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CASE REPORT

Interstitial pneumonia suspected during regorafenib administration and exacerbated by subsequent therapy with lenvatinib for unresectable hepatocellular carcinoma

Kohei Kotani[1] · Masaru Enomoto[1] · Masako Okada[1] · Kanako Yoshida[1] · Hiroyuki Motoyama[1] · Hideki Fujii[1] · Atsushi Hagihara[1] · Sawako Uchida-Kobayashi[1] · Hiroyasu Morikawa[1] · Yoshiki Murakami[1] · Akihiro Tamori[1] · Norifumi Kawada[1]

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Abstract
Recently, three tyrosine kinase inhibitors (TKIs) have become available for treatment of unresectable hepatocellular carcinoma (HCC). We herein report a case of a 59-year-old man with interstitial pneumonia that was suspected during regorafenib administration and was exacerbated by subsequent lenvatinib treatment for advanced HCC. After sorafenib was discontinued due to progressive HCC, regorafenib treatment was started. Progressive HCC was again noted and reticular shadows were suspected in both lower lung fields at 2 months after starting regorafenib administration. Subsequent treatment with lenvatinib obtained a partial response for HCC, but the reticular shadows became marked and dyspnea on effort emerged, followed by hypoxemia and an increased Krebs von den Lungen-6 (KL-6) value. Because we suspected acute interstitial pneumonia, due to these TKIs, intravenous pulse steroid therapy was started immediately after discontinuing lenvatinib. Within 1 week after starting steroid therapy, the patient's respiratory condition and hypoxemia gradually began improving. No previous case of pulmonary interstitial changes that appeared in association with regorafenib administration for HCC and that were exacerbated by subsequent treatment with lenvatinib has been reported. This case emphasizes that it is necessary to observe the patient's respiratory condition and to perform imaging examinations to monitor for adverse events during TKI treatment.

Keywords Hepatocellular carcinoma · Interstitial pneumonia · Lenvatinib · Regorafenib · Tyrosine kinase inhibitor

Introduction

Sorafenib had been used as the only molecular-targeted therapy in unresectable hepatocellular carcinoma (HCC) for about 10 years [1, 2]. A randomized placebo-controlled comparative phase III trial (RESORCE study) was conducted for HCC cases refractory to sorafenib therapy, and regorafenib treatment was shown to result in a significant improvement in overall survival as compared to placebo [3]; thus, in Japan, regorafenib was approved as the secondary treatment for unresectable HCC in June 2017. Subsequently, for primary molecular-targeted therapy, the REFLECT trial showed non-inferiority of overall survival for lenvatinib to sorafenib in patients with advanced stage HCC [4]. Lenvatinib was approved in Japan for unresectable HCC in March 2018. Hence, due to the approval of these new tyrosine kinase inhibitors (TKIs), treatment of HCC is now at a major turning point.

Well-known adverse events of TKIs include palmar–plantar erythrodysesthesia, diarrhea, loss of appetite, hypertension, general fatigue, and proteinuria, among others. It is crucial that these adverse events are managed well to increase the therapeutic effect. However, there has been no previous detailed report on the adverse event of interstitial pneumonia associated with treatment using these new TKIs. We herein report a case of interstitial pneumonia in which reticular shadows were suspected in the lung field during regorafenib administration; these shadows became obvious and dyspnea appeared after changing regorafenib to lenvatinib therapy.

✉ Masaru Enomoto
enomoto-m@med.osaka-cu.ac.jp

[1] Department of Hepatology, Graduate School of Medicine, Osaka City University, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan

Case report

A 59-year-old man was diagnosed with liver cirrhosis and multiple HCC of both liver lobes 2 years before admission to our institute. His HCC was unresectable and at the advanced stage according to the Barcelona Clinic Liver Cancer classification. In terms of HCC etiology, he tested positive for hepatitis B (HB) surface antigen and his alcohol consumption was high (about 100 g/day). At his first outpatient visit, he tested negative for HB e-antigen and positive for e-antibody. He had no history of antiviral therapies, and his serum HBV–DNA level was 5.9 $\log_{10}$ IU/mL. Thus, entecavir therapy was started. Transarterial chemoembolization and/or transarterial infusion chemotherapy (TAI) with cisplatin (CDDP) were performed for HCC six times during a period of 15 months. A partial response was obtained, but allergic reaction to CDDP occurred at the seventh round of TAI therapy.

