The Toxicity and Outcomes of Continuous 5-fluorouracil/Cisplatin-based Chemotherapy Followed by Chemoradiation in Patients with Resected High-risk Gastric Cancer: Results of a Single Institute

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Abstract

Introduction: The majority of patients with gastric cancer relapse after definitive surgery and 5-year survival after surgery is very poor. The Intergroup 0116 study showed a modest survival benefit for postoperative bolus 5-fluorouracil-based chemoradiation with a high rate of toxicity. We hypothesised that treatment outcome could be further improved with feasible toxicity using a combination of bolus 5-fluorouracil, continuous 5-fluorouracil, and cisplatin followed by chemoradiation after 3 months of chemotherapy. Materials and Methods: Thirty-six patients with stages Ib through IV adenocarcinoma of the stomach or gastroesophageal junction who had undergone gastric resection and negative margins were assigned to postoperative chemoradiation. The treatment consisted of 6 cycles of continuous 5-fluorouracil (600 mg/m²) for 24 hours, push 5-fluorouracil (400 mg/m²) and leucovorin (LCV) (200 mg/m²) on day 1 to 2 every 2 weeks, cisplatin (60 mg/m²) every 4 weeks followed by combined modality therapy using 45 Gy at 1.8 Gy per day concomitant with weekly bolus 5-fluorouracil (600 mg/m²) and LCV (50 mg). Results: The median age was 59 years (range, 29 to 75) and 25 patients were male. Thirty-five percent had proximal tumour, T3 or T4 were diagnosed in 92% of the patients and lymph nodes metastases were confirmed in 83%. Grade 3 or 4 neutropaenia was documented in 25%, and gastrointestinal toxicity in 16%. There was no toxic death, but 1 patient had long-term complications. The median disease-free survival was 37.4 months and the overall survival was 40.3 months. Conclusions: Postoperative chemoradiation with combination of bolus 5-fluorouracil, continuous 5-fluorouracil and cisplatin is a feasible and well-tolerated approach. Larger clinical trials should be conducted to further evaluate the toxicity and the efficacy of this regimen.

Key words: Adjuvant, Combined modality therapy, Gastric neoplasms

Introduction

Gastric carcinoma is the second most common cause of cancer mortality worldwide.1 Surgery is the only curative therapy, although 5-year survival rates remain poor even after curative resection. About two-thirds of the patients who undergo a complete resection will have locoregional recurrence.2 The benefit of adjuvant therapy has been controversial due to the lack of significant survival benefit in many randomised trials.3,4 Combined postoperative chemoradiation showed a significant survival advantage in the Gastric Surgical Adjuvant Trial (INT0116).5 The regimen consisted of bolus 5-fluorouracil and leucovorin (LCV): 1 cycle before chemoradiation and 2 cycles after the completion of chemoradiation.5

Despite the encouraging results, several concerns remained. Grade 3 and 4 toxicities were reported in 41% and 32% of cases respectively, and only 64% finished the treatment.5 In addition, the impact of bolus 5-fluorouracil on extra-abdominal recurrence was minimal, indicating a need for better systemic regimens.

In contrast to bolus 5-fluorouracil, continuous 5-fluorouracil is proposed to maximise the efficacy with less toxicity and better tolerability.6 Chemotherapy regimens including cisplatin and 5-fluorouracil have been reported to show high response rates in patients with metastatic gastric cancer.7,8
The aim of the present study was to evaluate the tolerability and the outcome of giving 5-fluorouracil using continuous and bolus infusions, concomitant with cisplatin followed by chemoradiation in unselected patients after complete resection of gastric cancer.

Materials and Methods

Gastric cancer patients with pathologically confirmed adenocarcinoma of the gastro-oesophageal junction or the stomach after complete resection were selected for treatment. The definition of complete resection included surgery with curative intent resulting in negative margins. All the patients had tumour stage T3-4 or N1-3, according to the 1988 staging criteria of the American Joint Commission on Cancer (AJCC). Eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, a serum creatinine (mg/dL) ≤ 1.5, total bilirubin ≤ 1.5 mg/dL, and alanine aminotransferase (ALT) ≤ 1.5 x upper limit of normal. Patients in the study did not receive preoperative chemotherapy. Treatment was begun as soon as possible and not later than 8 weeks after surgery. The pretreatment evaluations included physical examination, tumour markers and computed tomography (CT) to rule out metastatic disease.

The treatment consisted of 6 cycles of continuous 5-fluorouracil (600 mg/m²), bolus 5-fluorouracil (400 mg/m²) and LCV (200 mg/m²) on day 1 to 2 every 2 weeks, and cisplatin (60 mg/m²), was given on the day 1 every 4 weeks. Chemoradiation started a month after the last chemotherapy series with repeated CT and tumour marker. It consisted of 45 Gy at 1.8 Gy per day concomitant with weekly bolus 5-fluorouracil 600 mg/m² and LCV 50 mg total dose. Patients aged 70 years and above were treated with 5-fluorouracil without dose modification and carboplatin AUC2 instead of cisplatin. Dose modification of 20% was done after toxicity grade ≥ 2. In cases of life threatening toxicity, the treatment was stopped.

The 45 Gy of radiation was delivered in 25 fractions, 5 days per week, to the tumour bed, regional nodes 2 cm beyond the proximal and distal margins of resection. The tumour bed was defined by the preoperative CT imaging. The presence of proximal T3 lesions necessitated treatment of the medial left hemidiaphragm. All the patients were asked to sign an informed form consent prior to the beginning of treatment.

