Case report

Effectiveness of doxifluridine (5'-DFUR)/docetaxel against advanced/recurrent gastric cancer showing resistance to various anticancer drug regimens

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Abstract

A 58-year-old man was diagnosed as having type 3 gastric cancer (poorly differentiated adenocarcinoma). He underwent total gastrectomy with splenectomy, as well as D3 dissection, and received postoperative chemotherapy combining oral uracil and futrafur (UFT) with cisplatin (CDDP), but results showed recurrence of multiple abdominal lymph node metastases around the aorta. He therefore received various anticancer drug regimens (irinotecan [CPT-11]/CDDP; 1M tegafur-0.4M gimeracil-1M oteracil potassium [TS-1], methotrexate (MTX)/5-fluorouracil); however, final results showed growth of lymph node metastasis and simultaneous worsening of his general condition. The patient then received combined administration of doxifluridine (5'-DFUR)/docetaxel (5'-DFUR, 1000 mg/body [666.7 mg/m²], given by consecutive daily administration, orally, for days 1–14; and docetaxel, 80 mg/body [60 mg/m²], on day 8, by venous drip, every 3 weeks). Three courses of this regimen resulted in approximately 90% reduction of the abdominal lymph node size, disappearance of the right cervical lymph node metastasis, reductions of the levels of two tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA]19-9), and improvement of his general condition. In total, seven courses of the regimen were carried out. The patient died on day 298 after starting this combined regimen and showed a response period of 126 days. The primary toxicity identified was neutropenia (grade 4), as well as other low-grade (grade 1, 2) hematological and nonhematological toxicities. In the field of gastric cancer treatment, especially for patients showing multiple resistance to anticancer drugs, an effective therapy is critically needed.

Key words Gastric cancer · Docetaxel · Doxifluridine · Combination chemotherapy · Multidrug resistance

Introduction

Although various combined chemotherapies have been in use for patients with advanced recurrent gastric cancer, there are few effective regimens available for clinical use. There are hardly any reports published on the efficacy of second- or third-line therapies in patients who have relapsed into progressive disease. A new drug regimen is thus strongly needed in the field of gastric cancer treatment, especially for patients that do not respond to conventional regimens.

We report here a patient with postoperative recurrent gastric cancer who showed ineffective results from various combined chemotherapies, but responded well to a new regimen with doxifluridine (5'-DFUR)/docetaxel.

Case report

The patient, a 58-year-old man, underwent total gastrectomy with splenectomy and D3 dissection on May 19, 1999. His tumor was judged as type 3 according to the macroscopic evaluation criterion designated by the *Japanese classification of gastric carcinoma* [1] and was found to exist at sites from the upper body of the stomach to the lower part of the lesser curvature. Histopathological examination of the resected specimens showed poorly differentiated adenocarcinoma, infiltrating into the muscularis propria, without vascular permeation, but with noticeable lymphatic permeation and perigastric lymph node metastasis. Neither peritoneal nor liver metastasis was observed (P0, H0, T2, [MP], N1, v [–], ly [++]). His past and family histories were of no concern.

Earlier chemotherapy courses (Figs. 1, 2)

Postoperatively, from June 21 to September 3, 1999, two courses of adjuvant chemotherapy with uracil and

Fig. 1. Clinical course of the patient. CEA, Carcinoembryonic antigen; CA-19-9, carbohydrate antigen 19-9; UFT/CDDP, uracil and futrafur/cisplatin; CPT-11, irinotecan; TS-1, 1M tegafur-0.4M gimeracil-1 M oteracil potassium; MTX-5-FU, methotrexate-5-fluorouracil; 5-DFUR/TXT, doxifluridine/docetaxel

Fig. 2A–F. Computed tomography (CT) scans. **A,C,E** Right cervical lymph node; **B,D,F** abdominal lymph node. **A,B** Before combination chemotherapy with 5'-DFUR/TXT. **C,D,E,F** After combination chemotherapy with 5'-DFUR/TXT (**C** day 72; **D** day 64; **E** day 177; **F** day 134)

futrafur (UFT)/cisplatin (CDDP) [2] were conducted (course 1, UFT, 500mg/body [360mg/m²], days 1–21; and CDDP, 100mg/body [66.7mg/m²], day 8. Course 2, UFT, 400mg/body [266.7mg/m²] days 1–21; and CDDP, 80mg/body [53.3mg/m²], day 8). The results showed the occurrence of multiple abdominal lymph node me-

tastases around the aorta on October 26, 1999, i.e., on day 53 after completing the postoperative adjuvant chemotherapy.

