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CASE REPORT

Anlotinib helps alleviate radiation pneumonitis: A case report

Jiazhen Chen | Cunliang Wang | Xudong Hu

Department of Radiotherapy, Shandong Cancer Hospital and Institute, Shandomg First Medical University (Shandong Academy of Medical Sciences)

Correspondence
Xudong Hu, Department of Radiotherapy, Shandong Cancer Hospital and Institute, Shandomg First Medical University (Shandong Academy of Medical Sciences), No. 440, Jiyan Road, Huaiyin, Jinan, Shandong, China.
Email: drhuxudong@163.com

Abstract

Radiation pneumonitis is a serious side effect of thoracic radiotherapy with no established treatment currently. Anlotinib is a small-molecule tyrosine kinase inhibitor (TKI) with anti-angiogenic effects. The effect of TKIs in the treatment of radiation pneumonitis remains to be elucidated. We investigated whether anlotinib could alleviate radiation pneumonitis. We report a case of a patient with esophageal cancer who received anlotinib for radiation pneumonitis following radiotherapy. We also reviewed related studies to address this issue. The results in this patient suggest that anlotinib may be a valid treatment option for radiation pneumonitis.

KEYWORDS
anlotinib, esophageal cancer, radiation-induced lung injury, tyrosine kinase inhibitors

1 | INTRODUCTION

Radiotherapy is one of the conventional methods for the treatment of thoracic cancers such as lung cancer, esophageal cancer, breast cancer, and mediastinal tumors.[1] Lung tissue is sensitive to the toxic response of radiotherapy, therefore it is the most essential dose-limiting organ for radiotherapy.[2] Radiation-induced lung injury reduces the local control rate of the tumor to a certain extent, becomes an important limiting factor of radiotherapy dose, and may lead to dyspnea, pulmonary fibrosis, and decline in quality of life, which has an important impact on the prognosis of patients.[3,4] In this report, we describe a patient with esophageal cancer and radiation pneumonitis that was successfully managed using anlotinib. To the best of our knowledge, this is the first report of the use of anlotinib for the treatment of radiation pneumonitis.

2 | CASE REPORT

A 61-year-old male patient with a history of smoking and alcohol consumption was admitted to the hospital for dysphagia. Gastroscopy revealed an esophageal space-occupying lesion, which was pathologically confirmed as poorly differentiated squamous cell carcinoma (Figure 1). Computed tomography (CT) detected eccentric thickening of the middle and lower segments of the esophagus, hence esophageal cancer was considered. Esophageal barium meal radiography also suggested esophageal cancer.

The patient refused surgical intervention, and radical radiotherapy and chemotherapy were initiated. After eliminating the contraindications of radiotherapy, the masses on the middle and lower segments of the esophagus and mediastinal lymph nodes were treated with radiotherapy of 50.4 Gy/28f from 8 April 2018 to 18 May 2018, followed by docetaxel/nedaplatin chemotherapy for four cycles. The patient showed a partial response and the treatment effect was considered to be significant, therefore the patient received two cycles of the original regimen treatment. However, esophageal cancer progressed. Thus, the first-line regimen of chemotherapy was suspended, and oxaliplatin/tegafur chemotherapy was administered for four cycles. Consequently, the esophageal cancer did not progress after two cycles. The patient had chest tightness and dyspnea on 25 December 2018. A subsequent CT confirmed disease progression and the presence of inflammatory fibrous foci in the lungs on 7 January 2019. Therefore, the patient received low-dose dexamethasone treatment. Considering the disease progression after second-line chemotherapy, the patient

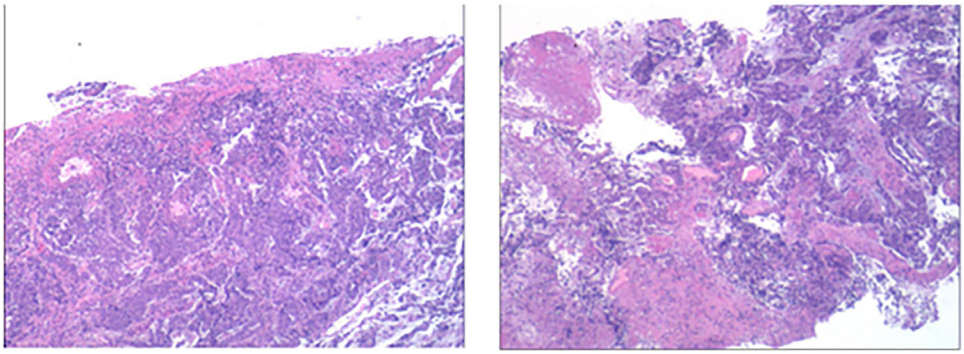

FIGURE 1 Pathological examination showed poorly differentiated squamous cell carcinoma

