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ORIGINAL ARTICLE

Prognostic factor analysis of third-line chemotherapy in patients with advanced gastric cancer

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Abstract
Background Almost all patients with advanced gastric cancer will eventually develop progressive disease after first-line chemotherapy. However, the role of subsequent salvage chemotherapy remains controversial. The purpose of this study was to evaluate prognostic factors for the survival of patients with advanced gastric cancer who received third-line chemotherapy.
Methods We reviewed 502 patients with advanced gastric cancer who received palliative chemotherapy at the Oncology Department of Hwasun Chonnam National University Hospital (2004–2008). Among them, 174 received third-line chemotherapy. To evaluate the clinicopathologic factors that affected overall survival, univariate and multivariate analyses were performed on the baseline factors before beginning third-line chemotherapy.
Results Multivariate analysis found 4 prognostic factors affecting poor survival following third-line chemotherapy: performance status of 2–3 (hazard ratio [HR] 1.46, 95% confidence interval [CI] 1.06–2.02; $P = 0.022$), serum albumin level < 4 mg/dL (HR 1.82, 95% CI 1.32–2.53; $P < 0.00$), poor histologic type (HR 1.77, 95% CI 1.27–2.47; $P = 0.001$), and progression-free survival of <2.7 months following second-line chemotherapy (HR 1.51, 95% CI 1.09–2.08; $P = 0.012$). A prognostic index was constructed, dividing patients into low- (0–1 factor), intermediate- (2 or 3 risk factors), or high- (4 risk factors) risk groups. Median survival times for each group were 11.8, 6.7, and 3.3 months, respectively ($P < 0.00$).
Conclusions This analysis suggests that some clinicopathologic factors might be helpful in identifying the subgroup of patients most likely to benefit from third-line chemotherapy for advanced gastric cancer.

Keywords Advanced gastric cancer · Third-line chemotherapy · Prognostic factor · Survival

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Introduction

Gastric cancer is the fourth most common cancer and second most common cause of cancer-related deaths worldwide [1]. Even though efforts for early detection are made in Asia, more than two-thirds of patients present with inoperable advanced or metastatic disease [2]. In addition, the recurrence rate following curative surgery has been reported to be 40–60% [3, 4]. Therefore, palliative chemotherapy may play a very important role in the treatment of patients with advanced gastric cancer.

Previous studies have shown that palliative chemotherapy attenuates symptoms, enhances quality of life, and prolongs survival [5–7]. In the meta-analysis reported by Wagner et al. [8] overall survival (OS) was prolonged by approximately 6 months.

Many chemotherapeutic agents have been investigated over the past decades, such as 5-fluorouracil (5-FU), cisplatin, anthracyclines, taxanes, oral fluoropyrimidine, irinotecan, oxaliplatin, and targeted agents including trastuzumab [9–15]. Despite the recently reported benefits of

chemotherapeutic agents, the 5-year survival rate for advanced or recurrent gastric cancer is still around 5–20%, and the median survival time of these patients remains between 8 and 13.8 months [10–15].

Most patients with advanced gastric cancer eventually progress after first-line chemotherapy. Because of the acceptable toxicity of new chemotherapeutic agents and the improvements in supportive care, the number of patients who maintain a good general condition after the failure of first-line chemotherapy has increased. As a result, the number of patients who are good candidates for second-line and subsequent chemotherapy has also increased. However, there is no established subsequent salvage chemotherapy for gastric cancer following failed first-line chemotherapy. Only one recent randomized prospective trial, which compared irinotecan-based second-line chemotherapy with the best supportive care, suggested the potential role of second-line chemotherapy [16]. Despite the lack of evidence of the benefit of salvage chemotherapy, a common practice is to offer further chemotherapy for selected patients after first-line failure. According to many retrospective analyses, second- and third-line chemotherapy is used in 20–50% and 15–30% of patients, respectively [17–21].

In this situation, the selection of patients for further chemotherapy has become an important issue. There are several reports of prognostic factors for survival time in second-line chemotherapy [18–20]. These include performance status, serum albumin level, the presence of liver or peritoneal metastases, and progression-free survival (PFS) on first-line chemotherapy. However, the prognostic factors in third-line chemotherapy remain unclear.

The aim of this analysis was to identify clinicopathologic factors of survival in patients with advanced gastric cancer who received third-line chemotherapy. Consideration of these factors may assist clinicians in the selection of patients for subsequent salvage chemotherapy.

Patients and methods

We screened patients with advanced gastric cancer who had received palliative chemotherapy between June 2004 and December 2008 at Hwasun Chonnam National University Hospital.

