Metastatic renal cell carcinoma complicated with diffuse alveolar hemorrhage: a rare adverse effect of sunitinib

著者	Yamada Tadaaki, Ohtsubo Koushiro, Izumi Kouji, Takeuchi Shinji, Mouri Hisatsugu, Yamashita Kaname, Yasumoto Kazuo, Ghenev Peter, Kitagawa Satoshi, Yano Seiji
journal or publication title	International Journal of Clinical Oncology
volume	15
number	6
page range	638-641
year	2010-12-01
URL	http://hdl.handle.net/2297/24813

doi: 10.1007/s10147-010-0104-3

**Metastatic renal cell carcinoma complicated with diffuse alveolar
hemorrhage: a rare adverse effect of sunitinib**

Tadaaki Yamada¹, Koushiro Ohtsubo¹, Kouji Izumi¹, Shinji Takeuchi¹,
Hisatsugu Mouri¹, Kaname Yamashita¹, Kazuo Yasumoto¹, Peter Ghenev¹,
Satoshi Kitagawa², and Seiji Yano¹

¹ Cancer Center, Kanazawa University, Kanazawa, Japan

² Department of Molecular and Cellular Pathology, Kanazawa University

Address correspondence and reprint requests to:

Tadaaki Yamada, M.D., Ph.D.,

Cancer Center, Kanazawa University, 13-1 Takara-machi, Kanazawa 920-8641,

Japan

Tel: +81-76-265-2794, Fax: +81-76-234-4524

E-mail: tadaakiy@med.kanazawa-u.ac.jp

Running Head: Diffuse alveolar hemorrhage by sunitinib in RCC

Abstract

We report a 67-year-old man with metastatic papillary renal cell carcinoma in whom bloody sputum developed after administration of sunitinib. Chest computed tomography revealed diffuse ground-glass opacity lesions, and bloody bronchoalveolar lavage fluid was obtained by flexible bronchoscopy. The abnormal shadows promptly regressed after withdrawal of sunitinib. In four cycles of sunitinib treatment, he suffered from controllable diffuse alveolar hemorrhage. Finally, he died of respiratory failure eight months after onset.

This is the first case report of diffuse alveolar hemorrhage as an adverse effect of sunitinib in metastatic papillary RCC. Care should be taken with pulmonary hemorrhage in the use of anti-angiogenesis agents in not only squamous cell lung cancer but also metastatic lung tumors.

Key words:

sunitinib, alveolar hemorrhage, adverse effect, papillary renal cell carcinoma, vascular endothelial growth factor

Introduction

Renal cell carcinoma (RCC) is the most common kidney tumor, and the incidence has been increasing over the last several decades (1). Although almost histological type of RCC is clear cell carcinoma, papillary carcinoma occupies 7% to 14% of RCC (2). Treatment of advanced RCC with cytokines, such as interferon- α and interleukin-2, had been standard practice for a number of years (3). Although the median survival period of patients with metastatic papillary RCC was reported as only 5.5 months and no patients survived beyond 2 years (4), a recent study indicated a 5-year survival rate of papillary RCC of 10% (5). Thus, the prognosis was improved because novel molecular therapeutic agents had demonstrated significant clinical activity in advanced RCC and altered the standard therapy in this disease. Of these therapies, sunitinib, a new oral multitargeted receptor tyrosine kinase inhibitor (TKI), is promising in the treatment of RCC patients. In phase III trial, progression-free survival was longer and response rate was higher in patients with untreated metastatic RCC who received sunitinib than in those receiving interferon- α as conventional therapy (6). The patients with papillary RCC treated with sunitinib had prolonged median progression-free survival of 11.9 months, although overall clinical responses remained low (7). On the other hand, this agent shows a

broad range of adverse effects 3 to 4 weeks after initiation of treatment, such as neutropenia, thrombocytopenia, asthenia, hypertension, and bullous skin toxicity. However, pulmonary bleeding as an adverse effect has been seldom reported. Here, we report a case of metastatic papillary RCC complicated with diffuse alveolar hemorrhage by sunitinib.

Case report

At the age of 67 years, the patient complained of non-productive cough in June 2008 and was subsequently hospitalized in July 2008.

He was a non-smoker. Although he had no family history of cancer, he had a history of tuberculous epididymitis at the age of 20, and was treated with oral therapy for diabetes mellitus and hypertension. The patient's blood cell counts were as follows (normal ranges are shown in parentheses): hemoglobin, 12.1 g/dL (13.5 – 17.0 g/dL); hematocrit, 36.1% (39.7% – 51.0%); white blood cells, 7920/mm³ (3,300 – 8,800/mm³); and platelets, 373,000/mm³ (130,000 – 350,000/mm³). The results of renal function, coagulation, and collagen studies, such as myeloperoxidase – anti-neutrophil cytoplasmic antibody (MPO – ANCA), were normal. Whole-body computed tomography (CT) revealed a huge left renal tumor with multiple lung and liver nodules, and mediastinal lymph node swelling. In addition, positron emission tomography (PET) demonstrated accumulating spots in multiple bone tumor lesions. Pathological diagnosis using renal and pulmonary CT-guided needle biopsies showed type 1 papillary RCC with lung metastases. The clinical stage was determined as T3bN0M1 (primary left renal tumor with lung, bone, liver, and mediastinal lymph node metastases) in TNM classification in August 2008.

