Original Article

A Randomized Phase 2 Study of Docetaxel and S-1 Versus Docetaxel and Cisplatin in Advanced Gastric Cancer With an Evaluation of SPARC Expression for Personalized Therapy

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BACKGROUND: The purpose of this study was to compare 2 weekly docetaxel-based regimens as first-line treatments for advanced gastric cancer and to investigate the expression of secreted protein acidic and rich in cysteine (SPARC) and its abilities to predict treatment-related clinical outcomes. **METHODS:** Patients were randomly selected to receive 3 weekly cycles of docetaxel (35 mg/m^2 on days 1 and 8) plus S-1 (35 mg/m^2 each twice daily on days 1-14) (DS), or docetaxel plus cisplatin (35 mg/m^2 each on days 1 and 8) (DC). Endpoints included overall response rate (primary), survival, toxicity, and quality of life (secondary). SPARC expression in prechemotherapy specimens of primary gastric tumors was evaluated via immunohistochemical analysis. **RESULTS:** Eighty patients were enrolled in the study. Confirmed overall response rates were 46% (95% confidence interval, 30%-62%) for DS and 24% (95% confidence interval, 11%-38%) for DC via intent-to-treat analysis. Median progression-free survival was 7.3 and 4.9 months and overall survival was 16.0 and 8.3 months for DS and DC, respectively. The most common grade $\geq$3 toxicity was neutropenia. Grade $\geq$3 mucositis (18%) and hand-foot syndrome (8%) were the toxicities most associated with DS, whereas anorexia (20%) and lethargy (20%) were more common with DC. High SPARC expression was related to early progression (hazard ratio, 3.67; $P = .042$) and poor overall survival (hazard ratio, 2.01; $P = .010$) in docetaxel chemotherapy on multivariate analysis. **CONCLUSIONS:** The outcomes in this study favored DS over DC for further phase 3 study. The findings suggest that split-dose weekly docetaxel alleviates hematological toxicity without compromising efficacy, and that SPARC expression may help individualize therapy in advanced gastric cancer. ***Cancer* 2011;117:2050–7.** © *2010 American Cancer Society.*

KEYWORDS: gastric cancer, chemotherapy, clinical trial, biomarker, SPARC, docetaxel.

Randomized studies of advanced gastric cancer (AGC) reveal the benefits of combination chemotherapy for survival and quality of life, but a globally accepted standard regimen has not been established. Old triplet regimens have been rapidly replaced by newer drugs, including taxanes, irinotecan, and oxaliplatin, that are more effective and better tolerated by patients. Docetaxel was the first of these drugs to be confirmed in prospective studies, and phase 2 trials of docetaxel plus cisplatin (DC) have shown promising efficacy.[1,2] Two recent randomized studies have suggested that combining docetaxel with fluorouracil and cisplatin (DCF) increases survival, response, and clinical benefits.[3,4] However, this regimen consistently produces high rates of neutropenia and nonhematological toxicity, underscoring the value of careful patient selection and comprehensive monitoring.[3,4] Therefore, dose optimization and selection of a combination partner are emerging questions in the clinical application of docetaxel.

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S-1 is one of the preferred agents for the treatment of gastric cancer in Asia. Recent randomized trials yielded encouraging results for S-1-containing doublets.[5-7] Docetaxel showed synergism with S-1 in vitro, and the response rate was 46%-67% in several phase 2 trials.[9-11] Based on these findings, we designed a randomized phase 2 study to determine whether S-1 or cisplatin shows greater promise as a combination partner of docetaxel for a subsequent phase 3 study. We adopted a weekly docetaxel regimen to assess whether split administration improves drug tolerability and tested the predictive values of biomarkers for treatment-related outcomes.

