RESEARCH COMMUNICATION

Adjuvant Bi-Weekly Combination of Cisplatin, Infusional 5-fluorouracil and Folinic Acid Followed by Concomitant Chemoradiotherapy with Infusional Fluorouracil for High Risk Operated Gastric and Gastroesophageal Junction Adenocarcinoma

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Abstract

Purpose: Chemotherapy and radiotherapy are approved in clinical practice of adjuvant treatment of gastric carcinoma. In present study, we retrospectively evaluated the efficacy and tolerability of an adjuvant treatment protocol including bi-weekly cisplatin, infusional 5-fluorouracil (5-FU) and folinic acid followed by continuous 5-FU infusion during radiotherapy. Patients and Methods: Between May 2005 and Dec 2008, 65 curatively resected gastric and gastroesophageal junction adenocarcinoma patients (stage III in 38 and stage IV M0 in 27) received chemotherapy including 50 mg/m^2 cisplatin, 200 mg/m^2 iv folinic acid, 5-FU 400 mg/m^2 iv bolus followed by 5-FU 1600 mg/m^2 46h-continuous infusion (CFF) bi-weekly. After 4 cycles of CFF, concomitant 200 mg/m^2/day continuous infusion 5-FU and 4500 cGy radiotherapy were administered for 5 weeks. After this chemoradiotherapy an additional 4 cycles of CFF were given. Results: The median follow-up was 15 (6-36) months. Fifty seven (87.7%) patients completed at least 90% of the planned treatment. Median disease free survival was 18 months (95% CI:13.9-22.0) and median overall survival was 19 months (95% CI:15.2-22.8). Common adverse events of all grades were nausea and vomiting (53.8%), leucopenia (42.6%), anemia (30.7%) and diarrhea (20%). The most common grade 3 and 4 toxicities were leucopenia (9.2%), anemia (7.6%), febrile neutropenia (6.1%) and diarrhea (4.6%). Conclusion: Bi-weekly CFF chemotherapy followed by continuous 5-FU infusion during radiotherapy is an effective and tolerable regimen for locally advanced operated gastric and gastroesophageal junction adenocarcinoma.

Keywords: Gastric cancer - adjuvant - chemoradiotherapy - cisplatin - 5-fluorouracil - folinic acid

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Introduction

Surgery is the only treatment with curative potential for gastric cancer. However, the five-year survival in patients with curative resection is 20-30% (Faivre et al., 1988; Hundhal et al., 1997; 2000). Worldwide efforts have been put in the recent years to develop effective adjuvant treatment regimens to increase postoperative survival in gastric cancer patients who had undergone radical resection. However, since adjuvant chemotherapy studies did not suggest an advantage over surgery, an effective standard regimen could not be defined (Coombes et al., 1990; Lise et al., 1995; Macdonald et al., 1995). Recent meta-analyses reported small but significant increases such as 3-5% in 5-year survival rates (Earle and Maroun, 1999; Mari et al., 2000; Panzini et al., 2002). However, these meta-analyses should be interpreted carefully due to their methodological flaws such as patient data being obtained from the literature.

The high locoregional failure rate up to 70% following curative resection has formed the rationale to use radiotherapy as neoadjuvant or adjuvant therapy. Radiation complementary to surgery was shown to increase locoregional control without significant impact on overall survival (Hallissey et al., 1994; Zhang et al., 1998).

The US Intergroup 0116 study was the first large randomized study suggesting the significant advantage of adjuvant combined chemoradiotherapy on progression

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free and overall survival (Macdonald et al., 2001). The chemotherapy regimen used in this study included 5 cycles of bolus 5-fluorouracil (FU) and folinic acid combination administered according to the Mayo Clinic protocol, 2 and 3rd cycles being administered during radiotherapy with reduced doses. The relapse patterns in the treatment and control arms showed that such an adjuvant treatment was more effective on decreasing local recurrence than distant metastasis, suggesting that bolus 5-FU/folinic acid be insufficient in reducing distant metastasis. The MAGIC study, where a more intense chemotherapy was used, suggested that perioperative epirubisin, cisplatin and infusional 5-FU (ECF) increased resectability, reduced distant metastasis and increased overall survival (Cunningham et al., 2006). Regimens such as continuously infused 5-FU, folinic acid plus cisplatin (PLF), ECF or regimens including novel agents such as docetaxel, paclitaxel, oxaliplatin or irinotecan, have been shown to have a substantially higher activity in metastatic disease than 5-FU/folinic acid alone, which makes them an attractive option for the use in the adjuvant setting (Vanhoefer et al., 2001; Louvet et al., 2002; Ross et al., 2002; Bouche et al., 2004; Van Cutsem et al., 2006).