Administration of 800 mg sorafenib per day had been introduced 6 months previously, because hepatic functional reserve was maintained at a Child–Pugh score of 5 (grade A), while his Eastern Cooperative Group Performance status was 0. No significant adverse events were observed, other than grade 1 hypertension, but computed tomography (CT) showed an increase in the size of the intrahepatic HCC lesion and emergence of left lung metastasis (Fig. 1a, b). Therefore, therapy had been changed from sorafenib to 160 mg/day regorafenib 4 months previously. No significant adverse events were observed, except for grade 2 palmar–plantar erythrodysesthesia and grade 3 hypertension. Palmar–plantar erythrodysesthesia was controlled well with by a humectant, and hypertension was also controlled well by a calcium channel blocker. However, 2 months before, an increase in the size of the intrahepatic HCC and lung

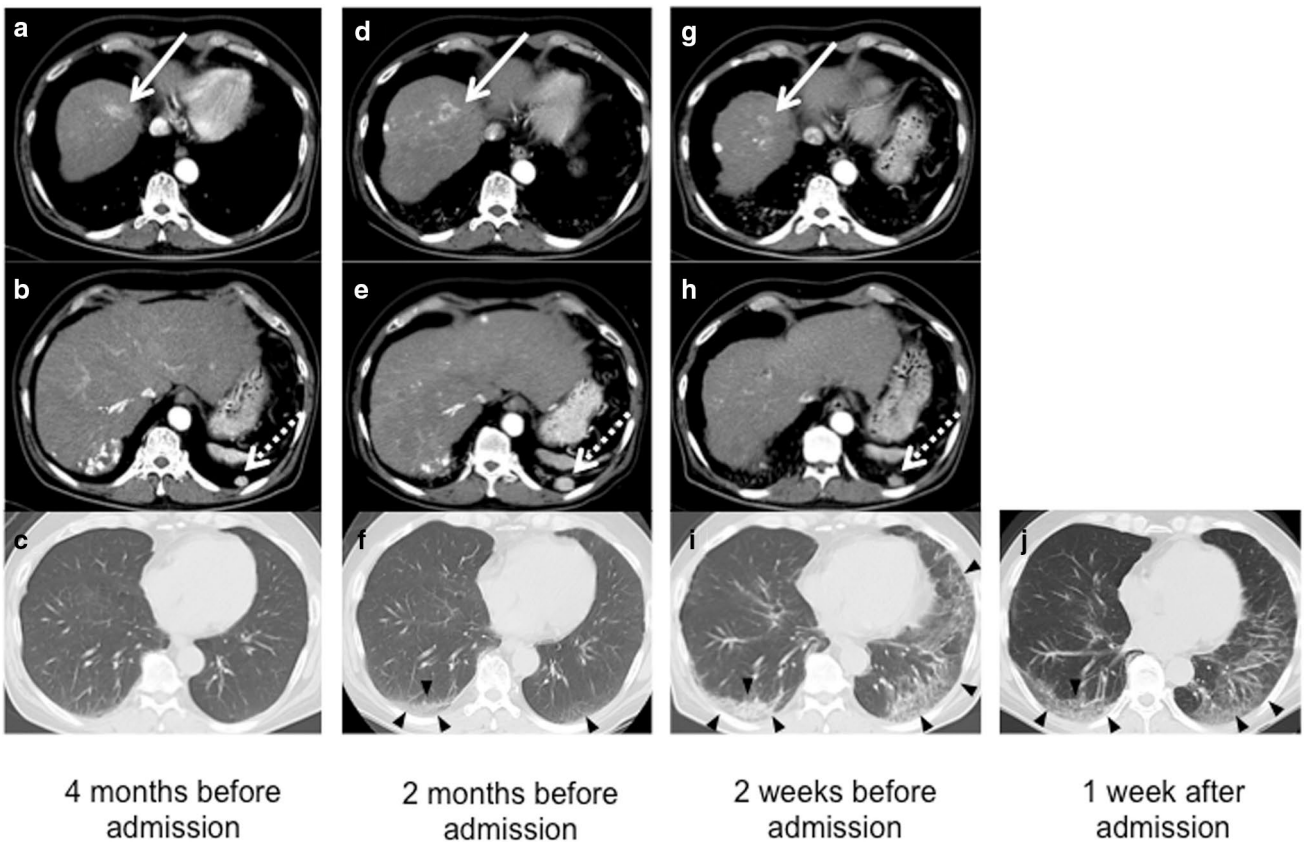

Fig. 1 Computed tomography (CT) image before introduction of regorafenib, 4 months before admission (**a–c**). **a** Intrahepatic hepatocellular carcinoma (HCC) (arrow) and **b** lung metastasis in the left lower lung field (broken line arrow) are observed. **c** There is no shadow suspicious of pneumonia in the lung field. CT image taken 2 months after starting regorafenib treatment (**d–f**). **d** Intrahepatic HCC (arrow) and **e** lung metastasis (broken line arrow) tend to increase. At that time, **f** reticular shadows appear in both lower lung fields (arrowheads). CT image obtained 1 and a half months after changing regorafenib to lenvatinib treatment (**g–i**). **g** Intrahepatic HCC (arrow) and **h** lung metastasis (broken line arrow) show a decrease. **i** Reticular shadows of both lower lung fields have increased (arrowheads), suggestive of interstitial pneumonia. **j** CT image obtained 1 week after discontinuation of lenvatinib and starting steroid therapy. The reticular shadows in both lower lung fields have decreased (arrowheads)

metastasis were noted on CT (Fig. 1d, e). Regorafenib was then discontinued due to the progression of the HCC.

At the termination of regorafenib, reticular shadows were suspected in both lower lung fields on CT images (Fig. 1f), but no specific treatment was required, because the patient had no respiratory symptoms. The patient's body weight was 64 kg. Administration of 12 mg/day of lenvatinib was started one and a half months before admission to our institute, and a partial response was obtained (reduction in the size of the intrahepatic lesion and lung metastasis on CT) 2 weeks before admission to our institution (Fig. 1g, h). However, lenvatinib therapy was discontinued due to grade 3 dyspnea on effort. In addition, chest CT showed an increase in the reticular shadows in both lower lung fields (Fig. 1i). The patient was admitted to our hospital for treatment of symptomatic interstitial pneumonia.

