J Korean Med Sci 1998; 13: 612-6
ISSN 1011-8934

Combination Chemotherapy of oral 5'-deoxy-5-fluorouridine and Cisplatin in Advanced Gastric Cancer: A Phase II Study

This study was designed to test the activity and feasibility of 5'-deoxy-5-fluorouridine (5'-DFUR) and cisplatin combination therapy in the treatment of advanced gastric cancer. Nineteen patients with inoperable and/or metastatic gastric cancer, which was histologically proven, were orally administered 5'-DFUR 1,200 mg/m^2 on days 1 to 4 and days 15-18 combined with 70 mg/m^2 of cisplatin being repeated every 4 weeks. Five partial responses (PRs) were achieved. Seven patients had stable disease and 6 progressed on therapy. The overall response rate was 27.7% (95% confidence interval: 9.69% to 53.5%). The median survival duration of all 18 patients was 25 weeks (9-64). The majority of patients had WHO grade I/II toxicity, but there was no treatment-related death. These data support that the combinations of oral 5'-DFUR and cisplatin are well tolerable and have a moderate activity with low toxicity in the treatment of advanced gastric cancer.

Key Words: *Stomach neoplasms; Floxuridine, 5'-DFUR; Cisplatin; Drug therapy, combination*

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Received: April 20, 1998
Accepted: July 21, 1998

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INTRODUCTION

Gastric cancer still remains a leading cause of cancer death in the world. Because the majority of patients reveal inoperable or metastatic disease at presentation, new chemotherapeutic agents with both high activity and low toxicity are needed to manage patients with advanced gastric cancer.

5'-deoxy-5-fluorouridine (doxifluridine, 5'-DFUR) is a synthetic prodrug of 5-fluorouracil (5-FU) (1). It is converted to active metabolite, 5-FU by pyrimidine nucleoside phosphorylase, mainly by uridine phosphorylase in mouse and by thymidine phosphorylase in human tumors, which are more abundant in tumors than in normal tissues except for the intestinal tract (2-4). The selective antitumor activity of 5'-DFUR has been shown to be mainly attributable to the unique tissue distribution patterns of the enzymes, responsible for its conversion to the active metabolite 5-FU (5). 5'-DFUR has been shown to have a therapeutic index that is 10 to 15 times greater than that of 5-FU or other fluoropyrimidines when tested against several experimental rodent tumors and also has less toxicity, including immunosuppressive activity (6-11).

The clinical use of intravenous 5'-DFUR as a bolus injection or short term infusion has been limited because of more severe and more frequent neurological toxicity compared to 5FU as well as unexpected cardiac toxicity (11). The bioavailability of oral 5'-DFUR is high and reproducible compared to that of 5-FU (6, 12). Experimental data in tumor-bearing rats treated with 5'-DFUR and 5-FU show a significant difference in therapeutic activity after the oral administration of these two agents (13). Previous studies using the intermittent oral administration of 5'-DFUR indicate that doses of between 1,000 and 1,400 mg/m^2 have antitumoral activity and an acceptable rate of side effects (14, 15).

Recently, combination therapies, including cisplatin have been investigated and are reported to have a high response rate in gastric cancer (16). Among them, the combined use of cisplatin and 5-FU was reported as exhibiting a synergistic effect in some basic studies and excellent clinical results have also been reported for the regimen with gastric cancer (17, 18). With a single agent of 5'-DFUR, its response rate against inoperable or recurrent gastric cancer was 14.3% (19). It has been reported that combination chemotherapy of 5'-DFUR and cisplatin showed a 50% response rate in gastric cancer (20).

We conducted a phase II study to investigate the efficacy and the toxicity of the combination therapy of

5'-DFUR and cisplatin in patients with advanced or metastatic gastric cancer.

MATERIALS AND METHODS

Patient eligibility

The criteria for eligibility included histologically confirmed inoperable advanced and/or metastatic gastric cancer. Patients have not been previously treated with any chemotherapy regimen. The patients also had to have a life expectancy of at least 4 weeks and a performance status ≤ 3 according to Eastern Cooperative Oncology Group criteria. Patients with severe intercurrent infections or metabolic disease, WBC count less than 4,000/μL, platelet count less than 100,000/μL, abnormal renal function (creatinine >1.5 mg/dL and blood urea nitrogen >50 mg/dL), and/or bilirubin level greater than 3 mg/dL, were excluded from the study. Of the 19 patients who entered the study, one patient was unable to be evaluated due to failure at follow-up after the first cycle. All patients gave informed written or oral consent before entry.