In present study, we retrospectively evaluated the efficacy and tolerability of adjuvant treatment protocol including bi-weekly cisplatin, infusional 5-FU, folinic acid chemotherapy followed by continuous 5-FU infusion during radiotherapy for locally advanced gastric and gastroesophageal junction adenocarcinoma patients after curative resection.

Patients and Methods

Patients and treatment protocol

Between May 2005 and December 2008, 65 curatively resected gastric and gastroesophageal junction adenocarcinoma patients (stage III in 38 patients and stage IV M0 in 27 patients) were included in our study. A juguler venous titanium port catheter was inserted in each patient. The treatment protocol included 50 mg/m^2 cisplatin, 200 mg/m^2 iv bolus folinic acid, 5-FU 400 mg/m^2 iv bolus followed by 5-FU 1600 mg/m^2 46h-continuous infusion (CFF) be-weekly. After 4 cycles of CFF, chemoradiotherapy (CRT) was started on day 15 with 180 cGy/day X 25 frx = 4500 cGy as parallel anteroposterior/posteroanterior administration on the tumor bed and regional lymphatics as well as concurrent 200 mg/m^2/day continuous infusion 5-FU. A booster dose of 10 cGy was added in patients with surgical margin positivity. Fifteen days after CRT additional 4 cycles of CFF were given (Figure 1).

Staging was accomplished according to the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system 2002 classification and toxicity was determined according to the NCI (National Cancer Institute) Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Treatment was interrupted for up to 15 days in patients who developed grade III / IV toxicity. Drug dose was subsequently reduced by 25% in those with persisting toxicity.

Statistical Analysis

Disease-free survival was considered as the time from gastrectomy to last visit, relapse or death and overall survival was determined by the time from gastrectomy to last visit, or death and both were expressed by months. Survival data of patients were updated in December 2008 and was assessed retrospectively. SPSS 13.0 for Windows package program was used for statistical analysis. Survival rates were calculated according to Kaplan-Meier Method.

Results

Treatment

Demographic characteristics of the patients are shown in Table 1. In 9 (13.8%) patients, the tumor was located in the gastroesophageal junction. Fifty-one (78.5%) patients had undergone D2 or D3 lymph node dissection. The median number of examined lymph nodes was 24 (6-66) and the median number of involved nodes was 11 (1-46). Seven or more lymph nodes metastasis were present in the majority of patients (75.4%). Similarly, the tumor had poorly differentiated in the majority of the patients (64.6%). Surgical margins were positive pathologically

Table 1. Clinical and Histopathologic Characteristics of Patients and Surgical Procedures

Characteristic	n (%)
Patients	65 (100)
Median age (min-max)	55 (26-72)
Gender	
Male	48 (73.8)
Female	17 (26.2)
ECOG performance status	
0	9 (13.8)
1	48 (73.9)
2	8 (12.3)
Surgical procedure	
Total gastrectomy	35 (53.8)
Subtotal gastrectomy	30 (46.2)
Surgical margin	
Positive	8 (12.3)
Negative	57 (87.7)
Tumor localization	
Stomach	56 (86.2)
Gastroesophageal junction	9 (13.8)
Type nodal dissection	
D1	14 (21.5)
D2	44 (67.7)
D3	7 (10.8)
Histological differentiation	
Well	3 (4.6)
Intermediate	20 (30.8)
Poor	42 (64.6)
Depth of invasion	
pT2	8 (12.3)
pT3	53 (81.5)
pT4	4 (6.2)
Nodal status	
pN1	16 (24.6)
pN2	25 (38.5)
pN3	24 (36.9)
TNM Stage	
III	38 (58.5)
IV (M0)	27 (41.5)

Figure 1. Treatment Schema. Schematic Appearance of the Treatment Protocol. OP, Operation; CFF, Cisplatin, 5-fluorouracil, Folinic Acid; RT, Radiotherapy; CI Continuous Infusion

