RESEARCH COMMUNICATION

Limited Efficacy of Cisplatin, UFT and Hydroxyurea Treatment in a Retrospective Evaluation of Patients with Metastatic Gastric Cancer

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Abstract

Background: Most gastric cancer cases are diagnosed at advanced stage and the prognosis is therefore poor. Combination chemotherapy regimens like FAM, FAMTX, ECF, ELF are recommended in advanced gastric cancer. Of particular interest is the HLFP protocol (hydroxyurea, leucovorin, 5-FU, cisplatin) which is reported to give good response rates. In the present study we evaluated the efficacy of oral UFT instead of 5-FU and leucovorin. Methods: We retrospectively evaluated the efficacy of cisplatin, UFT, and hydroxyurea in combination in 14 patients with metastatic gastric cancer. Patients with brain metastasis were excluded. The doses of agents were: oral hydroxyurea 1.5 g/day on days 1-3; cisplatin 80 mg/m2 infusion on day 1 for two hours; and UFT capsule 400 mg/day dose on days 1 to 14. Results: The results were progressive disease in 8 (57%) patients, stable disease in 2 (17%) patients and partial response in 1 (7%) patient. The overall survival was 7.9 months (3-15), progression free survival was 3.4 (1-7) months. Conclusions: Due to high toxicity and low response rates, cisplatin, UFT and hydroxyurea combination demonstrated limited activity against gastric cancer and was not found to be effective for the treatment of advanced gastric cancer.

Key words: Gastric cancer - Cisplatin - UFT - Hydroxyurea - retrospective study

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Introduction

Gastric cancer is the second leading cause of death due to malignancy worldwide. Approximately 95% cases of gastric cancers are adenocarcinoma. Other histologic types are gastric primary lymphoma, squamous cell carcinoma, small-cell carcinoma, and carcinoid tumors. It generally occurs at advanced ages. Most patients are diagnosed with gastric cancer at advanced stage and the prognosis is poor.

Chemothearpy should be offered to newly diagnosed advanced stage gastric cancer patients with good performance status. The single agents has been used for treatment of advanced gastric cancer are 5-FU, cisplatin, mitomycin, etoposide, anthracyclines, taxanes, irinotecan, oral fluoropyrimidines, and S-1. For the treatment of gastric cancer, 5-FU and cisplatin are the most widely used ones either as single agent or in combination with other drugs. However, response rates are higher at combination therapy in gastric cancer so that several different combination regimens including FAM (5-FU, doxorubicin, mitomycin), FAMTX (5-FU, doxorubicin, methotrexate), ECF (etoposide, carboplatin, 5-FU), ELF (etoposide, leucovorin, 5-FU), are being used. In a recent study, HLFP protocol (hydroxyurea, leucovorin, 5-FU, cisplatin) has been used in 102 patients with locally advanced or metastatic gastric cancer. The complete response rate was 5.9% and partial response rate was 56.5% with an overall response rate of 62.4%. There was also 17.6% stable disease and the median survival was 11 months (Louvet et al., 2003). In this study we evaluated the efficacy of oral UFT instead of 5-FU and leucovorin. The efficacy of cisplatin, UFT and hydroxyurea combination was evaluated retrospectively in 14 patients with metastatic gastric cancer.

Materials and Methods

Patients with metastatic, pathologically proved gastric adenocarcinoma were involved. ECOG performance statuses of patients were 0-2, and the median age was 55 (36-71) years. Patients with brain metastasis were excluded from the study. The complete blood count (CBC), liver and renal functions were in normal range. The doses of agents were; oral hydroxyurea 1.5 g/day on days 1 to 3; cisplatin 80 mg/m2 infusion on day 1 for two hours; and UFT capsule 400 mg/day dose on days 1 to 14. The chemotherapy regimen was repeated every 3

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Table 1. Patient Characteristics