A variety of human malignancies, including gastric cancer, overexpress secreted protein acidic and rich in cysteine (SPARC), and high SPARC expression in the primary tumor is correlated with metastasis and poor prognosis.[12,13] $SP^{-/-}$ mice exhibit increased sensitivity to cisplatin, and SPARC is known to interact with tubulin during development. These findings may indicate SPARC's role in mitosis and led us to select SPARC as a candidate marker for docetaxel treatment.[14,15]

MATERIALS AND METHODS

Eligibility

Inclusion criteria were histologically confirmed gastric adenocarcinoma, recurrent or metastatic disease, age $\geq$18 years, performance score $\leq$2 by Eastern Cooperative Oncology Group criteria, no prior chemotherapy for advanced disease (adjuvant chemotherapy completed $\geq$6 months before enrollment), $\geq$1 measurable lesion, and adequate organ function. The latter was defined as a neutrophil count $\geq$1500/μL, platelet count $\geq$100,000/μL, serum creatinine level $\leq$1.5 mg/dL, total bilirubin level $\leq$1.25 (or 1.5) $\times$ upper limit of normal, and serum transaminase levels $\leq$2.5 (or 5.0) $\times$ upper limit of normal in the absence (or presence) of liver metastasis. Patients were excluded if they had concurrent active malignancy, brain metastasis, or uncontrolled comorbidity. The institutional ethics committee approved the trial, and all patients gave written informed consent.

Treatment Schedule

Patients were randomly assigned to receive 3 weekly cycles of docetaxel (35 mg/m^2 on days 1 and 8) plus S-1 (35 mg/m^2 each twice daily on days 1-14) (DS), or docetaxel plus cisplatin (35 mg/m^2 each on days 1 and 8) (DC). S-1 was prescribed according to body surface area as previously reported.[16] Chemotherapy was administered until the occurrence of disease progression, unacceptable toxicity, or patient withdrawal.

Granulocyte-colony stimulating factor (G-CSF) was permitted not prophylatically but therapeutically in the event of grade 4 and/or febrile neutropenia. The next cycle was not started unless the neutrophil count exceeded 1500/μL and the platelet count exceeded 100,000/μL. Day 8 treatment was skipped if any hematological toxicity grade $\geq$2 (except anemia) or nonhematological toxicity (except alopecia, nausea, and vomiting) occurred. If toxicity grade $\geq$3 occurred, the dose for the next cycle was reduced according to a predetermined dose modification plan. Patients were excluded if they required $\geq$4 weeks of rest for recovery from toxicity or if they required a dose reduction beyond the predetermined level.

Response and Toxicity Assessment

Baseline evaluations included medical history, physical examination, complete blood count with differential, serum chemistry/electrolytes, and electrocardiography. Baseline tumor measurements were performed at least 3 weeks prior to treatment. During treatment, laboratory and physical examinations were performed weekly. Toxicity was evaluated weekly and graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

Tumor measurement was conducted every 2 cycles according to Response Evaluation Criteria in Solid Tumors guidelines (version 1.0). All responses were confirmed by a panel of independent intramural radiologists. Patients were considered response-assessable if they had overt clinical or radiological evidence of early progressive disease (PD) within the first 2 cycles, or if they had received a minimum of 2 cycles of treatment with at least 1 tumor measurement.

Immunohistochemistry

Immunohistochemistry for SPARC was performed in formalin-fixed, paraffin-embedded primary gastric tumors using the EnVision method.[17] Briefly, 4-μm-thick tissue sections were deparaffinized and rehydrated. After removal of endogenous peroxidase activity and retrieval of antigen, the slides were incubated with a 1:50 dilution of anti-SPARC monoclonal antibody (Zymed Laboratories, CA) at room temperature for 1 hour. The slides were then incubated with EnVision detection system reagents (Dako, CA) and stained using diaminobenzidine tetrahydrochloride/peroxidase reaction (Dako). Slides were counterstained with Mayer's hematoxylin (Sigma, CA)

and scored for SPARC expression using a weighted histoscore.[18] Histoscores were calculated according to the following formula: (1× percentage of cells staining weakly positive) + (2× percentage of cells staining moderately positive) + (3× percentage of cells staining strongly positive).

Statistical Analysis

The primary endpoint was overall response rate (ORR). Secondary endpoints included survival, safety, and biomarker implementation. We hypothesized that the ORR for DS and DC would be 50% and 20%, respectively. Using a 2-sided test and assuming $\alpha = 0.05$ and $\beta = 0.20$ (80% power), 36 patients in each treatment arm who met tumor response evaluation were acquired. Assuming a 10% dropout rate, the final number of patients was 40 per treatment arm. The ORR was evaluated according to both intent-to-treat and per-protocol analyses.

