Abstract

The first patient, a 68-year-old woman, presented neutropenic fever and hemorrhagic diarrhea on the sixth day of a combination chemotherapy of carboplatin and paclitaxel. The second patient, a 30-year-old man, presented neutropenia and diarrhea on the tenth day of the second cycle of a combination chemotherapy of cisplatin and vinorelbine. In both patients, abdominal computed tomography scan showed thickening of the colon wall and pericolic edema, and the ultrasonography revealed echogenic thickening of the colon walls. These findings confirmed the diagnosis of neutropenic enterocolitis. After the treatments, we changed the anticancer drug regimen; and successfully achieved partial responses.

Key words: neutropenic enterocolitis, lung cancer, chemotherapy

Introduction

Non-small cell lung cancer (NSCLC) is moderately sensitive to the currently available cytotoxic drugs. Patients treated with cisplatin-based regimens showed a 27% reduction in risk of death compared with best supportive care, equivalent to a 10% absolute improvement in 1-year survival or a 1.5-month increase in median survival (1). In recent years, several new active agents such as paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan have demonstrated promising antitumor activity against NSCLC. In recent phase III trials in advanced NSCLC, the combination of carboplatin and paclitaxel was equally effective, less toxic and better tolerated than other treatments (2). In addition, the combination of cisplatin and vinorelbine produced an equivalent response rate and survival for the combination of carboplatin and paclitaxel (3).

Neutropenic enterocolitis was first reported as submucosal hemorrhage and appendiceal perforation in children with leukemia in 1933 (4). Neutropenic enterocolitis may involve the intestinal mucosa of terminal ileum, ascending colon and cecum. The term typhlitis is also used for enterocolitis that is confined to the appendix. The pathogenesis of neutropenic enterocolitis had been explained as follows: anticancer drugs induce necrotizing inflammation of the colon, followed by invasion of bacteria into the damaged mucosa and their rapid proliferation because of neutropenia. Moreover, the production of bacterial endotoxins could induce intramural hemorrhage, ulceration, ischemia, and, in some cases, necrosis and perforation of the bowel wall (5).

A variety of solid tumors are treated with combination therapy that induces neutropenia, there are a few case reports of neutropenic enterocolitis. Since the introduction of new drugs for NSCLC described above, occurrences of this complication, especially in association with taxanes and vinca alkaloid drugs, have been noted in several clinical studies (6–11). Early diagnosis and appropriate treatment is important because neutropenic enterocolitis may be lethal.

We describe two cases of neutropenic enterocolitis with findings of computed tomography and ultrasonography and summarize the previous reports of this condition associated with taxanes or vinca alkaloid.

Case Reports

Case 1

A 68-year-old woman was diagnosed as having adeno-
carcinoma of the lung with multiple bone metastases. She was treated with palliative radiation therapy for multiple bone metastases on June 19, 2002, and with a combination chemotherapy of carboplatin (at a dose calculated to produce an area under the concentration-time curve of 6.0 mg per milliliter per minute based on Calvert’s formula) and paclitaxel (210 mg/m²) on the next day. She presented with grade 4 hemorrhagic diarrhea with abdominal pain, and fever [defined according to the National Cancer Institute Common Toxicity Criteria: NCI-CTC (12)] on the sixth day of the first course. Her laboratory findings were as follows: leukocyte count 2,050/μl (neutrophil 1,350/μl), C-reactive protein 8.4 mg/dl and lactate dehydrogenase 2,102 IU/l. Her stools were negative for Clostridium difficile. Abdominal computed tomography (CT) scan showed nonspecific colon distention with thickening of the wall throughout the colon (Fig. 1A). The abdominal ultrasonography (US) revealed the echogenic thickening of the colon walls, and the swelling being especially dominant from the cecum to the hepatic flexure. The thickness of the colon wall was measured at 10.8 mm (Fig. 1B). These findings supported the diagnosis of neutropenic enterocolitis. The patient was treated with broad-spectrum antibiotics (cefepime dihydrochloride 1 g every 12 hours) for 11 days, total parenteral nutrition, rhG-CSF, anti-thrombin III and gabexate mesilate. She started to improve on the sixth day after appearance of the symptoms, and as a result of the treatments, his symptoms and radiological findings were normalized. We changed the anticancer drug regimen to single-agent gefitinib and he achieved a partial response.