Male/Female ratio		8/6
Mean age		55 (36-71)
Performance status	0	2 (14%)
	1	1 (79%)
	2	1 (7%)
Primary location	Cardia	1 (7%)
	Corpus	8 (57%)
	Antrum	4 (29%)
	Fundus	1 (7%)
Previous operation history		
	Yes	1 (7%)
	No	13 (93%)
Previous chemotherapy		
	Yes	3 (21%)
	No	11 (79%)
Metastasis	Liver	5
	Lung	1
	Peritonitis carcinomatosa	5
	Ovary	1
	Bone	1
	Adrenal	1
No of cycles	1 cycle	2 (14%)
	2 cycles	2 (14%)
	3 cycles	6 (43%)
	6 cycles	4 (29%)

weeks if CBC, liver, and renal functions were in normal range. Each patient was hydrated before and after each cycle. The patients were evaluated after 3 cycles for the response . In case of progressive disease or severe toxicity the chemotherapy was stopped. Prior to treatment, all patients were evaluated with clinical examination, upper gastroscopy, chest x-ray (thoracic computed tomography for lung metastasis), abdominal computed tomography, CBC, and biochemical parameters (liver and renal function tests). Toxicitiy was recorded according to the World Health Organization (WHO) criteria. Local ethical application is not recommended in retrospective analysis in Gaziantep University.

Results

Table 2. Toxicity Events in 14 Patients after 47 Cycles

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	9 (19%)	2 (4%)	0	0
Nausea-vomiting	14 (30%)	22 (47%)	2 (4%)	0
Constipation	22 (47%)	0	0	0
Stomatitis	3 (6%)	0	0	0
Neutropenia	5 (11%)	2 (4%)	3 (6%)	1 (2%)
Alopecia	5 (11%)	0	0	0
Allergic reaction	0	0	0	0
Febrile Neutropenia		2 (4%)		

Table 3: Response Rates after Chemotherapy

Response	Number and percent of patients
Stable Disease	2 (14%)
Partial response	1 (7%)
Progressive disease	8 (57%)
Treatment Failure	3(22%)
Overall survival	7.9 (3-15) months
Progression Free Survival	3.4 (1-7) months

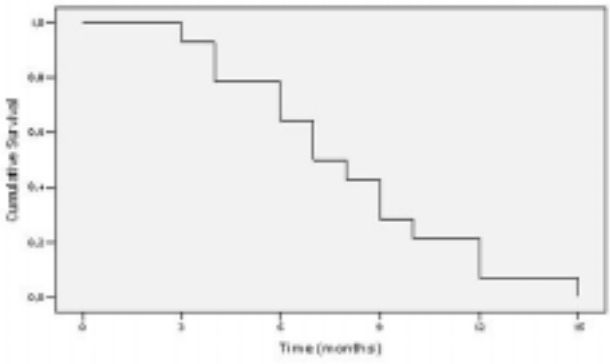

Figure 1. The Kaplan-Meier Survival Curve

The patient characteristics are shown in Table 1. Fourteen patients (8 male, 6 female) were included in the chemotherapy protocol. The mean age of patients was 55, and the ECOG performance statuses of 93% of patients were 0-1. The mean number of performed chemotherapy protocol was 3.36 cycles(1-6 cycles). Toxicity profile is shown in table 2. The most common toxicities were nausea and vomiting (81%). Bone marrow toxicity was observed as grade 3 and 4 neutropenia, 6% and 2%, respectively. Febrile neutropenia occurred in 2 cycles (4%) of chemotherapy. One patient could not tolerate the therapy and discontinued after the first cycle and the other one discontinued after the second cycle. After the first cycle, progressive bilirubin elevation was determined in one patient and after the third cycle, deep venous thrombosis was observed in another patient and chemotherapy was stopped in both of them.

One partial response (7%), 2 stable disease (17%), and progressive disease in 8 (57%) of patients were observed (Table 3). The overall survival was 7.9 months (3-15 months), and progression free survival was 3.4 (1-7) months. Kaplan-Meier survival curve is shown in Figure 1.

Discussion

The prognosis of gastric cancer remains poor. The reasons for this are multifactorial. There are neither specific defined risk factors nor clinic symptoms. The only potentially curative treatment for gastric cancer is surgical resection.

Gastric cancer is uncurable at advanced stage but most of histopathologic types are chemosensitive. Chemotherapy should be offered to newly diagnosed advanced stage gastric cancer patients with good performance status.