Treatment group differences in ORR were tested using the Cochran-Mantel-Haenschel test. The Kaplan-Meier method was used to estimate the distribution of time to events. Progression-free survival (PFS) was determined from the date of treatment to PD or death from any cause. Overall survival (OS) was calculated from the date of treatment to death from any cause. Logistic regression and Cox proportional hazards model were used to determine the contributions of clinico-pathological or biological factors to endpoints.

RESULTS

Patient Characteristics

Eighty patients were recruited from July 2005 to April 2007. One DS patient was ineligible due to concomitant malignancy. Four patients were excluded from efficacy analysis after the first cycle (3 withdrew consent [all DC] and 1 [DS] died of toxicity). Thus, the remaining 75 patients (DS, n = 37; DC, n = 38) were evaluated for response. The baseline characteristics of the 2 groups were well balanced (Table 1).

Sixty-three patients (79%) had metastatic disease, and the other 17 patients had recurrent disease after curative resection. All patients had at least 1 site of distant metastasis at the time of accrual (median, 2.5; range, 1-6), and the median size of measurable lesions was 18 mm (range, 10-108 mm). The most common nonmeasurable lesion was primary gastric mass (n = 59), and computed tomography scans revealed peritoneal seeding in 26 patients (33%).

Treatment Results

In total, 321 cycles of DS and 218 cycles of DC were administered, with a median of 6 cycles for DS (range, 1-26) and 4 cycles for DC (range, 1-16). The median treatment duration was 24 weeks (range, 3-64 weeks) for DS and 13 weeks for DC (range, 3-82 weeks). Dose reduction was more common in DS than DC (61% vs 39%), but the incidence within cycle 4 was more common with DC (DS, 50%; DC, 81%, $P = .056$). Reasons for dose reduction included neutropenia (n = 21), nonhematological toxicity (n = 15), poor patient compliance (n = 2), and investigator discretion (n = 2).

The incidence of toxicity-related dose delays by cycle 4 was similar in both groups (DS, 26%; DC, 27%). During the entire treatment period, more treatment delays occurred in DS due to the longer treatment duration; total delays were 72 weeks for DS and 37 weeks for DC, with a median of 1 week (range, 1-3 weeks) for both groups. Treatment cessation due to unacceptable toxicity and patient refusal occurred more frequently with DC (DS, 10%; DC, 24%). Treatment cessation decided by the investigator occurred mainly with DS, in cases of treatment sufficient in duration without disease progression (≥12 cycles) where further benefit might not be achieved without unacceptable toxicity.

Overall, the median relative dose intensity (RDI) of docetaxel was 0.88 for DS (range, 0.57-1.04) and 0.94 for DC (range, 0.47-1.03). The RDI of S-1 and cisplatin were 0.91 (range, 0.54-1.06) and 0.94 for DC (range, 0.47-1.03), respectively. In DS, the planned RDI was maintained until cycle 4, and then slowly declined to ≈0.8, whereas the RDI in DC declined steeply after cycle 2.

Efficacy and Survival

The confirmed ORR was 46% for DS (95% confidence interval [CI], 30%-62%) and 24% for DC (95% CI, 11%-38%) by intent-to-treat analysis ($P = .041$). Early PD (defined as PD or clinical deterioration within the first 2 cycles of treatment) occurred in 7 (18%) DS patients and 11 (27%) DC patients. Response duration was 8.6 months for DS and only 4.9 months for DC**.** On multivariate analysis, treatment arm (DS or DC) was the only independent factor selected for response, with a hazard ratio (DS/DC) of 0.38 (95% CI, 0.15-0.97; $P = .044$).

