

Postoperative chemotherapy in gastric cancer, consisting of etoposide, doxorubicin and cisplatin, followed by radiotherapy with concomitant cisplatin: A feasibility study

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Received December 15, 2011; Accepted February 6, 2012

DOI: 10.3892/ol.2012.617

Abstract. The prognosis following surgical treatment of gastric carcinoma (GC) or gastroesophageal junction (GEJ) adenocarcinoma remains poor. Although adjuvant chemo-radiotherapy with 5-fluorouracil has been shown to be beneficial, a high rate of distant failure has been reported. Thus, the toxicity profile and efficacy of an intensified chemo-radiotherapy regimen following complete or near-complete resection of GC was evaluated. Patients who underwent surgery for GC were eligible for evaluation. Treatment consisted of four cycles of modified EAP: etoposide 100 mg/m², days 1-3; cisplatin 27 mg/m², days 1-3; and adriamycin 40 mg/m², day 1; every 21 days, followed by a course of radiotherapy (45 Gy; 1.8 Gy/fr) combined with weekly cisplatin 40 mg/m². In total, 40 patients were included in the analysis. Median follow-up was 34 months from the onset of chemotherapy. Microscopic stage IV disease and/or R1 resection were found in 11 patients. For these patients, the median progression-free survival was 6.5 months, and overall survival 9.5 months, compared to 25 and 54 months, respectively, for the remaining 29 patients. In the latter subgroup, longer disease-free survival was associated with average dose intensity of >90% for the four cycles of EAP. The predominant grade 3-4 toxicities during EAP-chemotherapy were hematological adverse events. Nevertheless, the rate of severe non-hematologic toxicity reached 60%. There was one toxicity-related mortality. During the chemo-radiotherapy course, 39% of patients experienced grade 3-4 non-hematologic toxicities. It was concluded that the high toxicity rate of this regimen does not justify further evaluation of this postoperative protocol. Chemo-radiotherapy for R1 or pathological microscopic M1 patients does not appear to be justified.

Introduction

Despite advances in the surgical treatment of gastric and distal esophageal carcinoma, the prognosis of gastric carcinoma (GC) remains poor (1). Moreover, GC is only moderately sensitive to chemotherapy and radiation therapy. Consequently, the potential role of neo-adjuvant and adjuvant treatments has yet to be determined. Over the past decade, improvements in disease-free survival (DFS) and overall survival (OS) were achieved with the adjuvant chemo-radiotherapy approach used in the SWOG9008/INT0116 study (2), as well as perioperative chemotherapy, based on the MRC adjuvant gastric infusional chemotherapy 'MAGIC' trial (3). Although the use of intensified perioperative chemotherapy in place of adjuvant chemo-radiotherapy is growing, this approach remains under debate (4,5). The different surgical techniques and approaches to lymph node resection render these trials incomparable for the purpose of assessing the local control effect; in addition, the two trials retain the problem of distant recurrence. Various strategies are presently under investigation, including the introduction of new chemotherapy drugs and the use of CT-based planning systems for radiation treatment (6). While the best timing for adjuvant treatment remains under investigation, postoperative chemo-radiotherapy is the only approach with proven efficacy for patients who undergo surgical resection.

Chemotherapy in the SWOG9008/INT0116 trial was based on 5-fluorouracil (5FU) alone. To achieve improved results, we designed a phase II study of a postoperative chemo-radiotherapy protocol in patients with adenocarcinoma of the stomach or gastroesophageal junction (GEJ) using a combination of etoposide, cisplatin and adriamycin (modified EAP), a regime reported by our center (7), as postoperative chemotherapy. This treatment was followed by radiotherapy combined with weekly doses of cisplatin.

Patients and methods

Patients. Following approval of the study protocol by the institutional ethics committee, a retrospective analysis of the medical records of patients who underwent radical surgery

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Key words: gastric cancer, adjuvant chemo-radiotherapy, cisplatin, adriamycin, etoposide

for gastric or gastroesophageal adenocarcinoma and were treated with four cycles of modified EAP protocol followed by a radiotherapy course concomitant with weekly cisplatin was undertaken. Radical surgery was defined as complete resection of the tumor mass and involved lymph nodes. Patients with minimal microscopic peritoneal metastatic disease, revealed on the pathology report only, as well as those with microscopic focally positive surgical margins (R1), were also eligible. Disease stage was defined according to the American Joint Committee on Cancer (AJCC) TNM staging classification for carcinoma of the stomach (7th edition).

