Optimal indications for second-line chemotherapy in advanced gastric cancer

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As it remains uncertain whether patients with advanced gastric cancer who progress after first-line chemotherapy should receive second-line chemotherapy, we attempted to identify the optimal indications for second-line chemotherapy. In this retrospective study, 101 patients were included in univariate and multivariate analyses to identify clinicopathological variables independently associated with longer survival postprogression (SPP), defined as the time from recognition of disease progression on first-line chemotherapy to death from any cause or last follow-up. The median SPP was 340 days. On multivariate analysis, performance status 2 [hazard ratio (HR), 14.234; 95% confidence interval (CI), 2.766–73.258], serum albumin level less than 3.5 g/dl (HR, 2.088; 95% CI, 1.047–4.060) at initiation of second-line chemotherapy, and time to progression less than 170 days on first-line chemotherapy (HR, 2.497; 95% CI, 1.227–5.083) were identified as independent prognostic factors associated with shorter SPP. The median SPP was 496, 375, and 232 days in patients with 0, 1, and 2 of these 3 negative prognostic factors, respectively ($P=0.0002$). The present study suggests that second-line chemotherapy would not be beneficial in patients with two or more of the following three negative prognostic factors: performance status 2, serum albumin less than 3.5 g/dl at initiation of second-line chemotherapy and time to progression less than 170 days on first-line chemotherapy. ***Anti-Cancer Drugs*** **23:465–470** © **2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Gastric cancer is the second leading cause of cancer-related death worldwide, despite a recent decline in its global incidence [1–3]. Surgical resection is the mainstay of curative treatment for gastric cancer; however, the disease is often too advanced at initial diagnosis to allow for curative surgery. For such patients, the goals of chemotherapy are symptom palliation and prolongation of survival [4]. Despite considerable efforts to develop effective chemotherapy regimens, advanced gastric cancer (AGC) remains a challenging malignancy, with a median survival of 9–13 months [5–8]. Although there are no globally accepted standard regimens for AGC, doublet combinations containing 5-fluorouracil or oral fluoropyrimidines such as S-1 and capecitabine with platinum agents are the most commonly used first-line treatments worldwide [5,7,9]. In Japan, other regimens such as S-1 plus irinotecan [10], S-1 plus a taxane (paclitaxel or docetaxel) [11,12], and irinotecan plus cisplatin [8] have also been vigorously evaluated as first-line treatment in phase II/III trials. In addition, triplet regimens consisting of S-1, cisplatin, and a taxane have recently shown promising results, with a median survival over 15 months [13–15].

Although first-line chemotherapy effectively reduces tumor size in approximately half of patients with AGC, it ultimately fails and leads to disease progression after 4–6 months [5–8]. Whether every patient who progresses after first-line chemotherapy should go on to receive second-line chemotherapy remains under debate. In Japan, Korea, and Italy, on the basis of the results of several studies on second-line chemotherapy [16–20], more than half of patients with AGC receive second-line treatment in clinical practice [21]. Taxanes and irinotecan are the most commonly used agents as second-line chemotherapy [16–20,22]. Recently, in a small randomized phase III study with 40 patients with AGC, best supportive care (BSC) plus second-line irinotecan improved overall survival (OS) over BSC alone [23]. However, patient selection for second-line chemotherapy remains uncertain. Several factors such as performance status (PS), extent of disease, cumulative toxicity of the first-line treatment, history of the agents used, and efficacy of first-line chemotherapy should be taken into consideration when selecting patients who are likely to benefit from second-line chemotherapy [21]. We therefore attempted to identify the optimal indications for second-line chemotherapy in patients with AGC.

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Patients and methods

Patients

Of the 157 patients with primary unresectable or recurrent gastric cancer treated at our institution between April 2000 and January 2010, 101 fulfilled the following inclusion criteria for this retrospective study: (a) histologically proven unresectable or recurrent gastric adenocarcinoma; (b) treatment with second-line chemotherapy after first-line chemotherapy failed; (c) maximum Eastern Cooperative Oncology Group PS of 2 at initiation of second-line chemotherapy; (d) adequate bone marrow function (white blood cell count 3000–12 000 mm^{-3}, platelet count $\geq$ 100 000 mm^{-3}, and hemoglobin $\geq$ 8.0 g/dl), hepatic function (total bilirubin $\leq$ 1.5 mg/dl, serum transaminases $\leq$ 100 U/l), and renal function (serum creatinine $\leq$ upper institutional limit) at initiation of second-line chemotherapy; and (e) no other concurrently active malignancies.