At the median follow-up duration of 10.2 months (range, 0.4-37.5 months), 77 patients exhibited disease progression, and 71 patients had expired. The median PFS was 7.3 months for DS (95% CI, 5.3-9.3 months)

Table 1. Patient Characteristics

Characteristics	Docetaxel + S-1	Docetaxel + Cisplatin	Total
No. of enrolled patients	39	41	80
No. of evaluable patients	37	38	75
Age, y, median (%)	26-71 (56)	22-75 (60)	22-75 (58)
Sex, n			
Men	31	28	59
Women	8	13	21
Performance status, no. (%)			
ECOG 0-1	35 (90)	35 (85)	70 (87)
ECOG 2	4 (10)	6 (15)	10 (13)
BSA, m^2, mean ± SD	1.67 ± 0.13	1.64 ± 0.18	1.66 ± 0.15
CCr, mL/min, mean ± SD	90.2 ± 20.5	90.4 ± 23.2	90.3 ± 21.2
Disease status, no. (%)			
Metastatic	29 (74)	34 (83)	63 (79)
Recurrent	10 (26)	7 (17)	17 (21)
Previous treatment, no. (%)			
None	27 (69)	32 (78)	59 (74)
Gastrectomy only	7 (18)	6 (15)	13 (16)
Gastrectomy + adjuvant chemotherapy	5 (13)	3 (7)	8 (10)
Histology, no. (%)			
Well/moderately differentiated	17 (43)	15 (36)	32 (40)
Poorly differentiated	13 (33)	19 (46)	32 (40)
Signet ring cell	7 (18)	6 (15)	13 (16)
Other	2 (6)	1 (3)	3 (4)
Measurable lesion, no. (%)			
Lymph node	30 (55)	32 (54)	62 (54)
Liver	10 (19)	10 (17)	20 (18)
Neck node	6 (11)	5 (9)	11 (10)
Other	8 (15)	12 (20)	20 (18)
Nonmeasurable lesion, no. (%)			
Stomach	30 (50)	29 (48)	59 (49)
Peritoneum	14 (23)	12 (20)	26 (22)
Abdominal mass	4 (7)	7 (12)	11 (9)
Other	12 (20)	12 (20)	24 (20)
No. of involved organs, no. (%)			
1	2 (5)	5 (12)	7 (9)
2	14 (36)	9 (22)	23 (29)
3	10 (26)	16 (39)	26 (32)
4	13 (33)	11 (27)	24 (30)
No. of target lesions per patient, no. (%)			
1	3 (8)	7 (17)	10 (13)
2	10 (26)	12 (29)	22 (27)
3	4 (10)	4 (10)	8 (10)
4	22 (56)	18 (44)	40 (50)

ECOG indicates Eastern Cooperative Oncology Group; BSA, body surface area; CCr, creatinine clearance.

and 4.8 months for DC (95% CI, 2.8-6.8 months), with a hazard ratio (DS/DC) of 0.63 (95% CI, 0.38-1.05). The median OS was 16.0 months for DS (95% CI, 10.1-21.9 months) and 8.2 months for DC (95% CI, 5.1-11.3 months), with a hazard ratio (DS/DC) of 0.56 (95% CI, 0.35-0.88). The estimated 1-year survival rates were 59% for DS and 34% for DC.

Toxicity

There were 2 treatment-related deaths with DS from febrile neutropenia and infection. The most common grade ≥3 hematological toxicity was neutropenia. Febrile neutropenia occurred in 4 DS patients (10%). The number of granulocyte-colony stimulating factor injections was similar in both groups (8 DS patients; 11 DC patients).

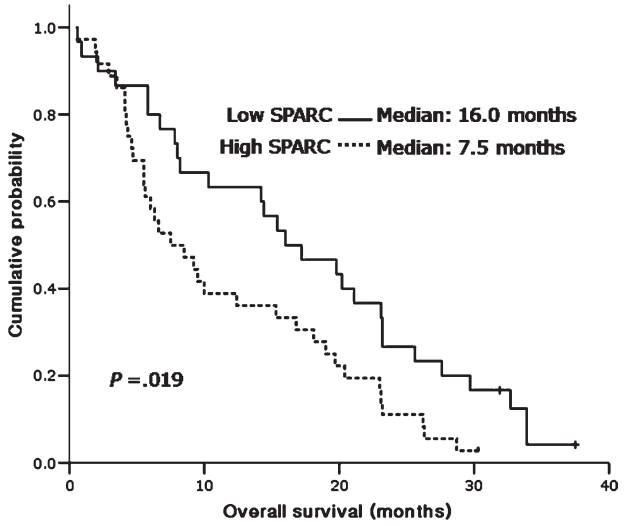

Figure 1. Overall survival according to expression level of secreted protein acidic and rich in cysteine (SPARC) is shown.