The peripheral oxygen saturation value (SpO_2) was 88% in room air and body temperature was 36.7 °C on admission. There was no history of pulmonary disease, but his smoking history was 45 pack-years; his Brinkman index was 1000. On physical examination, mild fine crackles in both lower lung fields were audible. In arterial blood gas analysis, hypoxemia and respiratory alkalosis were observed, with a pH of 7.467, PaO_2 of 59 mmHg, $PaCO_2$ of 27 mmHg, base excess of − 2.7 mEq/L, and HCO_3 of 19.2 mEq/L. Laboratory tests showed an elevated white blood cell value of 11900 cells/μL, an elevated C-reactive protein value of 0.79 mg/dL, an elevated aspartate aminotransferase value of 213 U/L, an elevated alanine aminotransferase value of 178 U/L, an elevated lactate dehydrogenase (LDH) value of 602 U/L, an elevated Krebs von den Lungen-6 (KL-6) value of 1283 U/mL, and an elevated total immunoglobulin E value of 4300 U/mL. No specific autoantibody suggestive of collagen disease-associated interstitial lung disease tested positive. No yellowish sputum was observed, no pathogen was detected in the blood and sputum cultures, and no image of lobar or bronchial pattern characteristic of infectious pneumonia was shown on CT. As interstitial shadows appeared during regorafenib administration and were exacerbated after switching from regorafenib to lenvatinib and respiratory symptoms appeared, acute interstitial pneumonia caused by these drugs was considered, although drug-induced lymphocyte stimulation test results for these drugs were negative. We performed steroid pulse infusion therapy with 500 mg/day of methylprednisolone for 3 days, following oral therapy with 40 mg/day of prednisolone. Within 1 week of starting steroid therapy, SpO_2 increased to 98%, the dyspnea on effort also improved, and the reticular shadows in both lower lung fields reduced in density and became unclear on CT (Fig. 1j). Laboratory tests on hospital day 19 showed that the LDH value had decreased to 487 U/L, and the KL-6 value also decreased to 909 U/mL. Owing to the entecavir treatment, the serum HBV–DNA level was sustained at < 1.0 $\log_{10}$ IU/mL during the steroid therapy. We gradually decreased the dosage of steroid every 2 weeks and he was discharged on hospital day 32 (Fig. 2).