Eligibility criteria for the study included age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, no prior chemotherapy or radiotherapy, complete recovery after surgery, normal serum creatinine and bilirubin levels, adequate bone marrow function (WBC >4,000, PLT >100,000) and no known contraindications to the chemotherapy drugs included in the modified EAP regimen (7).

Treatment. The modified EAP regimen consisted of etoposide 100 mg/m² on days 1-3, cisplatin 27 mg/m² on days 1-3 and adriamycin 40 mg/m² on day 1 administered every 21 days, for four cycles. Doses of the three drugs were reduced by 10% in all patients >65 years of age. Primary prophylaxis with granulocyte colony-stimulating factor (GCSF) was routinely used.

Radiation treatment of 45 Gy in 25 fractions was initiated 3-4 weeks following completion of the last chemotherapy cycle. Weekly cisplatin (40 mg/m²) was scheduled concomitantly. For the delineation of target volumes and critical structures, 3D CT-based planning was used. Simulation was performed in the supine arms-up position, intravenous contrast agent was administered during the scan, and CT slice thicknesses were up to 3 mm. Radiation was delivered using 6-18 MV photons with a linear accelerator. Clinical target volume (CTV) and the design of radiation treatment fields depended on the primary tumor location and the extent of lymph node involvement. Lymph node stations in the radiotherapy field included perigastric celiac, splenic, suprapancreatic, pancreatico-duodenal and porta hepatis. Radiotherapy fields for patients with GEJ tumors also included periesophageal lymph nodes, although pancreatico-duodenal nodes were excluded. The planning target volume consisted of the CTV with a 1 cm margin. Relevant organs at risk were contoured and use of a dose-volume-histogram (DVH) was mandatory. The dose homogeneity within the volume had to be maintained within -5% and +7% of the prescribed dose.

Follow-up. On completion of the treatment plan, patients were followed-up every 3-6 months. Imaging studies, endoscopy and determination of serum CEA and CA-19 were carried out at the discretion of the physician.

Toxic effects were graded by the National Cancer Institute Common Toxicity Criteria (CTCAE), version 4.0.

Statistical analysis. Survival and recurrence-free survival were measured from the first day of chemotherapy, using the Kaplan-Meier product limit method. Loco-regional recurrence was defined as a recurrence within the radiation field, while other recurrences were defined as distant. Two-tailed p-values

Table I. Characteristics of patients treated with etoposide/cisplatin/adriamycin followed by radiotherapy of 45 Gy with concomitant cisplatin.

Characteristics	No.
No. of patients	40
Age: median (range)	58 (42-80)
Male/female	27/13
Stage	
II	4
IIIA	18
IIIB	8
IIIC	3
IV	7
Tumor site	
Gastroesophageal junction	15
Fundus/cardia	5
Stomach body	10
Antrum	10
PS	
0	8
1	17
2	15
PS, performance status.	

of 0.05 or less were considered as statistically significant. Statistical analysis was performed with using SPSS (Statistics Products Solutions Services) 18.0 software for Windows.

Results

Patient characteristics. Between October 2004 and May 2009, 40 consecutive patients were treated in accordance with the protocol described in Patients and methods. The major characteristics of these patients are shown in Table I. The majority of patients had stage III disease; minimal peritoneal metastatic spread near the primary gastric tumor, identified by the pathology report only, was defined as stage IV disease. Six patients had R1 resection of the primary tumor (stage III, four patients; stage IV, two patients). Re-operation was ruled out by secondary surgical consultation.

All 40 patients received at least one cycle of chemotherapy (range, 1-6); 70% of the patients completed the four planned chemotherapy cycles. EAP was discontinued in 12 patients due to toxicity (8 patients) and tumor progression (4 patients).

Five patients did not receive chemo-radiotherapy due to rapid disease progression. Of the remaining 35 patients, 8 patients were treated without concomitant cisplatin (at the discretion of the physician). Another 4 patients received carboplatin (AUC 2/weekly) due to previous cisplatin toxicity.

Evaluation of treatment efficacy was performed separately for the group of patients who achieved R0 resection (stage II and III, n=29) and for the group with R1 resection and/or metastatic disease (n=11).

