Association of fluoropyrimidines, platinum agents, taxanes, and irinotecan in any line of chemotherapy with survival in patients with advanced gastric cancer

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Abstract

Background Although fluoropyrimidines, platinum agents, taxanes, and irinotecan are used in the treatment of advanced gastric cancer (AGC), it remains unclear whether these agents in any line of chemotherapy are associated with overall survival (OS) in these patients.

Methods We retrospectively analyzed 704 patients with AGC. To avoid possible lead-time bias, we applied time-varying covariate analysis for chemotherapy with four agents in any line.

Results Median OS was 12.3 months. The frequency of exposure to each agent class during all lines of treatment was 92.6% for FU (5-fluorouracil or oral fluoropyrimidine), 48.2% for platinum agents, 65.1% for taxanes, and 39.1% for irinotecan. According to a multivariate Cox model with exposure to each agent class as a time-varying covariate, the hazard ratios (HRs) of death were 0.41 (95% confidence interval [CI], 0.27–0.57; $p < 0.001$) for FU, 0.71 (95% CI, 0.58–0.84; $p < 0.001$) for platinum agents, 0.51

(95% CI, 0.41–0.63; $p < 0.001$) for taxanes, and 0.53 (95% CI, 0.43–0.65; $p < 0.001$) for irinotecan. Although other agents were used in 18.6% of the patients, they did not affect survival.

Conclusions Each of the four agent classes (FU, platinum agents, taxanes, and irinotecan) appears to be independently associated with improved OS in patients with AGC regardless of timing. This result suggests the importance of developing strategies which make these active agents available to all patients with AGC to prolong OS.

Keywords Gastric cancer · Chemotherapy · Fluorouracil · Platinum agent · Paclitaxel · Irinotecan

Introduction

Gastric cancer is the fourth most common malignancy in the world (989,000 cases in 2008, 7.8% of the total number of cases of malignancy) and the second leading cause of cancer death (737,000 deaths, 9.7% of the total number of cancer deaths) [1]. The prognosis of patients with advanced or recurrent gastric cancer (AGC) remains poor; chemotherapy confers only a minimal survival advantage, with a median survival of approximately 1 year. The most commonly used regimens are combination chemotherapy consisting of a fluoropyrimidine [FU; 5-fluorouracil (5-FU) or oral fluoropyrimidine] plus a platinum agent [2–7]. While docetaxel and anthracyclines are also used in first-line combination regimens in western countries [2, 3], docetaxel or paclitaxel is commonly used as second- or third-line chemotherapy in Japan [4, 8, 9]. Although irinotecan has been evaluated as a first-line agent [10–12], results have shown no survival benefit, partially reflecting its use in post-disease progression in trial control arms [10, 11].

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In contrast, a recent small randomized study has suggested its efficacy as second-line chemotherapy [13].

Because these agents are variously used in any of several lines of chemotherapy, in both clinical studies and clinical practice, their individual impact on overall survival (OS) in AGC patients in any line of treatment has not yet been clarified. Here, we used a novel time-varying covariate (TVC) analysis to retrospectively evaluate the impact of exposure to different classes of agents on OS in AGC patients who had undergone chemotherapy.

Patients and methods

Patients

This was a retrospective cohort study of AGC patients who received chemotherapy. Other principal inclusion criteria were the presence of histologically proven, inoperable gastric cancer; Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; and sufficient bone marrow, liver, and renal function.

Between March 2001 and April 2009, 758 consecutive patients with AGC were treated with chemotherapy in our institution, of whom 704 met the inclusion criteria. FU (5-FU or S-1), cisplatin, docetaxel, and paclitaxel were approved for use and consistently available throughout this period. Written informed consent for treatment was obtained from all patients. Chemotherapeutic regimens were selected individually by the attending physician or within the context of a clinical trial. Dosing and scheduling of most regimens were performed as reported in the literature [4, 8–11, 14].

Statistical methods

The primary objective of this study was to evaluate the association between exposure to each class of chemotherapeutic agent; namely, FU (5-FU or oral fluoropyrimidine), platinum agents (cisplatin or oxaliplatin), taxanes (docetaxel or paclitaxel), irinotecan, or others, and OS.