Staging and response assessment

Pretreatment evaluations, included a detailed medical history and physical examinations, blood test, complete blood chemistry, renal and hepatic function tests, chest X-ray, gastrofiberscopic examination, double contrast upper gastrointestinal radiographs, abdominal ultrasonograph or computed tomographic (CT) scan, ECG, and other diagnostic procedures appropriate to the extent of disease. All procedures performed baseline work-up and repeated at the time of response evaluation.

Treatment

Patients received oral 5'-DFUR 1,200 mg/m^2/day on days 1 to 4, and 15 to 18 and 70 mg/m^2 of cisplatin intravenous infusion on day 1, with the cycles being repeated every 4 weeks. 5'-DFUR was supplied in the form of 500 mg tablet. Antiemetic prophylaxis, including ondansetron 24 mg intravenous infusion on day 1, dexamethasone 10 mg iv push, and lorazepam 1.0 mg iv push and pre- and post-hydration with normal saline were prescribed for cisplatin infusion.

Evaluation of response and toxicity

Response to treatment was assessed every two cycles according to World Health Organization (WHO) criteria. A complete response (CR) was considered as the complete disappearance of all evident tumor as estimated by two observation not less than 4 weeks apart; partial response (PR) as a greater than 50% decrease in the cross-sectional areas of the measurable lesions; stable disease (SD) as a change of less than 25% in the extent of the disease, with no appearance of new lesions; and progressive disease (PD) as an increase of greater than 25% in the area of measurable disease or the appearance of new lesions. Side effects were graded according to WHO criteria and evaluated at the beginning of each cycle. In the case of grade III leukopenia or grade III diarrhea or mucositis, therapy was discontinued until recovery and then restarted at 50% of the dose. In the case of grade III toxicity at two consecutive evaluations or whenever grade IV toxicity was recorded, therapy was definitively stopped.

Statistical methods

The response duration was calculated from the time the response was achieved. Overall survival and time to treatment failure were calculated from the start of the treatment, and the curves of survival was plotted using the Kaplan-Meier method.

RESULTS

Patient characteristics

The patient characteristics are listed in Table 1. A total of 19 eligible patients were enrolled in the study and all the patients except one were assessable for response. All the patients had primary gastric cancer and seven of them with liver metastasis, six of them with distant lymph node metastasis, 11 of them with peritoneum.

Response to treatment

A total of 61 cycles were delivered, with a median of three for each patient (range, 1-6). After two cycles of chemotherapy, 5 partial responses (PRs) were achieved. Seven patients had stable disease and 6 progression on therapy. The overall response rate was 27.7% (5 of 18; 95% confidence interval: 9.7% to 53.5%) (Table 2). Responses were observed in liver (2 of 7), peritoneum (2 of 11), and lymph nodes (2 of 6), respectively.

The median duration of response was 20 weeks (range, 8-38) and the median time to progression was 13 weeks (range, 4-44). The median duration of survival was 25 weeks (range, 9-64) in evaluated patients (Fig. 1).

Table 1. Patient characteristics

Total number of patients	19
Male / Female	16 / 3
Age, years	
Median	59
Range	32-75
Performance status	
1	4
2	9
3	6
Previous treatment	
None	10
Palliative bypass	9
Site of metastasis	
Liver	7
Peritoneum	11
Distant lymph nodes	6
Others	1
Assessment	
Measurable disease	10
Evaluable disease	9

Toxicity

Toxicity was evaluated in all 19 patients receiving total 61 cycles of treatment. Treatment was well tolerated and acute side effects were manageable and reversible, and there was no cumulative side effects. As expected, the main toxicity was gastrointestinal such as 86.7% (53 of 61) of nausea/vomiting, 14.7% (9 of 61) of diarrhea and 29.5% (18 of 61) of mucositis confined to grade I/II, but only 1.6% (1 of 61) of patients had grade III vomiting. Only 3.3% (2 of 61) showed grade I leukopenia (Table 3). There was no toxic death associated with the treatment.

