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Successful Management of Crizotinib-Induced Neutropenia in a Patient with Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer: A Case Report

Jun Osugi Yuki Owada Takumi Yamaura Satoshi Muto Naoyuki Okabe Yuki Matsumura Mitsunori Higuchi Hiroyuki Suzuki Mitsukazu Gotoh

Department of Regenerative Surgery, Fukushima Medical University, School of Medicine, Fukushima, Japan

Key Words
Crizotinib · Anaplastic lymphoma kinase gene rearrangement · Neutropenia · Alectinib · Non-small cell lung cancer

Abstract
Crizotinib, the first clinically available inhibitor of anaplastic lymphoma kinase (ALK) gene rearrangement, is generally well tolerated. In contrast, neutropenia induced by crizotinib is a commonly reported grade 3 or 4 adverse event. In such cases, interruption and dose reduction of crizotinib might be necessary for some patients with severe neutropenia. However, information concerning clinical experience and management of severe neutropenia is currently limited. In this report, the successful management of crizotinib-induced neutropenia by dose reduction of crizotinib in a patient with ALK-positive non-small cell lung cancer is described.

Introduction

Crizotinib is the first clinically available inhibitor of anaplastic lymphoma kinase (ALK) gene rearrangement and has shown notable antitumor effects in patients with ALK-positive

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Jun Osugi
Department of Regenerative Surgery
Fukushima Medical University, School of Medicine
1 Hikarigaoka, Fukushima 960-1295 (Japan)
E-Mail josugi@fmu.ac.jp

non-small cell lung cancer (NSCLC) [1–3]. Crizotinib is generally well tolerated, because the severity of its most common adverse events (AEs), such as visual disturbance, nausea, diarrhea, constipation, vomiting, and peripheral edema, is grade 1 or 2 [1–3]. In contrast, the reported incidence of neutropenia was 9–14% in various clinical trials, and the severity of most of these cases of neutropenia was grade 3 or 4 (5.5–13.3%) [1–3]. However, there are currently few reports of detailed clinical experience and management of severe neutropenia in these patients. In this case report, the details of the clinical course of a patient with severe neutropenia induced by crizotinib are described.

Case Report

A 53-year-old woman was diagnosed with stage IA (cT1bN0M0) lung adenocarcinoma. She underwent a right lower lobectomy with lymph node dissection (ND2a-2) and was pathologically confirmed to have stage IIIA (pT1bN2M0) lung adenocarcinoma. She underwent four cycles of cisplatin and vinorelbine as adjuvant therapy. Her cancer relapsed 58 months after the lobectomy, and she developed pulmonary and mediastinal lymph node metastases. The PCR-Invader assay (BML, Tokyo, Japan) was used to perform EGFR mutation testing of a formalin-fixed, paraffin-embedded section from the previous surgical procedure, and the tissue specimen showed a wild-type status. The patient underwent 6 cycles of cisplatin, pemetrexed plus bevacizumab, and 12 cycles of maintenance bevacizumab with pemetrexed as first-line therapy. She subsequently underwent six cycles of carboplatin and tegafur/gimeracil/oteracil (TS-1®) as second-line therapy. During these multiple chemotherapy regimens, she developed neutropenia of no higher than grade 2 in severity according to the Common Toxicity Criteria for Adverse Events ver. 4 (CTCAE). Thereafter, ALK analysis was performed on the formalin-fixed, paraffin-embedded section from the previous surgical procedure; anti-ALK immunohistochemistry with the intercalated antibody-enhanced polymer method was positive, and EML4-ALK gene fusion was positive by fluorescence in situ hybridization. Crizotinib (500 mg/day, orally) was administered as third-line chemotherapy. Although grade 1 AEs including visual disturbance and nausea were noted 3 days after administration of crizotinib, a partial response was achieved at 4 weeks. At 8 weeks, a gradual decrease in neutrophil counts was observed which, by 36 weeks, had progressed to grade 4 neutropenia (neutrophil count: 240/μl). Thus, all medicines, including crizotinib, were discontinued at that time. After discontinuation, improvement of neutropenia (neutrophil count: 1,500/μl) was observed by 39 weeks, without resorting to granulocyte colony-stimulating factor support. Subsequently, crizotinib was re-administered at the initial dose. However, this resulted in a similar severity of neutropenia (neutrophil count: 342/μl) at 43 weeks. Therefore, we reasoned that the severe neutropenia was attributable to crizotinib, which was discontinued again. At 45 weeks, crizotinib was resumed at a reduced dose of 400 mg/day. However, grade 4 neutropenia (neutrophil count: 498/μl) was noted by 49 weeks, and further dose reduction to 250 mg/day was necessary at 51 weeks. The patient continued treatment with the same dose of crizotinib for 20 weeks and showed evidence of progressive disease (PD) with bone metastasis at 63 weeks. After the patient provided fully informed consent, including that regarding the risk of recurrent neutropenia, she began to undergo alectinib treatment (600 mg/day, orally) as fourth-line chemotherapy. As of this writing, she has continued this treatment for 12 weeks and has shown no evidence of neutropenia or disease progression. Figure 1 shows the time course of the patient.

Discussion

A case of crizotinib-induced neutropenia in a patient with ALK-positive NSCLC was described. This patient was treated with crizotinib for 71 weeks (17.7 months) by discontinuation and dose reduction until she achieved Response Evaluation Criteria in Solid Tumors (RECIST)-defined PD. She then successfully continued treatment with the next-generation ALK inhibitor alectinib without any toxicity, including severe neutropenia.