OS was defined as the number of days from the date of initial chemotherapy to the date of death or last follow-up visit. Disease progression associated with each line of chemotherapy was also measured from the beginning of treatment to the date of disease progression, as evaluated by the attending physician. Vital status and disease status were confirmed by checking medical records at the date of the last follow-up visit. In cases lost to follow-up, vital status was confirmed by census registration, which is conducted annually in Japan.

The impact of exposure to each agent class on OS was evaluated by univariate and multivariate analyses, using a

Cox proportional hazards model and presented as hazard ratio (HRs) and 95% confidence intervals (95% CIs). As the length of exposure to each agent class varied over time (i.e., between first-, second-, and third-line treatment), analyses might have been compromised by possible lead-time bias, which would have resulted in a false-positive association between a larger number of chemotherapeutic lines and longer survival. To minimize this potential bias, exposure to each agent class was analyzed as a simple prognostic factor or as a TVC. In addition, because disease progression was the primary reason for proceeding to the next line of chemotherapy, tumor progression during each line of chemotherapy was also included in the TVCs. Each TVC was constructed as a step function initially set at 0 and increased by 1 unit each time the corresponding event was observed (Fig. 1).

Models were constructed using forward and backward stepwise progression, with threshold *p* values for inclusion or exclusion in the model defined as 0.10 and 0.20, respectively. Other confounding variables considered in the univariate and multivariate analyses were age (<65 vs. ≥65 years), gender (male vs. female), ECOG PS (0–1 vs. 2), histological subtype (diffuse vs. intestinal), disease status (advanced vs. recurrent), prior gastrectomy (no vs. yes), prior adjuvant chemotherapy (no vs. yes), presence of peritoneal metastasis (no vs. yes), presence of liver metastasis (no vs. yes), number of metastatic sites (1 vs. ≥2), first-line chemotherapy (monotherapy vs. FU + platinum agent vs. other combinations), and date of initial chemotherapy (2001–2004 vs. 2005–2009). We applied the Kaplan–Meier product limit method to estimate survival probability at certain time points. Distribution of subject characteristics was assessed by the χ^2 test or Fisher's exact test, as appropriate. Statistical analyses were performed using STATA ver. 10 (Stata Corp LP, College Station, TX,

Fig. 1 Time-dependent variables describing exposure to each agent and tumor progression in an individual patient. S1 plus cisplatin was initiated in a patient as first-line chemotherapy in January 2005. Second-line paclitaxel and third-line irinotecan were administered, due to disease progression, beginning in May 2005 and September 2005, respectively

USA). All tests were two-sided, with p values less than 0.05 considered statistically significant.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. Median follow-up at the time of analysis was 47 months (range,

Table 1 Patient characteristics

Characteristic	All ($n = 704$)	
	n	%
Median age, years	62	–
Gender		
Male	470	67
Female	234	33
ECOG PS		
0–1	595	85
2	109	15
Histological type		
Diffuse	500	71
Intestinal	204	29
Disease status		
Advanced	472	67
Recurrent	232	33
Prior gastrectomy		
No	349	49
Yes	355	51
Adjuvant chemotherapy		
No	605	86
Yes	99	14
Peritoneal metastasis		
No	334	47
Yes	370	53
Liver metastasis		
No	504	72
Yes	200	28
No. of metastatic sites		
1	358	51
≥ 2	346	49
First-line chemotherapy		
Monotherapy	381	49
FU + platinum agent	198	28
Other combinations	125	18
Initiation of chemotherapy		
2001–2004	325	46
2005–2009	379	54

ECOG PS Eastern Cooperative Oncology Group performance status, FU 5-fluorouracil or fluoropyrimidine

