

Imatinib-induced interstitial lung disease and sunitinib-associated intra-tumour haemorrhage

Herbert H Loong 龍浩鋒
Winnie Yeo 楊明明

An ethnically Chinese patient with newly diagnosed metastatic gastro-intestinal stromal tumour initially treated with imatinib mesylate developed severe interstitial lung disease. As his condition improved after cessation of imatinib mesylate and treatment with corticosteroids, he was started on sunitinib malate. His clinical course was then unfortunately complicated with intra-tumour bleeding. This case report illustrates the dilemmas and complexities associated with treating patients with gastro-intestinal stromal tumours with the new tyrosine kinase inhibitors.

Case report

A 63-year-old man was referred to our department in January 2007 after being diagnosed with a recurrent gastro-intestinal stromal tumour (GIST). He was initially diagnosed with a duodenal GIST in January 2000 on presenting with symptoms of anaemia. A workup, including upper endoscopy, revealed an ulcerative growth over the third and fourth part of the duodenum. A computed tomographic (CT) scan showed a 4.5 x 5.5 cm soft tissue mass over the same area. A duodenectomy and duodeno-jejunostomy were performed and a pathological examination of tissue removed at surgery confirmed a low-grade GIST (S-100 positive; 4.5 cm in size, mitosis 6/10 high-power field, c-KIT positive). The resection margins were clear so he was managed with routine follow-up and observation. An abdominal ultrasound performed in 2003 showed no evidence of metastases.

He remained well until January 2007 when hepatomegaly was found during a physical examination. An abdominal CT scan showed multiple hypervascular tumour foci with cystic changes in both liver lobes. A histological examination of a liver biopsy specimen confirmed metastatic GIST. He was started on imatinib mesylate (Glivec; Novartis, Zurich, Switzerland) 400 mg daily in March 2007. Unfortunately he developed severe imatinib mesylate-induced interstitial lung disease in April 2007, presenting with increased shortness of breath and hypoxaemia requiring oxygen supplementation. A chest X-ray showed progressive interstitial lung shadows with honeycombing (Fig 1a) and a high-resolution CT thorax showed a predominantly reticular pattern and linear shadows as well as a ground-glass appearance consistent with interstitial lung fibrosis. His lung function test revealed a restrictive pattern. His condition improved with high-dose corticosteroids and the suspension of imatinib mesylate. Serial chest X-rays showed a dramatic improvement with resolution of the interstitial shadows (Fig 1b).

In view of his intolerance to imatinib mesylate, he was started on sunitinib malate 37.5 mg daily (Sutent; Pfizer, New York, US) in May 2007 but developed quite severe bullous eruptions over his hands and soles and hyperacanthosis over his plantar areas after 3 weeks of treatment. The treatment was suspended for 2 weeks and, with supportive management, his skin lesions subsided. He was subsequently re-challenged with sunitinib malate 25 mg daily and has tolerated this well.

In August 2007, he was admitted through our accident and emergency department for management of left upper quadrant abdominal pain, which had worsened progressively over 2 days. Blood tests revealed a drop in his haemoglobin from 104 g/L at baseline to 73 g/L. There were no symptoms suggestive of gastro-intestinal bleeding.

An urgent abdominal CT scan with contrast showed an intra-tumour haemorrhage with active bleeding (Fig 2a). There was no evidence of a subcapsular haematoma or intra-peritoneal haematoma. After consultation with our interventional radiologists, an urgent hepatic arteriogram was performed and this showed multiple foci of contrast extravasation from the left and right lobe tumours supplied by the left and right hepatic arterial branches. Embolisation with selective cannulation of the left and right hepatic arteries and gelfoam injection was done; the post-embolisation angiogram showed no contrast extravasation (Fig 2b).

Key words
Gastrointestinal stromal tumors; Protein-tyrosine kinases

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Department of Clinical Oncology,
Prince of Wales Hospital, The Chinese
University of Hong Kong, Shatin, Hong
Kong

HH Loong, MB, BS, MRCP (UK)
W Yeo, FRCP, FHKAM (Medicine)

Correspondence to: Dr HH Loong
E-mail: h_loong@clo.cuhk.edu.hk

由imatinib引致的肺間質病變及與sunitinib有關的腫瘤內出血

一名華籍病人有新近診斷的轉移性胃腸道基質瘤，起初以imatinib mesylate治療，出現嚴重的肺間質病變後停服，並改用皮質類固醇治療，情況好轉。其後以sunitinib malate治理，臨床病情併發腫瘤內出血。本報告顯示使用新的酪氨酸激酶抑制劑治理胃腸道基質瘤病人的困境和複雜性。