From November 4, 1999 to February 22, 2000, six cycles of combined chemotherapy with irinotecan (CPT-11)/CDDP [3] were administered every 2 weeks

(CTP-11, 84mg/body [60mg/m²]; CDDP, 42mg/body [30mg/m²]; total dose, CPT-11, 418mg; CDDP, 184mg). The results showed a partial response (PR; duration of response, 59 days) on computed tomography (CT) images, followed by both increased levels of tumor markers and the occurrence of abdominal lymph node enlargement.

From February 29 to May 16, 2000, the TS-1 (1M tegafur-0.4M gimeracil-1M oteracil potassium) regimen was carried out at 80–100mg/day, being administered on days 1–28, then discontinued for 14 days, for a total dose of TS-1 of 5440mg [4]. The results showed minor response (MR) on CT images, but, on May 16, 2000, the patient developed a metastatic focus in the right cervical lymph node (newly developed lesion).

From May 19 to July 11, 2000, time-lag alternating administration of methotrexate (MTX)/fluorouracil (5-FU) [5] was conducted every 2 weeks (MTX, 140mg/body; 5-FU, 840mg/body, with calcium folinate added as a toxicity-reducing measure. Total dose, MTX, 700mg; 5-FU, 4200mg). Results included: enlargement of abdominal lymph node; on July 25, 2000, a newly developed metastasis on the right axillary lymph node; and, at the same time, the patient's general condition worsened, according to the Eastern Cooperative Oncology Group (ECOG) performance status (PS), from grade 0 to 2, indicating progressive disease (PD).

Courses of combined chemotherapy with 5'-DFUR/docetaxel (Figs. 1, 2)

From July 18, 2000, combined chemotherapy with 5'-DFUR/docetaxel was started. One course of the regimen consisted of 5'-DFUR, 1000mg/body (700mg/m²), oral administration for 2 consecutive weeks (days 1–14), discontinuation of the regimen for a week; and docetaxel, 80mg/body (60mg/m²) administered by intravenous drip on day 8, every 3 weeks. After two courses of this regimen, the results showed 81% reduction of the abdominal lymph node tumor (from 5.0 × 4.3 to 3.5 × 3.7cm) and 40% reduction of the right cervical lymph node tumors (from 2.9 × 2.6 and 3.4 × 2.7 to 1.7 × 1.3 and 1.0 × 0.9cm). A further three courses of the regimen were given, resulting in approximately 90% reduction of the abdominal lymph node (1.1 × 0.8 to 1.2 × 0.7cm) and disappearance of the right cervical lymph node (Fig. 2A, B). The results also showed reductions in levels of two tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA]19-9), and improvements in his general condition from grade 2 before drug administration to grade 0 from the second course. The abdominal lymph node reduction and right cervical lymph node disappearance persisted. However, from

January 2001, bone marrow metastasis worsened and left hydronephrosis appeared. Thus, the condition of disease was evaluated as aggravated, and the combined drug administration was terminated after seven courses in total. The final response period lasted for 126 days; the patient died on day 298 after starting this combined regimen. As for hematological toxicity, leukocytopenia (grade 2) and neutropenia (grade 4) appeared from day 7 of the treatment, for which granulocyte colony-stimulating factor (G-CSF) was used in every course of the drug administration. Although a decrease in hemoglobin level (grade 2) was observed from day 7 of the treatment, no blood transfusion was conducted. Non-hematological toxicity included fever (grade 1), fatigue (grade 2), dysgeusia (grade 2), alopecia (grade 2), anorexia (grade 1), and nausea (grade 1). To control these toxicities, the patient was given an oral steroid, which decreased fever, fatigue, anorexia, and nausea. All other adverse events were within permissible limits. Efficacy of the combined regimen was assessed according to the "General rules for gastric cancer study" of the Japanese Research Society for Gastric Cancer (1995) [6], and toxicity associated with the regimen was evaluated according to the National Cancer Institute Common Toxicity Criteria, Version 2.0 (NCI-CTC, ver. 2.0) [7]. The patient was sufficiently advised of the combined drug treatment and his informed consent was obtained before the start of therapy.

