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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

A Phase 2 Study of Induction Chemotherapy Using Docetaxel, Cisplatin, and S-1 for Gastric Cancer with Peritoneal Metastasis (KUGC06)

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ABSTRACT

Background. The authors previously showed the significant efficacy of S-1 plus cisplatin for gastric cancer with limited peritoneal metastasis. They conducted a phase 2 study to evaluate the safety and efficacy of induction chemotherapy using a docetaxel, cisplatin, and S-1 (DCS) triplet regimen to treat gastric cancer with peritoneal metastasis.

Methods. The key eligibility criteria were gastric cancer with peritoneal metastasis or positive peritoneal cytology but no other distant metastases and capability of oral administration. The patients received three 28-day cycles of DCS (60 mg/m^2 of cisplatin, 40 mg/m^2 of docetaxel on day 1, and 80 mg/m^2 of S-1 from day 1 to day 14), then underwent D2 gastrectomy if R0 was possible. The primary end point was the R0 resection rate. The sample size was determined to have 80% power for detecting a 20% improvement in the R0 resection rate over a 45% baseline for a one-tailed alpha of 0.1.

Results. Among 30 enrolled patients, 24 completed three cycles of DCS. The most frequent grade 3 or 4 toxicity was neutropenia (60%). A complete response of peritoneal metastasis was observed in 16 patients, and 14 patients achieved R0 resection (47%; 95% confidence interval 28–66%). When the extent of peritoneal metastasis was classified as P0CY1, P1, P2, and P3 according to the Japanese classification, the R0 resection rates were respectively 63%, 60%, 46% and 0%.

Conclusions. Induction chemotherapy with DCS is safe and can achieve R0 resection for some patients with limited peritoneal metastasis or positive peritoneal cytology. The efficacy, however, appears similar to that of S-1 plus cisplatin.

Gastric cancer is the third leading cause of cancer death in the world. At the time of diagnosis, it often has penetrated the stomach wall and metastasized to the peritoneal cavity.

Because the prognosis for gastric cancer patients with peritoneal metastasis (PM) who have undergone upfront reduction surgery is extremely poor, with a median survival time of 5–8 months,[1,2] patients usually are considered incurable and given palliative chemotherapy. To improve the survival of these patients, hyperthermic intraperitoneal chemotherapy (HIPEC) has been evaluated in some specialized centers for patients with no other distant metastasis. However, HIPEC is associated with significant toxicity, and a recent meta-analysis showed its survival advantage only when used in a prophylactic setting.[3]

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We previously reported that induction systemic chemotherapy with S-1 plus cisplatin could eliminate limited PM, with some patients achieving R0 resection and long-term survival.[4] Although S-1 plus cisplatin is the standard first-line regimen for metastatic gastric cancer in Japan and a high response rate has been reported when it was used as neoadjuvant chemotherapy for patients with extensive lymph node metastasis, a more effective regimen is required to improve further the survival of patients with PM.

A triplet regimen using docetaxel, cisplatin, and S-1 (DCS), first reported in 2007, had a higher objective response rate than S-1 plus cisplatin.[5] Because intravenously administered docetaxel effectively penetrates ascites, a systemic regimen involving docetaxel would be ideal for treating patients with PM.[6] Although frequent febrile neutropenia was reported in the original paper on DCS, a modified regimen with manageable toxicity was reported by another group.[7] We expected that the modified DCS regimen would have superior efficacy to eradicate PM compared with S-1 plus cisplatin, and that more patients would become candidates for gastrectomy to achieve R0 resection. To explore the safety and efficacy of the DCS regimen for patients who have gastric cancer with PM, we conducted a multicenter phase 2 study.

