



Adjuvant chemoradiotherapy combined with cisplatin, 5-fluorouracil and folinic acid for locally advanced gastric cancer

Muharrem Kocar ^{a, *}, Ferhat Telli ^b, Berkant Sonmez ^a, Hande Kocar ^c

^a Department of Medical Oncology, Sanliurfa State Hospital, Sanliurfa, Turkey

^b Department of Medical Oncology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey

^c Department of Radiation Oncology, Sanliurfa State Hospital, Sanliurfa, Turkey

ARTICLE INFO

Article history:

Received 26 February 2016

Received in revised form

21 March 2016

Accepted 20 April 2016

Available online 2 July 2016

Keywords:

Adjuvant treatment

Chemotherapy

Cisplatin

Gastric cancer

Radiotherapy

ABSTRACT

Aim: This study retrospectively assessed the efficacy and tolerability of combination chemotherapy with cisplatin, infusional 5-fluorouracil and folinic acid given every two weeks and subsequent chemoradiotherapy with continuous infusions of 5-fluorouracil, in gastric cancer following curative resection. **Methods:** Between August 2007 and January 2014, 58 patients received adjuvant cisplatin 50 mg/m², leucovorin 400 mg/m², 5-fluorouracil 400 mg/m² IV bolus and 5-fluorouracil 2400 mg/m² as 48-h continuous infusion, every 14 days for gastric adenocarcinoma. After the first 2 cycles of chemotherapy, adjuvant radiation therapy was administered concurrently with the continuous infusion of 5-fluorouracil. Following the completion of radiation therapy, patients received another 4 cycles of combination chemotherapy.

Results: A total of 58 patients were included in this study and out of these, 41 patients were male and the median age was 53.5 years. 81% of the patients (n = 47) could complete 6 courses of planned chemotherapy. The median follow-up time was 31.4 (9.33–88.77) months, the median disease free survival (DFS) was 26.43 (95% CI: 49.38–69.95) months. The median overall survival (OS) was 28.53 (95% CI: 49.46–69.55) months. The estimated 3-year DFS and OS rates were 58.75% and 64.04% respectively. Common grade 3 and 4 side effects were weakness (18.9%), nausea and vomiting (12%), diarrhea (10.3%) and neutropenia (10.3%).

Conclusion: The addition of combination chemotherapy with cisplatin, infusional 5-fluorouracil and folinic acid before and after chemoradiotherapy was found to be safe and effective in patients with operated gastric cancer.

Copyright © 2016 Turkish Society of Medical Oncology. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Gastric cancer is one of the major causes of cancer-related death despite a decreasing incidence in Western populations.^{1–3} The 5-year survival rate ranges from 70% to 75% for stage 1 patients in Western countries, while this rate has been reported as 35% or less in stage 2 and more advanced disease.^{4–6} However, the diagnosis is frequently made at the advanced stages of the disease.

Surgical resection is the primary treatment for gastric cancer. However, surgical treatment alone offers a low 5-year survival rate

* Corresponding author. Department of Medical Oncology, Sanliurfa State Hospital, 63300, Sanliurfa, Turkey. Tel.: +90 414 3479932, +90 0506 586 2274 (mobile); fax: +90 414 3186812.

E-mail address: muharremkocar@hotmail.com (M. Kocar).

Peer review under responsibility of Turkish Society of Medical Oncology.

in patients with locally advanced gastric cancer.^{7–9} Therefore, adjuvant therapies such as radiation therapy (RT) and/or chemotherapy (CT) have been introduced in the management of gastric cancer in order to improve local control of the disease and survival rates. The benefits of adjuvant therapy have been demonstrated in a number of meta-analyses and although it has been widely accepted, any standard adjuvant therapy regimen has not been defined yet.^{10,11}

The INT 0116 study demonstrated a significant improvement in the disease free survival (DFS) and overall survival (OS) among the high relapse risk patients who received adjuvant chemoradiotherapy (CRT) in comparison to those who did not receive. In this study, bolus 5-fluorouracil (5-FU) and leucovorin were administered concomitantly as an adjuvant CT regimen.¹² However, this regimen has been considered as substantially toxic and inadequate in preventing distant metastases. Therefore, various CT

regimens have been increasingly used as adjuvant and neoadjuvant therapy in treating locally advanced gastric cancer patients and investigated in a number of studies.^{13–16}

Our study retrospectively assessed the efficacy and tolerability of combination CT with cisplatin, 5-FU and folinic acid given every two weeks and subsequent CRT with 5-FU infusions, in non-metastatic gastric cancer following curative surgical resection.