Discussion

Docetaxel is a newly developed anticancer drug that has a mechanism of action to promote tubulin polymerization and to inhibit the depolymerization of microtubules. In a phase II study conducted in Japan with the drug for patients with advanced gastric cancer, 80mg/body (60mg/m²) of docetaxel was given to the patients by drip infusion once every 3 to 4 weeks. The results showed a response rate of 23.7% (14/59 patients). 5'-Deoxy-5-fluorouridine; (generic name, doxifluridine; 5'-DFUR), which is a prodrug and an intermediate metabolite of capecitabine, is converted by pyrimidine nucleoside phosphorylase (PyNPase) to 5-FU and shows antitumor activity [8,9]. In a phase II study conducted in Japan, 5'-DFUR was given orally to gastric cancer patients at repeated doses of 800–1200mg/day. The results showed a response rate of 14.3% (20/140 patients) [10]. The drug was also shown to be useful in treating patients with other solid cancers [11–15].

In a recent basic study, docetaxel and several other anticancer drugs reportedly induced thymidine phosphorylase (TP), one type of PyNPase, in tumor tissues [16]. Furthermore, in tumors showing induced levels of

TP, concomitant administration of docetaxel and 5'-DFUR demonstrated a stronger synergistic efficacy than had been observed when other drugs were used. Animal studies comparing the effects of drug regimens, including 5'-DFUR, administered consecutively for 14 days, and combined single administrations of docetaxel on days 1, 8, or 15 showed that the strongest inhibitory effect on tumor growth occurred with the combined regimen on day 8 [17,18]. Based on this finding, clinical phase II and III studies were conducted in the breast cancer field, in which 5'-DFUR (14 consecutive days' administration) combined with docetaxel (administered on day 8) was repeatedly given every 3 weeks. From these results, it was recommended to administer the two drugs at the respective doses of 800mg/day and 60mg/m².

We employed this combined regimen for the present patient with advanced recurrent gastric cancer, and we obtained good results. This patient had received various anticancer drugs, including 5-FU and its derivatives, in previous regimens. Although shrinkage of tumors was identified, every one of them progressed to regrowth. It should be noted, however, that with this combined regimen, the patient showed a reduction of tumor size and improvement of his general condition. Yet, on the other hand, it was not clear why the combined treatment with 5'-DFUR/docetaxel showed efficacy. This result may be related to findings reported by basic studies whereby TP was induced by docetaxel [16] or the apoptosis-relating factor, Bcl2/Bax ratio, was reduced by capecitabine/5'-DFUR [19], both of which could enhance the antitumor effects of 5'-DFUR and docetaxel when used concomitantly. In the present, patient, because 5-FU or its derivatives had been administered in the previous three regimens, it may be assumed that docetaxel was responsible for the response of the patient, but at the same time, synergistic effects with fluorouracil may also be assumed to be responsible for the response.

Although the usefulness of anticancer drug treatment in patients with gastric cancer has been proven, the level of the sustained effect in prolonging life with anticancer drugs is insufficient. It is thus essential to establish more effective drug regimens and to introduce effective treatment for patients that show resistance to anticancer drugs. The present report suggests significant clinical evidence to support the idea that a combined regimen with 5'-DFUR/docetaxel could be an effective post-operative treatment for patients with advanced gastric cancer. But it should be noted at the same time that the present patient developed grade 4 neutropenia during every drug administration course; thus, patients receiving the combined drug therapy should be sufficiently monitored during the treatment courses. On the basis of the concept described above, we are conducting a clinical phase I study.

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