PATIENTS AND METHODS

Eligibility Criteria

The eligibility criteria included histologically proven gastric cancer, PM or positive peritoneal cytology confirmed by staging laparoscopy, absence of other distant or extra-regional lymph node metastasis, age of 20–75 years, performance status of 0–1, fair oral intake, written informed consent provided, and demonstration of adequate organ functions (white blood cells [WBC], $\geq$ 4000/mm^3, WBC $\leq$ 12,000/mm^3, neutrophils $\geq$ 2000/mm^3, hemoglobin $\geq$ 9 g/dL, platelets $\geq$ 100,000/mm^3, total bilirubin $\leq$ 1.5 mg/dL, aspartate aminotransferase [AST] $\leq$ 60 IU/L, alanine aminotransferase [ALT] $\leq$ 60 IU/L, creatinine clearance calculated by Cockcroft–Gault formula $\geq$ 60 mL/min, SpO_2 in room air $\geq$ 95%).

Patients were excluded from the study if they had peritoneal nodules larger than 2 cm or massive ascites confirmed with computed tomography (CT) scan; synchronous cancer; prior chemotherapy or radiotherapy; fresh bleeding from the tumor; severe comorbidities such as bowel obstruction, severe diarrhea, pulmonary fibrosis, or heart diseases; required medication with phenytoin or flucytosine; active infectious disease; or positive hepatitis B antigen.

Study Design and Statistical Consideration

The primary end point of this study was the R0 resection rate. The secondary end points were adverse events of induction chemotherapy, response rate based on the response evaluation criteria in solid tumors (RECIST), the response rate of PM, overall survival (OS), and progression-free survival (PFS). The histologic response rate, postoperative complication rate, and perioperative mortality were evaluated for patients who underwent surgical resection. Recurrence-free survival (RFS) and first site of recurrence were evaluated for patients who underwent R0 resection.

A total sample size of 30 patients was determined based on the hypothesis that the expected and threshold R0 resection rates were respectively 65% and 45% with the use of one-tailed testing at the 10% significance level having a power of 80%. The baseline R0 resection rate was determined according to previously published data of patients treated with S-1 plus cisplatin.[4]

The patients received three cycles of induction chemotherapy with the DCS regimen, and then were evaluated for the possibility of R0 resection. If R0 resection was considered possible, the patient underwent gastrectomy. The protocol treatment was terminated when R0 resection was impossible.

The study defined OS as the time from registration to death, PFS as the time from registration to the first event (i.e., progression, recurrence, or death from any cause), and RFS as the time from operation to the first event (i.e., recurrence or death from any cause). Data on patients shown to be event-free were censored on the date the patient was last seen. Recurrence was determined by clinical signs or imaging studies such as CT scan, magnetic resonance imaging (MRI), endoscopy, or gastrointestinal radiography. Patients were followed up regularly in the outpatient unit to check for symptoms suggesting recurrences. They were evaluated by CT scan/MRI, serum carcinoembryonic antigen (CEA), and CA19-9 a minimum of every 4 months for the first 3 years.

The protocol was first approved by the ethics review committee of Kyoto University on April 2011, and then approved by all the participating centers. The original accrual period was planned to be 3 years, with an additional 3 years of follow-up evaluation. The accrual period was extended to 4 years due to delayed accrual. All case report forms were collected by 6 April 2018, and data were locked on 27 April 2018. This trial was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000004932).

Patient Evaluation

All patients underwent CT scans of the neck, chest, abdomen, and pelvis; upper endoscopy; and staging laparoscopy to confirm eligibility for the study. During the staging laparoscopy, peritoneal lavage was performed using 50 mL of saline, and lavage fluid was collected from the Douglas' pouch, the left subphrenic space, or both for peritoneal cytology (CY). When PM was detected, a biopsy was taken for pathologic examination. Histologic type, macroscopic type of the tumor, tumor-node-metastasis (TNM) factor, and clinical stages were determined based on the 14th Japanese Classification of Gastric Carcinoma (3rd English edition).[8]

