RESEARCH COMMUNICATION

Second-Line Irinotecan after Cisplatin, Fluoropyrimidin and Docetaxel for Chemotherapy of Metastatic Gastric Cancer

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Abstract

Aim: Tumors of upper gastrointestinal tract are among the cancers that have a quite lethal course. Cytotoxic chemotherapy is the most efficient therapeutic modality for metastatic gastric cancer. In patients who do not respond to first-line treatment, the response rate to second-line therapies is generally low and the toxicity rates high. This study concerned the efficacy and the side effect profile of second-line therapy with irinotecan in the patients who were being followed-up with the diagnosis of metastatic gastric cancer in İzmir, Turkey. Materials and Methods: We retrospectively evaluated the efficacy and toxicity in 31 patients with metastatic gastric adenocarcinoma who presented to the polyclinic of Medical Oncology of Izmir Ataturk Education and Research Hospital between May 2008 and July 2011. All received chemotherapy regimens containing cisplatin, fluoropyrimidine (5-FU) and docetaxel as the first-line therapy for late stage disease. Irinotecan as a single agent was given at a dose of 210 mg/m^2 on each 21 days. Irinotecan (180 mg/m^2 on day 1), 5-FU (500 mg/m^2 on days 1-2) and leucovorin (LV; 60 mg/m^2 on days 1-2) as a combined regimen were given over a 14 day period. Results: Median age was 54 (range, 31-70). Irinotecan was given as a combined regimen for median 6 cycles (range, 3-12) and as a single agent for median 3 cycles (range, 1-10). Metastases were detected in one site in six patients (19%), in two different sites in 17 patients (55%) and in three or more sites in eight patients (26%). Four patients (12.9%) showed partial response and six patients (19.3%) showed stable disease. Progression-free survival (PFS) was found to be 3.26 months (95% CI, 2.3-4.2). Median overall survival (OS) was found to be 8.76 months (95% CI, 4.5-12.9). The most commonly seen grade 3/4 side effect was neutropenia but the the therapy was generally well-tolerated. Conclusions: In this study, it was demonstrated that second-line therapy with irinotecan given following the first-line therapy with cisplatin, fluoropyrimidine (5-FU) and docetaxel was efficient and safe. Further studies are needed for confirmation.

Keywords: Metastatic gastric cancer - irinotecan - second-line therapy

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Introduction

Gastric cancer is among the cancers that have a highly fatal course. Based on surveillance epidemiology and end results (SEER) data, overall 5-year relative survival was reported to be 23.6% between 2001 and 2007 (SEER Cancer Statistics, 2011). In the treatment for unresectable or metastatic gastric cancer, chemotherapy leads to a significant survival difference compared to best supportive care (Murad et al., 1993). Today, there is no standard regimen that is widely accepted for the first-line treatment of advanced gastric cancer. The efficacy of many cytotoxic agents was shown in the first-line therapy. In the second-line therapy, many cytotoxic agents, such as docetaxel, paclitaxel, oxaliplatin, irinotecan, were studied in accordance to the therapy received in the first-line treatment (Kodera et al., 2007; Sym et al., 2008; Giuliani et al., 2003; Seo et al., 2009). Today, there is not a standard therapy for the second-line treatment as well as the first-line treatment. In this study, we retrospectively evaluated the efficacy and the side effect profile of the therapy with irinotecan in the patients who have been previously diagnosed with metastatic gastric cancer and treated with fluoropyrimidine, platinum, and taxane-based chemotherapy regimen.