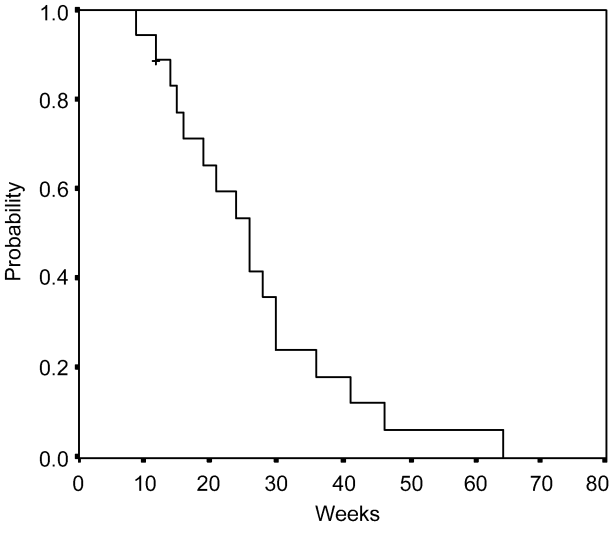

Fig. 1. Overall survival for all patients.

Table 2. Response to therapy

Evaluable	18
Total number of treatment	61
Median	3
Range	1-6
Response to treatment	
Partial Response	5
Stable Disease	7
Progressive Disease	6
Median duration of response (weeks)	20
Range	8-38
Median time to progression (weeks)	13
Range	4-44
Median duration of survival (weeks)	25
Range	9-64

Table 3. Incidence of side effects (total 61 treatments)

Side effects	WHO grade							
	I		II		III		IV	
	No	%	No	%	No	%	No	%
Nausea/Vomiting	33	54.0	20	32.7	1	1.6	-	
Diarrhea	8	13.1	1	1.6	-		-	
Stomatitis	8	13.1	10	16.4	-		-	
Leukopenia	2	3.3	-		-		-	
Neuropathy	1	1.6	-		-		-	

DISCUSSION

In our study, 5 of the 18 patients with inoperable and/or metastatic gastric cancer achieved 27.7% of response rates with combination of 5'-FUDR and cisplatin. Although the response rate is lower than the previous study of 5'-FUDR and cisplatin combination chemotherapy (20) in our study, this regimen was better than 5-FU alone or 5'-FUDR alone (19). There may be some explanations for our results. First, 31.6% of patients were poor performance status (ECOG$\leq$3) and over 70 years old patients (28%) were included. Second, no patients underwent palliative resection except bypass surgery for gastric cancer and any patient who recurred after curative resection was not included in our study, suggesting that most of the patients had a large tumor burden. Nevertheless, most of the patients were able to tolerate this regimen and there was no toxic death for the treatment. The majority of toxicity was mild and manageable. Koizumi et al. (20) reported 50% of response rate with oral 5'-DFUR and cisplatin combination chemotherapy, even though the dosage of 5'-DFUR and cisplatin was little higher than that of our study. These discrepancies may be attributed to the findings that patients with better performance and

lower tumor burden were included in the study.

The available data showed that recent more aggressive combination chemotherapy for advanced gastric cancer is capable of achieving 40-50% objective response rate according to the authors with marginal improvement in survival (21-24). Although some combination regimens achieved high remission rate, the toxicity of chemotherapy was essential. The combination chemotherapy of etoposide, doxorubicin, and cisplatin (EAP) has been reported to be effective in 43-64% of response rate, including 0-21% of complete response. However, the median survival has been limited to 6 to 9 months even in responders, and moreover there was severe side effects and high toxic death rate with the regimen (25-27).

In that sense, there may be some advantages for our regimen. Although we did not systematically analyze the quality of life, most of the patients were able to tolerate the regimen. And even half of the patients were able to receive chemotherapy on the outpatient basis. There also was no alopecia associated with this regimen. Moreover, there was no more than grade III toxicity in this regimen therefore, we were able to administer this treatment to the older and poor performance patients. Nevertheless, the median survival time with this regimen is comparable to other regimens.

In conclusion, we report that oral chemotherapy with 5'-DFUR and cisplatin combination chemotherapy might be an effective, safe, and have low toxicity in the palliative treatment of patients with advanced gastric cancer. Further trials in large population groups are needed to determine the effectiveness of this regimen in the treatment of patients with good performance.

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