Overall survival and efficacy of first-line chemotherapy

Survival postprogression (SPP) was defined as the time from disease progression on first-line chemotherapy to death from any cause or last follow-up. Time to progression (TTP) on first-line chemotherapy was defined as the interval between initiation of first-line chemotherapy and recognition of disease progression.

During first-line chemotherapy, each patient with a measurable lesion was assessed for response according to the Response Evaluation Criteria in Solid Tumors [24], with computed tomography (CT) scans performed every 2 or 3 months until disease progression. Patients with only nonmeasurable lesions were considered to have stable disease (SD) if neither complete disappearance (CR) nor obvious progression (PD) of the recurrent disease was observed on CT scans.

Statistical analysis

SPP and TTP were calculated using the Kaplan–Meier method and compared with the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to identify clinicopathological variables independently associated with SPP. Hazard ratios (HR) and 95% confidence intervals (CI) were also calculated. *P*-values less than 0.05 were considered statistically significant and all *P*-values correspond to two-sided significance tests. All statistical analyses were carried out using SAS statistical software 5.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics

The clinicopathological characteristics of the 101 patients at the initiation of second-line chemotherapy are shown in Table 1. There were 68 men and 33 women, with a median age of 69 (range, 25–85) years. The majority of patients had a good PS (0 or 1); there were five patients with PS 2. Histologically, 43 patients had intestinal-type adenocarcinoma and 58 had diffuse-type adenocarcinoma. Fifty-two patients had primary unresectable gastric cancer and 49 had recurrent disease. There were 61 patients with measurable metastatic lesions, and multiple metastatic sites were present in 13 patients. Sixty-two patients had serum albumin (Alb) levels of 3.5 g/dl or greater, and 84 patients had C-reactive protein (CRP) values below 1.0 mg/dl, whereas 33 patients were anemic, with hemoglobin (Hb) less than 10 g/dl.

Table 1 Patient characteristics at initiation of second-line chemotherapy

Number of patients	101
Sex (males/females)	68/33
Age (years), median (range)	69 (25–85)
ECOG performance status	
0–1/2	96/5
Histology (Lauren classification)	
Intestinal/diffuse	43/58
Primary tumor	
Present/absent	52/49
Site of primary tumor	
Cardia/body/antrum/total	14/40/44/3
Measurable lesion	
Present/absent	61/40
Number of metastatic sites	
1/ $\geq$ 2	88/13
Metastatic site	
Lymph node/liver/peritoneum/lung/bone/brain	31/30/42/7/3/1
Serum albumin (Alb)	
$<$3.5 g/dl/ $\geq$ 3.5 g/dl	39/62
C-reactive protein (CRP)	
$<$1.0 mg/dl/ $\geq$ 1.0 mg	84/17
Hemoglobin (Hb)	
$<$10 g/dl/ $\geq$ 10 g/dl	33/68

ECOG, Eastern Cooperative Oncology Group.

Chemotherapy regimens

Table 2 summarizes the first-line and second-line chemotherapy regimens that the patients received. Most patients (96/101) received S-1-based regimens, with five patients treated with irinotecan plus cisplatin. The majority of patients were participants in clinical trials who were treated according to trial protocols. Chemotherapy regimens for nontrial participants were based on the treating physician's discretion.

Second-line regimens included S-1-based regimens (41), taxane monotherapy (30), irinotecan-based regimens (29), and cisplatin plus paclitaxel (1).

Survival time postprogression

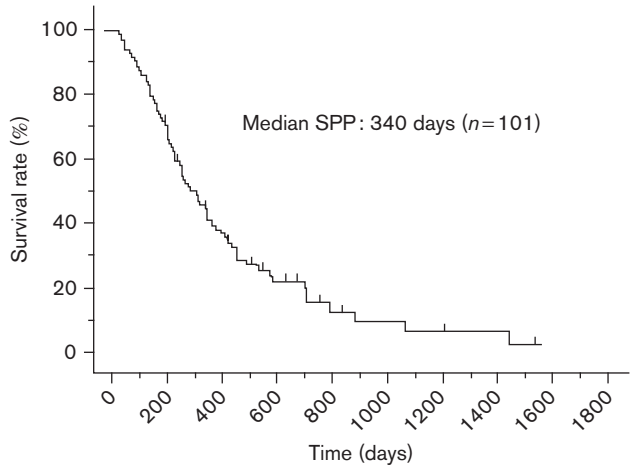
The median follow-up for all 101 patients was 490 days. Seventy-one deaths occurred during the study period. The median SPP was 340 days, as shown in Fig. 1. The median TTP on first-line chemotherapy was 178 days. The median SPP was significantly longer in the 54 patients with TTP $\geq$ 170 days (median, 434 days) than in the 47 patients with TTP $<$ 170 days (median, 291 days) ($P = 0.0087$), as shown in Fig. 2.

