A Case of Progressive Digital Ischemia after Early Withdrawal of Gemcitabine and S-1 in a Patient with Systemic Sclerosis

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Received December 5, 2010; accepted March 7, 2011

The safety of chemotherapy for patients with systemic sclerosis is unclear, and there are few published reports documenting the side effects of chemotherapy in patients with this condition. Here, we report the case of a patient with systemic sclerosis who developed severe digital ischemia during combination gemcitabine/S-1 chemotherapy for pancreatic cancer. In spite of aggressive treatment, the digital ischemia progressively worsened and gangrenous changes developed in multiple fingers and toes. In this patient, the systemic sclerosis had been well controlled, with no digital ischemic symptoms for the previous 6 years, so this progressive clinical course in spite of aggressive treatment strongly suggests that the chemotherapy triggered or aggravated the digital necrosis. To the best of our knowledge, this is only the third reported case of a patient with systemic sclerosis developing digital necrosis after gemcitabine-based chemotherapy. The incidence of digital necrosis during chemotherapy in patients with systemic sclerosis is unknown, and the mechanism by which it occurs is unclear, but the three reports published to date, including the present case, suggest that physicians should be very cautious about administering gemcitabine-based chemotherapy to patients with systemic sclerosis. Any resulting digital ischemia might be refractory to treatment and worsen progressively, even if chemotherapy is withdrawn in the early stages of digital ischemia.

Key words: gemcitabine – necrosis – S-1 – systemic scleroderma – toxicity

INTRODUCTION

Patients with systemic sclerosis (SSc) are at increased risk of cancer (1), so it seems likely that a not inconsiderable number of SSc patients require and receive chemotherapy in daily clinical practice. Over 90% of SSc patients experience Raynaud’s phenomenon, which, in a small number of cases, progresses to digital necrosis (2,3). Anti-cancer drugs have the potential to cause vascular toxicity, including digital necrosis (4–9), so patients with SSc may be more susceptible than others to vascular toxicity arising from treatment with anti-cancer drugs. However, the risks for SSc patients of the vascular toxicity associated with chemotherapy are poorly understood.

CASE REPORT

Here, we report a patient with SSc who developed digital ischemia after gemcitabine/S-1 combination therapy, which became gangrenous in spite of the best available treatment.
controlled by oral sulfonylurea. He had given up smoking 19 years earlier, before which he had had a smoking habit of 22 packs/year. There was no history of allergic disease. Although there had been no symptoms of digital ischemia over the previous 6 years, we were reluctant to treat the pancreatic cancer with systemic chemotherapy because it might increase the risk of digital necrosis. We strongly cautioned the patient about this risk, but he was firm in his wish to receive chemotherapy treatment.

Combination chemotherapy using gemcitabine (400 mg/m², days 1 and 8) and S-1 (80 mg/day, days 1–14) every 3 weeks was started in December 2008. Given the risk of digital necrosis, a low dose of gemcitabine was selected. This regimen effectively controlled the pancreatic cancer, and no significant hematological or non-hematological adverse events related to chemotherapy were observed until day 1 of the 10th cycle, in July 2009, when the patient experienced Raynaud’s phenomenon. The patient had previously experienced Raynaud’s phenomenon, but not during the previous 6 years.

At this stage, we strongly recommended suspension of chemotherapy; however, the patient refused to discontinue chemotherapy for fear of the pancreatic cancer progressing. The Raynaud’s phenomenon was treated with vasodilators, antiplatelet drugs and prostaglandin, but despite the treatment, ischemic changes became evident (Fig. 1A). In August 2009, chemotherapy was discontinued and the patient was hospitalized for treatment of the digital ischemia. Coagulation tests (prothrombin time, partial prothrombin time, fibrinogen, D-dimer) revealed no significant abnormalities except for a slightly prolonged prothrombin time (international normalized ratio of 1.32). Ultrasound tests performed in September 2009 revealed no vessel disease in the lower extremities.

