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ORIGINAL RESEARCH

Maintenance Chemotherapy with S-1 Following SOX Regimen Chemotherapy Improves Prognosis of Stage 3 Gastric Cancer After D2 Gastrectomy: A 5-Year Analysis

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Objective: To assess the effectiveness and safety of treatment consisting of maintenance chemotherapy (MCT) with S-1 following S-1 plus oxaliplatin (SOX) chemotherapy for stage 3 gastric cancer (GC) after D2 gastrectomy.

Methods: In this retrospective study, we enrolled 255 patients with stage 3 GC who underwent D2 gastrectomy between February 2011 and May 2014. The SOX regimen chemotherapy was administrated to all of the patients as adjuvant therapy. The SOX regimen consisted of S-1 (for patients with a body surface area [BSA] of less than 1.25 m^2, 80 mg/d; 100 mg/d for BSA=1.25 m^2- <1.5 m^2, and 120 mg/d for BSA≥1.5 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 SOX chemotherapy, 122 of these patients received maintenance chemotherapy (the MCT group) with S-1, whereas 133 patients (the control group) received no MCT. The MCT consisted of S-1 (80, 100, or 120 mg daily based on BSA, 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 MCT group exhibited a distinctly higher 5-year OS (P=0.0425) and RFS (P=0.0479) than those of the control group. The incidence of hand-foot syndrome was markedly greater in the MCT group (P=0.0026). No toxicity-related death occurred.

Conclusion: Maintenance chemotherapy with S-1 following the SOX regimen chemotherapy provides significant survival benefit for stage 3 GC after D2 gastrectomy.

Keywords: gastric cancer, chemotherapy, overall survival, recurrence-free survival

Introduction

With increasing incidence and prevalence, gastric cancer (GC) is considered a global health issue.[1] Approximately 1 million new cases are diagnosed and more than 700,000 deaths arising from GC are reported annually.[2] Surgery 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.[3–5] Despite D2 gastrectomy, patients with stage 3 GC have evidently lower long-term survival than patients with earlier-stage GC. Thus, innovative adjuvant therapy modalities for stage 3 GC need to be explored.

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Improved survival has been observed in patients with stage 3 GC who undergo longer adjuvant chemotherapy after radical surgery.[6] Similarly, completion of postoperative chemotherapy improves survival in patients with stage 3 GC.[7] 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, and the number of cycles of chemotherapy mostly depends on the reactivity and tolerability of the treatment in the patient, as well as the preferences of the physician. This retrospective study was designed to assess the effectiveness and safety of maintenance chemotherapy (MCT) with S-1 following S-1 plus oxaliplatin (SOX) for patients with stage 3 GC after D2 gastrectomy.

Methods

Patients

We enrolled 255 patients with stage 3 GC who underwent open D2 gastrectomy between February 2011 and May 2014. Our inclusion criteria were as follows: pathologically confirmed stage 3 GC [per the American Joint Committee on Cancer (AJCC) staging system, 7th edition]; 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 MCT group and the control group on the basis of whether they received MCT.

We conducted this study in accordance with the Declaration of Helsinki and Good Clinical Practice recommendations. Collection and archiving of patient data was performed with written informed consent, and the study was approved by the Medical Research Ethics Committee of the Huzhou Normal College. The patient data used in the study were confidential.

Chemotherapy Administration

Patients with stage 3 GC started the adjuvant chemotherapy within 21 d after D2 gastrectomy. The SOX regimen consisted of S-1 (for patients with a body surface area [BSA] of less than 1.25 m^2, 80 mg/d; 100 mg/d for BSA=1.25 m^2- <1.5 m^2, and 120 mg/d for BSA≥1.5 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 SOX chemotherapy, physicians illustrated the potential advantages and disadvantages of MCT with S-1 for the patients. The patients then decided, based on their own assessment, whether to receive MCT and then signed the consent form.

Overall, 122 patients agreed to receive MCT; hence, the MCT group was administered with S-1 (80, 100, or 120 mg daily per their BSA in 2 divided doses for 14 d), which was repeated every 21 d for 8 cycles. Meanwhile, 133 patients without MCT after the SOX 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.[8] 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,[9] 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 SOX chemotherapy or 3 cycles of MCT were not included.

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 until their death. In the case of recurrence, the patients received chemotherapy, radiofrequency ablation, or palliative treatment.