The inclusion criteria were as follows: (1) histologically proven gastric adenocarcinoma; (2) treatment with third-line chemotherapy after first- and second-line chemotherapy, due to disease progression, unacceptable toxicity, or patient's refusal; (3) presence of measurable or evaluable lesions; and (4) availability of clinical data for palliative chemotherapy. Of the 502 patients screened, 174 fulfilled the inclusion criteria and were enrolled in this retrospective analysis.

Performance status (PS) was evaluated according to the Eastern Cooperative Oncology Group (ECOG) criteria. The clinical tumor response was assessed after every 2 or 3 courses of chemotherapy, according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0).

Chemotherapy regimens were divided as follows: (1) taxane (paclitaxel or docetaxel) monotherapy; (2) taxane and cisplatin; (3) taxane, cisplatin, and 5-FU; (4) irinotecan monotherapy; (5) irinotecan and 5-FU; (6) oxaliplatin and 5-FU; (7) infusional 5-FU and cisplatin; (8) oral fluoropyrimidine (capecitabine or S-1) and cisplatin; and (9) oral fluoropyrimidine monotherapy.

Factors included in the univariate analyses were as follows: age, sex, PS, hemoglobin, serum albumin, carcinoembryonic antigen (CEA) level, previous gastrectomy, histologic grade, Lauren classification, tumor location, metastasis to liver, metastasis to peritoneum, number of metastatic sites, objective response to first- and second-line chemotherapy, disease control in first- and second-line chemotherapy, and the PFS of first- and second-line chemotherapy. Laboratory variables were initially recorded as continuous variables and later dichotomized according to the median value of each variable.

The primary endpoint of this study was OS. OS was measured from the first date of the third-line chemotherapy to death from any cause or the last follow-up visit. OS and PFS were estimated according to the Kaplan–Meier method, and the statistical significance of differences in survival curves between 2 groups was tested with a log-rank test. A prognostic model was established by searching all variables that significantly influenced OS at P values of <0.05 in the univariate analysis. Multivariate analysis for prognostic factors was performed using Cox's proportional hazards regression model. P values of <0.05 were considered statistically significant, and all P values corresponded to 2-sided significance tests. All statistical calculations were carried out using the SPSS 18.0 software package (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 502 patients received first-line chemotherapy in this study period, and 352 patients (70.1%) received second-line chemotherapy. Of the 502 patients, 174 (34.7%) met the eligibility criteria. The baseline clinicopathologic characteristics of the patients at the start of third-line chemotherapy are shown in Table 1. The median age of the

Table 1 Patient characteristics at the start of third-line chemotherapy ($n = 174$)

Characteristics	No. of patients	%
Age, years, median (range)	58 (19–76)	
Sex		
Male	121	69.5
Female	53	30.5
ECOG performance status		
0–1	90	51.7
2–3	84	48.3
Laboratory findings		
Hemoglobin, median (range)	10.6 g/dL (6.7–14.4)	
Albumin, median (range)	4.0 g/dL (1.6–4.9)	
CEA, median (range)	4.94 ng/mL (0.64–18,411)	
Histologic grade		
Adenocarcinoma, WD	12	6.9
Adenocarcinoma, MD	53	30.5
Adenocarcinoma, PD	75	43.1
Signet ring cell carcinoma	34	19.5
Lauren classification		
Diffuse	41	23.6
Intestinal	102	58.6
Not known	31	17.8
Tumor location		
GEJ-cardia	11	6.3
Body	101	58.1
Antrum	62	35.6
Disease status		
Initial metastasis	111	63.8
Recurrence after gastrectomy	63	36.2
Previous gastrectomy		
Yes	97	55.7
No	77	44.3
Number of metastases		
1–2	165	94.8
≥3	9	5.2
Liver metastasis		
Yes	108	62.1
No	66	37.9
Peritoneal metastasis		
Yes	115	66.1
No	59	33.9

ECOG Eastern Cooperative Oncology Group, *CEA* carcinoembryonic antigen, *WD* well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *GEJ* gastroesophageal junction

patients was 58 years, with a range of 19–76 years. A total of 121 patients (69.5%) were male, and 84 patients (48.3%) had an ECOG PS of 2–3. A total of 97 patients (55.7%) had had a previous gastrectomy, in either a curative or a palliative setting.