Grading of PM extent was determined based on laparoscopic findings according to the Japanese classification and the peritoneal carcinomatosis (PC) staging system.[9] The Japanese classifications were as follows: P0 (no implants to the peritoneum), P1 (cancerous implants adjacent to the stomach), P2 (several scattered metastases to the distant peritoneum and ovarian metastasis only), and P3 (numerous metastases to the distant peritoneum).[10] The PC stages were as follows: stage 1 (malignant granulations smaller than 5 mm and localized in one part of the abdomen) stage 2 (malignant granulations smaller than 5 mm and diffused to the whole abdomen), stage 3 (malignant granulations 5 mm to 2 cm in size), and stage 4 (malignant cakes (larger than 2 cm).[9]

Induction Chemotherapy, Adverse Events, and Response Evaluation

The patients received three 28-day cycles of induction chemotherapy with a DCS regimen (80 mg/m^2 of S-1 from day 1 to day 14, 60 mg/m^2 of cisplatin on day 1, 40 mg/m^2 of docetaxel on day 1). Adverse events were assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE, version 4.0). The S-1 course was interrupted when patients had grade 3 or 4 hematologic toxicity, febrile neutropenia, or non-hematologic toxicity of grade 2 or higher, including diarrhea, hearing impairment, and neurologic or cardiac disorders. Initiation of the next course was postponed until recovery and fulfillment of the following criteria: WBC $\geq$ 3000/mm^3, neutrophils $\geq$ 1500/mm^3, platelets $\geq$ 100,000/mm^3, total bilirubin $\leq$ 1.5 mg/dL, AST/ALT $\leq$ 60 IU/L, and creatinine clearance $\geq$ 60 mL/min. Docetaxel, cisplatin, and S-1 doses were reduced when the following adverse events occurred in the previous course: febrile neutropenia, grade 4 neutropenia, grade 4 thrombocytopenia, grade 2 or higher elevated AST/ALT, and grade 3 or 4 fatigue. The S-1 dose was reduced in the event of grade 3 or 4 diarrhea or grade 3 stomatitis. The cisplatin dose was reduced in the event of grade 2 hearing impairment, neurologic or cardiac disorders, or creatinine clearance less than 30 mL/min. The docetaxel dose was reduced in the event of grade 2 or higher neurologic or cardiac disorders.

Patients were reevaluated during the recovery period after the first and third course of induction chemotherapy by endoscopy/upper gastrointestinal series, CEA, CA19-9, and CT scan/MRI. A second diagnostic laparoscopy to evaluate the response of PM after the third course of chemotherapy was mandatory except for patients whose initial diagnosis was P0CY1 or when the extent of PM was P1 according to the Japanese classification. The response to chemotherapy was determined by evaluation of these findings according to RECIST, version 1.1.[11] The response of PM to induction chemotherapy was determined based on the second diagnostic laparoscopic findings or the surgical findings when the patient underwent surgery without a second diagnostic laparoscopy. A complete response of peritoneal disease was defined as the disappearance of macroscopic peritoneal implants and negative cytology. When scarred peritoneum was observed, biopsy was performed for pathologic examination. The pathologic response was graded according to the Japanese gastric cancer classification.[8]

Surgery

Surgery was scheduled to be performed within 3 to 6 weeks after the last administration of S-1, when the following criteria were fulfilled: a neutrophil count of at least 1500/μL, no signs of infection, and R0 resection considered possible based on findings of a CT scan and diagnostic laparoscopy. When a second diagnostic laparoscopy confirmed complete disappearance of peritoneal nodules or only a few nodules that could be resected, R0 resection was considered possible. Palliative surgery was allowed only when patients had symptoms to be palliated, such as obstruction or bleedings.

Standard gastrectomy with D2 lymphadenectomy was the basic operation performed. A combined resection of the involved organ or an extended lymphadenectomy was acceptable to achieve R0 resection. However, no systemic or wide peritonectomy procedures were allowed. The protocol was discontinued when surgery was not performed or resection was considered to be R1 or R2.