On admission, his performance status was 1, but he suffered systemic metastases and the tumor growth progressed rapidly. Tumor doubling time was 42 days. Therefore, he was spared cytoreductive nephrectomy for standard therapy and treated with sunitinib, a novel angiogenic inhibitor, as first-line systemic therapy on September, 2008. Daily treatment with sunitinib showed efficacy with progression control in targeting primary and multiple lung and liver metastatic lesions. However, he suffered a small amount of bloody sputum (grade 1; Common Terminology Criteria for Adverse Events ver. 3.0) on day 5 and slight malaise (grade1) on day 7. Administration of sunitinib was then interrupted because thrombocytopenia (grade 3) developed on day 18. On the same day, the chest CT scan revealed diffuse ground-glass opacity lesions around lung metastatic nodular shadows (Figure 1-A). To investigate the abnormal shadows, flexible bronchoscopy was performed and obtained serous bloody bronchoalveolar lavage fluid was obtained from the superior lingular segment (Figure 2). After stopping sunitinib, he was treated with carbazochrome sodium sulfonate hydrate 100 mg against diffuse alveolar hemorrhage, resulting in marked reduction of the lesions determined by CT on day 40 (Figure 1-B). Although he was treated with interferon- α after cessation of sunitinib, tumor growth indicated a rapidly progressive course. Then, he received four cycles of

sunitinib, until diffuse alveolar hemorrhage (grade 2) or thrombocytopenia (grade 3) was observed. In four cycles of sunitinib, controllable diffuse alveolar hemorrhage developed as well as first administration. Finally, the patient died of respiratory failure eight months after the onset, due to the progression of multiple lung and mediastinal lymph node metastases, and pleuritis carcinomatosa and lymphangitic carcinomatosis.

In the lung autopsy, diffuse peripheral alveolar hemorrhage was confirmed around the lung metastases (Figure 3-A). To investigate the mechanism of diffuse alveolar hemorrhage by sunitinib, immunohistochemistry was performed for VEGF in the autopsy specimens of both lung tumors and primary renal tumor in addition to renal biopsy specimens. Although about 60% of tumor cells demonstrated weak cytoplasmic staining for VEGF in renal biopsy, almost all tumor cells showed strong staining in both lung metastases and primary renal tumor in the autopsy (Figure 3-B).

Discussion

Here, we report the first case of diffuse alveolar hemorrhage as an adverse effect of sunitinib in metastatic papillary RCC. Sunitinib is an oral multitargeted TKI against VEGFR1 and 2, platelet-derived growth factor (PDGF) receptors α and β , c-KIT, FLIT-3, and ret protooncogene (RET). Substantial clinical activity of sunitinib has been demonstrated in imatinib-resistant gastrointestinal stromal tumors, breast cancer, and other tumors (8). Similar to other cancers, sunitinib has a major clinical impact for RCC.

Recently, pulmonary bleeding has been reported as an adverse effect with the development of antiangiogenic therapeutic approaches. Bevacizumab, a recombinant humanized monoclonal antibody that binds to VEGF, showed an adverse effect with fatal tumor-related bleeding, especially centrally located lung tumor or squamous cell histology, in patients enrolled in a randomized study for non-small cell lung carcinoma (9). Sunitinib led to fatal pulmonary bleeding events in two patients with advanced squamous cell lung cancer in a phase II trial of previously treated advanced non-small cell lung cancer (10). Therefore, ongoing trials for antiangiogenic agents tend to eliminate patients with squamous cell lung cancer. Furthermore, a retrospective study suggested that baseline tumor cavitation may be a potential risk factor for pulmonary

hemorrhage in first-line advanced non-small cell lung cancer treatment with carboplatin and paclitaxel plus bevacizumab (11).

The present case represents a timely warning regarding the clinical use of sunitinib for some reasons as follows: 1) histological diagnosis was metastatic lung adenocarcinoma from RCC, but not squamous cell lung cancer, in which sunitinib-related diffuse alveolar bleeding has been reported; 2) lung metastatic tumors with hemorrhage were located in the peripheral side without cavitations; 3) the frequency of the use of sunitinib would be anticipated to increase in the future. Therefore, care should be taken with regard to the adverse effects of sunitinib in cases of RCC lung metastases. However, the mechanism and clinical condition of sunitinib-associated pulmonary hemorrhage remain unclear.

VEGF is one of the principal proangiogenic factors in solid tumors and plays a pivotal role in vascular development, stimulating both angiogenesis and vasculogenesis (12, 13). Papillary RCC tumors also show high levels of VEGF immunoreactivity (14) and elevated VEGF mRNA levels in papillary RCC tumors were associated with short survival (15). In addition, this growth factor is known as both a proangiogenic and survival factor for endothelial cells. Inhibition of VEGF results in inhibition of vascular development and significant alteration of epithelial development, suggesting that VEGF coordinates proper development

of the normal lung epithelium and vasculature (16). Therefore, it seems possible that inhibition of VEGF may decrease the regenerative capacity of the endothelial cells, resulting in endothelial dysfunction in the supporting layers of the blood vessels (17).