Table 2 Regimens in each line of chemotherapy ($n = 174$)

	No. of patients	%
First-line chemotherapy		
Taxane/cisplatin	84	48.3
Taxane/cisplatin/5-FU	39	22.4
Irinotecan/5-FU	7	4
Oxaliplatin/5-FU	16	9.2
5-FU (oral or infusional fluoropyrimidine)/cisplatin	14	8.0
Oral fluoropyrimidine	14	8.0
Second-line chemotherapy		
Taxane	6	3.4
Taxane/cisplatin	27	15.5
Taxane/cisplatin/5-FU	6	3.4
Irinotecan/5-FU	39	22.4
Oxaliplatin/5-FU	32	18.4
Oral fluoropyrimidine/cisplatin	6	3.4
Oral fluoropyrimidine	58	33.3
Third-line chemotherapy		
Taxane	8	4.6
Taxane/cisplatin	19	10.9
Taxane/cisplatin/5-FU	4	2.3
Irinotecan	7	4.0
Irinotecan/5-FU	36	20.7
Oxaliplatin/5-FU	60	34.5
Oral fluoropyrimidine/cisplatin	3	1.7
Oral fluoropyrimidine	37	21.3

Taxane docetaxel or paclitaxel, *5-FU* 5-fluorouracil, *oral fluoropyrimidine* capecitabine or S-1

Treatment

The most commonly used first-line chemotherapy regimens were taxanes and cisplatin ($n = 84$, 48.3%) (Table 2). For second-line chemotherapy, oral fluoropyrimidine monotherapy ($n = 58$, 33.3%) or an irinotecan and 5-FU combination ($n = 39$, 22.4%) were frequently used. Third-line chemotherapy consisted mostly of regimens containing oxaliplatin and 5-FU ($n = 60$, 34.5%), oral fluoropyrimidine monotherapy ($n = 37$, 21.3%), and irinotecan and 5-FU ($n = 36$, 20.7%). As far as possible, no patients were treated with the same anticancer drug as that used previously, to avoid possible cross-resistance and potential cumulative toxicity. However, one patient was treated with S-1 in third-line chemotherapy, which had been used in second-line chemotherapy.

Response and survival

A complete response to third-line chemotherapy was achieved in two patients (1.1%), and a partial response was

Table 3 Results of each line of chemotherapy ($n = 174$)

	No. of patients	%
First-line chemotherapy		
Response		
CR	9	5.2
PR	61	35.1
SD	60	34.4
PD	44	25.3
ORR (CR + PR)	70	40.3 (95% CI, 33–47.6)
DCR (CR + PR + SD)	130	74.7 (68.2–81.2)
PFS-1, median		4.8 months (4.4–5.2)
MST-1, median		18 months (16.8–19.0)
Second-line chemotherapy		
Response		
CR	3	1.7
PR	23	13.2
SD	50	28.8
PD	98	56.3
ORR (CR + PR)	26	14.9 (9.6–20.2)
DCR (CR + PR + SD)	76	43.7 (36.3–51.1)
PFS-2, median		2.7 months (2.4–3.0)
MST-2, median		11 months (9.8–12.2)
Third-line chemotherapy		
Response		
CR	2	1.1
PR	16	9.2
SD	50	28.7
PD	106	60.9
ORR (CR + PR)	18	10.3 (5.8–14.8)
DCR (CR + PR + SD)	68	39.1 (31.8–46.4)
PFS-3, median		2.6 months (2.4–2.8)
MST-3, median		6.4 months (5.3–7.4)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* overall response rate, *DCR* disease control rate, *95% CI* 95% confidence interval, *PFS* progression-free survival from the first date of each line of chemotherapy, *MST* median survival time from the first date of each line of chemotherapy

achieved in 16 patients (9.2%), giving an overall response rate of 10.3% (95% CI 5.8–14.8) and a disease control rate of 39.1% (95% CI 31.8–46.4).

The median PFS was 4.8 months (95% CI 4.4–5.2) in first-line, 2.7 months (95% CI 2.4–3.0) in second-line, and 2.6 months (95% CI 2.4–2.8) in third-line chemotherapy.

The median survival time from the start of first-line chemotherapy was 18 months (95% CI 16.8–19.0); it was 11 months (95% CI 9.8–12.2) from the start of second-line chemotherapy, and 6.4 months (95% CI 5.3–7.4) from the start of third-line chemotherapy (Table 3).

Univariate and multivariate analyses

In the univariate analysis (Table 4), seven variables were significantly associated with a shorter survival time: ECOG PS of 2–3, serum albumin < 4.0 g/dL, poor histologic grade, diffuse type, non-disease–controlled group for first-line chemotherapy, non-disease–controlled group for second-line chemotherapy, and a PFS of second-line chemotherapy of <2.7 months.

