

Gastric perforation related to concurrent use of nintedanib and ramucirumab

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Keywords

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Abstract

The prevalence of lung cancer in idiopathic pulmonary fibrosis (IPF) patients ranges from 9.8 to 38%. Nintedanib, a small molecule receptor tyrosine kinase inhibitor (TKI) of platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR), has been approved for IPF after phase III INPULSIS trials in 2014. Ramucirumab, a monoclonal antibody for VEGFR-2, combined with docetaxel, has been approved for advanced non-small cell lung cancer (NSCLC) after the phase III REVEL trial in 2014. Physicians will have more IPF patients being treated with nintedanib, who subsequently develop NSCLC, and therefore will likely be treated with ramucirumab plus docetaxel. We report the first case of 70-year-old man taking nintedanib for his IPF and treated with ramucirumab plus docetaxel as a seventh-line therapy for his pulmonary adenocarcinoma. On day 15 of his chemotherapy treatment cycle 2, after taking nintedanib for nine days, he developed gastric perforation.

Introduction

Nintedanib, a small molecule receptor tyrosine kinase inhibitor (TKI) of platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and vascular endothelial growth factor receptor (VEGFR), was approved as a treatment for idiopathic pulmonary fibrosis (IPF) in 2014. Ramucirumab, a monoclonal antibody against VEGFR-2, combined with docetaxel, has also been recently approved as a second-line chemotherapy for advanced non-small cell lung cancer (NSCLC). The prevalence of lung cancer in IPF patients is reported to range from 9.8 to 38% [1]. The number of patients taking nintedanib for their IPF who develop lung cancer, with the probability of being treated with ramucirumab plus docetaxel, will likely increase. We report the first case of gastric perforation related to the concurrent use of nintedanib for IPF and ramucirumab for NSCLC.

Case Report

A 70-year-old man with a smoking history of 47 pack-years was diagnosed with epidermal growth factor receptor

(EGFR) mutations, anaplastic lymphoma kinase (ALK), or c-ros oncogene 1 (ROS1) fusion genes negative stage IIIB (T1aN3M0) pulmonary adenocarcinoma in July 2015. He had chronic renal failure and combined pulmonary fibrosis and emphysema. He was treated with several lines of cytotoxic agents and nivolumab. Interstitial pneumonia progressed in January 2018 and was treated with prednisolone until May 2018. As his tumour started to progress rapidly, ramucirumab plus docetaxel were initiated as a seventh-line therapy in May 2018 and showed a favourable response. As his pulmonary fibrosis also started to progress, 200 mg/day of nintedanib was started on day 3 of the chemotherapy treatment cycle 2. He had fever and appetite loss from cycle 2 day 9 (C2D9) and made an unscheduled visit on C2D11. He was febrile with a body temperature of 37.6°C and was hypoxemic SpO₂ 89% at room air. His computed tomography (CT) scan showed infiltration in his left upper lobe. He was diagnosed with pneumonia and admitted to our hospital (white blood cells (WBC) 25,700/μL, C-reactive protein (CRP) 13 mg/dL, Hb 8.2 g/deciliter). Nintedanib was discontinued, and 1 g of

meropenem every 8 hours (q8h) was started. On day 2, his anaemia worsened (Hb 6.6 g/dL). As meropenem was not effective, 30 mg/day prednisolone was started on day 4, and the patient responded. He developed epigastric pain on day 5, and free air under the diaphragm was noted on a chest X-ray and CT scan the next day (Fig. 1A,B). Prednisolone was discontinued, and emergency surgery consisting of reefing of gastric perforation and coating with greater omentum was performed. A round perforation, 7 × 9 mm, was found on the posterior wall of the antrum of the lesser curvature of the stomach (Fig. 2A). His postoperative recovery was unremarkable. He started to eat on postoperative day 3. His pulmonary fibrosis was aggravated, and 30 mg/day of prednisolone was resumed on postoperative day 5. Prednisolone was continued, and his pulmonary fibrosis improved while chemotherapy was discontinued, and his lung cancer progressed. Follow-up gastroscopy performed on postoperative day 25 showed a well-healed scar without any carcinoma (Fig. 2B). He was discharged from our hospital on postoperative day 28.

Discussion

Ramucirumab is a monoclonal antibody against VEGFR-2. Ramucirumab plus docetaxel has been approved as second-line chemotherapy for advanced NSCLC. Gastrointestinal perforation has been reported in 0.8% patients

treated with ramucirumab monotherapy and in 1.5% of patients treated with ramucirumab plus docetaxel [2].

Nintedanib is a small molecule receptor TKI of PDGFR α and β , FGFR1-3, and VEGFR1-3. Pirfenidone and nintedanib are currently the only therapies approved for IPF [3]. Diarrhoea and liver dysfunction are the frequently reported adverse effects of nintedanib. Gastrointestinal perforation is rare and reported to occur in 0.2% of patients [4,5]. Nintedanib plus docetaxel was shown to be safe and effective for patients with advanced NSCLC previously treated with platinum-based therapy by phase III trials and has been approved by the European Medicines Agency as a second-line treatment. In addition, a randomized study of carboplatin plus nanoparticle albumin-bound paclitaxel with or without nintedanib for patients with advanced NSCLC and concurrent IPF is currently running in Japan. Nintedanib can suppress progression of both NSCLC and IPF and is probably safe to be used in combination with certain kinds of cytotoxic anticancer drugs.

