European Review for Medical and Pharmacological Sciences 2020; 24: 11344-11349

Extending chemotherapy with capecitabine following CAPOX chemotherapy improves survival of Stage 3 gastric carcinoma after radical surgery: a 5-year analysis

Y. FEI[1], S.-X. HUANG[1], M.-Y. FEI[1], X.-P. PAN[2]

[1]General Surgery Department of First People's Hospital affiliated to Huzhou Normal College, Huzhou, People's Republic of China
[2]Nursing Department of First People's Hospital affiliated to Huzhou Normal College, Huzhou, People's Republic of China

Abstract. – OBJECTIVE: To assess the effectiveness and safety of treatment consisting of extending chemotherapy (ECT) with capecitabine following capecitabine plus oxaliplatin (CAPOX) chemotherapy for stage 3 gastric carcinoma (GC) after D2 gastrectomy.

PATIENTS AND METHODS: In this retrospective study, we included 214 patients with stage 3 GC who underwent D2 gastrectomy between January 2012 and April 2014. The CAPOX regimen chemotherapy was administrated to all of the patients as adjuvant therapy. The CAPOX regimen consisted of capecitabine (1000 mg/m^2, in 2 divided doses for 14 d) and oxaliplatin (130 mg/m^2 given on Day 1), repeated every 21 d for 8 cycles. Following CAPOX chemotherapy, 102 of these patients received extending chemotherapy (the ECT group) with capecitabine, whereas 112 patients (the control group) received no ECT. The ECT consisted of capecitabine (1000 mg/m^2, in 2 divided doses for 14 d), repeated every 21 d for 8 cycles at most. The chemotherapy was discontinued if unacceptable toxicity or disease progression occurred or upon the request of the patient. All cases were followed up, and overall survival (OS), recurrence-free survival (RFS), and toxicities were compared.

RESULTS: The ECT group exhibited a distinctly higher 5-year OS (p=0.0468) and RFS (p=0.0483) than those of the control group. The incidence of hand-foot syndrome was markedly greater in the ECT group (p=0.0043). No toxicity-related death occurred.

CONCLUSIONS: Extending chemotherapy with capecitabine following the CAPOX regimen chemotherapy provides significant survival benefit for stage 3 GC after D2 gastrectomy.

Key Words:
Gastric carcinoma, Chemotherapy, Overall survival, Recurrence-free survival.

Introduction

Gastric carcinoma (GC) has become a worldwide health issue due to its increasing incidence and prevalence[1,2]. About 1 million new cases are diagnosed and more than 700,000 deaths arising from GC are reported annually[3,4]. Radical resection provides an opportunity to cure the disease, but more than 40% of the cases develop recurrence within 2 years postoperatively; thus, adjuvant treatment is crucial[5-7]. Despite D2 gastrectomy, patients with stage 3 GC have evidently lower long-term survival than patients with earlier-stage GC[8]. Thus, innovative adjuvant therapy modalities for stage 3 GC need to be explored.

Improved survival has been reported in patients with stage 3 GC who undergo extended duration of adjuvant chemotherapy after radical surgery[9]. Similarly, completion of postoperative chemotherapy improves survival in patients with stage 3 GC[10]. Therefore, the duration of adjuvant chemotherapy and submissiveness to chemotherapy can potentially be considered as prognostic factors, independently, in patients with stage 3 GC after radical surgery.

However, studies regarding the optimal duration of adjuvant chemotherapy are rarely reported. Number of cycles of chemotherapy mostly depends on the reactivity and tolerability of the treatment in the patient and the preferences of the physician. This retrospective study was designed to assess the effectiveness and safety of extending chemotherapy (ECT) with capecitabine following capecitabine plus oxaliplatin (CAPOX) for patients with stage 3 GC after D2 gastrectomy.

Corresponding Author: Xueping Pan, MD; e-mail: jxm_hzyy@sina.com

Patients and Methods

Patients

We included 214 patients with stage 3 GC who underwent open D2 gastrectomy between January 2012 and April 2014. Our inclusion criteria were as follows: pathologically confirmed stage 3 GC [per the American Joint Committee on Cancer (AJCC) staging system, 7th edition][11]; no prior anticancer therapy; Eastern Cooperative Oncology Group score of 0-2; recurrence-free survival (RFS) and overall survival (OS) > 6 months; ages 18-75 years. Patients were divided into the ECT group and the control group on the basis of whether they received ECT.

We conducted this study in accordance with the Declaration of Helsinki and Good Clinical Practice recommendations and with the approval of the Medical Research Ethics Committee of the Huzhou Normal College.

