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The Efficacy of Cytoreductive Surgery with Systemic Chemotherapy for Gastric Cancer with Peritoneal Dissemination

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Abstract

Background: Primary treatment for gastric cancer with peritoneal dissemination is systemic chemotherapy because the effectiveness of cytoreductive surgery remains unclear. This study aimed to investigate the efficacy of cytoreductive surgery with systemic chemotherapy for advanced gastric cancer with peritoneal dissemination.

Methods: From 2007 to 2014, 40 patients with peritoneal disseminated gastric cancer received cytoreductive surgery followed by systemic chemotherapy. Clinicopathological characteristics, survival, and prognostic factors were evaluated.

Results: Thirty-three patients (82.5%) received S-1 plus cisplatin as a first-line regimen, whereas 22 patients (55%) received second-line chemotherapy with taxane or irinotecan, and 7 patients (17.5%) received four agents (S-1, CDDP, CPT-11, and taxane). The overall survival time was 12 months, whereas the 3- and 5-year survival rates were 23% and 16%, respectively. Multivariate analysis revealed synchronous distant metastasis other than to the peritoneum (HR, 4.27; 95% CI, 1.31-13.89; P=0.016) as an independent prognostic factor for survival, but not systemic chemotherapy with four agents, lymph node metastasis, resectability, lymphatic invasion.

Conclusions: Although cytoreductive surgery followed by systemic chemotherapy with S-1, cisplatin, taxane, and irinotecan was not an independent prognostic factor for patients with peritoneal dissemination, the detection of distant metastasis before surgery was correlated with poor prognosis. Therefore, we should be administered the strategy to the patients without the detection of distant metastasis.

Keywords: Gastric cancer; Peritoneal dissemination; Cytoreductive surgery; Systemic chemotherapy

Introduction

Gastric cancer is the second leading cause of cancer death worldwide, although patient survival has improved because gastrectomy with D2 lymphadenectomy was adopted as a standard treatment [1-4]. However, the outcomes of patients with unresectable or recurrent gastric cancer remain poor, as more than 50% of potentially curable advanced gastric cancer patients die because of peritoneal recurrence [5]. The median overall survival time for gastric cancer patients with peritoneal dissemination is >6 months [6,7]. Although overall survival time is improved by systemic chemotherapy compared with best supportive care, there is currently no standard treatment regimen for gastric cancer with peritoneal dissemination [8,9]. In 2008, a randomized phase III study of S-1 alone *vs.* S-1 plus cisplatin in the treatment for advanced gastric cancer (SPIRITS trial) reported a significant increase in the median survival time of patients with advanced gastric cancer who received S-1 plus cisplatin, as compared with those who received S-1 alone (13.0 vs. 11.0 months) [10]. S-1 plus cisplatin is an effective regimen that is becoming a standard first-line treatment for patients with advanced gastric cancer in Japan. Camptothecin-11 (CPT-11) and taxane have shown potent effects for treatment of advanced gastric cancer as a second- or third-line régimen [11]. Cytoreductive surgery with systemic chemotherapy has been reported to improve prognosis of gastric cancer with peritoneal dissemination [12]. However, only a few studies have been conducted to investigate the efficacy of this treatment strategy [13-16]. The aim of the present study was to evaluate the survival benefit of cytoreductive surgery with systemic chemotherapy for gastric cancer patients with peritoneal dissemination.

Materials and Methods

Patients

From 2007 to 2014, 601 patients with gastric cancer underwent gastrectomy. The records of 40 patients with peritoneal disseminated gastric cancer who underwent reduction surgery followed by systemic chemotherapy were retrospectively reviewed. Eligibility criteria included the following: (i) histologically proven peritoneal dissemination arising from gastric cancer, (ii) an Eastern Cooperative Oncology Group performance status of ≤ 2, (iii) age of ≥ 20 years, (iv) expected survival of at least 3 months, and (v) adequate organ function (leukocyte count>2000/μl, platelet count>50,000/μl, transaminases<2.5 times the upper normal limit, total bilirubin <2 times the upper normal limit, and a serum creatinine level no greater than the upper normal limit). The criteria of the Japanese Gastric Cancer Association were used to classify disease stage and assess resected specimens [17].