Case 2
A 30-year-old man was diagnosed as having adenocarcinoma of the lung. He was treated with a combination chemotherapy of cisplatin (80 mg/m²) and vinorelbine (15 mg/m² on days 1, 8 and 15) on April 16, 2002. He presented with grade 3 diarrhea, abdominal pain, and fever (NCI-CTC) on the tenth day of the second cycle of the chemotherapy. The laboratory findings were: leukocyte count 1,200/μl (neutrophil 1,350/μl), C-reactive protein 8.4 mg/dl and lactate dehydrogenase 2,102 IU/l. Her stools were negative for Clostridium difficile. Abdominal computed tomography (CT) scan showed nonspecific colon distention with thickening of the wall throughout the colon (Fig. 2A). Abdominal US revealed echogenic thickening of the colon walls, and the swelling being especially dominant from the cecum to the hepatic flexure. The thickness of the colon wall was measured at 12.5 mm (Fig. 2B). These findings supported the diagnosis of acute neutropenic enterocolitis with disseminated intravascular coagulation. The patient was treated with broad-spectrum antibiotics (cefepime dihydrochloride 1 g every 12 hours) for 11 days, total parenteral nutrition, rhG-CSF, anti-thrombin III and gabexate mesilate. He started to improve on the tenth day after appearance of the symptoms, and as a result of the treatments, his symptoms and radiological findings were normalized. We changed the anticancer drug regimen to single-agent gemcitabine and he achieved a partial response.

Discussion
The previous cases and the cases of neutropenic enterocolitis induced by chemotherapy of the NSCLC are summa-
rized in Table 1. A total of 7 patients were found: The patient’s age ranged from 30 to 70, and there were 6 men and a woman. Four patients were treated with a single agent. The onset of symptoms varied from day 5 of the first cycle to day 10 of the seventh cycle of chemotherapy. Four patients underwent abdominal CT for diagnosis. All of the patients had abdominal pain, and 4 patients had hemorrhagic diarrhea. Two patients were treated only with antibiotics, and 5 patients were treated with antibiotics and rhG-CSF support. Two patients (cases 4, 5) died on the single-agent regimen of docetaxel.

In the previous phase II studies evaluating a single-agent regimen of paclitaxel or docetaxel, the incidence of mucositis or diarrhea (grade 3 or more) was at most 6% (range 0–6%) (13, 14). However, several cases of neutropenic enterocolitis have been reported in patients with solid tumors treated with taxane-based combination chemotherapy (6–11), and single-agent vinorelbine chemotherapy (8). Pestalozzi et al (7) described 2 patients with acute typhlitis associated with chemotherapy for metastatic breast cancer, on a regimen of combined paclitaxel and doxorubicin. It is noteworthy that these 2 patients continued with the same medication, at a lower dose, without a recurrence of symptoms. In the present 2 cases, however, we changed the regimen because of the severe hematological toxicity and severe gastrointestinal toxicity. In the recent phase II study, single-agent gefitinib or gemcitabine has shown a relatively mild toxicity profile in chemotherapy-naive patients, and a second-line treatment with single-agent gemcitabine or gefitinib was reported to yield a tumor response rate of 19% or 18.4%, respectively (15, 16). We were able to confirm this mild hematological toxicity profile in the second-line treatment setting.

Concerning CT and US investigations, these are non-invasive examinations, which are useful for the diagnoses. Previous reports indicated that the typical CT findings were...
thickening of the colon wall and signs of pericolic edema (17, 18). In the US examination with the high frequency probe, three layers, a mucous membrane layer, mucous membrane lower layers and muscle layers are easy to discern in the colon wall of healthy individuals. In the present patients, the US findings were mural thickening with different patterns of healthy individuals, such as complete effacement of the lumen with no discernible layers in the wall or reduced numbers of layers along with resolution in a heterogeneous zone of medium echogenicity. The degree of bowel thickening was correlated significantly with the outcome of patients with neutropenic enterocolitis. In particular, 60% of patients with a colon wall thickness of more than 10 mm died from this complication (19). We could successfully treat both patients, although the colon wall thickness was beyond 10 mm.

Sufficient attention for neutropenic enterocolitis is necessary in lung cancer chemotherapy. We emphasize the importance of symptoms such as abdominal pain and tenderness, fever and diarrhea in patients treated with anticancer drugs. These symptoms should be managed immediately and aggressively in the consideration of acute neutropenic enterocolitis. In such patients, both CT and US would be useful for the diagnosis.

References