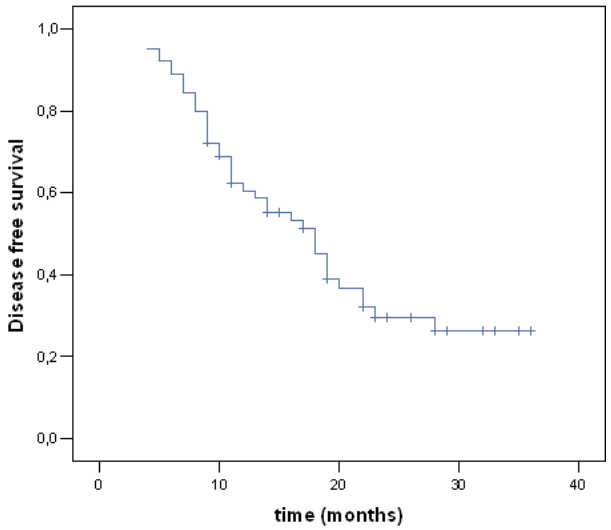

Figure 2. Disease Free Survival Curves. Kaplan-Meier Disease-free Survival Curve. Median 18 Months (95% CI:13.9-22.0)

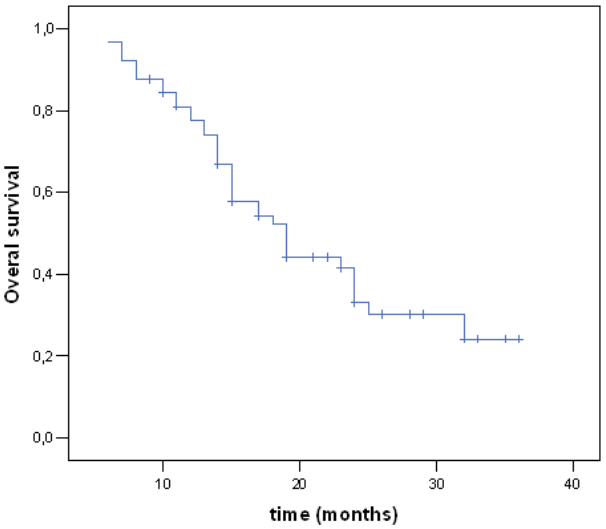

Figure 3. Overall Survival Curves. Kaplan-Meier Overall Survival Curve. Median 19 Months (95% CI:15.2-22.8)

in 8 (12.3%) patients.

The median number of chemotherapy cycles was 8 (1-8). Fifty-seven patients (87.7%) completed at least 90% (6 cycles CFF + CRT) of the preplanned treatment and 46 (70.8%) completed the whole treatment. Of the 19 (29.2%) patients who could not complete treatment, 7 (10.7%) stopped treatment voluntarily, of which 5 (7.7%) did not receive only the last course. Treatment was stopped due to progression in 5 (7.7%) patients and for toxicity in 7 (10.7%).

Sixty-one (93.8%) patients received the preplanned radiotherapy dose. Treatment was stopped before radiotherapy in 3 (4.6%) patients due to toxicity and in 1 (1.5%) patient due to progression. In 61 (93.8%) patients who received radiotherapy, 5-FU was administered by continuous infusion.

Table 2. Adverse Events Due to Treatment (CTCAE v 3.0)

Adverse event	Grade	
	I/II n (%)	III/IV n (%)
Leucopenia	22 (33.4)	6 (9.2)
Anemia	15 (23.1)	5 (7.6)
Thrombocytopenia	3 (4.6)	-
Diarrhea	10 (15.4)	3 (4.6)
Mucositis	12 (18.5)	1 (1.5)
Nausea and vomiting	35 (53.8)	-
Infection	6 (9.2)	1 (1.5)
Febrile neutropenia	-	4 (6.1)
Renal toxicity	(12.3)	-
Hepatotoxicity	5 (7.6)	-

Efficacy

The median follow-up time was 15 (6-36) months. The disease relapsed in 41 (63.1%) patients and 38 (58.5%) patients died during the follow-up. Median disease free survival was 18 months (95% CI:13.9-22.0) and median overall survival was 19 months (95% CI:15.2-22.8) (Figures 2 and 3).

Among the 41 relapsed patients, 12 developed peritoneal metastasis and 18 developed distant metastasis. The relapse pattern could not be determined in 11 patients, of which 7 were considered relapsing prior to death. The most common distant metastatic site was liver (13 patients). There was no only local relapse in any patient.