On the other hand, in phase II trials for several types of cancer, such as breast or renal cell carcinoma, combination therapy consisting of bevacizumab, a monoclonal antibody for VEGF, and multi-targeted TKI, such as sorafenib, pazopanib, or telatinib blocking VEGF signalling pathway, showed substantial toxicity and minimal efficacy, leading to these phase II trials being aborted.

The underlying mechanism of gastrointestinal perforation during antiangiogenic treatment is probably

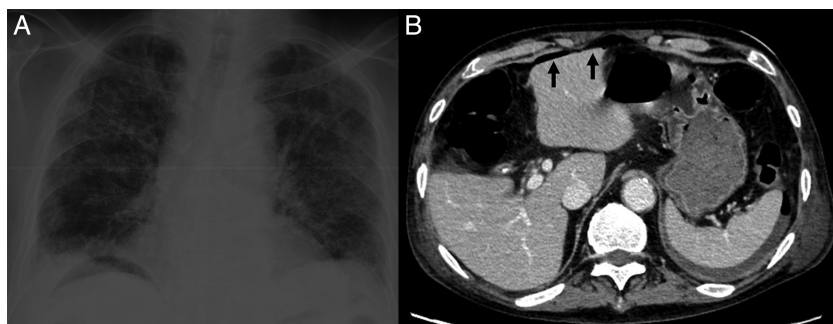


Figure 1. Free air under the right hemidiaphragm on chest X-ray (A) and computed tomography scan (B).

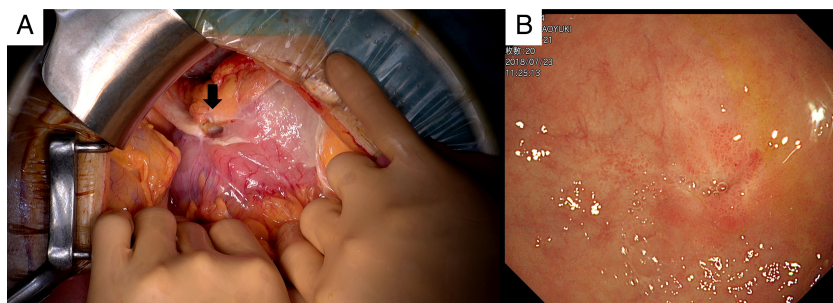


Figure 2. (A) A round perforation on the posterior wall at the antrum of lesser curvature of stomach noted at surgery. (B) Gastroscopy showed a well-healed scar without any carcinoma in the stomach 25 days after surgery.

regression of normal blood vessels by excessive VEGF inhibition, although the exact mechanism still remains unclear. Therefore, concurrent use of ramucirumab and nintedanib in our case probably increased gastrointestinal perforation risk by inhibiting VEGF signal more strongly than monotherapy with ramucirumab or nintedanib. Previous long-term prednisolone use might have also contributed to the gastric perforation.

Previous reported cases show that the major risk factors for gastrointestinal perforation associated with antiangiogenic treatment are three or more prior chemotherapy regimens, primary tumour site, recent history of endoscopy or abdominal radiotherapy, and abdominal surgery [6]. In our case, there was no carcinoma at the site of perforation, but ramucirumab plus docetaxel was the seventh line of treatment. Most gastrointestinal perforations occurred within the first 3 months of ramucirumab treatment. Similar to those reports, gastric perforation in our patient occurred one month after initiating ramucirumab.

In summary, the prevalence of lung cancer in IPF patients ranges from 9.8 to 38% [1]. The number of patients taking nintedanib for their IPF, and who may be prescribed ramucirumab plus docetaxel therapy for lung cancer, will likely increase. It is probably safer to stop nintedanib or to switch to pirfenidone when ramucirumab plus docetaxel chemotherapy is initiated in order to lower the risk of gastrointestinal perforation. Continuing patients on nintedanib, as opposed to changing to ramucirumab, is probably safe and reasonable, although there has been no clinical trial to compare the efficacy of docetaxel plus nintedanib versus docetaxel plus ramucirumab. In addition,

most importantly, gastrointestinal perforation should be considered in the differential diagnosis, when patients complain of abdominal pain during treatment with nintedanib and ramucirumab.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

References

1. Bouros D, Hatzakis K, Labrakis H, et al. 2002. Association of malignancy with diseases causing interstitial pulmonary changes. *Chest* 121:1278–1289.
2. The medical package insert for ramucirumab. 2018. Eli Lilly, Kobe, Japan.
3. Raghu G, Rochweg B, Zhang Y, et al. 2015. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. *Am. J. Respir. Crit. Care Med.* 192:e3–e19.
4. Guide for appropriate use of OFEV. 2017. Boehringer Ingelheim, Tokyo.
5. Mita Y, Nishimura K, Miura A, et al. 2018. A case of necrotizing diverticulitis of colon associated with nintedanib. *Ann. Jpn. Respir. Soc.* 7:263–266.
6. Walraven M, Witteveen PO, Lolkema MP, et al. 2011. Anti-angiogenic tyrosine kinase inhibition related gastrointestinal perforations: a case report and literature review. *Angiogenesis* 14:135–141.