Postoperative complications were graded according to the Clavien–Dindo classification.[12] The postoperative complication rate was calculated by dividing the number of patients with any event by the total number of patients who underwent surgery. Postoperative mortality was defined as death during the period of hospitalization or within 30 days after surgery.

Statistical Analysis

The time to the event end points was analyzed with Kaplan–Meier survival methods. Study treatment groups were compared using the log-rank test. All *P* values lower than 0.05 were considered to indicate statistical significance.

RESULTS

Patient Characteristics

From six hospitals in Japan, 30 patients were enrolled between October 2011 and April 2015. The characteristics of the 30 patients are shown in Table 1. The most common P category according to the Japanese classification was P2 ($n = 13$). One patient was considered ineligible because it became apparent that paraaortic lymph node metastasis was diagnosed before the initiation of induction chemotherapy. The patient received the protocol treatment, however, and was thus included in the analysis based on the intention-to-treat principle (Fig. 1).

Induction Chemotherapy and Adverse Events

Induction chemotherapy was initiated for all 30 patients, and 24 patients completed the three planned cycles. The reasons for chemotherapy discontinuation were patient refusal ($n = 2$), a severe adverse event ($n = 1$), delayed recovery from an adverse event ($n = 1$), and other ($n = 2$).

The worst grades of major adverse events according to the CTCAE are listed in Table 2. Grade 3 or 4 adverse events that occurred in more than 10% of the patients were neutropenia (60%), leukocytopenia (33%), appetite loss (27%), general malaise (13%), and anemia (10%). In addition, one patient had a grade 3 pulmonary embolism, and another patient had a grade 4 fresh bleeding from tumor that required endoscopic intervention for hemostasis. No treatment-related deaths occurred.

Response to Induction Chemotherapy

Among 10 patients who had target lesions, 5 exhibited a partial response, 2 exhibited stable disease, 2 exhibited progressive disease, and 1 was not evaluable. The objective response rate among the patients with target lesions based on the RECIST criteria was 50% (95% confidence interval [CI] 19–81%).

When a complete response of PM was defined as the disappearance of PM and negative peritoneal cytology, 16 patients achieved complete response (53%; 95% CI 34–72%), and PM progressed in 3 patients (10%).

TABLE 1 Background characteristics of patients

No. of patients	30
Median age: years (range)	60 (42–73)
Sex	
Male	15
Female	15
Performance status	
0	23
1	7
Histology	
Differentiated	6
Undifferentiated	24
Macroscopic types	
1	1
2	3
3	9
4	16
5	1
T category	
T3 (SS)	1
T4a (SE)	25
T4b (SI)	4
N category	
N0	5
N1	7
N2	15
N3	3
CY category	
CY0	8
CY1	19
CYX	3
P category	
P0	8
P1	5
P2	13
P3	4
PC stages	
0	8
1	3
2	13
3	6
4	0

SS subserosa, *SE* serosa, *SI* invasion of adjacent structures, *PC* peritoneal carcinomatosis

The relationship between the extent and response of PM is shown in Table 3. The extent of PM evaluated by both the Japanese classification system and the PC staging system was correlated with the complete response rate of PM ($P = 0.002$ and 0.010, respectively).

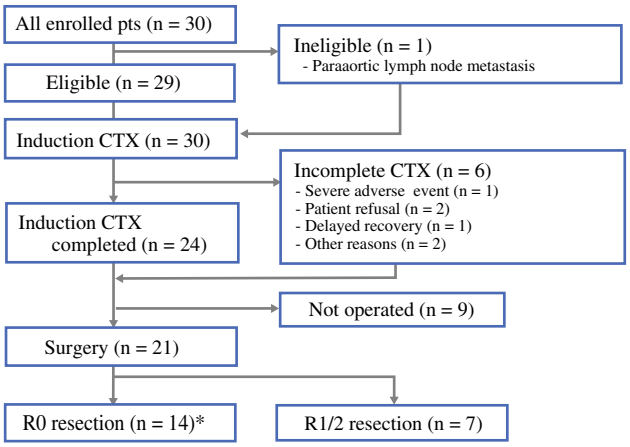

FIG. 1 Flow diagram of the 30 enrolled patients. *Including one ineligible patient. *CTX* chemotherapy, *pts* patients