2. Materials and methods

Patients aged 18 years and older, with the Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, who have adequate bone marrow, liver, kidney and cardiac functions and who were diagnosed with histologically proven gastric adenocarcinoma and underwent a curative surgical resection between August 2007 and January 2014, were assessed retrospectively. Patients who were staged as 1a or 1b (pT2N0) based on the American Joint Committee on Cancer (AJCC) staging system 2010, patients with a microscopic or macroscopic residual tumor, patients with distant metastasis and who were not expected to tolerate CT or RT due to other systemic diseases, were excluded from the study.

The adjuvant CT protocol included; cisplatin 50 mg/m² on the 1st day, leucovorin 400 mg/m² on the 1st day, bolus 5-FU 400 mg/m² on the 1st day and 5-FU 2400 mg/m² as 48-h continuous infusion. This CT regimen was administered every 14 days. After the first 2 cycles of CT, adjuvant RT was started concurrently with the continuous infusion of 5-FU at a dose of 200 mg/m²/day. RT was administered to the tumor bed and regional lymph nodes with a total dose of 45 Gy, 1.8 Gy per fraction in 25 fractions, following the completion of RT, another four cycles of CT were administered.

Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 3.0. The therapy was discontinued for one week in patients who developed grade 3 or 4 toxicity. CT was resumed with a dose reduction of 25%, after the resolution of the toxicity to grade 1. Therapy was permanently discontinued in case of a Grade 3 or 4 toxicity that lasted longer than 2 weeks in spite of an appropriate treatment.

Statistical Analysis: An NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) was used for the statistical analyses. Descriptive statistics (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used in the assessment of the data from the study. Student T Test was used for two-group comparisons of normally distributed quantitative data, while Mann Whitney U Test was used for the two-group comparisons of the parameters that were not normally distributed. Fisher's Exact Test and Yates' Continuity Correction Test (Yates corrected chi square test) were used for the comparisons of qualitative data. Kaplan Meier Survival and LogRank test were used for the survival assessments. P values of <0.01 and < 0.05 indicated statistically significant levels.

3. Results

A total of 58 patients were included in the study and out of these, 41 patients were male (70.7%) and 17 patients were female. The median age of the patients was 53.5 years (30–79 years). Descriptive characteristics of the patients are shown in Table 1. D1 dissection was performed in 50% (n = 29) of the cases, while D2 dissection was performed in 48.3% (n = 28) of the cases. The number of the lymph nodes that were resected ranged from 9 to 76 with a median of 27 lymph nodes, while the number of the positive lymph nodes ranged from 0 to 69 with a median of 5 lymph nodes. Lymphovascular invasion was detected in 87.9% (n = 51) of the

Table 1
The distribution of descriptive characteristics

Characteristic	n	%	
Patients	58	100	
Median age (min–max)	53,5	30–79	
Sex	Male	41	70.7
	Female	17	29.3
pT	2	4	6.9
	3	37	63.8
	4	17	29.3
pN	0	6	10.3
	1	11	19.0
	2	14	24.1
	3	27	46.6
Stage	2	14	24.1
	3	44	75.9
Grade	1	3	5.2
	2	18	31.0
	3	37	63.8
Type of surgical intervention	Subtotal gastrectomy	21	36.2
	Total gastrectomy	37	63.8
Dissection	D1	29	50.0
	D2	28	48.3
	D3	1	1.7
ECOG PS	0	36	62.1
	1	22	37.9
The number of chemotherapy cycles	3 cycles	2	3.4
	4 cycles	6	10.3
	5 cycles	3	5.2
	6 cycles	47	81.0

patients while, perineural invasion was detected in 74.1% (n = 43) of the patients.

The numbers of CT cycles administered to the patients ranged from 3 to 6 while the median number of the CT cycles was 6. All of the patients completed concomitant CRT following the first two cycles of chemotherapy. Forty-seven (81%) patients could complete 6 cycles of planned CT. No treatment-related mortality was observed. Most of the side effects were mild. However side effects necessitating a dose reduction were observed in 31% of the patients. Most common grade 3 or 4 side effects included weakness (18.9%), nausea and vomiting (12%), diarrhea (10.3%), neutropenia (10.3%), hand-foot syndrome (1.7%), anemia (1.7%), mucositis (1.7%).