Initially, the patient was treated with prostaglandin, vasodilators, antiplatelet drugs and antithrombin, but these
treatments brought about no improvements. Next, bosentan hydrate was administered and a sympathetic nerve block was implemented, but again neither of these treatments yielded any improvement in the digital ischemia. The digital ischemia progressively worsened and in September 2009 gangrenous changes developed in multiple fingers and toes (Fig. 1B). Because the digital ischemia was not complicated with infection, amputation was not performed. The digital ischemia stabilized after December 2009, but the patient died from multiple organ failure in January 2010.

DISCUSSION

To the best of our knowledge, this is only the third reported case in the English-language literature of an SSc patient developing digital necrosis after chemotherapy (5,6) (Table 1). In all three cases, gemcitabine was included in the chemotherapy regimen, and digital necrosis developed 3, 16 and 27 weeks after chemotherapy began, respectively. All three patients eventually developed gangrenous changes in spite of the best available treatment for the digital ischemia, whereas complete recovery from digital ischemia after chemotherapy has been reported for patients without SSc (6). Gemcitabine is known to cause digital ischemia in patients without SSc, with the vascular toxicity thought to be due to its causing endothelial damage or a hypercoagulable state (5–7). We could not find any reports in the literature documenting digital ischemia following S-1 treatment. In the present case it is not possible to conclude which agent played the greater role in the development of ischemia; determining whether gemcitabine is associated with a higher risk of vascular toxicity compared with other anti-cancer drugs in SSc patients requires further study.

In the present case, we cannot rule out the possibility that factors other than chemotherapy were involved in the development of digital ischemia. The patient had a history of smoking and diabetes mellitus, both of which could have increased the risk of digital ischemia. However, the diabetes mellitus had been well controlled for the past 16 years, and he had no diabetic retinopathy or nephropathy. Furthermore, ultrasound tests performed in September 2009 revealed no vessel disease in the lower extremities. Therefore, diabetes mellitus was unlikely to have been the main cause of the digital ischemia. Furthermore, considering that the patient had experienced no symptoms of digital ischemia over the previous 6 years, and had undergone a progressive clinical course in spite of aggressive treatment, we strongly suspect that chemotherapy triggered or aggravated the digital ischemia in this patient. Given that the digital ischemia had stabilized several weeks before the patient’s death, and the fact that there was no sepsis, it was unlikely to have been directly responsible for his death.

Vascular toxicity is a rare but serious side effect of chemotherapy (4–9). The precise incidence is unknown, and the mechanism by which chemotherapy causes digital necrosis in patients with SSc remains unclear, but in the light of previous case studies, the present findings strongly suggest that physicians should be very cautious about administering chemotherapy, especially gemcitabine-based chemotherapy, to SSc patients. The resulting digital ischemia might be refractory to conventional treatment and worsen progressively, even if chemotherapy is withdrawn at an early stage in the development of digital ischemia.

Table 1. Published case reports of digital necrosis following chemotherapy in patients with systemic sclerosis (SSc)

<table>
<thead>
<tr>
<th>Demographic and clinical features</th>
<th>Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (years)</td>
<td>Cloese et al. (8)</td>
</tr>
<tr>
<td>Patient sex</td>
<td>Female</td>
</tr>
<tr>
<td>Primary disease</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>SSc manifestation</td>
<td>Sclerodactyly, Raynaud’s phenomenon, sicca syndrome, esophageal involvement, carpal tunnel syndrome</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>Gemcitabine and carboplatin</td>
</tr>
<tr>
<td>Time of onset</td>
<td>3 weeks</td>
</tr>
<tr>
<td>Treatment for digital ischemia</td>
<td>Calcium channel blocker, prednisolone, cephalaxin, gabapentin, stellate ganglion block</td>
</tr>
<tr>
<td>Outcome</td>
<td>Gangrenous changes (amputation)</td>
</tr>
</tbody>
</table>

*Time of onset after start of chemotherapy.*
Conflict of interest statement

None declared.

References