Toxicity

Generally, treatment was well tolerated and there was no treatment related death. Most of the adverse events were mild (Table 2). The most common adverse events were nausea and vomiting (53.8%), leucopenia (42.6%), anemia (30.7%) and diarrhea (20%). The incidence of most common grade 3 and 4 toxicities was leucopenia (9.2%), anemia (7.6%), febrile neutropenia (6.1%) and diarrhea (4.6%). Empyema developed in 1 patient who had a history of thoracotomy due to tumor localization in cardia of the stomach. The port was withdrawn in 2 (3%) patients, 1 due to port infection and 1 for thrombosis. Seven patients were hospitalized for reasons other than transfusion or progression; five of those patients were hospitalized for infection.

Discussion

The results of the Intergroup 0116 study led to a change in the routine treatment of gastric cancer patients, and the new approach was concomitant radiotherapy and 5-FU based chemotherapy (Macdonald et al., 2001). Bolus 5-FU administration concurrently with radiotherapy was shown to reduce locoregional relapse, which is a significant marker for mortality. However, considering the common adverse events that developed during the administration of this regimen led to a search for optimal chemoradiotherapy regimens that could achieve better disease-free survival and overall survival with lower toxicity.

We examined the efficacy and tolerability of CFF and chemoradiotherapy protocol in patients with gastric and gastroesophageal junction adenocarcinoma who had undergone curative resection and who had local findings of advanced disease. Our patients had a high risk of relapse; most (75.4%) had N2 or N3 nodal involvement, 12.3% had histopathological surgical margin positivity and 64.4% had poorly differentiated tumor. Earle and Maroun (1999) reported that patients with high relapse risk might benefit more from adjuvant therapy strategies. In addition, Bajetta et al., (2002) suggested that 5-FU/cisplatin based chemotherapy protocols provided survival advantage over follow-up in patients with more than six metastatic lymph nodes and that adjuvant chemotherapy would be more beneficial in local advanced subgroups.

Gastrointestinal side-effects were the most common non-hematological toxicities in our study, but overall grade 3/4 gastrointestinal toxicities appeared to be less than literature. This may be due to the different 5-FU schedule used in our protocol with 5-FU given as a 46-h continuous infusion bi-weekly. MacDonald et al., (2001) reported 54% hematologic and 33% gastrointestinal grade 3/4 toxicity, 1% toxic death, and 17% of patients were excluded from the study due to toxicity. No patient died due to toxicity in our study. In another study from Turkey by Bese et al., (2005) 59 patients were treated with bolus 5-FU, folinic acid and levamizole and the toxic death rate was reported as 7%. This may be considered an indicator that the Intergroup 0116 treatment, which includes bolus 5-FU is a poorly tolerable regimen for Turkish patients. In a small phase II study in Germany, 45 patients received two cycles of 500 mg/m^2 folinic acid, 2 g/m^2 5-FU continuous infusion within 24 hours weekly every six weeks, 50 mg/m^2 cisplatin on week 2 and 5 and 220 mg/m^2/day 5-FU continuous infusion along with 45 Gy RT. The rate of hematological and non-hematological toxicity was 49% and 43% respectively (Kollmannsberger et al., 2005). The 5-FU and folinic acid doses were higher in that study than in our study and the dosing scheme was different. In addition, that study was the first chemoradiotherapy study in Germany and the high rate of adverse events was attributed to lack of previous experience.

The optimum extent of lymph node dissection (D1 vs D2/D3) in gastric cancer is still controversial and the general opinion is to perform systemic lymphadenectomy (Bonenkamp et al., 1999; Cuschieri et al., 1999). Whether in D2 or D3 lymph node dissection, which causes more extensive abdominal trauma, adjuvant therapy would be more toxic is yet to be determined. The acceptable results for toxicity in our study may suggest that D2 or D3 lymphadenectomy actually did not increase the toxicity of adjuvant chemotherapy.

Although all of the patients in the present study had stage III and IV (M0) disease, and had worse prognostic factors such as poorly differentiated tumor, the median overall survival was 19 months. In most of the adjuvant studies the survival rates was reported for all stages of the study group. To escape from misunderstanding we didn't compare our survival results with results of other studies. It can be suggested that survival rates for high risk groups may be given separately in the adjuvant gastric cancer studies.

In conclusion, bi-weekly cisplatin, infusional 5-FU, folinic acid chemotherapy followed by continuous 5-FU infusion during radiotherapy is an effective and tolerable regimen in gastric and gastroesophageal junction adenocarcinoma patients who had undergone surgical intervention and who have local findings of advanced disease. Further prospective randomized studies are needed for comparing treatment regimens including bolus 5-FU with those including infusional 5-FU for efficacy and adverse events.

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