In the present case, we speculated that the correlation with high-level production of VEGF from the tumor and anti-VEGF effect of sunitinib in the lung metastatic microenvironment may cause diffuse alveolar hemorrhage as adverse events, because tumor cells showed stronger expression of VEGF in both the primary site and the lung metastases at autopsy. On the other hand, Kontovinis *et al.* reported that plasma VEGF-A levels increased after treatment with sunitinib in clear-cell metastatic renal cell carcinoma (18). Therefore, we cannot rule out the possibility that anti-VEGF treatment itself might have induced the increased expression of VEGF in the autopsy specimens. In addition, pulmonary bleeding as an adverse effect of sunitinib has been reported only rarely in papillary RCC tumors. As we did not investigate other sunitinib-targeting molecules, such as PDGF, c-KIT, FLIT-3, and RET, further investigations regarding the mechanism of pulmonary hemorrhage are required.

In conclusion, we reported a case of metastatic papillary RCC with controllable diffuse alveolar hemorrhage as an adverse event associated with

sunitinib. Care should be taken with pulmonary hemorrhage in the use of anti-angiogenesis agents in not only squamous cell lung cancer but also metastatic lung tumors.

References

1. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. *JAMA* 281:1628-31, 1999.
2. Reuter VE. The pathology of renal epithelial neoplasms. *Semin Oncol* 33:534-43, 2006.
3. Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med* 353:2477-90, 2005.
4. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *N Engl J Med* 335:865-75, 1996.
5. Patard JJ, Leray E, Rioux-Leclercq N, Cindolo L, Ficarra V, Zisman, A, et al. Prognostic value of histologic subtypes in renal cell carcinoma: A multicenter experience. *J Clin Oncol* 23:2763-71, 2005.
6. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 356:115-24, 2007.
7. Choueiri TK, Plantade A, Elson P, Negrier S, Ravaud A, Oudard S, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. *J Clin Oncol* 26:127-31, 2008.
8. Socinski MA. The current status and evolving role of sunitinib in non-small cell

lung cancer. J Thorac Oncol 3:S119-23, 2008.

9. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 22:2184-91, 2004.

10. Socinski MA, Novello S, Brahmer JR, Rosell R, Sanchez JM, Belani CP, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. J Clin Oncol 26:650-6, 2008.

11. Sandler AB, Schiller JH, Gray R, Dimery I, Brahmer J, Samant M, et al. Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non-small-cell lung cancer treated with Carboplatin and Paclitaxel plus bevacizumab. J Clin Oncol. 27:1405-12, 2009.

12. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 9:669–76, 2003.

13. Hanahan D, Weinberg R. The hallmarks of cancer. Cell 100:57–70, 2000.

14. Jacobsen J, Grankvist K, Rasmuson T, Bergh A, Landberg G, Ljungberg B. Expression of vascular endothelial growth factor protein in human renal cell

carcinoma. BJU Int 93:297-302, 2004.

15. Ljungberg BJ, Jacobsen J, Rudolfsson SH, Lindh G, Grankvist K, Rasmuson T. Different vascular endothelial growth factor (VEGF), VEGF-receptor 1 and -2 mRNA expression profiles between clear cell and papillary renal cell carcinoma. BJU Int 98:661-7, 2006.

16. Zhao L, Wang K, Ferrara N, Vu TH. Vascular endothelial growth factor co-ordinates proper development of lung epithelium and vasculature. Mech Dev 122:877-86, 2005.

17. Cho YJ, Murgu SD, Colt HG. Bronchoscopy for bevacizumab-related hemoptysis. Lung Cancer 56:465-8, 2007.

18. Kontovinis LF, Papazisis KT, Touplikioti P, Andreadis C, Mouratidou D, Kortsaris AH. Sunitinib treatment for patients with clear-cell metastatic renal cell carcinoma: clinical outcomes and plasma angiogenesis markers. BMC Cancer 9:82, 2009.

Figure legends

Figure 1

Chest computed tomography revealing diffuse ground-glass opacity lesions around lung metastases on day 18 after treatment with sunitinib (Fig. 1-A). The lesions disappeared on day 40 (Fig. 1-B).

Figure 2

Flexible bronchoscopy demonstrating bronchial hemorrhage from the superior lingular segment (Fig. 2-A). Serous blood in bronchoalveolar lavage fluid was observed (Fig. 2-B).

Figure 3

Histological findings of peripheral alveolar hemorrhage around lung metastases at autopsy (Fig. 3-A). Immunohistochemical findings showing strongly positive cytoplasmic staining for VEGF in lung metastases at autopsy (Fig. 3-B). A, H&E, x200; B, Immunostaining of VEGF, x200.

Figure 1

Figure 2

A

B

Figure 3