Patients were evaluated at intervals of 6 months for 3 years and yearly thereafter. The follow-up consisted of physical examination, complete blood count and liver-function tests, CEA, CA19-9, and chest, abdominal and pelvis CT scan. Recurrence was ascertained by clinical, radiological and (when possible) histological examinations. Patients were followed until the first occurrence of a neoplastic event or until death.

Primary end points were the determination of the toxicity and the efficacy of the combined adjuvant treatment. Survival curves were estimated using the Kaplan-Meier method. Statistical analysis was performed using the SPSS program.

Results

Thirty-six patients (25 men and 11 women) were enrolled to the protocol between 15 May 2001 and 1 August 2004. Patient characteristics are outlined in Table 1. The median age was 59 years (range, 29 to 75). Lesions were present in the gastro-oesophageal junction in about one-third of the patients. The patients were at high risk for recurrence; 92% had T3 or T4 tumours and lymph node metastases were confirmed in 83%. D1 dissection is routinely performed in our institute with a median of 15.4 removed lymph nodes per patient. In 4 patients, the regimen did not include cisplatin; 2 were older than 70 years, 1 had heart disease and 1 patient refused consent.

Toxicities experienced during treatment are showed in Table 2. The most common haematologic toxic effect was
neutropaenia; 5 patients (13.9%) experienced Grade 4 toxicity and 4 patients (11.1%) had grade 3 toxicity. Neutropaenic fever was noted in 1 patient. Thrombocytopenia and anaemia were mild and none of the patients experienced grade 3 or 4 toxicity. Non-haematologic toxicity included grades 3 to 4 nausea or vomiting (8.3%), diarrhoea (8.3%) and stomatitis (2.7%). Overall, 1 severe toxic episode (grade 3 to 4) was reported at least once in 38.9% of the patients. During the follow-up period, no neurotoxicity was noted.

Of the 36 patients assigned to the mentioned protocol, 25 (69.4%) completed all the programmed treatments and 11 (30.6%) stopped chemotherapy secondary to toxicity; 3 patients (8.3%) did not finish both chemotherapy and radiotherapy and another 8 patients did not complete the chemotherapy but received the planned radiotherapy. Except for 1 patient, all the patients received at least 4 cycles of chemotherapy. In addition, 9 patients had dose modification. Twenty-two patients completed radiotherapy (88.9%), but 7 patients did not finish concomitant chemotherapy.

The median disease-free survival duration was 37.4 months and the median overall survival was 40.3 months. All the patients who relapsed had locoregional recurrence and 22% had both distant and locoregional recurrence. No treatment-related death was observed.

**Conclusions**

In patients with curative resection of gastric cancer, the combination of local and distance recurrence provided the rationale for adjuvant combined chemoradiation therapy. The improvement in overall survival was first demonstrated by the INT0116. Continuous efforts are underway to improve the toxic profile and the outcome of these patients. Our results demonstrate that our regimen is more tolerable without compromising its efficacy.

Grade 3 or 4 toxicities were observed in 14 patients (38.9%), with the most frequent side effect being neutropaenia (9 patients, 25%) followed by gastrointestinal toxicity (7 patients, 19.4%). Haematological and gastrointestinal side effects were also the most frequent in the INT0116, but the incidence was about half in our protocol: neutropaenia in 25% compared to 54% in the INT0116, and gastrointestinal toxicity in 19.4% compared to 33% respectively. The reduction mainly in haematological toxicity is supported by previous studies, which showed fewer side effects in the 5-fluorouracil given as a 24-h continuous infusion compared to 5-fluorouracil given as a bolus. Our toxicity rates are better than those reported by Kollmannsberger et al., using 5-fluorouracil given as a 24-h continuous infusion in a phase II study. In the INT0116 and the trial reported by Kollmannsberger et al., the chemoradiation was given between the first and second cycles of chemotherapy, which resulted in substantially increased toxicity during second-cycle chemotherapy. Our schedule included chemoradiation only after the completion of chemotherapy, and all patients except for 1 received at least 50% of the programmed cycles.

In spite of the better toxic profile, almost one-third of the patients did not complete the treatment. Theses rates are similar to those of other reports, including the INT0116. A high proportion of early treatment cessation may reflect the differences between analyses of unselected groups compared to phase II or III studies.

Although similar rates of patients completed the treatment, the disease-free survival and the overall survival were better than those of the INT0116; 37 months compared to 30 months in disease-free survival and 40 months compared to 36 months in overall survival. Several reasons may explain these findings. First, using 5-fluorouracil as continuous infusion compared with 5-fluorouracil as bolus may improve tolerability and efficacy. Second, the addition of cisplatin may improve efficacy, although several studies failed to demonstrate a better outcome in the adjuvant setting. Third, we began chemoradiation only after the cessation of chemotherapy, which may improve the toxic profile as well as the systemic response to chemotherapy.

Many different approaches have been recently suggested for the treatment of operable gastric cancer, including preoperative and postoperative use of chemotherapy, combination of chemotherapy and chemoradiation, selection of various drugs and the mode of delivery. Over the last few years, continuously infused 5-fluorouracil has become more common than bolus 5-fluorouracil in the adjuvant setting. To the best of our knowledge, the tolerability and the outcome of the treatment with a regimen consisting of continuously infused 5-fluorouracil followed by chemoradiation after the completion of chemotherapy has not been published. It must be pointed out that we had a relatively small number of patients, and short follow-up and that the present study is not a phase III trial. However, the toxicity profile was acceptable, and the disease-free survival and overall survival were very encouraging. Further trials should address the toxicity and the efficacy of this regimen.

**REFERENCES**


