[原著] A pilot study of docetaxel and TS-1 combination chemotherapy for advanced gastric cancer

A pilot study of docetaxel and TS-1 combination chemotherapy for advanced gastric cancer

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ABSTRACT

PURPOSE: The aim of this study was to assess the efficacy and safety of combination chemotherapy with docetaxel and TS-1. PATIENTS AND METHODS: Five patients with advanced gastric cancer were treated with a combination chemotherapy regimen consisting of docetaxel and TS-1. All patients had undergone prior chemotherapy. Docetaxel at a dose of 30 mg/m^2 was intravenously administered on Day 1 and 8, and TS-1 at a dose of 80mg/m^2/day was orally administered for 2 weeks followed by 1 drug-free week. RESULTS: Three of the 5 patients showed a partial response, of a response rate of 60%. Two of the 5 patients had stable diseases. One patient experienced grade 3 leukocytopenia, grade 2 diarrhea and grade 2 alopecia. In the other patients, only low grade toxicities (grade 1 or 2 leukocytopenia, neutrocytopenia and anemia) were seen. CONCLUSION: The combination chemotherapy of docetaxel and TS-1 was found to be effective and well tolerable by advanced gastric cancer patients. This combination may be useful as a second-line chemotherapy. *Ryukyu Med. J., 23(1, 2) 21～24, 2004*

Key words: docetaxel, TS-1, chemotherapy, gastric cancer

INTRODUCTION

Gastric cancer is a major intestinal health problem, with a particularly high incidence in Asia, Eastern Europe and tropical South America[1]. Advanced gastric cancer continues to demonstrate a poor prognosis and remains a leading cause of death from malignant neoplasms in these countries and also in Japan[2]. Advanced gastric cancer is considered to be poorly chemosensitive over a long period, although for patients with recurrent or unresectable gastric cancer, palliative chemotherapy is often the only therapeutic option[3-5]. In recent years, however, high response rates have often been achieved in gastric cancer chemotherapy using newly developed anticancer drugs or combination regimens[6].

Docetaxel is a tubulin-inhibiting agent of the taxane family with a broad anti-tumor activity, which acts as mitotic spindle poison and induces a mitotic block. The toxicity profile of docetaxel in gastric cancer is closely comparable to that seen in other types of tumor. TS-1 is a novel combination of the 5-FU prodrug tegafur with new modulating agents, namely 5-chloro-2,4-dihydropyrimidine (gimeracil, is an inhibitor of the catabolic enzyme dihydropyrimidine dehydrogenase) and potassium oxonate (oteracil, inhibits 5-FU phosphorylation in the gastrointestinal tract) at a molar ratio of 1:0.4:1. This drug has recently been approved for treatment of gastric cancer in Japan, based on the encouraging response rates in Japanese trials[7].

The combination of taxanes with CDDP and/-or 5-fluorouracil (or an oral substitute) has become very popular in the United States, where it is associated with good response rates and an effective palliation of symptoms[7]. Docetaxel and TS-1 are both

Table 1 Patient characteristics

Case no.	Gender	Age	Performance status	Disease status	Site of disease	Prior Chemotherapy
Case 1	Male	64	0	recurrence	Lymph node Peritoneum	TS-1
Case 2	Male	67	1	inoperable	Primary Peritoneum	docetaxel+5-FU+CDDP
Case 3	Male	75	0	inoperable	Primary Peritoneum	TS-1+CDDP
Case 4	Male	76	0	inoperable	Primary Liver Lymph node	TS-1+CDDP
Case 5	Male	82	2	inoperable	Primary Lymph node Liver Lung	TS-1,TS-1+CDDP

active agents against gastric cancer and they have different mechanisms of action. It was thus hypothesized that this combination may provide an additive or synergistic effect against gastric cancer.

The aim of this study was to assess the efficacy and safety of a combination chemotherapy regimen using docetaxel and TS-1 in patients with advanced gastric cancer.

PATIENTS AND METHODS

Five male patients were recruited for this study. All patients were histologically proven to have locally advanced and/or metastatic gastric cancer with measurable or evaluable lesions. One patient had a recurrent gastric cancer and four patients had inoperable gastric cancer. All patients (Cases 1-5) had undergone prior chemotherapy: case 1 had received TS-1 chemotherapy, case 2 had received docetaxel+5-FU+CDDP chemotherapy, cases 3 and 4 had received TS-1+CDDP chemotherapy, and case 5 had received TS-1 and TS-1+CDDP chemotherapy. The patient's age ranged between 64 and 82 years (median, 72 years). Their World Health Organization (WHO) performance statuses (PS) were 0-2 with adequate organ functions. All the patients gave their informed consent before entering the study (Table 1).

Docetaxel was administered at a dose of 30 mg/m^2 by 2 hours intravenous infusion on Days 1 and 8, and TS-1 was orally administered at a dose of 80 mg/m^2/day daily for 2 weeks followed by 1 drug-free week. The combination therapy was repeated if no disease progression was observed. Three out of the 5 patients underwent the docetaxel and TS-1 combination chemotherapy as outpatients.