TABLE 2 Adverse events associated with induction chemotherapy

Adverse event	Gr 1	Gr 2	Gr 3	Gr 4	Gr 3/4 (%)
	No. of patients				
Hematologic					
Leukocytopenia	0	10	10	0	33.3
Neutrocytopenia	0	8	13	5	60.0
Anemia	4	15	2	1	10.0
Thrombocytopenia	8	1	1	0	3.3
Total bilirubin	0	2	0	0	0
AST	5	0	0	0	0
ALT	9	1	0	0	0
Creatinine	5	0	0	0	0
Non-hematologic					
Nausea	8	8	2	NA	6.7
Vomiting	8	0	2	0	6.7
Diarrhea	10	0	2	0	6.7
Appetite loss	7	8	8	0	26.7
Stomatitis	3	2	1	0	3.3
General malaise	10	4	4	NA	13.3
Skin reaction	2	0	0	0	0
Pigmentation	2	0	0	0	0

Gr grade, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *NA* not available

Surgical Procedure and Outcomes

After reevaluation that followed induction chemotherapy, surgery for R0 resection was planned for 18 patients. Three additional patients for whom R0 resection was considered impossible underwent palliative/reduction surgery. The extent of resection was total gastrectomy for 19 patients and distal gastrectomy for 2 patients. Except for one patient who underwent D1 + lymphadenectomy, D2/D2 + lymphadenectomy was performed. Seven patients underwent splenectomy, and four patients underwent pancreaticosplenectomy for D2 total gastrectomy. The gallbladder (n = 5), transverse colon (n = 1), and jejunum (n = 1) also were resected in some patients. Among 18 patients for whom curative surgery was intended, 14 achieved R0 resection. In 12 patients, PM disappeared, and 2 patients achieved R0 resection through clearance of residual limited peritoneal nodules. The reasons for R1/2 resection in four patients were positive surgical margins (n = 3) and PM (n = 1). The R0 resection rate among all the patients was 47% (95% CI 28–66%).

No patient had a pathologic complete response. A pathologic response of grade 2 (degeneration or necrosis in more than two thirds of the original tumorous area) and grade 1b (degeneration or necrosis in more than one third of the original tumorous area) was observed in five patients each.

Postoperative complications of any grade occurred for 10 patients (48%). The following complications of grade 3a or higher occurred for six patients (29%): pancreatic fistula (n = 2), intraabdominal abscess (n = 1), anastomotic leakage (n = 1), anorexia (n = 1), renal vein thrombosis (n = 1), cystitis (n = 1), AST increase (n = 1), ALT increase (n = 1), γGTP increase (n = 1), pulmonary embolism (n = 1), and liver infarction (n = 1). No postoperative mortality occurred.

Survival

All but one patient were followed longer than 3 years or until death. The median survival time was 21.1 months (range, 13.3–28.9 months), and the 3-year OS rate was 32.5%. The median PFS was 15.3 months (range, 10.6–20.0 months), and the 3-year PFS was 16.7% (Fig. 2a).

When OS was compared between patients with macroscopic PM and patients with peritoneal positive cytology only (P0CY1), OS was significantly longer for the patients with P0CY1 (P = 0.002; Fig. 2b). The OS for the patients who underwent R0 resection was significantly better than for the patients with R1/2 resection or without resection (P = 0.046; Fig. 2c).