Written informed consent was obtained from all patients before enrollment in the study.

Cytoreductive surgery and chemotherapy

Based on the surgical findings, all patients underwent subtotal or total gastrectomy with regional lymph node dissection (D1+α, β or D2), including peritonectomy by the Sugarbaker procedure when the tumor involved the peritoneal surface. Combined resection was performed for locally advanced lesions (T4b) or lymph node dissection. We excluded patients who underwent exploratory laparotomy. Staging laparoscopy to evaluate disseminated disease was not performed.

All patients postoperatively received systemic chemotherapy within 4 weeks. As shown in Figure 1, the treatment regimens included S-1 alone, S-1 plus CDDP, S-1 plus paclitaxel, CPT-11 plus CDDP, docetaxel plus CDDP plus S-1 (DCS), paclitaxel plus CDDP plus S-1 (PCS), and paclitaxel alone. For the S-1 alone regimen, S-1 (80 mg/m^2) was administered daily for the first 3 weeks, followed by 2 weeks of rest. For the S-1 plus CDDP regimen, S-1 (80 mg/m^2) was administered daily for the first 3 weeks, followed by 2 weeks of rest. Low-dose CDDP (10 mg) was administered on days 1-5 and 8-12 (total, 10 days). For the S-1 plus paclitaxel regimen, S-1 (80 mg/m^2) was administered daily for 2 weeks, followed by 2 weeks of rest. Paclitaxel (60 mg/m^2) was administered on days 1, 8, and 15 every 3 weeks. For the CPT-11 plus CDDP regimen, the duration of every cycle was 5 weeks. CPT-11 (80 mg/m^2) was administered on days 1 and 8. Low-dose CDDP (10 mg) was administered on days 2-6 and 9-13 (total, 10 days). For the DCS regimen, S-1 (80 mg/m^2) was administered daily for 2 weeks, followed by 2 weeks of rest. Docetaxel (40 mg/m^2) was administered on day 1. Low-dose CDDP (10 mg) was administered on days 1-5 and 8-12. For the PCS regimen, S-1 (80 mg/m^2) was administered daily for 2 weeks, followed by 2 weeks of rest. Paclitaxel (160 mg/m^2) was administered on day 1. Low-dose CDDP (10 mg) was administered on days 1-5 and 8-12. For the paclitaxel alone regimen, paclitaxel (60 mg/m^2) was administered on days 1, 8, and 15, and duration of each cycle was 4 weeks.

Statistical analysis

The Kaplan-Meier method was used to plot survival curves, and the log-rank test was used to compare variables in univariate analysis. Multivariate analysis was conducted using a Cox proportional hazards model to evaluate prognostic factors. Those variables showing statistical significance in the univariate analysis were subjected to multivariate analysis using a logistic regression model. A probability (P) value of <0.05 was considered statistically significant.

Results

Patient characteristics

This study included 29 (72.5%) males and 11 (27.5%) females, with a mean age of 70.1 ± 9.3 years (Table 1). The most common site of lesion was the middle third (50%) of the stomach and the most common type of resection was total gastrectomy (80%). Histopathological examinations confirmed that the majority of patients had lymph node involvement (97.5%) and 39 cases (97.5%) had pT4a or pT4b disease. Four (10%) patients underwent curative resection and 36 (90%) underwent non-curative resections (R1 or R2). Eighteen patients (45%) underwent combined resection. Six patients (15%) had synchronous distant metastasis without peritoneal dissemination.

Variables	Patients (n=40)
Mean age (years, mean ± SD)	70.1 ± 9.3
Sex	
Male	29 (72.5%)
Female	11 (27.5%)
Mean tumor size (cm, mean ± SD)	9.1 ± 3.5
Tumor location	
Upper	9 (22.5%)
Middle	20 (50.0%)
Lower	11 (27.5%)
Histological type	
Well differentiated	10 (25.0%)
Undifferentiated	30 (75.0%)
Borrmann type	
I-II	5 (12.5%)
III-IV	35 (87.5%)
Depth of invasion	
T3	1 (2.5%)
T4a	32 (80.0%)
T4b	7 (17.5%)
Lymph node involvement	
N0	1 (2.5%)
N1	2 (5.0%)
N2	4 (10.0%)
N3a	11 (27.5%)
N3b	22 (55.0%)
Distant metastasis	
Peritoneum	40 (100%)
Liver	5 (12.5%)
Distant lymph node	1 (2.5%)
Resection type	
Subtotal gastrectomy	8 (20.0%)
Total gastrectomy	32 (80.0%)
Combined resection	
Spleen	11 (27.5%)
Pancreas	5 (12.5%)