Combination chemotherapy regimens resulted in better overall survival and quality of life at advanced gastric cancer (Pyrhonen et al., 1995, Murad et al., 1993, Glimelius et al., 1994) . In a study of North Central Cancer Treatment Group (NCCTG), there was no survival difference among FAM protocol versus 5-FU alone versus 5-FU plus doxorubicin; but there was higher response rates at combination regimens (Cullinan et al., 1985). Also FAM versus FAMTX (Wils et al., 1991), FAMTX versus ECF (Webb et al., 1997), FAMTX versus ELF versus cisplatin alone have been studied extensively (Vanhoefer et al.,

2000). However, cisplatin and/or 5-FU based chemotherapy protocols are recommended for the treatment of advanced gastric cancer. In a recent phase III study, docetaxel, cisplatin, and 5-FU combination chemotherapy improved time to progression, survival and response rate compared with cisplatin and 5-FU combination in untreated advanced gastric cancer patients (Van Cutsem et al., 2006). Apart from chemotherapy, new categories of agents like vaccines, antiangiogenic agents and receptor antagonists (CCK receptors, etc.) are new area of interest in treatment of gastric cancer. Although there is no standard second-line chemotherapy protocol for advanced stage gastric cancer, the patients who are resistant to cisplatin/5-FU regimen in the first-line, showed 16% partial and 25% stable response rates in a phase II study in which the cisplatin and docetaxel combination was used as the second line chemotherapy regimen (Polyzos et al., 2006).

Single agents like 5-FU, mitomycin, etoposide (Macdonald et al., 1992), cisplatin (Lacave et al., 1983), paclitaxel (Einzig et al., 1995, Ohtsu et al., 1998, Ajani et al., 1998), docetaxel (Sulkes et al., 1994, Einzig et al., 1996, Taguchi et al., 1998), irinotecan (Diaz-Rubio 2004), UFT (Takiuchi et al., 1998), oral etoposide (Ajani et al., 1999), S-1 (Koizumi et al., 2000, Ohtsu et al., 2000, Maehara, 2003, Takahashi et al., 2003, Ajani 2006), have shown activity against gastric cancer. 5-FU and cisplatin are most widely used drugs either as single agent or in combination with other drugs. Hydroxyurea is also known to be an active agent in gastric cancer. A synergy has been demonstrated between 5FU and hydroxyurea in vitro: hydroxyurea inhibits the ribonucleotide reductase and lowers the dUMP pool, allowing the 5-FU metabolite 5-FdUMP to bind more effectively to thymidylate synthase (Hashino et al., 1985).

An oral anticancer agent, UFT, a combination of uracil and tegafur (TGF), results in a higher fluorouracil concentration in the tumor tissues. The uracil slows degradation of 5-FU by dihydropyrimidine dehydrogenase. UFT is well tolerated, but nausea, vomiting and diarrhea are dose and schedule dependent toxic effects. UFT has a more favorable toxicity profile than intravenous 5-FU (Takiuchi et al., 1998).

The Eastern Cooperative Oncology Group (ECOG) conducted a randomized phase II trial in patients with advanced gastric cancer. At this trial patients were divided in two groups; first group received FHIG protocol (fluorouracil, infusional hydroxyurea and interferon-alpha-2a) and the second group received AD protocol (doxorubicin, docetaxel). The response rates were only one partial response in FHIG arm (8.3%) and none in AD arm and the median survival was 6.6 and 10.1 months, respectively (Wadler et al., 2002).

In a French study published in 2003, HLFP protocol (hydroxyurea, leucovorin, 5-FU, cisplatin) was studied in 102 patients with locally advenced or metastatic gastric cancer. The results were 5.9% complete response, 56.5% partial response and 17.6% stable disease. The median survival was 11 months (Louvet et al., 2003). In patients with gastric cancer, UFT alone has a response rate of approximately 20%. UFT is also a part of the standard adjuvant chemotherapy for gastric carcinoma in Japan (Takiuchi et al., 1998). It also inhibits the repair of cisplatin-induced DNA damages and enhances cisplatin's toxicity (Albain et al., 1992).

In the present study, we planned to use UFT instead of 5-FU and leucovorin because of higher in vitro activity. The efficacy of cisplatin, UFT and hydroxyurea combination has been evaluated retrospectively in 14 patients with metastatic gastric cancer. However, compared to HLFP regimen, we could not obtain good response with cisplatin, UFT and hydroxyurea combination. It may be due to effective dose difference between infusional 5-FU and oral drug UFT. In addition, UFT dose might be less effective in this protocol or race related factors might impact on this manner. Since the toxicity profile of this combination were worse than expected, it was thought that UFT dose was acceptable or might be reduced. In contrast to the synergistic effect of 5-FU and hydroxyurea has been widely recognized, the combination of UFT and hydroxyurea may be harmful.

In conclusion, cisplatin, UFT and hydroxyurea combination is less effective and can not be offered for the treatment of advanced gastric cancer.

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