On first-line chemotherapy, six patients achieved CR and 38 patients achieved a partial response (PR). SD was

Table 2 Chemotherapy regimens

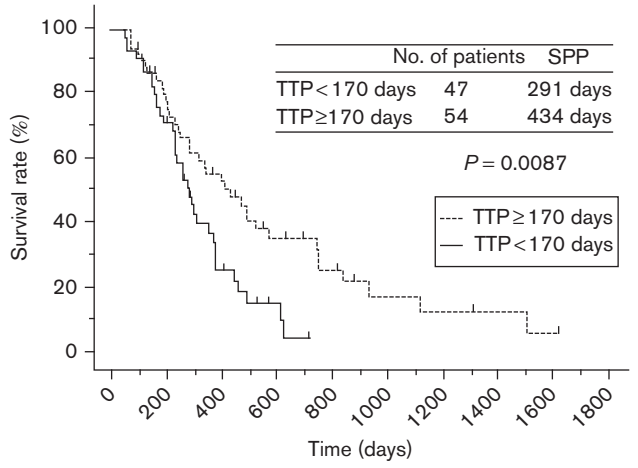
	Number of patients
First-line chemotherapy	
S-1 alone	37
S-1 + cisplatin or oxaliplatin	27
S-1 + irinotecan	9
S-1 + paclitaxel or docetaxel	15
S-1 + cisplatin + taxane	8
Irinotecan + cisplatin	5
Second-line chemotherapy	
S-1 alone	6
S-1 + cisplatin	9
S-1 + irinotecan	17
S-1 + paclitaxel or docetaxel	9
Taxane	30
Irinotecan	17
Irinotecan + cisplatin	12
Cisplatin + paclitaxel	1

Fig. 1



Survival postprogression (SPP).

Fig. 2



Survival postprogression (SPP) according to time to progression (TTP) on first-line chemotherapy.

Table 3 Prognostic factors for survival postprogression

Prognostic factors	Median SPP (days)	*P*	HR	95% CI	*P*
Sex					
Males	382	0.6839	1.491	0.738–3.013	0.2658
Females	314		1		
Age (median)					
<69 years	315	0.8443	1.076	0.596–1.943	0.8077
≥69 years	321		1		
Performance status					
2	262	0.4812	14.234	2.766–73.258	0.0015
0–1	351		1		
Histology					
Intestinal	314	0.4326	1.363	0.693–2.681	0.3697
Diffuse	351		1		
Primary tumor					
Present	321	0.0433	0.877	0.415–1.855	0.7315
Absent	358		1		
Measureable lesion					
Absent	340	0.8342	1.040	0.544–1.990	0.9056
Present	375		1		
Number of metastatic site					
≥2	178	0.0110	2.140	0.858–5.338	0.1027
0 or 1	376		1		
Albumin (g/dl)					
<3.5	246	0.0295	2.088	1.047–4.060	0.0300
≥3.5	401		1		
CRP (mg/dl)					
<1.0	375	0.2119	0.910	0.452–1.830	0.7905
≥1.0	278		1		
Hemoglobin (g/dl)					
<10	285	0.2133	0.960	0.522–1.765	0.8947
≥10	382		1		
TTP on the first-line chemotherapy median					
<170 days	291	0.0087	2.497	1.227–5.083	0.0116
≥170 days	434		1		
Response to the first-line CTX					
SD or PD	314	0.8922	1.270	0.693–2.327	0.4385
PR or CR	351		1		

CI, confidence interval; CR, complete response; CRP, C-reactive protein; CTX, chemotherapy; HR, hazard ratio; PD, progressive disease; PR, partial response; SD, stable disease; SPP, survival postprogression; TTP, time to progression.