Table II. Adverse events during chemotherapy of etoposide/cisplatin/adriamycin followed by radiotherapy of 45Gy with concomitant cisplatin.

	Etoposide/cisplatin/adriamycin			Radiotherapy of 45 Gy with cisplatin		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Non-hematological						
Diarrhea	2 (5%)	2 (5%)	1 (2.5%)	2 (6%)	-	-
Nausea	14 (35%)	2 (5%)	-	8 (23%)	3 (9%)	1 (3%)
Vomiting	12 (30%)	-	-	9 (26%)	1 (3%)	-
Abdominal pain	2 (5%)	2 (5%)	-	5 (15%)	3 (9%)	-
Stomatitis/esophagitis	3 (7.5%)	1 (2.5%)	1 (2.5%)	6 (18%)	-	-
Asthenia	12 (30%)	2 (5%)	-	9 (26%)	5 (15%)	-
Infection	-	7 (17.5%)	-	-	-	-
Hearing loss	4 (10%)	-	-	-	-	-
Sensory neuropathy	4 (10%)	-	-	-	-	-
Other	3 (7.5%)	1 (2.5%)	1 (2.5%)	-	-	-
Hematological						
Leucopenia	7 (17.5%)	9 (21.5%)	8 (20%)	4 (10%)	-	-
Neutropenia	2 (5%)	5 (12.5%)	19 (47.5%)	3 (7.5%)	-	-
Thrombocytopenia	4 (10%)	3 (7.5%)	3 (7.5%)	7 (21%)	1 (3%)	-
Anemia	11 (27.5%)	3 (7.5%)	-	-	-	-
Febrile neutropenia	-	6 (15%)	1 (grade 5)	-	1 (3%)	-

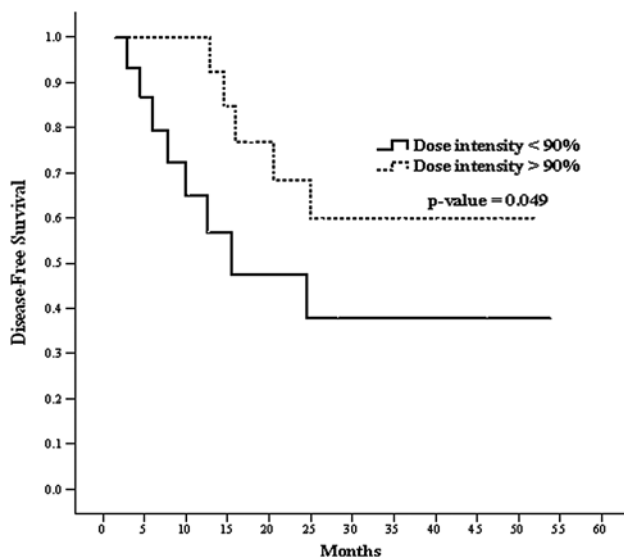


Figure 1. DFS in the group of patients after curative surgery (n=29), comparing patients receiving EAP with an average dose intensity for the 4 cycles of >90% (n=13) versus <90% (n=16). DFS, disease-free survival; EAP, etoposide/cisplatin/adriamycin.

DFS in the group of patients after curative surgery. In the group of patients undergoing curative resection, an average dose intensity of >90% for the four cycles of modified EAP was associated with a longer DFS compared to a lower average dose intensity ($p=0.049$) (Fig. 1). No correlation was found between DFS and other parameters, such as age, gender, pathological grade or number of lymph nodes dissected. The lack of correlation between outcome and disease stage was explained

by the fact that >70% of the patients had stage III disease. The most common sites of recurrence were the peritoneal cavity (n=5), tumor bed (n=3) and ovary (n=3).

Median OS was 53 months, with 66% surviving for two years and 57% for three years. A trend to improved OS (40 months versus 15 months, $p=0.06$) was correlated with a full dose of EAP treatment in consecutive cycles.

Median time to tumor progression (TTP) and OS were 5.5/9.5 and 9.0/15.5 months, respectively, in the patient groups with residual microscopic disease R1 and resected M1.

Toxicity and adverse events. All 40 patients were eligible for a toxicity assessment. One patient succumbed to the disease 33 days after initiation of the first cycle of chemotherapy with pancytopenia, neutropenic fever and profound electrolyte changes, and later, fulminant multi-organ insufficiency.