The median follow up time was 31.4 (9.33–88.77) months, the median DFS was 26.43 (95% CI: 49.38–69.95) months (Fig. 1). Thirty-nine (67.2%) out of 58 study participants survived, while 19 patients died. The median OS was 28.53 (95% CI: 49.46–69.55) months (Fig. 2). The estimated 3-year DFS and OS rates were 58.75% and 64.04% respectively. No significant difference was found between the types of dissection (D1 vs D2–3) in DFS and OS (p > 0.05).

Locoregional recurrence was defined as tumor recurrence in the lymph nodes located at RT fields, at duodenal stump, anastomosis site and at the tumor bed. The recurrences at the areas other than those stated above (peritoneum, liver, lymphnode involvement in the areas apart from the radiation therapy field) were defined as distant metastasis. Five (8.6%) out of 23 (39.6%) patients with relapsing disease had local recurrence while 18 (31%) patients had distant metastasis.

4. Discussion

The management of gastric cancer shows variations around the world. While adjuvant CT is the treatment of choice in Asian countries, perioperative CT is administered in Europe. Post-operative CRT is frequently recommended to the patients in the US. A complete resection with an adequate lymph node dissection is the most important factor in disease control. However, the prognosis of locally advanced gastric cancer still remains poor.

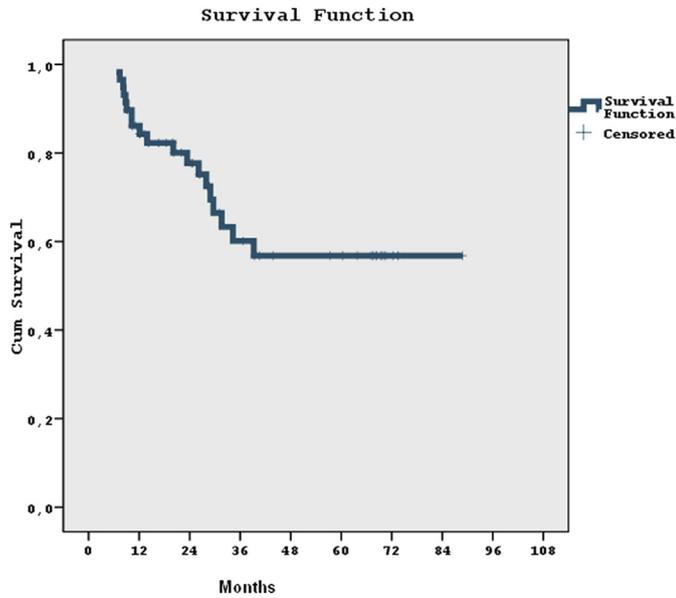


Fig. 1. Disease free survival curves. Kaplan–Meier disease free survival curve. Median 26.43 months (95% CI: 49.38–69.95)

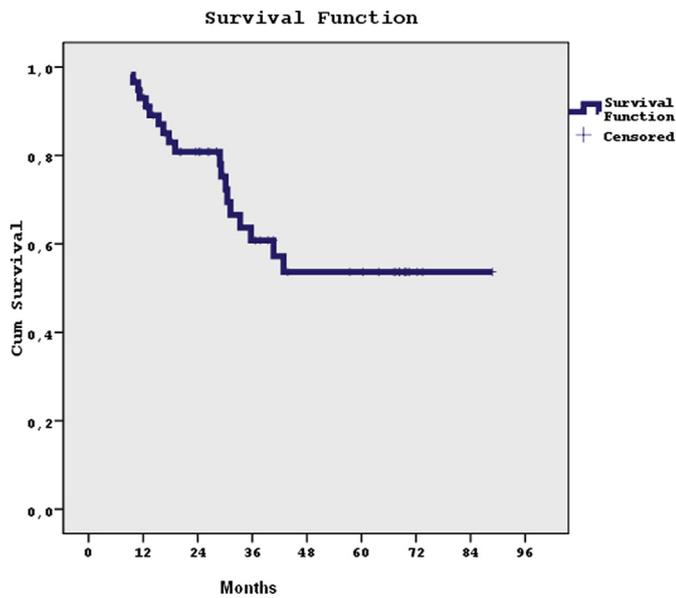


Fig. 2. Overall survival curves. Kaplan–Meier overall survival curve. Median 28.53 months (95% CI: 49.46–69.55)

The first large phase 3 study on adjuvant CRT was the SWOG INT-0116 study and DFS and OS rates were found to be significantly longer in the group of patients who received CRT. Three-year disease-free (48 versus 31 percent) and overall survival rates (50 versus 41 percent) were significantly better with combined modality therapy, and median survival was significantly longer (36 versus 27 months).¹² However, the common side effects that were observed in this study prevented to define an optimal therapy regimen.