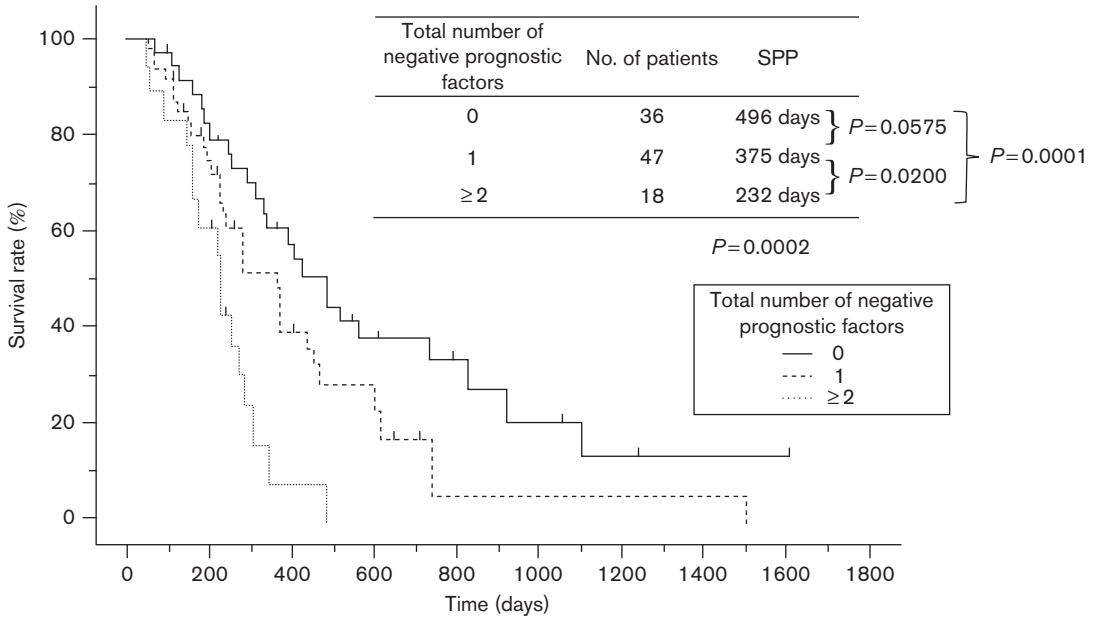
observed in 39 patients, and 18 patients had PD. When categorized by response, the median SPP was 915, 382, 302, and 261 days in patients with CR, PR, SD, and PD, respectively ($P = 0.1671$) (data not shown).

Prognostic factors

The results of univariate and multivariate analyses on the association between various factors, such as sex, age, PS, histology, presence of primary tumor, presence of measurable lesions, number of metastatic sites, TTP on first-line chemotherapy, response to first-line chemotherapy, and Alb, CRP, and Hb values at initiation of second-line chemotherapy and SPP, are summarized in Table 3. PS 2 (HR, 14.234; 95% CI, 2.766–73.258), Alb < 3.5 g/dl (HR, 2.088; 95% CI, 1.047–4.060) at initiation of second-line chemotherapy, and TTP < 170 days on first-line chemotherapy (HR, 2.497; 95% CI, 1.227–5.083) were identified as significant independent prognostic factors for shorter SPP.

In addition, patients were classified according to the number of these three negative prognostic factors they possessed (PS 2, Alb < 3.5 g/dl, and TTP < 170 days on

Fig. 3



Survival postprogression (SPP) according to the number of negative prognostic factors.

first-line chemotherapy) as follows: 36 patients without any negative prognostic factors were scored as 0, 47 patients with one out of three negative prognostic factors were scored as 1, and 18 cases with two or more factors were scored as 2. The median SPP was 496, 375, and 232 days in patients scored as 0, 1, and 2, respectively, with a statistically significant difference between scores of 0–1 and 2 ($P = 0.0002$), as shown in Fig. 3.

Discussion

For patients with AGC, chemotherapy plays an important role in improving survival and symptom alleviation. Even if patients with AGC initially respond to first-line chemotherapy, they ultimately have disease progression. Recently, the combined analysis of two Japanese phase III trials involving 327 patients has demonstrated that second-line chemotherapy contributes to prolonging OS in patients with AGC [25]. In addition, the efficacy of second-line chemotherapy has clearly been demonstrated for the first time in a prospective randomized phase III study, in which second-line irinotecan significantly prolonged OS over BSC in 40 patients with AGC [23]. However, it remains uncertain whether we can distinguish patients who are likely to benefit from second-line chemotherapy from those who would not.