Materials and Methods

Patients

We retrospectively evaluated the efficacy and the toxicity profile of second-line therapy with irinotecan in 31 patients with metastatic gastric adenocarcinoma who were admitted to the polyclinic of Medical Oncology of Izmir Ataturk Education and Research Hospital between May 2008 and July 2011. All of these patients had histologically proven gastric or esophagogastric adenocarcinomas. These

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patients had measurable metastatic lesions in at least one site. All the patients received cisplatin, fluoropyrimidine (5-FU) and docetaxel-containing chemotherapy regimens as the first-line treatment. Before the irinotecan therapy, progressive disease was radiologically shown in all the patients. Eastern Cooperative Oncology Group (ECOG) performance status was between 0 and 2. Pre-treatment evaluation included a complete medical history, physical examination, complete blood cell counts, serum biochemistry assays, carcino-embryogenic antigen (CEA), CA 19-9 and computed tomography of the abdomen and/or thorax in cases for evaluating target lesions.

Treatment Plan

Irinotecan therapy was given as a single agent or as a combination therapy with 5-FU and Leucovorin (LV). As a single agent, it was given at a dose of 210 mg/m^2 each 21 days. As a combination regimen, irinotecan (180 mg/m^2 on day 1) , 5-FU (500 mg/m^2 on days 1-2) and LV (60 mg/m^2 on days 1-2) were given each 14 days. The patients did not undergo primary prophylaxis with GCSF. The following treatment course of irinotecan was given on schedule if there was no evidence of tumor progression and the following criteria were methemoglobin 9.0 g/dL (after transfusion if necessary), neutrophils 1,500/μL, and platelets 100,000/μL. Patients continued therapy until disease progression or unacceptable toxicity. All patients underwent complete physical examination and toxicity assessment (including blood counts and biochemical parameters) on every pre-treatment period. Patients were evaluated for hematological and non-hematological toxicities and were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria.

Response Evaluation

Response rate, progression free survival (PFS), duration of response and overall survival (OS) were evaluated in this group. Tumor response was assessed according to response evaluation criteria in solid tumors (RECIST) as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The overall response rate (ORR) was defined as the percentage of patients with CR or PR (Therasse et al., 2000; Eisenhauer et al., 2009).

Statistical Evaluation

PFS was accepted as duration between the time of beginning of irinotecan regimen and the time of determining the first objective evidence of progression. OS was accepted as duration between the time of the beginning of the irinotecan regimen and death. The duration was calculated from the date of first response to the first date of documented progression. PFS and OS were calculated with Kaplan- Meier method. SPSS (Statistical Package for Social Sciences) v. 15.0 software was used for statistical analysis.

Results

We retrospectively evaluated the data of 31 patients with metastatic gastric adenocarcinoma who received second-line irinotecan therapy between May 2008 and July 2011. Patient characteristics are shown in Table 1. Irinotecan was given as a single agent to 25 patients (77.4%) and as a combined regimen to 7 patients (22.6%). Irinotecan was given as a combined regimen for median 6 cycles (range, 3-12) and as a single agent for median 3 cycles (range, 1-10). Median duration of the irinotecan therapy was determined to be 2. 4 months (range, 0. 70-9. 13 months). Nine patients (29%) showed elevated CEA, 16 patients (51.6%) showed elevated CA19-9, 3 patients (9.7%) showed elevated AFP and 7 patients (22.6%) showed elevated CA 125. Elevation of both CEA and CA19-9 was observed in 8 patients (25.5%). While 8 of 9 patients with elevated CEA showed 2 metastases in 2 or more sites, 14 of 16 patients with elevated CA 19-9 showed 2 metastases in 2 or more sites.

Responses and survival

Overall response rate was found to be 32.2% (4 Partial Responses, 6 Stable diseases). Clinical response rates are given in Table 2.

For all the patients who were enrolled to the study, median PFS was 3.26 (95% CI, 2.3-4.2) months and median OS from the onset of irinotecan therapy was 8,76 (95% CI, 4.5-12.9) months (Figure 1-2). At the time when the data were reviewed, 17 patients (54.8%) had died.

