one patient required discontinuing of treatment due to an AE. These results suggest that the toxicity and PKs of crizotinib are related to the effects of body weight and ABCB1 SNPs.

The dose escalation phase I trial of 1001/NCT00585195 determined that the maximum tolerated dose of crizotinib was 250 mg twice daily.4,16 Several later clinical studies reported the efficacy and safety of crizotinib in patients with malignant solid tumors, including advanced ALK-positive NSCLC. Crizotinib is currently the standard of care for patients with advanced ALK-positive NSCLC and is under development for ROS1-rearranged NSCLC and MET mutated or amplified NSCLC.17–20 Nevertheless, only a few PK studies of crizotinib have been reported, and most data were extracted primarily from documents submitted for drug approval.21–23 The phase I documents reported that peak plasma concentration of crizotinib after a single oral dose of 50–300 mg was reached at approximately 4 h, followed by a multiexponential decline with a terminal half-life of 43–51 h. After multiple doses, the steady state was reached within 15 days with a mean AUC of 3880 ng h/mL (CV 36%) and a mean Cmax of 411 ng/mL (CV 44%). Steady-state Ctrough levels with a twice daily dose of 250 mg were stable with median Ctrough ranging from 242 to 319 ng/mL.23

In this study, Japanese patients appeared to develop toxicities of all grades more frequently than patients in the previous trials. The PK parameters at steady state, with a mean AUC of 5410 ng h/mL and a mean Cmax of 525 ng/mL, also appear to be higher than patients in the previous trials (Table 3). Moreover, the geometric mean of AUC0–12h on day 15 was significantly increased in the five patients with clinically significant AEs compared to the three (13 467 ng h/mL and 1216 μg/mL, respectively). This was the same patient who developed grade 3 QTc prolongation.
Table 5. Polymorphisms in ABCC1 in Japanese non-small-cell lung cancer patients (n = 8) treated with crizotinib

| Age, years | Sex | Race | BW, kg | FISH | Shrinkage rate, % | Reason for discontinuation | Clinical significance AE | Reason for ALK Shrinkage |
|------------|-----|------|--------|------|------------------|---------------------------|------------------------|-------------------------|
| #1         | 50  | Female | 53.0   | CC   | 40               | Yes                       | PD                     | PD                      |
| #2         | 56  | Female | 42.8   | CC   | 302              | Yes                       | Ongoing                | PD                      |
| #3         | 72  | Male   | 49.7   | CC   | 255              | No                        | No                     | PD                      |
| #4         | 46  | Female | 45.0   | CT   | 374              | Yes                       | Yes                    | PD                      |
| #5         | 48  | Male   | 61.0   | CC   | 32   | Yes              | AE                      | PD                      |
| #6         | 66  | Female | 42.4   | CT   | 70               | Yes                       | PD                     | Ongoing                 |
| #7         | 69  | Female | 43.3   | CT   | 138              | Yes                       | PD                     | PD                      |
| #8         | 62  | Female | 48.6   | CC   | 301              | Yes                       | PD                     | PD                      |

†Rate of positive cells in FISH (%).
‡Percent change at maximum reduction from baseline according to Response Evaluation Criteria in Solid Tumors version 1.1.
§This patient had a previous history of crizotinib treatment.

AE, adverse event; BW, body weight; FISH, fluorescence in situ hybridization; PD, progressive disease; PS, progression-free survival.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

**Fig. S1.** CONSORT diagram of this study.

**Fig. S2.** Tumor responses to crizotinib from baseline in Japanese non-small-cell lung cancer patients with ABBC1 polymorphism.

**Fig. S3.** Progression-free survival in Japanese non-small-cell lung cancer patients with ABBC1 polymorphism treated with crizotinib.

**Fig. S4.** Overall survival in Japanese non-small-cell lung cancer patients with ABBC1 polymorphism treated with crizotinib.

**Fig. S5.** Mean plasma concentration–time curves of crizotinib on days 1 (■) and 15 (○) (mean ± standard deviation) in Japanese non-small-cell lung cancer patients with ABBC1 polymorphism.

**Table S1.** Pharmacokinetic parameters of crizotinib in Japanese non-small-cell lung cancer patients with ABBC1 polymorphism adjusted by (A) body weight and (B) body surface area.