In our study, a retrospective assessment was carried out on the efficacy and tolerability of the combination CT with adjuvant cisplatin, 5-FU and leucovorin given every two weeks and subsequent CRT with continuous 5-FU infusion, in non-metastatic locally advanced gastric cancer (pT3, T4 or N+) following curative surgical resection.

The phase 2 study of the Radiation Therapy Oncology Group (RTOG) study, failed to show the superiority of adjuvant CRT with cisplatin paclitaxel combination CT to the adjuvant CRT with concomitantly administered 5-FU.¹⁷

In the ARTIST study adjuvant capecitabine plus cisplatin CT was compared to capecitabine plus cisplatin with concurrent capecitabine RT. Although CRT did not contribute to overall DFS, CRT significantly prolonged the DFS in the group of high risk patients with lymph node metastasis (three-year DFS 76 versus 72 percent, $p = 0.004$).¹⁸

Fuchs et al investigated the benefits of ECF combination CT given before and after 5-FU based adjuvant CRT and the addition of ECF to CRT did not prolong the DFS. Overall survival, the primary endpoint, was not significantly better with ECF (at three years, 52 versus 50 percent for ECF and FU/LV, respectively).¹⁹ Another study conducted by Li et al demonstrated the benefits of the addition of ECF combination CT to CRT and a positive correlation was found between the OS and the number of the cycles of CT.²⁰ Furthermore, the addition of ECF combination CT to CRT was found to be appropriate and safe in a study conducted by Trans-Tasman Radiation Oncology Group.²¹

In another retrospective study, Uncu et al evaluated the efficacy and toxicity of the cisplatin given before and after 5-FU based CRT. This study included the patients who had undergone an R1 resection and most of the patients had lymph node metastases. It was concluded that this therapy regimen was effective and tolerable.²²

In our study the majority of the patients had locally advanced stage pT3–4 (93.1%), pN1–N3 (89.7%). In addition, 63.8% of the patients had a grade 3 tumor. We aimed at investigating the benefits and side effect profile of cisplatin added to adjuvant therapy in the group of the patients with a high risk of relapse. The median DFS was 26.43 months and median OS was 28.53 months in the high-risk group. The estimated 3-year DFS and OS rates were 58.75% and 64.04% respectively. On the other hand, the 3-year OS was 50% in the CRT arm of INT-0116 study.¹²

All of the patients tolerated concurrent CRT after the first two cycles of CT. Moreover the majority of the patients (81%) could receive all of the planned therapy regimens. However, in the INT-0116 study, only 64% of the patients could complete their planned therapy. In the chemoradiotherapy group, grade 3 and grade 4 acute toxic effects occurred in 41 and 32 percent of patients, respectively, while three (1 percent) died from treatment-related toxicity. The most frequent grade 3 or worse adverse effects were hematologic (54 percent), gastrointestinal (33 percent), infectious (6 percent), and neurologic (4 percent).¹² On the other hand 75% of the patients in the CRT arm could complete their planned therapy in the ARTIST study.¹⁸ A dose reduction was required only in 31% of the patients due to grade 3 or 4 side effects. Gastrointestinal side effects and weakness constituted the major part of the side effects. No toxicity-related death was observed. The prevalence of grade 3 and 4 hematological and non-hematological side effects was found to be significantly lower in comparison to their prevalence in the medical literature.^{12,18,23}

Although the type of the lymph node dissection that should be chosen is still controversial, D2 dissection has been recommended in several studies.^{24,25} In our study, D1 dissection was performed in half of the patients while D2 or D3 dissection was performed in the other half. The DFS and OS rates and side effect profiles did not differ between the dissection groups. A criticism of INT-0116 trial was the limited extent of the surgical procedure in most cases. Although D2 lymph node dissection was recommended, it was only performed in 10 percent of cases, and 54 percent did not even have clearance of the D1 nodal regions.

In our study 5 (8.6%) out of 23 (39.6%) patients with relapsing disease had local recurrence while 18 (31%) patients had distant

metastasis. A later pattern of failure analysis of INT-0116 study disclosed a similar frequency of distant metastasis (16 versus 18 percent in the chemoradiotherapy and control groups, respectively), but fewer local (2 versus 8 percent) and regional (22 versus 39 percent) recurrences with chemoradiotherapy.²⁶

In conclusion the addition of combination CT with cisplatin, 5-FU, folinic acid before and after 5-FU based CRT, was found to be safe and effective in surgically resected gastric cancer patients with a high risk of relapse. These results should be supported by prospective studies with larger sample size.

