—Case Reports—

A Case of Gastric Cancer with Perforation Caused by Chemotherapy with Docetaxel and S-1

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Abstract

We treated a patient who had gastrointestinal perforation during chemotherapy with docetaxel and S-1 which was successfully treated with percutaneous drainage. A 66-year-old man was admitted to our hospital with complaints of abdominal pain. Gastric cancer (T3N1M0) had been diagnosed 3 years earlier, and distal gastrectomy had been performed. Two years later, intrapelvic recurrence of the cancer was diagnosed. We administered docetaxel and S-1. After 3 courses of chemotherapy, he complained of abdominal pain of sudden onset. Computed tomography showed free air and limited ascites, and gastrointestinal perforation was diagnosed. We performed percutaneous drainage. The abdominal pain improved 3 days later, and he was able to eat meals 15 days after the onset of abdominal pain. He was discharged 27 days after admission. Because the patient's general condition was poor, we started providing best supportive care only. He died 10 months after the perforation was found.


Key words: gastric cancer, gastrointestinal perforation, docetaxel, S-1

Introduction

Gastric cancer is the most common malignancy in Japan. At present, the only potentially curative treatment is surgical resection; however, recurrence is common, both locally and at distant sites. The standard treatment for advanced or relapsed gastric cancer is chemotherapy, which aims to prolong survival. Compared with best supportive care, chemotherapy appears to increase median survival. However, chemotherapy may induce febrile neutropenia, gastrointestinal bleeding, and gastrointestinal perforation.

In particular, perforations that occur during chemotherapy are life-threatening because of immunosuppression. The mortality rate of surgery for perforated gastric cancer during chemotherapy is 40% to 80%, and some patients die of sepsis, myelosuppression, or hypoproteinemia. The prognosis of patients receiving chemotherapy is poorer than that of patients who are not treated with an anticancer agent.

Docetaxel and S-1 are key drugs for gastric cancer chemotherapy, and S-1 is the drug used most frequently for gastric cancer in Japan. We report on a patient with gastric cancer in whom spontaneous gastrointestinal perforation occurred during
chemotherapy with docetaxel and S-1.

Case

A 66-year-old man was admitted to our hospital with complaints of abdominal pain. An abdominal X-ray film revealed free air under the diaphragm (Fig. 1a), and computed tomography (CT) confirmed the free air (Fig. 1b) and showed limited ascites (Fig. 1c).

Gastric cancer had been diagnosed 3 years earlier. An upper gastrointestinal series showed advanced gastric cancer (type 2) in the angulus. Histopathological analysis revealed a well-differentiated adenocarcinoma. However, CT showed no metastatic lesions in the liver or lungs. Distal gastrectomy (Billroth II) was performed (T3N1M0, stage IIIA). Two years after the operation, intrapelvic recurrence of the gastric cancer was diagnosed (Fig. 2). As first-line chemotherapy, S-1 (100 mg/body) was administered for 2 months, but treatment was stopped owing to a marked loss of appetite. As second-line chemotherapy, paclitaxel (80 mg/m²) and cisplatin (25 mg/m²) were administered biweekly for 4 months. Widespread skin eruptions developed mainly on the upper limbs and were diagnosed as an allergic reaction to paclitaxel or cisplatin. Therefore, third-line chemotherapy was started with docetaxel (40 mg/m²) administered on days 1 and 8 and S-1 (100 mg/body) administered on days 1 to 14 every 21 days. We also administered granisetron (3 mg) and dexamethasone (8 mg) to prevent allergic reactions. Generally, treatment to prevent an allergic reaction to docetaxel is not required. However, we were worried about an allergic reaction to docetaxel because the patient had had an allergic reaction to

Fig. 1  a: Abdominal plain roentgenogram at the onset of abdominal pain. The arrow indicates a soft drain inserted in the epigastric region.  
b: CT at the onset of abdominal pain. The arrow indicates free air.  
c: CT at the onset of abdominal pain. There was small amount of ascites fluid (arrow).

Fig. 2  CT at the time of recurrence. The arrow indicates a recurrent tumor.
concluded that the perforation was minor. In addition, a systemic inflammatory response syndrome had not developed, and the recovered fluid did not contain fecal matter. We concluded that perforation was not in the colon. However, we believed that digestive tract perforation had occurred because culture of the ascites fluid yielded *Escherichia coli* and *Streptococcus salivarius*.

The abdominal symptoms had improved after 3 days, and the patient was able to tolerate oral feeding 15 days after the perforation was found. A CT examination 3 weeks later (Fig. 3) showed no ascites, metastasis to the liver, or intra-abdominal masses. Although gastroduodenal endoscopy was important for planning the treatment after the perforation healed; at that time, we were concerned about applying great pressure to the perforation site.