In several clinical trials, severe neutropenia has been reported in 5.5–13.3% of patients who undergo crizotinib treatment [1–3]. For any grade 3–4 hematologic toxicity except lymphopenia, the Summary of Product Characteristics recommends withholding treatment until recovery to grade ≤2, then resuming treatment with dose reduction (400 mg/day) in patients with grade 4 hematologic toxicity; if further reduction is necessary, the dose should be further decreased to 250 mg once daily [4]. Interruption and reduction of crizotinib to 400 mg/day were performed in the present case because of grade 4 neutropenia, and further dose reduction to 250 mg/day was necessary because of recurrent grade 4 neutropenia. Although the present patient required a double dose reduction during crizotinib treatment, it was possible to continue crizotinib for 71 weeks (17.7 months) until RECIST-defined PD occurred. The duration of crizotinib treatment in our case is superior to the median progression-free survival of 7.7–9.7 months in several clinical trials [1–3]. In this respect, the present case indicates that the appropriate management of AEs is essential to continue crizotinib as long as the patient derives a benefit from this treatment.

Following crizotinib treatment, the present patient was started on alectinib treatment because second-generation ALK inhibitors, including alectinib, demonstrated antitumor activity in patients with ALK-positive NSCLC after failure of crizotinib in a recent clinical trial [5]. A notable difference in the myelotoxicity between crizotinib and alectinib treatment was observed in the present patient. Crizotinib differs from alectinib in that crizotinib is a multitarget receptor tyrosine kinase inhibitor of both ALK and mesenchymal epithelial growth factor (c-Met)/hepatocyte growth factor (HGF) receptor kinases, whereas alectinib is highly selective for ALK [6, 7]. A previous study proved that HGF stimulates epithelial cell proliferation, motility, morphogenesis, and angiogenesis via tyrosine phosphorylation of its receptor, c-Met, and plays a role in self-repair of various injured organs [8]. Additionally, HGF is reportedly produced by bone marrow stromal cells and plays a role in promoting hematopoiesis via the c-Met receptor [9]. In a phase II study of tivantinib (ARQ197), which is a selective oral inhibitor of c-Met, the incidence of severe neutropenia was 14% [10]. Furthermore, this clinical trial confirmed that the incidence of severe neutropenia was higher in the high-dose group than in the low-dose group. In line with this, it can be presumed that the inhibitory action of crizotinib against the c-Met receptor might induce neutropenia in a dose-dependent manner.

Toyota et al. [11] recently reported a case of severe neutropenia induced by crizotinib, similar to the present case, and they proposed that such neutropenia might be an idiosyncratic drug-induced neutropenia mediated by the immune response. Immune-mediated neutropenia often occurs within days to a few weeks after beginning the drug, and drug rechallenge, even at low doses, is characteristically associated with prompt recurrence of neutropenia [12]. In the present case, however, neutropenia first developed at 8 weeks and was not observed with rechallenge by dose-reduction of crizotinib. Thus, we conclude that the pathogenesis of neutropenia in the present case might be associated with the inhibitory action against the c-Met receptor rather than an immune-mediated reaction.

Several studies have confirmed that alectinib is an effective alternative in patients for whom crizotinib has been discontinued because of serious AEs such as dysgeusia and esophageal ulceration [13, 14]. The present case also showed that alectinib was effective and well-tolerated as a posttreatment agent after the development of RECIST defined-PD with crizotinib treatment. Limited clinical experience and information concerning the management of AEs associated with both crizotinib and alectinib treatment is currently available. The pathogenesis of crizotinib-induced neutropenia is still controversial, and this is the first report concerning and discussing the treatment of crizotinib-induced neutropenia with dose reduction of crizotinib and subsequent administration of alectinib in a patient with ALK-positive NSCLC. Further information sharing would be of value to optimize the management of AEs and treatment in patients with ALK-positive NSCLC.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report.

Disclosure Statement

All authors have no potential conflicts of interest.

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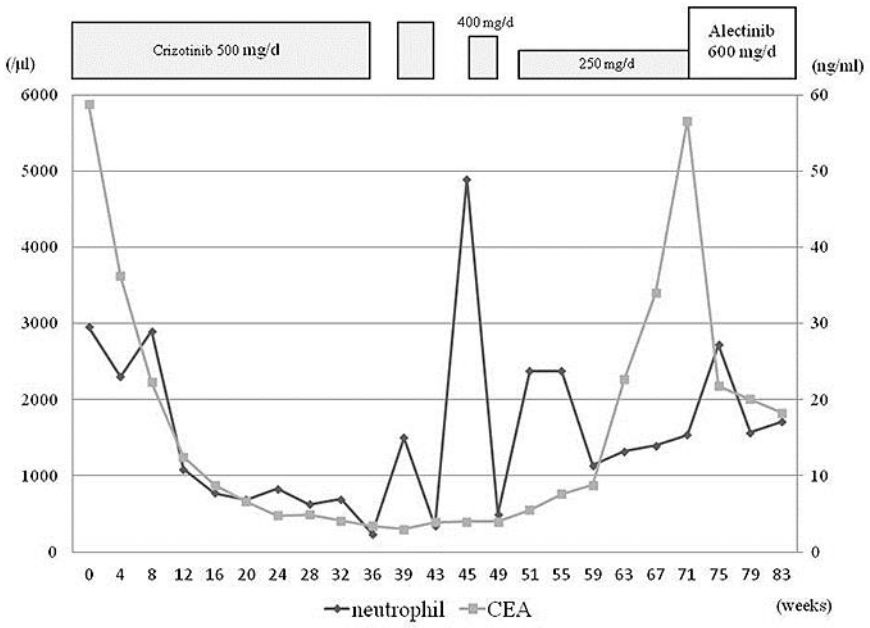

Fig. 1. Clinical course after administration of crizotinib. d = Day; CEA = carcinoembryonic antigen.