Conflicts of interest

All authors state that they have no conflicts of interest.

References

- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
- Bertuccio P, Chatenoud L, Levi F, et al. Recent patterns in gastric cancer: A global overview. *Int J Cancer.* 2009;125:666–673.
- Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin.* 2014;64:9–29.
- Howlander N, Ries LA, Stinchcomb DG, Edwards BK. The impact of under-reported Veterans Affairs data on national cancer statistics: Analysis using population-based SEER registries. *J Natl Cancer Inst.* 2009;101:533–536.
- Yang D, Hendifar A, Lenz C, et al. Survival of metastatic gastric cancer: Significance of age, sex and race/ethnicity. *J Gastrointest Oncol.* 2011;2:77–84.
- Agboola O. Adjuvant treatment in gastric cancer. *Cancer Treat Rev.* 1994;20:217–240.
- Faivre J, Forman D, Estève J, Gatta G. Survival of patients with oesophageal and gastric cancers in Europe. EUROCARE Working Group. *Eur J Cancer.* 1998;34:2167–2175.
- Hundhal SA, Menck HR, Mansour EG, Winchester DP. The National Data Base report on gastric carcinoma. *Cancer.* 1997;80:2333–2341.
- Hundhal SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy; Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the “different disease” hypothesis. *Cancer.* 2000;88:921–932.
- Janunger KG, Hafström L, Glimelius B. Chemotherapy in gastric cancer: A review and updated meta-analysis. *Eur J Surg.* 2002;168:597–608.
- Panzini I, Gianni L, Fattori PP, et al. Adjuvant chemotherapy in gastric cancer; A meta-analysis of randomized trials and a comparison with previous meta-analyses. *Tumori.* 2002;88:21–27.
- 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.* 2001;345:725–730.
- Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Eng J Med.* 2006;355:11–20.
- Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase 3 trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage 2 or 3 gastric cancer. *J Clin Oncol.* 2011;29:4387–4393.
- Di Costanzo F, Gasperoni S, Manzione L, et al. Adjuvant chemotherapy in completely resected gastric cancer: A randomized phase III trial conducted by GOIRC. *J Natl Cancer Inst.* 2008;100:388–398.
- Boige V, Pignon J, Saint-Aubert B, et al. Final results of a randomized trial comparing preoperative 5-fluorouracil (F)/cisplatin (P) to surgery alone in adenocarcinoma of stomach and lower esophagus (ASLE): FNLCC ACCORD07-FFCD 9703 trial. *J Clin Oncol.* 2007;25:4510.
- Schwartz GK, 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.* 2009;20:1956–1962.
- Lee J, Lim do H, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection; the ARTIST trial. *J Clin Oncol.* 2012;30:268–273.
- Fuchs CS, Tepper JE, Niedzwiecki D, et al. Postoperative adjuvant chemotherapy 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/LV before and after CRT: Intergroup trial CALGB 80101. *J Clin Oncol.* 2011;29:4003.
- Li G, Zhang Z, Ma X, Zhu J, Cai G. Postoperative chemoradiotherapy combined with epirubicin-based triplet chemotherapy for locally advanced adenocarcinoma of the stomach or gastroesophageal junction. *PLoS One.* 2013;8:54233.
- Leong T, Lim Joon D, Willis D, et al. Adjuvant chemoradiation for gastric Cancer using ECF before and after 3D-Conformal radiotherapy with CI 5-FU; a multicentre study of the Trans-Tasman Radiation Oncology Group (TROG). *Int J Radiat Oncol Biol Phys.* 2011;79:690–695.
- Uncu D, Ozdemir NY, Aksoy S, et al. 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. *Asian Pac J Cancer Prev.* 2010;11:1493–1497.
- Kollmannsberger C, Budach W, Stahl M, et al. Adjuvant chemoradiation using 5-fluorouracil/folinic acid/cisplatin with or without paclitaxel and radiation in patients with completely resected high-risk gastric cancer; two cooperative phase II studies of the AIO/ARO/ACO. *Ann Oncol.* 2005;16:1326–1333.
- Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol.* 2010;11:439–449.
- Jiang L, Yang KH, Chen Y, et al. Systematic review and meta-analysis of the effectiveness and safety of extended lymphadenectomy in patients with resectable gastric cancer. *Br J Surg.* 2014;101:595–604.
- Smalley SR, Benedetti JK, Haller DG, et al. Updated analysis of SWOG-directed intergroup study 0116: A phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. *J Clin Oncol.* 2012;30:2327.