Chemotherapy Administration

Patients with stage 3 GC started the adjuvant chemotherapy within 21 d after D2 gastrectomy. The CAPOX regimen consisted of capecitabine (1000 mg/m^2, in 2 divided doses for 14 d) and oxaliplatin (130 mg/m^2 given on Day 1), repeated every 21 d for 8 cycles in the first phase of chemotherapy. At the end of the CAPOX chemotherapy, physicians illustrated the potential advantages and disadvantages of ECT with capecitabine for the patients. The patients then decided whether to receive ECT based on their own assessment and then signed the consent form.

Overall, 102 patients agreed to receive ECT; hence, the ECT group was administered with capecitabine (1000 mg/m^2, in 2 divided doses for 14 d), which was repeated every 21 d for 8 cycles. Meanwhile, 112 patients without ECT after the CAPOX chemotherapy phase were observed as the control group.

Toxicities of chemotherapy were scaled in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. We reduced the chemotherapy dose by 25% in succeeding cycles if any of the following occurs: grade 4 neutropenia and/or grade 3 or 4 thrombocytopenia and anemia, grade 2 or 3 hand-foot syndrome, or another grade 3 or 4 acute non-hematologic adverse event. Meanwhile, we terminated the chemotherapy if any of the following occurs: prolonged recovery (more than 2 weeks) from the toxicities of chemotherapy, recurrence, or the patient requests termination. Patients who were administered fewer than 3 cycles of CAPOX chemotherapy or 3 cycles of ECT were excluded.

Patient Evaluation and Follow-up

We assessed the patients before each chemotherapy session during the treatment period. Subsequently, we followed them up each month in the 1st year post-surgery and then every 3 months thereafter or until their death. In the case of recurrence, the patients received chemotherapy, radiofrequency ablation, or palliative treatment.

Statistical Analysis

All data are presented as mean ± SD. We used Student's *t*-test, the chi-square test, or Fisher's exact test to examine the clinical data. Using Ridit analysis, we compared the toxicities of chemotherapy of the two groups. In this study, we described RFS as the interval from the surgery date to the date of the (i) first recurrence, (ii) death from any cause, or (iii) last follow-up. OS was described as the interval between the surgery date and the date of either death from any cause or the last follow-up. We used the log-rank test to evaluate the survival curves acquired from the Kaplan-Meier estimates. $p<0.05$ indicated statistical significance.

Results

Patient Characteristics

No significant difference was found in the characteristics of the patients, including gender, surgery date, age, tumor differentiation, tumor site, tumor size, tumor stage, and blood loss during the operation between the ECT group and the control group (Table I).

Toxicities of Chemotherapy and Treatment Outcomes

The toxicities of chemotherapy are listed in Table II. Compared with the control group, the ECT group showed a markedly greater incidence of hand-foot syndrome ($p=0.0043$). Most of the toxicities were controlled and managed using symptomatic therapy and dose reduction. No toxicity-associated fatality was reported.

In the CAPOX chemotherapy phase, all patients completed 8 cycles of CAPOX chemotherapy. However, 20 patients from the control group and 15 from the ECT group received dose reduction. Subsequently, 94 patients in the ECT group completed 8 cycles of ECT. Among the 94 patients,

Table I. Patient characteristics.

		Control group (n = 112)	ECT group (n = 102)	*p*-value
Age (year)		55.16 ± 7.27	54.91 ± 6.92	0.7974
Tumor Size (cm)		4.21 ± 1.58	4.36 ± 1.62	0.4939
Operating Time (min)		139.28 ± 29.51	141.66 ± 29.75	0.5578
Blood Loss During Surgery (ml)		104.57 ± 35.21	106.48 ± 36.44	0.6971
Gender				0.8346
	Male	91	84	
	Female	21	18	
Tumor Stage				0.9772
	IIIA	24	22	
	IIIB	39	35	
	IIIC	49	45	
Tumor Differentiation				0.9159
	Well	18	17	
	Moderately	25	21	
	Poorly	54	50	
	Signet ring cell	15	14	
Tumor Location				0.9898
	Lower	45	39	
	Middle	24	22	
	Upper	33	32	
	Entire	10	9	

13 were administered dose reduction. We discontinued ECT in 3 patients because of disease recurrence and 5 patients due to refractory grade 3 hand-foot syndrome and grade 4 thrombocytopenia. These patients underwent at least 3 cycles of ECT and were included in the analysis.

Recurrence-Free Survival

In the first 5 years post-surgery, 48 patients in the control group and 33 patients in the ECT group reported recurrence. Patients in the ECT group showed markedly improved 5-year RFS relative to those in the control group (p=0.0483) (Figure 1). The hazard ratio for recurrence was 0.6442 [95% CI, 0.4167 to 0.9961] in the ECT group relative to that in the control group. The sites of relapse are listed in Table III.