Statistical Analysis

Data are presented as mean ± SD and analyzed with SPSS software (version 17.0). 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. 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

Table 1 Patient Characteristics

	Control Group (n=133)	MCT Group (n=122)	*P* value
Age (year)	56.44±6.14	57.62±7.21	0.16
Tumor Size (cm)	3.87±1.24	4.14±1.47	0.11
Operating Time (min)	144.74±24.21	148.57±25.68	0.22
Blood Loss During Surgery (mL)	112.47±18.25	116.12±21.17	0.14
Gender			0.69
Male	94	89	
Female	39	33	
Tumor Stage			0.90
IIIA	37	32	
IIIB	51	49	
IIIC	45	41	
Tumor Differentiation			0.54
Well	27	24	
Moderately	44	48	
Poorly	52	42	
Signet ring cell	10	8	
Tumor Location			0.73
Lower	61	57	
Middle	39	41	
Upper	21	14	
Entire	12	10	

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 MCT group and the control group (Table 1).

Toxicities of Chemotherapy and Treatment Outcomes

The toxicities of chemotherapy are listed in Table 2. Compared with the control group, the MCT group showed a markedly greater incidence of hand–foot syndrome (P=0.0026). Most of the toxicities were controlled and managed using symptomatic therapy and dose reduction. No toxicity-associated fatality was reported.

In the SOX chemotherapy phase, all patients completed 8 cycles of SOX chemotherapy. However, 22 patients from the control group and 20 from the MCT group received dose reduction. Subsequently, 109 patients in the MCT group completed 8 cycles of MCT. Among the 109 patients, 15 were administered dose reduction. We discontinued MCT in 4 patients because of disease recurrence and 9 patients due to refractory grade 3 hand–foot syndrome and grade 4 thrombocytopenia. These patients were given at least 3 cycles of MCT and were included in the analysis.

Recurrence-Free Survival

In the first 5 years post-surgery, 55 patients in the control group and 38 patients in the MCT group reported recurrence. Patients in the MCT group showed markedly

Table 2 Toxicities

Event	Control Group				MCT Group				*P* value
	Grade				Grade				
	1	2	3	4	1	2	3	4	
Neutropenia	68	39	23	3	55	41	22	4	0.38
Thrombocytopenia	54	61	4	1	50	54	3	3	0.97
Anemia	62	51	2	0	54	48	4	0	0.62
Nausea/Vomiting	69	61	3	0	64	57	3	0	0.86
Diarrhea	22	10	3	0	19	11	4	0	0.71
Nephrotoxicity	5	3	0	0	4	2	0	0	0.70
Hepatic toxicity	11	7	0	0	13	8	0	0	0.42
Stomatitis	17	12	5	0	18	11	5	0	0.71
Hand-foot Syndrome	57	3	2	-	60	5	11	-	0.0026
Paresthesia	32	10	0	0	29	9	0	0	0.94

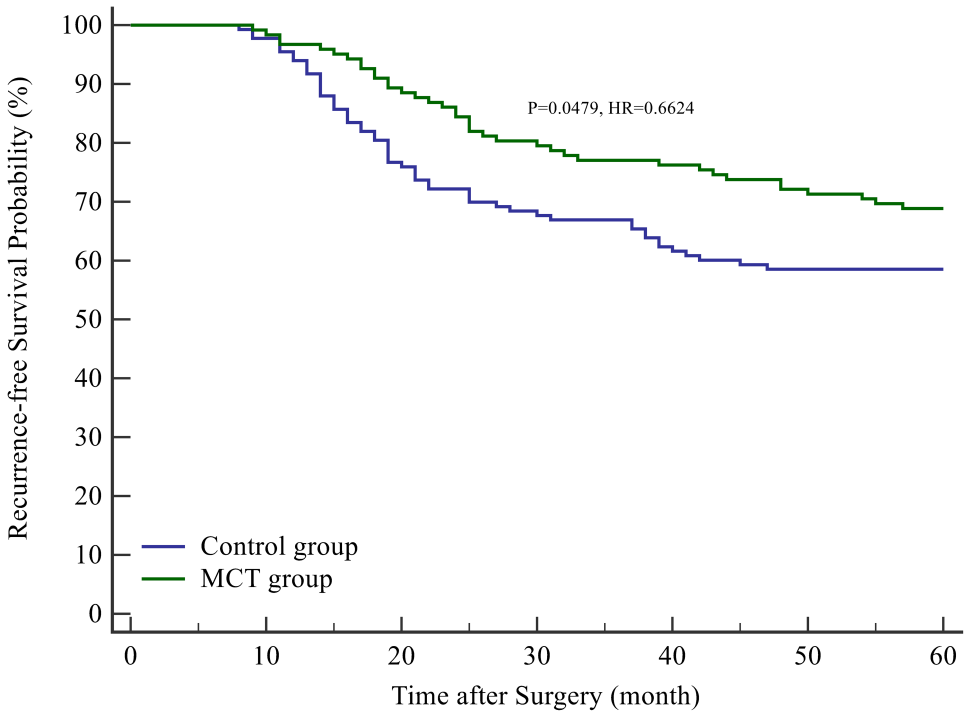

Figure 1 Recurrence-free survival curves of the 2 groups. In the initial 5 years post-surgery, recurrence was observed in 55 patients in the control group and 38 patients in the maintenance chemotherapy (MCT) group. The MCT group had a significantly higher 5-year RFS than that of the control group (P=0.0479) (Figure 1). The hazard ratio for recurrence in the MCT group, relative to the control group, was 0.6624 [95% confidence interval (CI), 0.4411 to 0.9947].

improved 5-year RFS relative to those in the control group (P=0.0479) (Figure 1). The hazard ratio for recurrence was 0.6624 [95% CI, 0.4411 to 0.9947] in the MCT group relative to that in the control group. The sites of relapse are listed in Table 3.