DISCUSSION

This multicenter phase 2 study demonstrated the safety of DCS induction chemotherapy for gastric cancer patients with PM. A complete response of PM was achieved by 53% of the patients. The observed R0 resection rate did not, however, reach the expected value of 65%. The study failed to show sufficient efficacy of the DCS regimen for

TABLE 3 Extent and response of peritoneal metastasis

Number	*n*	Response				R0 resection *n* (%)
		CR *n* (%)	Non-CR/non-PD	PD	NE	
All patients	30	16 (53)	6	3	5	14 (47)
Japanese classification						
P0	8	8 (100)	0	0	0	5 (63)
P1	5	3 (60)	0	0	2	3 (60)
P2	13	5 (38)	6	2	0	6 (46)
P3	4	0 (0)	0	1	3	0 (0)
PC stages						
0	8	8 (100)	0	0	0	5 (63)
1	3	1 (33)	0	1	1	1 (33)
2	13	5 (38)	5	1	2	7 (54)
3	6	2 (33)	1	1	2	1 (17)

CR complete response, *PD* progressive disease, *NE* not evaluable, *PC* peritoneal carcinomatosis

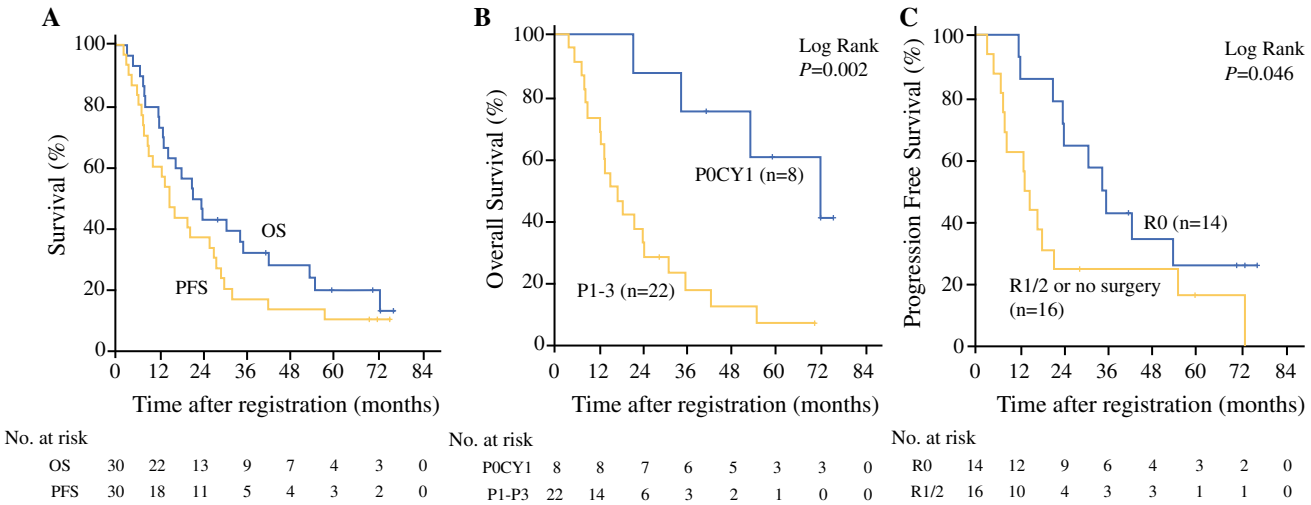

FIG. 2 **a** Kaplan–Meier curves of overall and progression-free survivals for the 30 enrolled patients. **b** Overall survival curves by status of peritoneal metastasis and **c** status of residual tumor. P0CY1, positive peritoneal cytology without visible peritoneal metastasis; P1–P3, gross peritoneal metastasis; R0, complete resection with no residual tumor; R1/2, microscopic or gross residual tumor

the following surgical intervention. One possible reason for this failure was the low dose intensity of S-1. Although the regimen consists of three drugs, the dose intensity of S-1 was lower than that of the S-1 plus cisplatin doublet regimen.