10–108 months). Median OS of all patients was 12.3 months (95% CI; 11.5–13.1 months), with 576 patients (81.8%) already dead. Treatment regimens are shown in Fig. 2. A total of 198 (28.1%) patients received FU plus a platinum agent as first-line chemotherapy. Other patients received other combinations ($n = 131$; 18.6%) or monotherapy ($n = 375$; 53.3%). Second-line chemotherapy was used in 513 patients (72.9%), third-line in 264 patients (37.5%), and fourth-line in 117 patients (16.6%). Exposure frequencies to each agent class in all courses of treatment were as follows: FU, 92.6%; platinum agents, 48.2%; taxanes, 65.1%; irinotecan, 39.1%; and other agents, 18.6%. The median OS of patients exposed to one ($n = 145$; 20.6%), two ($n = 233$; 33.1%), three ($n = 191$; 27.1%), or four agents ($n = 135$; 19.2%) was 6.5 (95% CI, 5.0–8.1), 10.2 (95% CI, 9.1–12.1), 14.8 (95% CI, 12.9–16.5), and 20.4 months (95% CI, 16.2–21.7), respectively.

Fig. 2 Treatment regimens and lines of chemotherapy. FU 5-Fluorouracil or fluoropyrimidine, PD progressive disease

Table 2 Univariate and multivariate analyses with or without TVCs

Baseline and clinical features	Univariate analysis without TVC			Multivariate analysis without TVC			Multivariate analysis with TVC ^a		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Exposure to agents									
FU	0.48	0.35–0.66	<0.001	0.37	0.26–0.51	<0.001	0.41	0.27–0.57	<0.001
Platinum agent	0.67	0.57–0.79	<0.001	0.73	0.60–0.88	0.001	0.71	0.58–0.84	<0.001
Taxane	0.67	0.56–0.79	<0.001	0.68	0.56–0.82	<0.001	0.51	0.41–0.63	<0.001
Irinotecan	0.66	0.56–0.78	0.006	0.79	0.65–0.97	0.022	0.53	0.43–0.65	<0.001
Others	0.92	0.75–1.11	0.47	1.00	0.80–1.26	0.94	0.87	0.69–1.10	0.25

Values in italics denote significant differences

TVC time-varying covariate, HR hazard ratio, CI confidence interval, FU 5-fluorouracil or fluoropyrimidine, ECOG PS Eastern Cooperative Oncology Group performance status

^a Adjusted by age, gender, ECOG PS, histological type, disease status, prior gastrectomy, adjuvant chemotherapy, presence of peritoneal metastasis, presence of liver metastasis, number of metastatic sites, first-line chemotherapy, time of initiation of chemotherapy, and tumor progression during each line of chemotherapy

Fig. 3 Overall survival (OS) according to period of initiation of chemotherapy. The median OS of patients in whom chemotherapy was initiated between 2001 and 2004 ($n = 325$) was 12.0 months and that of patients in whom chemotherapy was initiated between 2005 and 2009 ($n = 379$) was 12.5 months, with no statistically significant improvement on multivariate analysis (HR 0.93; 95% CI, 0.78–1.12; $p = 0.44$). HR hazard ratio, CI confidence interval

TVC analyses of exposure to each agent class and survival

Table 2 shows the results of univariate and multivariate analyses of exposure to each agent class as prognostic factors, including exposure to each agent as TVCs. Exposure to each agent class remained significant on multivariate analyses. The rightmost column of Table 2 also shows the results of multivariate analyses with exposure to each agent class as a TVC. Exposure to each agent class remained significantly associated with better survival, with the HR of death being 0.41 (95% CI, 0.27–0.57; $p < 0.001$) for FU, 0.71 (95% CI, 0.58–0.84; $p < 0.001$) for platinum agents, 0.51 (95% CI, 0.41–0.63; $p < 0.001$) for taxanes, and 0.53 (95% CI, 0.43–0.65; $p < 0.001$) for irinotecan. In contrast, other agents had no impact on survival (HR, 0.87; 95% CI, 0.69–1.10; $p = 0.25$).

Table 3 Exposure to each agent between 2001–2004 and 2005–2009

Agent	Exposure to agents	
	2001–2004 (%)	2005–2009 (%)
FU	94	91
Platinum	40	54*
Taxane	65	62
Irinotecan	36	36
Any three drugs	43	49
Four drugs	18	20

* $p < 0.05$

Comparison of the periods 2001–2004 and 2005–2009

The median OS of patients for whom chemotherapy was initiated between 2001 and 2004 ($n = 325$) was 12.0 months, while that of patients who started on chemotherapy between 2005 and 2009 ($n = 379$) was 12.5 months, showing no statistically significant improvement on multivariate analysis (HR 0.93; 95% CI, 0.78–1.12; $p = 0.44$, Fig. 3). The proportion of patients who received each drug and any three drugs was not significantly different between the two periods, although exposure to platinum was slightly higher in 2005–2009 (Table 3).