Twenty-four DS patients and 16 DC patients had nonhematological toxicity grade ≥3. The median time to grade ≥3 nonhematological toxicity was longer for DS (4 cycles; range, 1-15 cycles) than for DC (1 cycle; range, 1-9 cycles). Eight DS patients (33%) experienced grade ≥3 toxicity within the first 2 cycles, compared with all but 2 DC patients (88%). Diarrhea, mucositis, and hand-and-foot syndrome were common in DS; however, all patients recovered with conservative care. Anorexia and lethargy were more common in DC patients. One DS patient underwent gastrectomy after cycle 2 for intractable bleeding due to cancer progression.

Association of SPARC Expression With Treatment Outcome

SPARC was mainly localized in the cytoplasm or membranes of cancer cells. Histoscores for SPARC expression did not differ between treatment groups ($P = .877$, Mann-Whitney U test) or other clinico-pathological parameters (data not shown). Grouping patients as "high SPARC" or "low SPARC" according to the median value of histoscore revealed an association of high SPARC with early PD ($P = .042$). On logistic regression, high SPARC expression was the only independent variable that predicted early PD ($P = .042$), with a relative risk of 3.67 (95% CI, 1.05-12.86).

On univariate analysis, patients with high SPARC had significantly shorter OS than patients with low SPARC (7.5 vs 16.0 months, $P = .019$) (Figure 1). On multivariate analysis, SPARC expression remained in the final model for OS along with treatment arm (DS vs DC). High SPARC showed a hazard ratio for death of 2.01 (95% CI, 1.18-3.40; $P = .010$) (Table 2).

DISCUSSION

When designing this study, we already knew the randomized phase 2 trial in which DCF gave a higher ORR than DC.[19] Nonetheless, we chose DC as a treatment arm because it had similar OS to DCF but a more favorable nonhematological toxicity profile. The other main consideration in study design was docetaxel dosage. Early studies evaluated triweekly docetaxel at 85-100 mg/m^2 combined with 75 mg/m^2 cisplatin based on phase 1 results. Subsequent studies, however, consistently raised concerns about toxicity, notably neutropenia.[1,20,21] Preclinical studies have demonstrated that docetaxel modulates the intracellular metabolism of other drugs (5-FU and cisplatin), which explains the mechanism underlying the synergistic effect.[22,23] Therefore, we hypothesized that split-dose weekly administration of docetaxel is a rational approach to procure dose intensity without increasing toxicity. Even with the strict weekly follow-up of complete blood count mandated by the protocol, only 27% of patients suffered grade ≥3 neutropenia, which is remarkable compared with previous data indicating that >80% of DCF patients have grade ≥3 neutropenia.[4,19] Therefore, we suggest that split-dose docetaxel offers a safer approach than a triweekly schedule and that combination with S-1 has high efficacy for gastric cancer. However, we also found that this weekly strategy is yet to be justified with cisplatin. For DC treatment, the toxicity profile seems better compared with previous data, but it is possible that the efficacy was also compromised, leading to decreased response and survival.

We observed that DS and DC had different toxicity profiles in nonhematological toxicities. The major adverse event of DS was mucocutaneous toxicity, and 8% of patients suffered grade ≥3 hand-and-foot syndrome. This toxicity profile is similar to weekly docetaxel plus capecitabine, which proved to be promising in gastric cancer, as shown by some phase 2 trials.[24,25] Although the incidence is not high, this toxicity may be troublesome for patients. Docetaxel-induced hand-and-foot syndrome is known to be related to the cumulative dose and occur more frequently in a weekly schedule.[26] Mucositis and nail changes that advanced to onycholysis are also combined. Mucocutaneous toxicity, which usually began to appear