Common adverse events during EAP chemotherapy and chemo-radiation treatment are shown in Table II. Although a primary prophylaxis with GCSF was administered during chemotherapy cycles, the most significant grade 3-4 hematological toxicities were neutropenia (60%) and thrombocytopenia (15%). Seven (17.5%) patients developed one episode of neutropenic fever. Red blood cell (RBC) transfusion was indicated in 11 patients. Grade 3-4 non-hematological toxicities were predominantly gastro-intestinal issues (nausea, vomiting, abdominal pain, diarrhea and stomatitis) and infections. Together with dose-independent toxicities (cardiotoxicity n=2, renal toxicity n=1, neurotoxicity n=4, and oto-toxicity n=4), these had a marked effect on chemotherapy dose intensity. Dose reductions due to toxicity were indicated in 38% of patients.

The majority of adverse events during the chemo-radiotherapy course were grade 2-3 gastro-intestinal adverse events and asthenia (Table II). Two years after treatment completion, one patient suffered a non-pathological fracture of the lumbar vertebra (L3) treated with vertebroplastia; this was potentially a late radiotherapy adverse event.

Discussion

Perioperative chemotherapy is becoming a common strategy in operable GC. However, the benefits of this approach over surgery followed by adjuvant therapy has to be confirmed in a prospective phase III study. Furthermore, a considerable number of GC patients continue to be referred to an oncologist following surgery. The standard postoperative adjuvant therapy for GC is based on the INT 0116 trial and contains 5FU and leucovorin administered as bolus IV both prior to and concomitantly with radiotherapy. Possible disadvantages of this regime are the relatively low activity of the 5FU-leucovorin combination and the high gastrointestinal toxicity associated with concomitant radiation and 5FU. According to the INT 0116 trial, reported grade 3-4 GI toxicity with 5FU was high (33%) (2).

In the current study, modified EAP was selected in light of our previous experience with this regime, showing a relatively high activity in advanced GC (7), as well as promising results as an adjuvant protocol (8). We substituted 5FU with cisplatin as the radio-sensitizer, with the intention of reducing the GI toxicity associated with concomitant chemo-radiotherapy.

The intensification of chemotherapy treatment in the adjuvant setting for stomach carcinoma patients has a leading priority in the literature. Several phase II trials that used modern multi-agent chemotherapy regimens (9-11) reported promising results and good safety profiles prior to and post chemo-radiotherapy. However, the latest reported results in the CALGB-80101 phase III trial showed that an ECF regimen failed to improve survival compared to bolus 5FU/leucovorin prior to and following 5FU/XRT (12). In the present study, the trend for improved survival in patients treated with an average EAP dose intensity of >90% may support the role of intensive adjuvant chemotherapy for GC. However, the sample size used is limited and conclusions regarding the efficacy of this protocol are insufficient. Furthermore, the safety profile of the regimen is problematic, having resulted in dose reductions during the treatment for the majority of the patients.

In a randomized phase II study, the RTOG 0114 study compared a combination of paclitaxel and cisplatin with and without 5FU (13). In the interim analysis of this study, severe GI toxicity in the arm containing 5FU resulted in the early discontinuation of the trial. Findings of this study showed severe GI toxicity was low (only 15%), thereby justifying a regimen without 5FU for adjuvant chemo-radiotherapy treatment in stomach carcinoma patients.

Hematological toxicity is consistently high in the majority of studies of adjuvant treatment for stomach carcinoma patients. For instance, the rate of grade 3-4 toxicity with and without 5FU in the RTOG 0114 trial was 67 and 40%, respectively (13). Although prophylactic GCSF was administered in this study, grade 3-4 hematological toxicity was relatively high

and, together with neutropenic fever, was the main reason for low-dose chemotherapy intensity.

The option of administering adjuvant chemotherapy only was renewed recently with promising results from a small, randomized, phase III trial (14) supporting the use of adjuvant platinum/docetaxel chemotherapy instead of chemo-radiotherapy. That trial found no differences between the groups, but was underpowered to exclude a beneficial effect of radiotherapy. The sub-analysis showed a prognostic role of ERCC1 expression. Patients with ERCC1-positive tumors had significantly longer median DFS and OS, and intensified adjuvant chemotherapy may be justified for those patients (14). In the recent presentation of results from the CLASSIC trial (15), a marked improvement in DFS (primary endpoint) and a trend to OS improvement was demonstrated in a group of Asian patients who received an adjuvant XELOX protocol, compared to observation alone.