Liver	1 (2.5%)
Colon	1 (2.5%)
Resectability	
R0	4 10.0%)
R1	4 (10.0%)
R2	32 (80.0%)
Lymph node dissection	
D1+	8 (20.0%)
D2	32 (80.0%)

Table 1: Clinicopathologic findings in 40 patients.

Postoperative complications

As shown in Table 2, postoperative complications occurred in 7 patients (17.5%). Surgical site infection was the most frequent complication, occurring in 4 patients (10%). Pancreatic fistula, abdominal abscess, and pneumonia occurred in other cases. No re-operations were required and there were no postoperative deaths.

	First line	Second line	Third line
S-1+CDDP	33	1	1
CPT-11+CDDP	3	7	1
DCS	1	4	2
PCS	1	1	1
S-1	2	6	0
S-1+PTX	0	2	2
PTX	0	4	1
Total no. of patients (%)	40 (100%)	25 (62.5%)	8 (20.0%)

Table 2: Postoperative morbidity and mortality.

Systemic chemotherapy and survival rates

Systemic chemotherapy regimens are shown in Table 3. The majority of patients (33 patients; 82.5%) received the S-1 plus CDDP regimen as a first-line treatment, followed by CPT-11 plus CDDP (3 patients; 7.5%), S-1 alone (2 patients; 5.0%), DCS (1 patient; 2.5%), and PCS (1 patient; 2.5%). As a second-line chemotherapy, 25 patients (62.5%) received a taxane-based regimen (11 patients; 44.0%) or a CPT-11-based regimen (7 patients; 28.0%) or a different regimen. Furthermore, 8 patients (20.0%) received third-line chemotherapy, whereas seven patients (17.5%) were administered four agents (S-1, cisplatin, CPT-11, and Taxane) following second-line chemotherapy.

	No. of patients	%
Morbidity	7	17.5
Surgical site infection	4	10
Pancreatic fistula	2	5
Abdominal abscess	1	2.5
Pneumonia	2	5
Mortality	0	0

Table 3: Chemotherapy regimen.

The overall survival time for all patients was 12.0 months, whereas the 3- and 5-year overall survival rates were 23% and 16%, respectively. There was a significant survival difference between patients with synchronous distant metastasis with or without peritoneal dissemination (Figure 1). Prognosis was significantly improved in patients without synchronous distant metastasis other than peritoneal dissemination, as compared with those with distant metastasis (Overall survival time, 13.0 vs. 7.0 months).

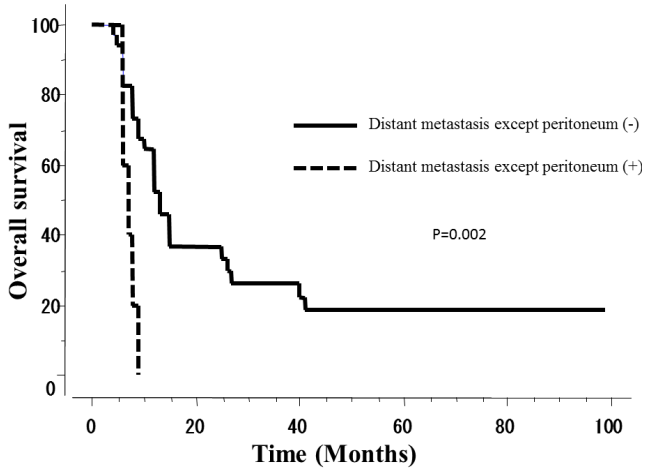

Figure 1: Kaplan-Meier curves of overall survival in patients with or without distant metastasis except peritoneum.

Prognostic factors

Multivariate analysis using the Cox proportional hazards model identified distant metastasis other than to the peritoneum (HR, 4.27; 95% CI, 1.31–13.89; P=0.016) as an independent prognostic factor for survival. However, systemic chemotherapy with four agents, lymph node metastasis, resectability, lymphatic invasion, and tumor diameter were not independent survival factors (Table 4).