Discussion

Regorafenib has been approved in Japan for use in patients with unresectable, advanced colorectal cancer as the 3rd line treatment, and in patients with advanced gastrointestinal stromal tumor exacerbated after chemotherapy [5, 6]. Thereafter, in June 2017, it was also approved for use in patients with unresectable, advanced HCC as a secondary treatment [3]. Although there have been several reports of drug-induced lung injury accompanying administration of sorafenib for treatment of HCC [7–10], no previous report described the appearance of interstitial pneumonia as an adverse event associated with regorafenib administration.

Severe interstitial lung disease is known to be caused by administration of epidermal growth factor receptor–tyrosine kinase inhibitors (EGFR–TKIs), such as gefitinib and erlotinib. Male sex, smoking, and a history of lung disease have been listed as risk factors for interstitial lung disease caused by these TKIs [11, 12]. Although the mechanism underlying the onset of interstitial pneumonia caused by TKIs remains unclear, it has been reported that both cytotoxic pulmonary injury and immune-mediated pulmonary injury are involved [13]. Acute injury appears to progress to chronic inflammation, aided by T-lymphocytes and macrophages, resulting in continued exposure to an antigen or the failure of the intrinsic anti-inflammatory mechanisms of the lungs. Chronic inflammation stimulates the ability of fibroblasts to migrate, proliferate, and produce the extracellular matrix, which leads to parenchymal fibrosis [14]. In addition, the inappropriate regeneration of the sequentially injured epithelium is sufficient to stimulate fibroblasts, without the need for ongoing inflammation [15], which implies that alterations in the epithelial cells function as a trigger for fibrogenesis.

EGFR plays a role in maintaining the structure and function of bronchiolar epithelial cells [16]. EGFR inhibition by gefitinib prolongs neutrophil sequestration and worsens acute lung injury, and up-regulated expression of genes involved in the airway microenvironment, prolonged inflammation, and potentiated acute lung injury have been observed in murine microarray analysis [17]. Another report showed that an EGFR–TKI up-regulated interleukin-6 expression in cancer cells and induced development of interstitial pneumonia in humans [18].

On the other hand, the association between inhibition of the vascular endothelial growth factor (VEGF) signaling pathway and interstitial pneumonia has also been suggested [19, 20]. VEGF is a potent inducer of vascular permeability and acts, at least in part, by increasing the expression of