Discussion

In this study, we found that each of the four classes of agents examined—FU, platinum agents, taxanes, and irinotecan—was independently associated with improved OS in patients with AGC according to TVC analysis. Although several pivotal studies [2–6, 8, 10–15] and one meta-

analysis [16] have demonstrated the efficacy of each of these agent classes as first-line chemotherapy, to our knowledge this is the first study to simultaneously evaluate exposure to each agent class in all lines of treatment. Based on the present results, we speculate that it is important to make these active agents available to all patients with AGC to prolong OS.

Because there was no exposure to any of these four classes of agents prior to the initiation of chemotherapy, a false association between exposure to each agent class and patient outcome, due to the tendency of more lines of chemotherapy and more agents to result in a better prognosis (lead-time bias) might have been expected, as shown in our results (6.5 months with one agent vs. 20.4 months with four agents). To address our *a priori* hypothesis, we therefore used Cox proportional hazards models to remove confounding factors and we used exposure to each agent as TVCs. This is one of the strengths of this study. In contrast to the four agent classes above, agents classified as “other” did not affect survival. This result also supports the assumption that the level of false-positive associations due to lead-time bias is low.

These results suggest the importance of making these active agents available to all patients with AGC. A similar strategy is warranted for metastatic colorectal cancer, for which exposure to three effective cytotoxic agents (5-FU, oxaliplatin, and irinotecan) has been shown to prolong survival [17]. The low proportion of patients eligible to receive third-line therapy (37.5%) in the present study suggests the importance of using effective agents in first- and second-line treatments. Although an early report of triplet combination chemotherapy for AGC showed a high frequency of toxicity [2], a more recent study of a modified regimen demonstrated more acceptable toxicity [18]. Future evaluation to determine optimal treatment strategies in patients with AGC is therefore warranted.

It is important to note the methodological strengths and limitations of the present study. First, while admittedly this was a retrospective cohort study, the conduct of a prospective study would have been hampered by the difficulty in gathering detailed information about all courses of treatment or disease progression with each line of chemotherapy, given that most studies to date have been conducted primarily to evaluate the efficacy of a single agent or regimen in a single treatment line. In contrast, the present study was designed to comprehensively evaluate the impact of each agent class regardless of treatment line, using TVC analysis, which is one of its strengths. On the other hand, TVC analysis was not necessarily perfect in the setting of our study, because this method may be valid under a strong assumption of an association between treatment selection at the time of events and the history up to the events [19]. Second, potential confounders such as PS, histological type, and metastatic site

were considered in the multivariate analyses; therefore, although any associations observed were theoretically independent of confounders, the effect of residual confounding by factors not evaluated cannot be completely ruled out. Third, although current standard treatment for AGC is FU plus a platinum agent, fewer than half of the patients in the present analysis received such first-line combination chemotherapy, because FU monotherapy (5-FU or S-1) was the standard chemotherapy regimen during the earlier part of this study (prior to publication of the results of the SPIRITS trial [4]). However, we included the first-line chemotherapy regimen as a confounder in the multivariate analysis. Additionally, when we limited our analysis to patients who received FU plus a platinum agent as first-line chemotherapy, the impact of taxanes and irinotecan on survival in this cohort was similar to that in the overall patient population (data not shown). Finally, because the treatment regimens used in each line of therapy were quite variable due to the retrospective nature of this analysis, a variety of different treatment indications may also have been used by individual physicians, which may have affected the results. With regard to the strengths of this study, these include its relatively large sample size and the availability of detailed clinical information.

In conclusion, our findings indicate that each of the four agent classes (FU, platinum agents, taxanes, and irinotecan) evaluated in the present study is independently associated with improved OS in patients with AGC. This finding may indicate the importance of strategies to make all of these active agents available to all patients with AGC to prolong OS.

Conflict of interest None of the authors has financial or personal conflicts of interest to disclose.

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