Overall Survival

In the first 5 years post-surgery, 43 patients in the control group and 28 patients in the ECT group died. Patients in the ECT group showed a markedly improved 5-year OS relative to those in the control group (p=0.0468) (Figure 2). The hazard ratio for death in the ECT group was 0.6214 [95% CI, 0.3902 to 0.9896] relative to that in the control group.

Table II. Toxicities.

	Control group				ECT group				
	Grade				Grade				
Event	1	2	3	4	1	2	3	4	*p*-value
Neutropenia	45	38	26	3	39	33	27	3	0.6373
Thrombocytopenia	47	51	2	2	44	49	3	2	0.3622
Anemia	50	42	3	0	47	44	4	0	0.1255
Nausea/Vomiting	57	53	2	0	51	49	2	0	0.8893
Diarrhea	18	12	1	0	16	13	1	0	0.7370
Nephrotoxicity	6	4	0	0	7	2	0	0	0.9500
Hepatic toxicity	10	8	0	0	12	9	0	0	0.4016
Stomatitis	16	13	4	0	17	14	4	0	0.4608
Hand-foot Syndrome	43	4	3	–	53	7	5	–	0.0043
Paresthesia	27	11	0	0	23	9	0	0	0.6860

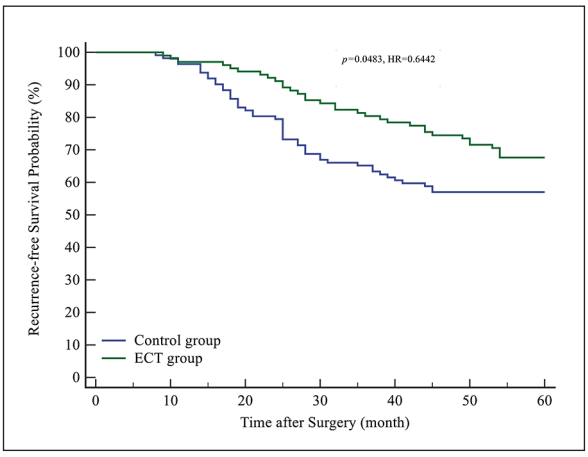

Figure 1. Recurrence-free survival curves of the 2 groups. In the first 5 years post-surgery, 48 patients in the control group and 33 patients in the ECT group reported recurrence. Patients in the ECT group showed markedly improved 5-year RFS relative to those in the control group (p=0.0483). The hazard ratio for recurrence was 0.6442 [95% CI, 0.4167 to 0.9961] in the ECT group relative to that in the control group.

Discussion

Radical surgery constitutes the only curative therapy for localized GC, and adjuvant chemotherapy is obligatory to improve long-term survival for patients with stage 3 GC after curative surgery[12]. The benefit of adjuvant chemotherapy to the survival of patients with advanced GC after D2 gastrectomy has been well demonstrated in several clinical trials and systematic reviews[13,14]. In the CLASSIC trial, disease-free survival (DFS) was improved by 44% in randomly assigned patients who received capecitabine combined with oxaliplatin (XELOX) relative to the patients who received observation after radical surgery[15]. Therefore, XELOX chemotherapy for 6 months is considered as the standard postoperative adjuvant treatment for patients with resectable stage 2 or 3 GC.

Due to tumor progression, patients with stage 3 disease have considerably poorer long-term survival than those with GC at an earlier stage[8]. Therefore, further research on innovative adjuvant therapeutic approaches for stage 3 GC has to be conducted. Extending the duration of chemotherapy is one of the exploratory strategies that can potentially achieve promising long-term survival in patients with stage 2 and stage 3 GC[9]. Another study showed that extending the duration of chemotherapy after surgery improved survival even in patients with stage 4 GC[16]. In Japan, S-1 monotherapy for 1 year was established as the standard adjuvant chemotherapy after surgery for GC owing to findings of the ACTS-GC clinical trial[17]. It may suggest that 1-year post-operative chemotherapy is an ideal treatment modality and tolerable for GC. To achieve a favorable long-term survival, capecitabine monotherapy for an additional period of 6 months was administered as extending chemotherapy in the ECT group following 6-month CAPOX regimen chemotherapy after D2 gastrectomy in this study.

Our findings indicate that fewer patients experienced recurrence in the ECT group than in the control group in the initial 5 years post-surgery. The ECT group exhibited a markedly higher 5-year RFS relative to that of the control group arm [p=0.0483; HR, 0.6442; 95% CI, 0.4167 to 0.9961]. Thus, fewer patients died in the ECT group than in the control group in the first 5 years post-surgery. The ECT group showed a markedly higher 5-year OS, compared with the control group (p=0.0468; HR, 0.6214; 95%CI, 0.3902 to 0.9896). Despite the extended duration of chemotherapy received, the ECT group reported chemotherapy-related toxicities mostly comparable to those of the control group, except for hand-foot syndrome. A significant number of patients in the ECT group developed hand-foot syndrome (p=0.0043).