Toxicity Analysis

Treatment-related toxicities are explained in Table 2. All treatment-related grade 3/4 adverse events developed in 7 patients (22.5%). Among grade 3/4 hematologic and non-hematologic toxicities, neutropenia was observed

Table 1. Patient Characteristics

Characteristics		No. (%)
No. of patients		31
Median age (year)		54 (31-70)
Range:	<65	24 (77, 4)
	≥65	7 (22, 6)
Sex:	Male	22 (71)
	Female	9 (29)
Primary tumor site:	Esophagogastric junction	11 (35, 5)
	Other	20 (64. 5)
Localization of metastasis:	Liver	20 (64, 5)
	Peritoneum	14 (45, 2)
	Lung	9 (29)
	Bone	1 (3, 2))
	Lymph nodes	7 (22, 6)
	Other	4 (12, 9)
Number of sites with metastasis:	1	6 (19)
	2	17 (55)
	>2	8 (26)

Table 2. Clinical Response Results

Clinical Response (no.)	no (%)
CR	-
PR	4 (12.9)
SD	6 (19.3)
PD	21 (67.8)

* 'CR: Complete Response; PR: Partial Response; SD: Stable disease; PD: Progressive disease

Table 3. Treatment-Related Toxicity Results

Toxicity	Grade 1-2 No	Grade 3-4 No
Hematology		
Neutropenia	4	4
Anemia	8	1
Trombocytopenia	1	1
Febrile neutropenia	1 patient	
Non-hematologic		
Stomatitis	1	-
Diarrhea	3	-
Vomiting	2	1

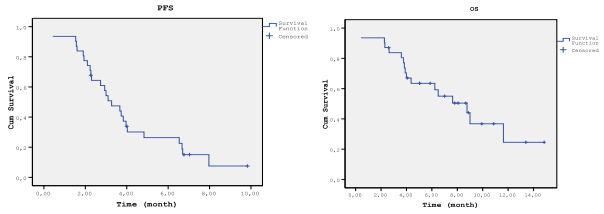

Figure 1. A) Progression-free survival, B) Overall survival.

in four patients, anemia was seen in one patient, thrombocytopenia was detected in one patient and nausea-vomiting was observed in one patient. Uncomplicated neutropenic fever was observed in one patient.

Discussion

For the treatment of metastatic gastric cancer, there is no standard regimen to be used in the second-line therapy of the patients who showed progression after the first-line therapy. Generally, second-line regimen is empirically selected. In many phase II studies with small numbers, many drugs were studied. In these studies, PFS was reported to range between 2.2 and 4.5 months, whereas OS was reported to vary between 3. 5 and 8 months (Graziano et al., 2000; Giuliani et al., 2003; Chun et al., 2004; Cho et al., 2006; Kodera et al., 2007; Jeong et al., 2008; Sym et al., 2008; Baize et al., 2009; Seo et al., 2009; Kim et al., 2010). In our study, PFS was 3.26 months and OS was 8.76 months. For survival, these rates were consistent with the literature. In the phase II studies cited in the literature, overall response rate was reported to be 17-48.6%. In our study, it was found to be 32.2% consistent with these data (4 Partial Responses, 6 Stable diseases, no complete response). In the study performed by Park . 2002 patients with advanced gastric cancer who showed progression with first-line therapy with fluoropyrimidines and a platinum agent received docetaxel or irinotecan (Park et al., 2011). In the intent-to-treat population, a significant difference in OS (5.1 months for Second-line therapy v 3.8 months for BSC) was observed (hazard ratio, 0.63; 95% confidence interval, 0.47-0.86; P=0.004). Thereby, it was demonstrated that second-line therapy provided an advantage of survival over BSC. In the study presented by Thuss-Patience et al. this result was supported with a randomized phase III study that compared BSC and second-line irinotecan (Thuss-Patience et al., 2011). In this study, median OS was reported to be 2.4 months (95% CI 1.7-4.9) vs 4.0 months (95% CI 3.6-7.5) for BSC vs. irinotecan, respectively. Side effect profile observed in our study was consistent with the literature.