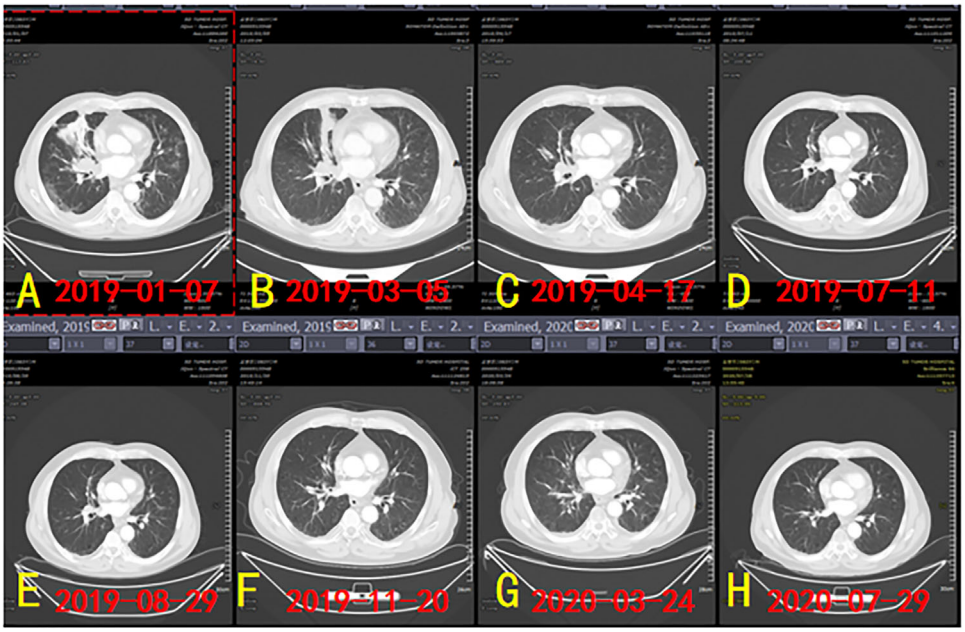

FIGURE 2 (A) CT image before anlotinib treatment. (B–H) CT images after anlotinib treatment

was instructed to take anlotinib for molecular targeted therapy on 7 January 2019. The patient did not receive any anti-inflammatory treatment after discharge from the hospital. Regular CT re-examination revealed no disease progression and inflammatory fibrous foci of both lungs almost disappeared (Figure 2).

3 | DISCUSSION

Esophageal cancer is one of the most common digestive tract tumors because many patients have hidden symptoms in the early stage and are diagnosed at an advanced stage. It is ranked fourth among the five major causes of cancer-related deaths in China.[5] Esophageal cancer can be categorized into two main histological types: esophageal adenocarcinoma and esophageal squamous cell carcinoma (ESCC), which is the predominant type.[6] The main treatments for patients with esophageal cancer include surgical resection, radiotherapy, and chemotherapy. Esophagectomy with lymphadenectomy is the primary treatment for patients with locally advanced esophageal cancer.[7]

In the majority of malignancies, tyrosine kinase inhibitors (TKIs) have been shown to play a significant role in cellular proliferation, migration, and metastasis of the cells. Receptor tyrosine kinase activity depends on the phosphorylation of signaling molecules and activation of transcription factors that mediate target gene expression in response to ligands.[8]

Anlotinib is a new oral TKI, independently developed in China, which effectively inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, fibroblast growth factor receptor, c-Kit, and other kinases, and has an effect on angiogenesis and tumor growth.[9,10] Some studies have shown that VEGF is highly expressed in patients with esophageal cancer and is related to prognosis and sensitivity to radiotherapy and chemotherapy.[11] Anlotinib is highly selective to VEGFR2. It acts on the catalytic pocket of the Adenosine triphosphate (ATP) binding site of VEGFR2 kinase and inhibits the activity of the indole ring in the ATP binding site by inter-

acting with the aspartic acid-phenylalanine-glycine module (Asp-Phe-Gly (DFG)-motif), thereby inhibiting the activity of VEGFR2 kinase and blocking angiogenesis.[9] The results of the ALTER-1102 study of anlotinib for second-line and above treatment of advanced ESCC were officially announced at the 2019 ASCO GI, which brought a new choice for Chinese patients with esophageal cancer. In this study, 165 Chinese patients with esophageal cancer were randomly divided into two groups at 2:1 ratio and given anlotinib or placebo 12 mg/d for 2 weeks, every 3 weeks as a course of treatment, until the disease progressed, or intolerable adverse reactions occurred. The results showed that the median Progress-free survival (PFS) of the anlotinib group was significantly longer than that of the placebo group (3.02 months *vs.* 1.41 months, HR 0.46, 95% CI 0.32–0.66, $p < 0.01$), Disease control rate (DCR) was significantly improved (64% *vs.* 18%, $p < 0.01$), and the adverse reactions were relatively less. The most common 3/4 grade adverse reactions were hypertension (15.6%) and anorexia (5.5%).[12] In this case, the patient was treated with anlotinib after the failure of second-line chemotherapy, and the lymph node metastasis was smaller than before anlotinib treatment, indicating its strong effect.

Radiation-induced lung injury is a common complication of radiotherapy for thoracic tumors. It usually comprises radiation pneumonitis at an early stage and radiation-induced pulmonary fibrosis at the late stage. Receptor tyrosine kinase is a family of signaling molecules involved in multiple signaling pathways in the body and is closely related to fibrotic diseases, therefore it is a potential therapeutic target.[13] However, there are few studies on the use of anlotinib in the treatment of radiation-induced lung injury. Phase III clinical trials confirmed that it was effective in the treatment of non-small-cell lung cancer, ovarian cancer, and idiopathic pulmonary fibrosis.[14] A recent study showed that anlotinib had visible inhibitory effects on lung inflammation, oxidative stress, and pulmonary fibrosis in mice.[15] The patient in the present case had severe pulmonary fibrosis after radiotherapy. Surprisingly, the inflammatory fibrous foci gradually decreased after oral administration of anlotinib, suggesting that anlotinib is likely to be an option for radiation-induced lung injury.

4 | CONCLUSION

The results of this case suggest that anlotinib can alleviate radiation pneumonitis. However, there are few studies on the use of anlotinib in the treatment of radiation-induced lung injury. Further studies should be conducted to validate these findings.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

ORCID

Jiazhen Chen https://orcid.org/0000-0002-1813-9751

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