The patient was discharged from the hospital 27 days after the perforation was found. Because his general condition was poor (Eastern Cooperative Oncology Group performance status, 2), we provided best supportive care only. He died of peritonitis carcinomatosa 10 months after the perforation was found.

### Discussion

The present case is, to our knowledge, the second reported case of gastrointestinal perforation developing during chemotherapy with docetaxel and S-1 for gastric cancer. Only a single case of gastric

| Table 1 |
|-----------------|----------|
| White blood cell count | 10.630 /μL |
| Red blood cell count | 363 /μL   |
| Hemoglobin         | 11.8 /μL  |
| Hematocrit         | 34.6 %    |
| Platelet count     | 15.7×10⁴ /μL |
| Total protein      | 6.1 g/dL  |
| Albumin            | 3.7 g/dL  |
| Blood urea nitrogen| 24.9 mg/dL|
| Creatinine         | 1.25 mg/dL|
| Aspartate aminotransferase | 35 U/L |
| Alanine aminotransferase | 28 U/L |
| Lactate dehydrogenase | 210 U/L |
| Na                 | 137 mEq/L |
| K                  | 5.3 mEq/L |
| Cl                 | 100 mEq/L |
| C-reactive protein | 6.48 mg/dL|

Fig. 3 CT 3 weeks after onset. There was no ascites.
perforation occurred among patients who had participated in a phase I clinical trial of S-1 and weekly docetaxel®.

Oncological gastrointestinal perforation can be due to the following causes®. The first is spontaneous tumor rupture. When the tumor progresses rapidly, it can perforate the gastrointestinal tract. The second is rapid tumor shrinkage and necrosis due to chemotherapy. The third is drugs, such as anticancer agents or corticosteroids, that are administered to prevent side effects.

CT showed no tumor progression, neither when the perforation was found nor 3 weeks later. We concluded that rapid tumor shrinkage was not the cause of the perforation because CT images obtained 3 months earlier did not show a large mass. We could not rule out adverse effects of S-1, docetaxel, and corticosteroids as causes of the perforation.

The mechanism by which cancer chemotherapies induce gastrointestinal injury is incompletely understood. Such injury is thought to result from a combination of factors, including intestinal epithelial cytotoxicity, inflammation, ulceration, and increased bowel-wall permeability®.

S-1 is an oral fluoropyrimidine (5-FU) and is the drug most commonly used for gastric cancer chemotherapy in Japan. There is no direct evidence that 5-FU causes perforation of the gastrointestinal tract. However, 5-FU is toxic to the gastrointestinal mucosa and induces gastroduodenal ulceration, gastritis, and duodenitis®.

Colucci et al. have reported a case of colonic perforation caused by the combination therapy of docetaxel, cisplatin, and 5-FU®. Rose and Piver have reported 14 cases of gastrointestinal perforation with a 57% mortality rate during the period of chemotherapy with paclitaxel, which has a similar structure to docetaxel®. They described the possibility that paclitaxel can induce duodenal necrosis and gastritis. That is, S-1 or docetaxel may cause perforation, and which drug causes the perforation cannot yet be determined.

In addition, we must also consider the effect of corticosteroids. Corticosteroids have been associated with severe complications involving the gastrointestinal tract. Gastrointestinal perforation is a life-threatening complication in corticosteroid-treated patients and has high rates of mortality and morbidity. Perforations of peptic ulcers and of colonic diverticula are the most frequent complications®. Dayton et al. have reported on 8 patients with gastroduodenal perforation who were treated with corticosteroids®. Moreover perforation can be cause by S-1, docetaxel, or corticosteroids, and there were no findings ruled out the possibility that 1 of the 3 drugs had caused perforation.

Identifying the perforation site is important for treatment planning. However, the present patient and his family wished only for palliative care after he recovered; therefore, we did not perform gastroduodenal endoscopy. The properties of the ascites fluid were similar to those of the fluid drained through a gastric tube, and enteric bacteria were detected through culture of the ascites fluid. These findings suggest perforation of the upper digestive tract.

Percutaneous drainage is effective for treating mild ascites and mild inflammation resulting from perforation. Percutaneous drainage has localized effects but is less invasive than other treatments. Septic shock did not develop, the abdominal findings were limited to the epigastric region, and we diagnosed gastric perforation, not colorectal perforation. Thus, we chose to perform percutaneous drainage. In cases of colorectal perforation or panperitonitis leading to septic shock, percutaneous drainage should not be selected.

It is important to observe the course of treatment carefully, and if percutaneous drainage is insufficient, open drainage should be considered. This strategy is recommended for unresectable gastric cancer, and avoidance of an invasive procedure allows chemotherapy or palliative care to be started immediately. As a matter of course, gastrectomy is an important option for radically resectable gastric cancer causing perforation.

Conflict of Interest: The authors have no conflicts of interest to declare.
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References


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