In our study, postoperative therapy following R1 resection or in patients with microscopic peritoneal M1 disease did not appear to improve prognosis, and survival in this subgroup of patients was similar to that expected in metastatic disease. The results do not support a beneficial effect of radiotherapy treatment for these patients.

In conclusion, the high toxicity rate of this regimen does not justify further evaluation of this postoperative protocol. Chemo-radiotherapy for R1 or pathological microscopic M1 patients does not appear to be justified.

References

- Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA and Hamilton SM: Gastric adenocarcinoma. Review and considerations for future directions. *Ann Surg* 241: 27-39, 2005.
- Macdonald JS, Smalley SR, Benedetti J, *et al*: Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 345: 725-730, 2001.
- Cunningham D, Allum WH, Stenning SP, *et al*: Perioperative chemotherapy versus surgery alone for respectable gastroesophageal junction carcinoma. *N Engl J Med* 355: 11-20, 2006.
- Goburn NG, Govindarajan A, Law CH, *et al*: Stage-specific effect of adjuvant therapy following gastric cancer resection: a population-based analysis of 4,041 patients. *Ann Surg Oncol* 15: 500-507, 2008.
- Fiorica F, Cartei F, Enea M, *et al*: The impact of radiotherapy on survival in respectable gastric carcinoma: a meta-analysis of literature data. *Cancer Treat Rev* 33: 729-740, 2007.
- Lim L, Michael M, Mann GB and Leong T: Adjuvant therapy in gastric cancer. *J Clin Oncol* 23: 6220-6232, 2005.
- Haim N, Tsalik M and Robinson E: Treatment of gastric adeno-carcinoma with combination of etoposide, adriamycin and cisplatin (EAP): comparison between two schedules. *Oncology* 51: 102-107, 1994.
- Bar-Sela G, Tsalik M, Steiner M, Wollner M and Haim N: Local recurrence following adjuvant chemotherapy without radiotherapy in completely resected stomach and gastroesophageal junction adenocarcinoma. *Anticancer Res* 29: 1853-1856, 2009.
- Leong T, Joon DL, Willis D, *et al*: Adjuvant chemoradiation for gastric cancer using epirubicin, cisplatin, and 5-fluorouracil before and after three-dimensional conformal radiotherapy with concurrent infusional 5-fluorouracil: a multicenter study of the Trans-Tasman Radiation Oncology Group. *Int J Radiat Oncol Biol Phys* 79: 690-695, 2011.
- Oechsle K, Bokemeyer C, Hartmann JT, Budach W, Trarbach T, Stahl M, *et al*: Four consecutive multicenter phase II trials of adjuvant chemoradiation in patients with completely resected high-risk gastric cancer: the experience of the German AIO/ARO/CAO group. *J Cancer Res Clin Oncol* 135: 163-172, 2009.

11. Orditura M, De Vita F, Muto P, Vitiello F, Murino P, Lieto E, Vecchione L, *et al*: Adjuvant chemoradiotherapy in patients with stage III or IV radically resected gastric cancer: a pilot study. *Arch Surg* 145: 233-238, 2010.
12. Fuchs C, Tepper J, *et al*: Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LCV before and after CRT: intergroup Trial CALGB 80101. ASCO abstract 4003, 2011.
13. Schwartz G, Winter K, Minsky BD, *et al*: Randomized phase II trial evaluating two paclitaxel and cisplatin-containing chemoradiation regimens as adjuvant therapy in resected gastric cancer (RTOG-0114). *J Clin Oncol* 27: 1956-1962, 2009.
14. Bamias A, Karina M, Papakostas P, *et al*: A randomized phase III study of adjuvant platinum/docetaxel chemotherapy with or without radiation therapy in patients with gastric cancer. *Cancer Chemother Pharmacol* 65: 1009-1021, 2010.
15. Bang Y, Kim Y, *et al*: Adjuvant capecitabine and oxaliplatin for gastric cancer: results of the phase III CLASSIC Trial. ASCO abs. 4002, 2011.