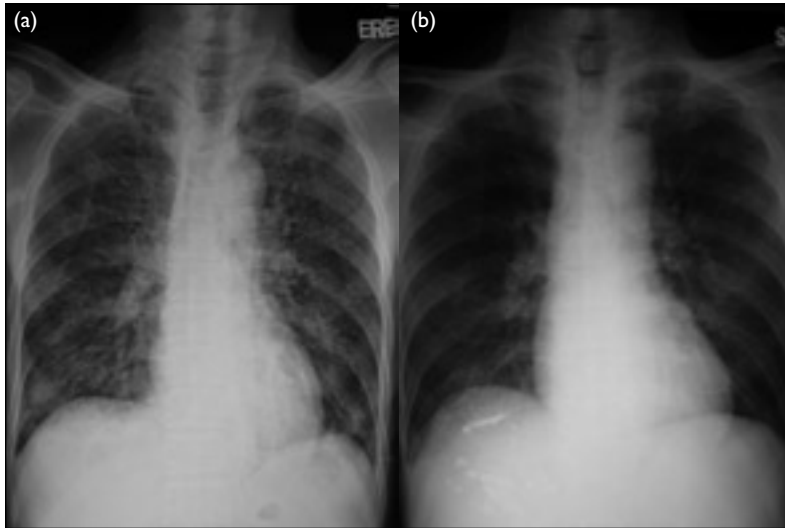


FIG 1. (a) Chest X-ray showing the presence of imatinib mesylate-induced interstitial lung disease with diffuse interstitial shadows and honeycombing. (b) Chest X-ray after cessation of imatinib mesylate and administration of steroids showing resolution of the interstitial lung shadows

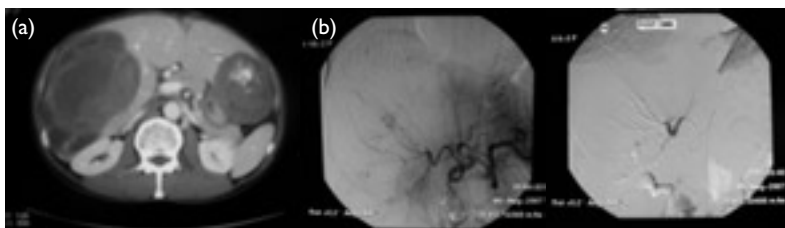


FIG 2. (a) Contrast computed tomographic abdomen showing haemorrhage within the metastasis in the left liver lobe. (b) Pre- and post-embolisation hepatic angiograms

The patient was given a top-up blood transfusion, remained stable and pain free over the next 2 days, and was subsequently discharged.

Discussion

Gastro-intestinal stromal tumours comprise a group of smooth muscle mesenchymal alimentary tract tumours of variable malignancy. These mesenchymal neoplasms are thought to arise from the intestinal cells of Cajal that are found throughout the gastro-

intestinal tract, regulating peristalsis.¹ Despite being notoriously resistant to conventional chemotherapy and radiotherapy, the discovery of gain-of-function mutations in the KIT proto-oncogene, reported in 1998 by Hirota et al,² and the subsequent development and approval of imatinib mesylate, drastically changed treatment. Not all GIST shows mutations in KIT however, and mutations of the platelet-derived growth factor receptor- α (PDGFR- α) have been shown to be an alternate pathway for oncogenesis, accounting for approximately 5% of mutations.^{3,4}

Imatinib mesylate is generally well tolerated with grade-3 and -4 non-haematological toxicity being relatively uncommon. Respiratory complications, mainly in the form of dyspnoea and cough, have been documented in 7 to 10% and 10 to 14% of patients receiving imatinib mesylate respectively.⁵ These have mostly been attributed to pulmonary oedema.

Nonetheless, imatinib mesylate-induced interstitial lung disease is now being recognised as a distinct toxic effect of imatinib mesylate treatment. In Japan, 27 cases of interstitial lung disease⁶ associated with imatinib mesylate therapy have been reported, along with other isolated case reports in Europe and North America. This epidemiological distribution suggests this condition may affect Asian orientals more than other ethnic groups.

It is unclear whether the mechanism is a drug hypersensitivity phenomenon, or a pharmacological effect of tyrosine kinase inhibition. The resolution of the diffuse ground-glass opacities seen on chest X-ray and CT scan on cessation of the drug and with use of corticosteroid therapy, suggest a hypersensitivity phenomenon, as has been reported in the literature.⁶ Alternatively, interstitial lung disease could conceivably be a pharmacological effect.

Platelet-derived growth factor (PDGF), one of the targets that imatinib mesylate acts upon, has been known to play a key role in acute lung injury. There is early evidence in animal models that tyrosine kinase inhibition can also increase the susceptibility of rat lungs to acute injury.⁷ Gefitinib, another tyrosine kinase inhibitor which is an epidermal growth factor receptor-tyrosine kinase inhibitor, has also been associated with interstitial lung disease. Nevertheless, there are no reports in the literature of prolonged inhibition of PDGF leading to interstitial lung disease. Thus the mechanism of imatinib mesylate-related interstitial lung disease remains unclear.