The original DCS regimen was first reported by Takayama et al.[13] with a very high response rate of 88% and severe toxicity. We used the modified regimen that was evaluated in a multicenter phase 3 study for unresectable gastric cancer, as well as in a phase 2 study of preoperative chemotherapy for gastric cancer with extensive lymph node metastasis or with a large type 3 or 4 tumor.[14,15]

Consistent with these previous studies, the adverse events were well manageable, and three courses of DCS regimen were completed for 80% of the patients. The surgical complication rate of grade 3 or higher was 29%. This also was comparable with the complication rates in two other studies with the same DCS regimen.[14,15] These demonstrated the safety of the DCS regimen in the induction setting, although the efficacy was insufficient.

To deliver drugs to the peritoneum more efficiently, HIPEC has been evaluated by several investigators during the last few decades, often combined with cytoreductive surgery. However, the survival benefit of HIPEC was shown only for patients with positive peritoneal cytology only or limited PM. Moreover, patients who received HIPEC plus cytoreductive surgery often experienced

significant systemic toxicity. To reduce toxicity, intraperitoneal chemotherapy using intraperitoneal port systems has been evaluated as another strategy.

A recent randomized phase 3 study comparing intraperitoneal and systemic chemotherapy in Japan suggested the possible clinical benefits of intraperitoneal paclitaxel, but failed to show its clear survival benefit.[16] To improve the survival of patients with PM, the development of a new regimen or a novel drug that would target PM more efficiently, by either systemic or intraperitoneal administration, is necessary.

Our strategy in the current study was to perform R0 resection when PM disappeared by systemic chemotherapy. We observed significantly better survival for the patients who underwent R0 resection. Controversy remains, however, as to whether gastric cancer patients with PM could be a target of a therapeutic strategy of induction chemotherapy followed by surgery or not. Both Japanese and Western current treatment guidelines recommend systemic chemotherapy for patients with distant metastasis. Whether R0 resection after a good response to systemic chemotherapy contributes to improving the survival of these patients is a matter of debate. Recent Japanese studies have shown that a significant proportion of patients with limited paraaortic lymph node metastasis achieved 5-year survival after neoadjuvant chemotherapy followed by extended surgery.[14,17] Studies of HIPEC and cytoreductive surgery for patients with gross PM have indicated that survival depends on the completeness of cytoreductive surgery.[3] These findings suggest that R0 resection after intensive chemotherapy is an important factor contributing to the longer survival of gastric cancer patients with PM.

There is consensus that the prognosis of patients with positive peritoneal cytology is extremely poor. Both the current TNM staging system and the Japanese Classification of Gastric Carcinoma classify patients with positive peritoneal cytology as stage 4. However, controversy remains regarding the optimal therapeutic strategy for patients who have peritoneal-positive cytology without visible PM (P0CY1). In Japan, these patients often undergo surgery first and receive adjuvant chemotherapy. When cytology was the only incurable factor, a prospective study reported a 5-year survival rate of 27%.[18] We previously reported the frequent negative conversion of cytology status after induction chemotherapy.[4] Other studies also have reported significantly better survival for patients with negative cytology after chemotherapy.[19,20] In the current study, although the number of patients was small, peritoneal cytology converted to negative status for all the patients with initial P0CY1 status, and the 5-year survival rate for these patients was 60%. Patients who have CY1 without macroscopic PM may have a better chance of cure by induction chemotherapy followed by surgery.

One limitation of the current study was its single-arm study design. We were able to estimate the R0 resection rate and the response rate of PM. However, a randomized controlled trial is needed to answer the question whether resection after significant response contributes to improvement of survival for these patients. Also, the number of patients in the current study was not sufficient for a subgroup analysis regarding the possible extent of PM. The current data suggested that the response and the prognosis may differ between patients with macroscopic PM and those with positive cytology only. We may need separate clinical trials for these two patient categories or could include more patients for a subgroup analysis.

In conclusion, induction chemotherapy with a DCS regimen was safe but did not improve the R0 resection rate for the patients with gastric cancer who had PM. To improve the survival of patients with PM, the development of a novel chemotherapeutic regimen that targets PM is required. When the initial diagnosis is positive peritoneal cytology without gross PM, R0 resection after a negative conversion of cytology by induction chemotherapy may improve patient survival.