Overall Survival

In the first 5 years post-surgery, 48 patients in the control group and 32 patients in the MCT group died. Patients in the MCT group showed a markedly improved 5-year OS relative to those in the control group (P=0.0425) (Figure 2). The hazard ratio for death in the MCT group was 0.6342 [95% CI, 0.4091 to 0.9831] 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.[10] 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.[11,12] 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.[13] Therefore, XELOX chemotherapy for 6 months

Table 3 Sites of Recurrence

	Peritoneum	Hematogenous	Lymph Nodes	Local
Sites of First Recurrence				
Control group	16	11	18	10
MCT group	10	9	12	7
Sites of Any Recurrence				
Control group	18	14	19	13
MCT group	13	10	15	10

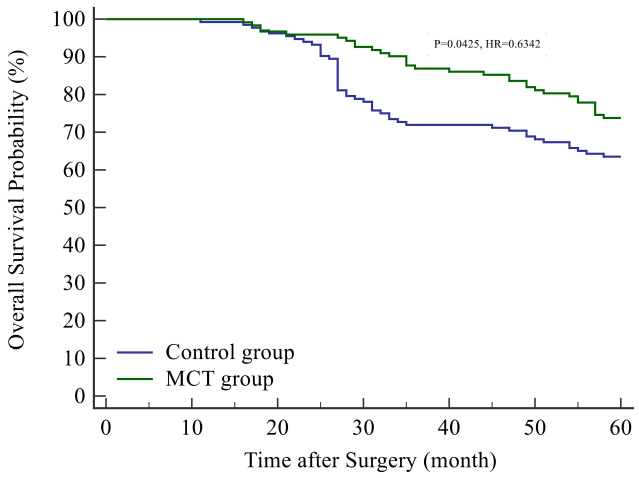

Figure 2 Overall survival curves of the 2 groups. In the initial 5 years post-surgery, 48 patients in the control and 32 patients in the maintenance chemotherapy (MCT) group died. The MCT group had a significantly higher 5-year OS than that of the control group (P=0.0425) (Figure 2). The hazard ratio for death in the MCT group, relative to the control group, was 0.6342 [95% CI, 0.4091 to 0.9831].

is considered as the standard postoperative adjuvant treatment for patients with resectable stage 2 or 3 GC.

S-1 constitutes an oral bioavailable anticancer drug consisting of tegafur, 5-chloro-2, 4-dihydroxypyridine, and potassium oxonate (1:0.4:1; molar ratio). This drug showed an estimated 40% response rate in patients with advanced or relapsed GC in the Phase II trials.[14,15] The doublet combination chemotherapy, SOX, significantly improved the DFS and exhibited tolerable toxicity in patients with resected GC after D2 surgery relative to S-1 alone.[16] It was also proved that SOX provided comparable advantages in survival to XELOX with tolerable toxicities in patients with GC after D2 gastrectomy.[17–19]

Owing to tumor progression, patients with stage 3 disease have considerably poorer long-term survival than those with GC at an earlier stage. 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.[6] A study showed that prolonging the duration of chemotherapy after surgery improved survival even in patients with stage 4 GC.[20] In Japan, S-1 monotherapy for 1 y was established as the standard adjuvant chemotherapy after surgery for GC owing to findings of the ACTS-GC clinical trial.[21] To achieve a favorable long-term survival, S-1 monotherapy for an additional period of 6 months was administered as MCT in the MCT group following SOX regimen chemotherapy after D2 gastrectomy in this study.

Our findings indicate that fewer patients experienced recurrence in the MCT group than in the control group in the initial 5 years post-surgery. The MCT group exhibited a markedly higher 5-year RFS relative to that of the control group arm [P=0.0479; HR, 0.6624; 95% CI, 0.4411 to 0.9947]. Thus, fewer patients died in the MCT group than in the control group in the first 5 years post-surgery. The MCT group showed a markedly higher 5-year OS, compared with the control group (P=0.0425; HR, 0.6342; 95% CI, 0.4091 to 0.9831). Despite the longer duration of chemotherapy received, the MCT 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 MCT group developed hand–foot syndrome (P=0.0026).

Therefore, MCT with S-1 following SOX 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.

Disclosure

The authors disclose no conflicts of interest in this work.

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