In this study, PS 0–1 and Alb $\geq$ 3.5 g/dl at initiation of second-line chemotherapy as well as TTP $\geq$ 170 days on first-line chemotherapy were identified as positive prognostic factors for SPP. In accordance with our findings, other studies have shown that PS 0–1 and TTP greater than 5–6 months on first-line chemotherapy were significantly associated with prolonged OS in patients receiving second-line chemotherapy for AGC [26–28]. Second-line chemotherapy would not be appropriate for patients with considerable PS deterioration and rapid disease progression on first-line chemotherapy. However, data from the Surveillance, Epidemiology, and End Results registry, which enrolls large numbers of patients with metastatic gastric cancer, demonstrate that age, sex, and tumor location were significant independent prognostic factors for OS [29]. When tumor location was included in the multivariate analysis, PS 2, Alb < 3.5 g/dl, and TTP < 170 days on first-line chemotherapy were still identified as independent prognostic factors, whereas age, sex, and tumor location were not (data not shown).

As observed in other studies [26–28,30–32], PS 2 had a significantly negative impact on survival in the multivariate analysis even though only 5% of the study cohort had PS 2. Irrespective of the sample size of patients with PS 2, PS classifications of 0–1 and 2 are generally used to stratify patients in the phase III trials on AGC [5–8,10] due to its well known impact on survival.

In this study, Alb of 3.5 g/dl and CRP of 1.0 mg/dl were adopted as cut-off values because both elevated CRP (> 1.0 mg/dl) and decreased Alb (< 3.5 g/dl) were reported to be significant negative prognostic factors in various types of cancer [33,34]. Although there has been some controversy over whether serum Alb is a useful prognosticator for SPP [28,30] as opposed to PS and TTP,

Alb was independently associated with OS in our cohort. Patients who maintain their nutritional status can better tolerate second-line chemotherapy, which may lead to durable SPP.

Anemia with Hb ≤ 10 g/dl is often found in patients with AGC due to bleeding from the primary lesion, chemotherapy-induced myelosuppression, or nutritional deficiency, and its negative prognostic value has been discussed in several studies [26,27,35]. In the present study, Hb level was not identified as a prognostic factor for SPP, partly due to the comparatively well maintained Hb level at the initiation of second-line chemotherapy (median, 10.6 g/dl) compared with other studies [26,27,35] that found low Hb to be a negative prognostic factor.

Regarding the association between response to the first-line chemotherapy and SPP, positive response (CR plus PR) as assessed by CT scan was not prognostically significant (Table 3). This finding is consistent with a previous report [36] that showed no significant association between positive response to the first-line chemotherapy and longer OS in AGC, despite a moderate correlation between positive response and durable TTP. In contrast, the tumor's metabolic response to chemotherapy, which is observable by PET as a decrease in fluorine-18 fluorodeoxyglucose uptake, has recently been reported to be an independent prognostic factor for OS in patients with AGC receiving preoperative chemotherapy [37,38]. Longer TTP on first-line chemotherapy, which was identified as a positive prognostic factor for SPP in this study, might be predicted by PET scans during first-line chemotherapy.

The total number of negative prognostic factors, such as PS 2, Alb < 3.5 g/dl, and TTP < 170 days, was prognostically significant in this study (Fig. 3). Approximately four-fifths of the patients with 0 or 1 negative factor achieved SPP over 1 year, whereas patients with two or more negative factors had a median SPP of 232 days. Similar prognostic scoring models have been reported in previous studies [26,27]. Catalano *et al.* [26] incorporated five prognostic factors (PS, Hb level, carcinoembryonic antigen value, number of metastatic sites, and TTP under first-line chemotherapy) into a prognostic score. Kanagavel *et al.* [27] proposed a model composed of PS, Hb level, and TTP under first-line chemotherapy. In accordance with our findings, their models were able to differentiate patient prognosis following second-line chemotherapy in good, intermediate, and poor risk categories with a median survival of 12.7–13.5, 6.0–7.1, and 2.0–3.3 months, respectively.

The optimal indications for second-line chemotherapy in patients with AGC are less clearly defined than those for first-line chemotherapy. The present study demonstrated that second-line chemotherapy would not be beneficial in patients with two or more of the following factors: PS 2, Alb < 3.5 g/dl at initiation of the second-line chemotherapy, and TTP < 170 days on first-line chemotherapy. The limitations of this study, which include its retrospective, single-institution nature and the relatively small sample size, need to be taken into account before generalizing the results to daily clinical practice until prospective, multicenter validation is available. However, we believe that our findings will help practitioners prognosticate on the disease course and facilitate decision-making regarding second-line chemotherapy by physicians, patients, and their caregivers.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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