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DISCLOSURE The authors declare that they have no conflict of interest.

REFERENCES

1. Miyashiro I, Takachi K, Doki Y, et al. When is curative gastrectomy justified for gastric cancer with positive peritoneal lavage cytology but negative macroscopic peritoneal implant? *World J Surg.* 2005; 29:1131–4.
2. Bando E, Yonemura Y, Takeshita Y, et al. Intraoperative lavage for cytological examination in 1297 patients with gastric carcinoma. *Am J Surg.* 1999; 178:256–62.
3. Desiderio J, Chao J, Melstrom L, et al. The 30-year experience: a meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. *Eur J Cancer.* 2017;79: 1–14.
4. Okabe H, Ueda S, Obama K, et al. Induction chemotherapy with S-1 plus cisplatin followed by surgery for treatment of gastric cancer with peritoneal dissemination. *Ann Surg Oncol.* 2009;16:3227–36.
5. Sato Y, Takayama T, Sagawa T, et al. Phase II study of S-1, docetaxel, and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. *Cancer Chemother Pharmacol.* 2010;66:721–8.

6. Tamegai H, Kaiga T, Kochi M, et al. Pharmacokinetics of docetaxel in gastric cancer patients with malignant ascites. *Cancer Chemother Pharmacol.* 2013;71:727–31.
7. Koizumi W, Nakayama N, Tanabe S, et al. A multicenter phase II study of combined chemotherapy with docetaxel, cisplatin, and S-1 in patients with unresectable or recurrent gastric cancer (KDOG 0601). *Cancer Chemother Pharmacol.* 2012;69:407–13.
8. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer.* 2011;14:101–12.
9. Gilly F, Carry P, Sayag A, et al. Regional chemotherapy (with mitomycin C) and intraoperative hyperthermia for digestive cancers with peritoneal carcinomatosis. *Hepatogastroenterology.* 1994;41:124–9.
10. Japanese Research Society for Gastric Cancer. The general rules for gastric cancer study. 1st ed. Tokyo: Kanehara Shuppan; 1995.
11. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–47.
12. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250:187–96.
13. Takayama T, Sato Y, Sagawa T, et al. Phase I study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. *Br J Cancer.* 2007;97:851–6.
14. Ito S, Sano T, Mizusawa J, et al. A phase II study of preoperative chemotherapy with docetaxel, cisplatin, and S-1 followed by gastrectomy with D2 plus para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis: JCOG1002. *Gastric Cancer.* 2017;20:322–31.
15. Hosoda K, Azuma M, Katada C, et al. A phase II study of neoadjuvant chemotherapy with docetaxel, cisplatin, and S-1, followed by gastrectomy with D2 lymph node dissection for high-risk advanced gastric cancer: results of the KDOG1001 trial. *Gastric Cancer.* 2018. https://doi.org/10.1007/s10120-018-0884-0.
16. Ishigami H, Fujiwara Y, Fukushima R, et al. Phase III trial comparing intraperitoneal and intravenous paclitaxel plus S-1 versus cisplatin plus S-1 in patients with gastric cancer with peritoneal metastasis: PHOENIX-GC trial. *J Clin Oncol.* 2018;36:1922–9.
17. Tsuburaya A, Mizusawa J, Tanaka Y, et al. Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with paraaortic lymph node dissection for gastric cancer with extensive lymph node metastasis. *Br J Surg.* 2014;101:653–60.
18. Kodera Y, Ito S, Mochizuki Y, et al. Long-term follow up of patients who were positive for peritoneal lavage cytology: final report from the CCOG0301 study. *Gastric Cancer.* 2012;15:335–7.
19. Mezhir JJ, Shah MA, Jacks LM, et al. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. *Ann Surg Oncol.* 2010;17:3173–80.
20. Jamel S, Markar SR, Malietzis G, et al. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. *Gastric Cancer.* 2018;21:10–8.