Consequently, it was demonstrated that, today, for advanced gastric cancer, second-line therapy provided a survival advantage compared to BSC. However, there is no comparative study about the selection of the second-line therapeutic modality. Nevertheless, in the patients who have previously received docetaxel-based chemotherapy, irinotecan therapy may be considered as a second-line therapy. In the patients who received platinum and fluoropyrimidines based chemotherapy, the regimen to be selected is not clear. Based on two phase III studies conducted on such patients, in which docetaxel was not used in the first-line therapy, docetaxel or irinotecan based chemotherapy regimen may be selected in the second-line therapy (O, P). In our study, it was demonstrated that irinotecan administered as the second-line therapy following cisplatin, fluoropyrimidine (5-FU) and docetaxel was efficient and safe. In this area, further studies are warranted.

References

Baize N, Abakar-Mahamat A, Mounier N, Berthier F, Caroli-Bosc FX (2009). Phase II study of paclitaxel combined with capecitabine as second-line treatment for advanced gastric carcinoma after failure of cisplatin-based regimens. *Cancer Chemother Pharmacol*, **64**, 549.

Cho BC, Kim JH, Kim CB, et al (2006). Paclitaxel and leucovorin-modulated infusional 5-fluorouracil combination chemotherapy for metastatic gastric cancer. *Oncol Rep*, **15**, 621.

Chun JH, Kim HK, Lee JS, et al (2004). Weekly irinotecan in patients with metastatic gastric cancer failing cisplatin-based chemotherapy. *Jpn J Clin Oncol*, **34**, 8.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). J New response evaluation criteria in solid tumours: revised RECIST guideline (version 1. 1). *Eur J Cancer*, **45**, 228.

Giuliani F, Gebbia V, De Vita F, et al (2003). Docetaxel as salvage therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico Italia Meridionale (G. O. I. M.). *Anticancer Res*, **23**, 4219.

Graziano F, Catalano V, Baldelli AM, et al (2000). A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer. *Ann Oncol*, **11**, 1263.

Jeong J, Jeung HC, Rha SY, et al (2008). Phase II study of combination chemotherapy of 5-fluorouracil, low-dose leucovorin, and oxaliplatin (FLOX regimen) in pretreated advanced gastric cancer. *Ann Oncol*, **19**, 1135.

Kim SH, Lee GW, Go SI, et al (2010). A phase II study of irinotecan, continuous 5-fluorouracil, and leucovorin (FOLFIRI) combination chemotherapy for patients with recurrent or metastatic gastric cancer previously treated with a fluoropyrimidine-based regimen. *Am J Clin Oncol*, **33**, 572-6.

Kodera Y, Ito S, Mochizuki Y, et al (2007)A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). *Anticancer Res*, **27**, 2667.

Murad AM, Santiago FF, Petroianu, et al (1993). Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer*, **72**, 37-41.

Park S, Lim D, Park K, et al (2011). A multicenter, randomized

trial comparing second-line chemotherapy plus best supportive care (BSC) with BSC alone for pretreated advanced gastric cancer (AGC) (Abstract 4004). *J Clin Oncol*, **29**, 257.

SEER Cancer Statistics http://www. seer. cancer. gov/statistics/ (Accessed on March 31, 2011).

Seo HY, Kim DS, Choi YS, et al (2009). Treatment outcomes of oxaliplatin, 5-FU, and leucovorin as salvage therapy for patients with advanced or metastatic gastric cancer: a retrospective analysis. *Cancer Chemother Pharmacol*, **63**, 433.

Sym SJ, Ryu MH, Lee JL, et al (2008). Salvage chemotherapy with biweekly irinotecan, plus 5-fluorouracil and leucovorin in patients with advanced gastric cancer previously treated with fluoropyrimidine, platinum, and taxane. *Am J Clin Oncol*, **31**, 151.

Therasse P, Arbuck SG, Eisenhauer EA, et al (2000). New guidelines to evaluate the response to treatment in solid tumors: European Organization for . Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*, **92**, 205.

Thuss-Patience PC, Kretzschmar A, Bichev D, et al (2011). Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer-a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer*, **47**, 2306-14.