The measurement and evaluation of lesions were repeated by X-ray, computed tomography (CT), and ultrasonography. During the administration period, hematological tests such as WBC counts, biochemical tests such as liver and renal function tests and urinalysis were repeatedly conducted.

The major endpoints of this study were the response rate and the incidence of adverse reactions. The antitumor effects and adverse reactions were evaluated in accordance with the criteria of the Japanese Gastric Cancer Association[8].

RESULTS

Response rate

Cases 1, 3 and 4 showed responses to the Docetaxel and TS-1 combination chemotherapy. There was a complete response (CR) in no patients, a partial response (PR) in 3 patients, stable disease (no change; NC) in 2 patients, and progressive disease (PD) in no patients. The response rate was 60%

Table 2 Treatment response and adverse reactions

Case no.	Site of disease	Response	Adverse reaction		
			Items	Grade	Treatment
Case 1	Lymph node Peritoneum	Stable disease Not evaluable	leukocytopenia alopecia	1 1	
Case 2	Primary Peritoneum	Stable disease Partial response	leukocytopenia diarrhea alopecia	3 2 2	G-CSF Fluid therapy
Case 3	Primary Peritoneum	Partial response Not evaluable	leukocytopenia	2	
Case 4	Primary Liver Lymph node	Partial response Complete response Stable disease	anemia*	2	Blood transfusion
Case 5	Primary Lymph node Liver Lung	Stable disease Stable disease Stable disease Stable disease	leukocytopenia anemia	2 1	

G-CSF, granulocyte colony stimulating factor
* anemia occurred due to bleeding from the tumor

(Table 2). Especially in case 4, the primary tumor decreased in size and liver metastasis vanished after 2 courses of combination chemotherapy.

Toxicity

Almost all of the patients experienced only low grade toxicities (grade 1 or 2) of leukocytopenia, neutrocytopenia, anemia, and alopecia. No serious toxicities of the renal function, liver function, or febrile neutropenia, were observed. The toxicities of leukocytopenia, neutrocytopenia, and anemia improved after 1 or 2 drug-free weeks. Only one patient, case 2, experienced grade 3 leukocytopenia, grade 2 diarrhea and grade 2 alopecia (Table 2). This patient also suffered more severe side effects than those he experienced when he received docetaxel+5-FU+CDDP chemotherapy. He was administered human granulocyte colony stimulating factor. None of the patients died from the toxicities of docetaxel and TS-1 combination chemotherapy.

Outcome

Case 1 continued to undergo combination chemotherapy as an outpatient for 4 months, but his disease progressed and thus was submitted to other chemotherapy regimen.

Cases 2 and 3 were administered the combination chemotherapy as a neoadjuvant chemotherapy on admission and thereafter underwent a total gastrectomy after two courses of this combination chemotherapy.

Case 4 continued to undergo this combination chemotherapy as an outpatient for 6 months.

Case 5 continued to undergo the combination chemotherapy as an outpatient, but after 3 months his disease progressed. The chemotherapy was thus discontinued and palliative care was instead given. Unfortunately, he died of the disease one month later.

DISCUSSION

For patients with advanced gastric cancer, palliative chemotherapy is usually the only therapeutic option, since chemotherapy has been reported to have some survival benefits when compared with the best available supportive care[9-11]. Several new drugs, such as taxanes, TS-1, and CPT-11, have recently emerged as potential new options for gastric cancer[7,12]. Multidrug combination chemotherapies using these drugs have been tried in numerous studies.

Docetaxel and paclitaxel, novel taxoids which act as mitotic spindle poisons and induce a mitotic

block, have potent antineoplastic activities. These taxoids, when combined with cisplatin and/or 5-FU, showed response rates of more than 50%, and could thus be attractive anticancer agents for advanced gastric cancer[13,14]. They are also associated with an effective palliation of symptoms.

TS-1 is an oral formulation consisting of ftorafur (FT), which is a prodrug of 5-fluorouracil (5-FU); 5-chloro-2,4-dihydropyrimidine (CDHP); and potassium oxonate (OXO) at a molar ratio of 1:0.4:1. CDHP inhibits dihydropyrimidine dehydrogenase (DPD), an enzyme associated with the degradation of 5-FU, resulting in sustained concentrations of 5-FU in the blood.

Therefore, the combination of taxanes and TS-1 is expected to be superior to the combination of taxanes and 5-FU. Docetaxel and TS-1 are both active agents against gastric cancer and have different mechanisms of action. As a result, this combination may provide an additive or synergistic effect against gastric cancer.

In fact, this combination chemotherapy showed a high response rate in the present study. The combination chemotherapy of docetaxel and TS-1 was effective with a low incidence of grade 3-4 adverse events in 3 of the 5 patients with advanced gastric cancer who had undergone prior chemotherapy. Furthermore, three patients were administered the docetaxel and TS-1 combination chemotherapy regimen as outpatients.

In conclusion, the combination chemotherapy with docetaxel and TS-1 was found to be effective and well tolerable by advanced gastric cancer patients. It may be useful as a second-line chemotherapy.

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