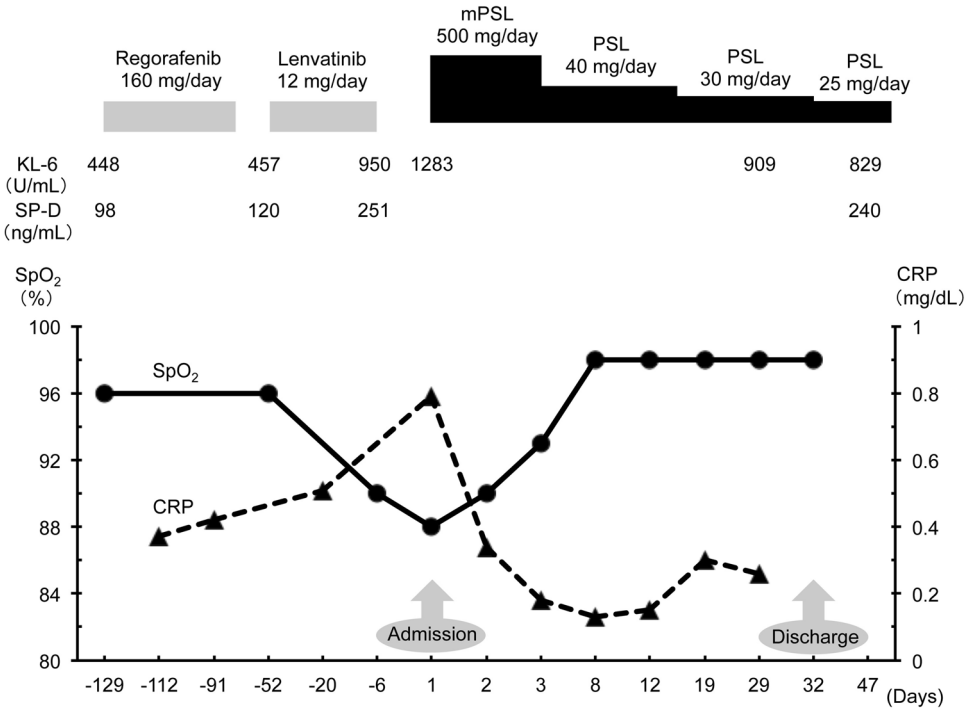

Fig. 2 Clinical course of the patient after starting regorafenib therapy. SpO_2 was maintained at 96% during regorafenib administration, but gradually decreased after changing from regorafenib to lenvatinib therapy, to as low as 90% 6 days before admission. Blood KL-6 and SP-D values gradually increased during treatment with these tyrosine kinase inhibitors. Before admission, chest CT showed exacerbation of reticular shadows in both lower lung fields, and the patient developed dyspnea on effort. On admission, SpO_2 was as low as 88%, the CRP value increased to 0.79 mg/dL, and the KL-6 value increased to 1283 U/mL. After steroid pulse infusion therapy with 500 mg/day of methylprednisolone for 3 days, SpO_2 showed an upward trend and the CRP value tended to decrease. Subsequently, oral steroid therapy with 40 mg/day of prednisolone was continued and SpO_2 improved to 98% on hospital day 8. The dosage of prednisolone was decreased every 2 weeks, and he was discharged on hospital day 32. *CT* computed tomography, *SpO_2* peripheral oxygen saturation values, *CRP* C-reactive protein, *KL-6* Krebs von den Lungen-6, *SP-D* surfactant protein-D, *mPSL* methylprednisolone, *PSL* prednisolone

matrix metalloproteinases, which are essential for extracellular matrix remodeling, wound healing, and angiogenesis, and have been implicated in the pathogenesis of idiopathic pulmonary fibrosis [21]. VEGF plays a role in maintaining the structure and function of alveolar capillary vessels [22, 23]. Therefore, inhibition of VEGF receptors (VEGFRs) is thought to induce apoptosis of alveolar epithelial cells, resulting in pulmonary structural remodeling and lung interstitial fibrosis [24, 25].

Regorafenib has a structure in which only a single fluorine atom is added to the phenyl ring at the center of sorafenib, and thus, its structure is markedly similar to that of sorafenib. Sorafenib targets mainly VEGFR2 and VEGFR3, platelet-derived growth factor receptor (PDGFR)-beta, fibroblast growth factor receptor 1 (FGFR1), v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT), rearranged during transfection (RET), v-raf-1 murine leukemia viral oncogene homolog 1, v-raf murine sarcoma viral oncogene homolog B1, etc., and in addition, regorafenib targets VEGFR1, PDGFR-α, and tyrosine kinase with Ig-like loops and epidermal growth factor homology domain-2 (TIE2) [26, 27]. Because these targets are similar, it is inferred that adverse events may be caused by the same mechanism as in sorafenib.

In Japan, lenvatinib was approved for use in patients with radioiodine-refractory thyroid cancer in May 2015 [28]. Thereafter, it was also approved for use in patients with unresectable HCC in March 2018 [4]. In the present case, administration of lenvatinib was associated with an increase in interstitial lung shadows, as well as dyspnea. Only one previous report described interstitial pneumonia associated with lenvatinib therapy, but rather than HCC, the original disease was squamous cell carcinoma of unknown primary [29]. Lenvatinib targets mainly VEGFR1–3, PDGFRα, FGFR1–4, KIT, and RET [30]. It may also inhibit the VEGF pathway and contribute to progression of interstitial pneumonia. In addition, male sex and heavy smoking may have been risk factors for the development of interstitial pneumonia in the present case.

In a clinical setting, increasing numbers of cases will be receiving regorafenib or lenvatinib therapy for HCC. In our case, fortunately, the respiratory condition improved

with discontinuation of lenvatinib and after steroid treatment. When the appearance of interstitial pneumonia as an adverse event of TKI is suspected, administration of this medicine should be discontinued promptly, and it is necessary to start steroid treatment without hesitation if cessation of lenvatinib alone does not improve the interstitial pneumonia [31].

In conclusion, we experienced a case of interstitial pneumonia in which interstitial shadows in both lower lung fields appeared during regorafenib administration and were exacerbated by subsequent lenvatinib therapy for advanced, unresectable HCC. Interstitial pneumonia might occur as one of the adverse events when administrating TKI. It is important to monitor patients for the occurrence not only of the frequent adverse events, such as palmar–plantar erythrodysesthesia, diarrhea, loss of appetite, or hypertension, but also respiratory conditions and changes on chest images during TKI treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for being included in the study.

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