Variables	X^2	P value	Hazard ratio	95% CI
Systemic chemotherapy with 4 agents (S-1, CDDP, CPT-11, and Taxane)	0.003	0.96	0.975	0.354-2.681
<N3 vs. ≥ N3	0.051	0.821	1.199	0.248-5.780

R0, 1 vs. R2	2.001	0.157	2.141	0.746-6.135
ly 1 vs. ly 2,3	0.845	0.358	2.519	0.352-17.857
Distant metastasis except peritoneum	5.81	0.016	4.274	1.310-13.889
Tumor diameter<10 cm vs. ≥ 10 cm	1.511	0.219	1.623	0.750-3.521

Table 4: Multivariate analysis of prognostic factors.

Discussion

There is currently no standard treatment strategy for peritoneal dissemination from gastric cancer. Because peritoneal dissemination is considered as incurable, surgery is not the primary treatment option except for patients with bleeding, perforation, or obstruction. Systemic or intraperitoneal chemotherapy was recently reported as a standard therapy for gastric cancer with peritoneal dissemination [18-22]. On the other hand, previous studies reported a survival advantage of salvage chemotherapy for pretreated gastric cancer compared with best supportive care [8,9]. For advanced colorectal cancer, the use of three agents (fluorouracil, CPT-11, and oxaliplatin) was found to improve survival. Overall survival was significantly correlated with the administration of all three agents in the course of disease [23]. As for advanced gastric cancer, the use of multi-agents or dual-agents with molecular target drug were suggested to improve prognosis [7,10,24,25].

Some recent studies revealed that cytoreductive surgery with perioperative chemotherapy or intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) confers a significant survival benefit for gastric cancer patients with peritoneal dissemination [13-16]. The reported overall survival time of adjuvant surgery following chemotherapy is in the range of 16.7 to 29.5 months [18-22], whereas that of cytoreductive surgery with HIPEC was 11.0-15.8 months [13-16].

The results of the present study demonstrated that overall survival time following cytoreductive surgery with systemic chemotherapy was 12.0 months, and the 3- and 5-year survival rates were 23% and 16%, respectively. For patients with synchronous distant metastasis other than peritoneal dissemination, the overall survival time was 13.0 months.

In this series, although patient survival tended to be lower than that reported in previous studies of adjuvant surgery following chemotherapy, it was satisfactory compared with that of cytoreductive surgery with HIPEC. Because adjuvant surgery was performed in patients without non-curative clinical factors during chemotherapy, survival tended to be longer compared with that of cytoreductive surgery with HIPEC.

The results of the present study demonstrated that distant metastasis other than to the peritoneum (HR, 4.27; 95% CI, 1.31-13.89; P=0.016) was the only independent prognostic factor. However, systemic chemotherapy with four agents (S-1, CDDP, CPT-11, and Taxane) was not an independent prognostic factor, unlike in advanced colorectal cancer. Previous studies have identified prognostic factors for gastric cancer patients with peritoneal dissemination following cytoreductive surgery with systemic chemotherapy or HIPEC. For example, synchronous peritoneal dissemination, positive cytology after neoadjuvant chemotherapy, completeness of cytoreduction, and cytoreductive surgery with HIPEC are known risk factors [14-16]. Canbay et al. [13] suggested that response to bidirectional intraperitoneal and systemic induction chemotherapy, optimal cytoreductive surgery, and limited peritoneal dissemination are the best outcomes [13]. Although cytoreductive surgery with systemic chemotherapy or HIPEC seems to be effective for treatment of patients with peritoneal dissemination, prognosis was poor for those with distant metastasis in addition to peritoneal dissemination even if cytoreductive surgery with systemic chemotherapy was performed.

Conclusion

Cytoreductive surgery with systemic chemotherapy with S-1, CDDP, CPT-11, and taxane was not an independent prognostic factor for gastric cancer with peritoneal dissemination. Although this strategy should not be applied to the gastric cancer patients with distant metastasis in addition peritoneal dissemination, prognosis was significantly improved in patients without synchronous distant metastasis.

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