Table 2. Univariate and Multivariate Analysis of Survival

Clinico-pathological Factors	n	Progression-Free Survival				Overall Survival			
		Median, mo	Univariate *P*	Multivariate *P*	HR (95% CI)	Median, mo	Univariate *P*	Multivariate *P*	HR (95% CI)
Sex									
Men	59	6.6	.440			10.4	.862		
Women	21	5.7				9.5			
Age									
<70	69	6.4	.784			10.4	.405		
≥70	11	5.6				9.2			
Functional status									
ECOG 0-1	70	7.0	.010			10.4	.028		
ECOG 2	10	3.0				5.8			
Previous gastrectomy									
No	59	6.2	.526			9.2	.159		
Yes	21	7.0				16.0			
Involved organ									
1-2 metastatic sites	34	6.4	.872			10.3	.479		
>2 metastatic sites	46	6.2				9.5			
Histology									
Differentiated	32	7.0	.289			10.4	.294		
Undifferentiated	47	5.8				10.0			
Treatment arm									
Docetaxel + S-1	39	7.3	.072	.012	1	16.0	.011	.008	1
Docetaxel + cisplatin	41	4.8			1.80 (1.13-2.85)	8.2			2.00 (1.20-3.36)
SPARC expression									
Below median	33	6.2	.357			16.0	.019	.010	1
Above median	33	5.7				7.5			2.01 (1.18-3.40)

HR indicates hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SPARC, secreted protein acidic and rich in cysteine.

after cycle 4, may have clinical implications; it causes pain and degrades quality of life enough to significantly delay the next treatment cycle. Therefore, early detection and symptomatic relief are essential for better application in clinical practice.

Although survival is not a primary endpoint, the remarkably long OS for PFS in DS patients is noteworthy. This discrepancy between PFS and OS may reflect multiple factors: First, DS had twice the response duration as DC, a higher disease control rate (80% vs 64%), and a trend toward longer disease stabilization (7.8 vs 6.2 months; $P = .076$). Second, survival may be partly influenced by the therapy that followed the study. More DS patients were transferred to salvage chemotherapy (69% vs 41%), and many of them received cisplatin (23%), a generally favorable salvage treatment in AGC.[27] *Ad hoc* analysis showed that 23% of the DS patients who received second-line treatment showed an objective response, compared with only 9% of DC patients. Third, inferior survival of DC patients possibly results from an altered schedule of weekly DC administration rather than a triweekly schedule. Finally, the favorable response and survival of DS patients may be attributable to molecular factors involved in drug metabolism or cell signaling.

Little is known about molecular biomarkers relevant to gastric cancer. A recent phase 3 study validated erbB2 as a criterion for treatment individualization in gastric cancer.[28] However, the prevalence of erbB2 positivity is low in gastric cancer,[29] and only 1 patient in our study showed erbB2 immunoreactivity. We hypothesized that pooling information from multiple pathways might yield a clearer picture of tumor behavior and potential sensitivity to therapy. We demonstrated that high protein expression of SPARC detected in primary gastric tumor helps to predict early PD and poor survival, which may correspond to primary resistance to docetaxel. The underlying mechanism between SPARC and chemosensitivity is currently unknown, but some previous studies have shown that SPARC protects cells from stress-induced apoptosis through interaction with integrin β1 heterodimers that enhance integrin-linked kinase activation and prosurvival activity.[13,30] Our study is only the first suggestion of an association between SPARC expression and clinical outcome of docetaxel treatment, and this preliminary finding awaits confirmation in larger study groups along with in vitro experiments. SPARC expression should be prospectively evaluated as a stratification factor in a randomized trial to determine whether it is truly predictive of benefit or response to docetaxel or other chemotherapy.

In conclusion, we favor DS over DC for further evaluation in terms of tumor response and survival. An Asian phase 3 trial (JACCRO GC03) comparing S-1 plus docetaxel to S-1 monotherapy has completed accrual.[31] This trial could provide more information on the combination of S-1 and docetaxel. However, the study design was different from ours (triweekly vs weekly treatment), and we tried higher dose intensity of docetaxel (13 vs 23 mg/m^2/week). We think that the potency of S-1-based combinations shown in the SPIRITS trial justifies further testing in future phase 3 trials.[5] We support the use of weekly docetaxel, and our results suggest that intratumoral SPARC expression provides molecular insights into patient survival and chemoresistance. A better understanding of the molecular signatures of cancer may lead to more rational and predictable chemotherapies and expand our ability to individualize the treatment of AGC.

CONFLICT OF INTEREST DISCLOSURES

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