Table III. Sites of recurrence.

		Peritoneum	Hematogenous	Lymph nodes	Local
Sites of first recurrence					
	Control group	14	7	17	10
	ECT group	10	5	11	7
Sites of any recurrence					
	Control group	15	9	19	12
	ECT group	13	8	13	10

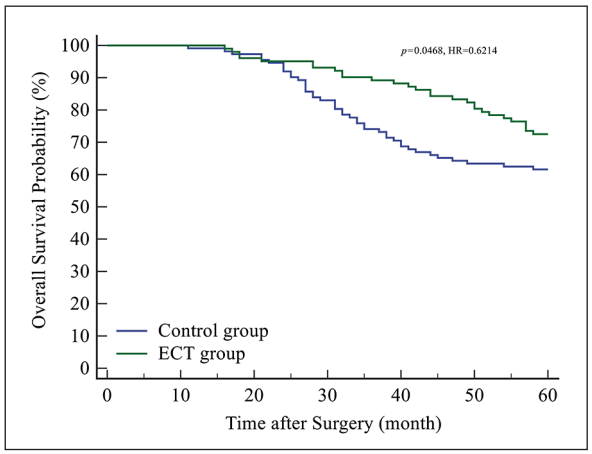

Figure 2. Overall survival curves of the 2 groups. In the first 5 years post-surgery, 43 patients in the control group and 28 patients in the ECT group died. Patients in the ECT group showed a markedly improved 5-year OS relative to those in the control group (p=0.0468). The hazard ratio for death in the ECT group was 0.6214 [95% CI, 0.3902 to 0.9896] relative to that in the control group.

Conclusions

To sum up, ECT with capecitabine following CAPOX regimen chemotherapy may significantly improve survival in patients with stage 3 GC after D2 gastrectomy. However, owing to the retrospective design and small sample size of this study, its findings have to be verified by a prospective study with a larger sample size.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

Yi Fei and Xueping Pan designed the study and wrote the manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

References

1) Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.
2) de Martel C, Forman D, Plummer M. Gastric cancer: epidemiology and risk factors. Gastroenterol Clin North Am 2013; 42: 219-240.
3) Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
4) Zhang J, Tian ZL, Zhang WT, Cheng LM, Liu J, Cao YX, Zhang ZR. Clinicopathological and prognostic significance of miR-4317 expression in gastric cancer patients. Eur Rev Med Pharmacol Sci 2019; 23: 2803-2808.
5) D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg 2004; 240: 808-816.
6) Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, Magic Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355: 11-20.
7) Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Geneve J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29: 1715-1721.
8) Graziosi L, Marino E, Cavazzoni E, Donini A. Prognostic value of the seventh AJCC/UICC TNM classification of non-cardia gastric cancer. World J Surg Oncol 2013; 11: 103.
9) Fujitani K, Kurokawa Y, Takeno A, Endoh S, Ohmori T, Fujita J, Yamasaki M, Takiguchi S, Mori M, Doki Y. Time to initiation or duration of S-1 adjuvant chemotherapy; which really impacts on survival in stage II and III gastric cancer? Gastric Cancer 2018; 21: 446-452.
10) Jang SH, Jung YJ, Kim MG, Kwon SJ. The prognostic significance of compliance with postoperative adjuvant chemotherapy in patients with Stage III gastric cancer: an observational study. J Gastric Cancer 2018; 18: 48-57.
11) Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-1474.
12) Aoyama T, Yoshikawa T. Adjuvant therapy for locally advanced gastric cancer. Surg Today 2017; 47: 1295-1302.
13) Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, Lee KW, Kim YH, Noh SI, Cho JY, Mok YJ, Ji J, Yeh TS, Button P, Sirzen F, Noh SH. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012; 379: 315-321.
14) Zhao SL, Fang JY. The role of postoperative adjuvant chemotherapy following curative resection for gastric cancer: a meta-analysis. Cancer Invest 2008; 26: 317-325.
15) Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, Kim HH, Choi JH, Kim HK, Yu W, Lee JI, Shin DB, Ji J, Chen JS, Lim Y, Ha S, Bang YJ. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an

open-label, randomised phase 3 trial. Lancet Oncol 2014; 15: 1389-1396.

16) Wang QW, Zhang XT, Lu M, Shen L. Impact of duration of adjuvant chemotherapy in radically resected patients with T4bN1-3M0/TxN3bM0 gastric cancer. World J Gastrointest Oncol 2018; 10: 31-39.

17) Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011; 29: 4387-4393.