Sunitinib malate is a newer oral multi-targeted receptor tyrosine kinase inhibitor that has shown antiangiogenic and antitumour activities. By inhibiting the phosphorylation of a greater number of tyrosine kinases including PDGFR- α and - β , vascular endothelial growth factor (VEGF) receptor-1, -2, -3 and Fms-like-tyrosine-kinase-3, sunitinib malate has been approved for treatment of advanced renal cell

carcinoma and GIST after disease progression or intolerance to imatinib mesylate.

Sunitinib malate is generally well tolerated. The most common adverse reactions, occurring in more than 20% of patients, include fatigue, asthenia, diarrhoea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, and hypertension. Nevertheless, early human trials done by Faivre et al⁸ showed that six of 22 patients on their phase I trial developed evidence of tumour necrosis leading to tumour cavitations in four patients and further development of fistulae in two patients. Lethal peritoneal haemorrhage was also reported in a patient with recurrent peritoneal GIST.

The mechanism of sunitinib malate-associated haemorrhage remains unclear. Vascular endothelial growth factor is known to stimulate endothelial cell proliferation and promote endothelial cell survival, thus maintaining vascular integrity. One possible hypothesis is that inhibition of VEGF could thereby diminish the regenerative capacity of endothelial cells and cause defects that expose pro-coagulant phospholipids on the luminal plasma membrane or underlying matrix, leading to thrombosis or haemorrhage.

Haemorrhagic events have been reported in phase III trials with sunitinib malate. In GIST Study A,⁹ a two-arm, international, randomised, double-blind, placebo-controlled trial of sunitinib in patients with GIST who had disease progression during prior imatinib mesylate treatment or who were intolerant of imatinib mesylate, 37% of patients on sunitinib developed haemorrhage or bleeding, with 14% being grade 3 or 4, compared with 17% and 9% in the placebo group, respectively. The most common haemorrhagic event was epistaxis, less common bleeding sites being rectal, gingival, upper gastrointestinal, genital and wounds. Treatment emergent grade-3 and -4 tumour haemorrhage occurred in five (2.5%) of 202 of patients with GIST receiving sunitinib malate in GIST Study A.

Spontaneous intra-tumoural bleeding appears to be a rarity in GIST with only one case described in the recent literature.¹⁰ However, GISTs, especially those pretreated with imatinib mesylate, have been known to be extremely friable due to treatment-induced necrosis and myxoid degeneration¹¹ and the centrally cystic nature of the metastases. The fact that this patient was treated with both imatinib mesylate

previously as well as sunitinib malate prior to the rupture event may have made him more prone to intra-tumoural bleeding.

Metastatic liver disease is a major determinant of survival in GIST with prior studies having shown that patients who underwent hepatic resection of all visible disease had a 1-year and 3-year overall survival rate of 90% and 58% respectively.¹²

Although now out of favour following the introduction of the tyrosine kinase inhibitors, imatinib mesylate and sunitinib malate, trans-arterial embolisation therapy has been used to manage metastatic GIST. Unfortunately most of the data available are based on small case series and are often fragmented.

Recently, Kobayashi et al¹³ from the MD Anderson Cancer Centre performed a retrospective analysis of 110 patients with metastatic GIST who underwent trans-arterial chemo-embolisation (TACE) from January 1993 to March 2005. Of the 110 patients identified, the radiologic response to TACE could be evaluated in 85 patients, 12 (14%) of whom demonstrated partial responses, 63 (74%) of whom demonstrated stable disease, and 10 (12%) of whom demonstrated progressive disease. The median progression-free survival time was 8.2 months. Patients who had more than five liver metastases or who underwent only one TACE session had a shorter progression-free survival compared to those with fewer metastases or those who received two or more than two TACE sessions. Extensive liver involvement, presence of extra-hepatic metastases, and progression of liver disease after TACE were all associated with poor overall survival.

To our knowledge, the use of intra-arterial embolisation in the acute management of intra-tumoural bleeding in metastatic GISTs has not been reported. The management and outcome of this case may present us with a salvage option should a similar situation arise.

As the use of imatinib mesylate and sunitinib malate becomes more prevalent in patients with GISTs, this case serves to illustrate potential complications of treatment. This patient's complications—imatinib mesylate-induced interstitial lung disease and intra-tumoural haemorrhage whilst on sunitinib malate—illustrate the complexity and challenges faced when managing patients with metastatic GISTs in the era of tyrosine kinase inhibition.

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