Cox multivariate analysis included all variables that were found to have prognostic significance in the univariate analysis (Table 5). The results of the analysis identified the following four independent prognostic factors that correlated with shorter survival time in third-line chemotherapy: ECOG PS of 2–3 (HR 1.46, 95% CI 1.06–2.02; $P = 0.022$), serum albumin < 4.0 g/dL (HR 1.82, 95% CI 1.32–2.53; $P < 0.001$), poor histologic grade (HR 1.77, 95% CI 1.27–2.47; $P = 0.001$), and PFS of second-line chemotherapy of < 2.7 months (HR 1.51, 95% CI 1.09–2.08; $P = 0.012$).

A prognostic index was constructed by incorporating all four prognostic factors. The prognostic grouping of the 174 patients was carried out according to the following criteria: low-risk group, patients with zero to one prognostic factor ($n = 41$); intermediate-risk group, patients with two or three prognostic factors ($n = 104$); and high-risk group, patients with four prognostic factors ($n = 29$). Figure 1 shows the survival of these three risk groups. There were highly significant survival differences among the three risk groups ($P < 0.00$). Median survival times for the low-, intermediate-, and high-risk groups were 11.8, 6.7, and 3.3 months, respectively. The one-year survival rates for each group were 41.5% (95% CI 34.1–48.8), 20.2% (95% CI 14.2–26.2), and 3.4% (95% CI 0–6.2), respectively. The six-month survival rates for each group were 75.6% (95% CI 69.2–82), 54.8% (95% CI 47.4–62.2), and 13.8% (95% CI 8.7–18.9), respectively. When compared with the low-risk group, the intermediate- and high-risk groups had 1.8-fold (HR 1.76, 95% CI 1.19–2.62) and 5.4-fold (HR 5.41, 95% CI 3.19–9.18) higher risks of death, respectively.

Discussion

Despite the development of new agents, many patients who receive palliative chemotherapy for advanced gastric cancer do not respond to first-line chemotherapy, and all patients eventually progress. The decision as to whether to use subsequent salvage treatment needs to be made. However, little is known about the survival benefit, feasibility, and prognostic factors of subsequent salvage chemotherapy after the failure of first-line chemotherapy. Nevertheless, at least half

Table 4 Univariate analysis of baseline clinicopathologic factors

Variable	MST-3 (months)	*P* value
Age		
≤58 years	5.8	0.212
>58 years	8.3	
Sex		
Male	7.9	0.342
Female	5.1	
ECOG performance status		
0–1	7.4	0.019
2–3	5.1	
Albumin		
<4 g/dL	4.5	<0.001
≥4 g/dL	8.9	
Hemoglobin		
<10.6 g/dL	5.9	0.585
≥10.6 g/dL	7.6	
CEA		
<4.94 ng/mL	6.4	0.339
≥4.94 ng/mL	6.3	
Histologic grade		
Good[a]	9.0	0.004
Poor	5.4	
Lauren classification		
Diffuse	6.2	0.02
Intestinal	7.5	
Tumor location		
GEJ to cardia	6.0	0.314
Body	6.2	
Antrum	8.0	
Disease status		
Initial metastasis	6.0	0.313
Recurrence after gastrectomy	7.2	
Previous gastrectomy		
Yes	6.6	0.243
No	6.0	
Number of metastatic sites		
0–1	6.3	0.559
≥3	11.8	
Liver metastasis		
Yes	8.3	0.568
No	6.1	
Peritoneal metastasis		
Yes	7.4	0.769
No	5.7	
Response (CR + PR) to first-line chemotherapy		
Yes	7.2	0.141
No	6.2	
Disease control (CR + PR + SD) to first-line chemotherapy		
Yes	7.2	0.028
No	5.9	
PFS of first-line chemotherapy		
<4.8 months	6.1	0.624
≥4.8 months	6.8	
Response (CR + PR) to second-line chemotherapy		
Yes	7.9	0.38
No	6.2	
Disease control (CR + PR + SD) to second-line chemotherapy		
Yes	6.9	0.049
No	6.2	
PFS of second-line chemotherapy		
<2.7 months	5.1	0.033
≥2.7 months	7.2	

ECOG Eastern Cooperative Oncology Group, *CEA* carcinoembryonic antigen, *GEJ* gastroesophageal junction, *PFS* progression-free survival, *CR* complete response, *PR* partial response, *SD* stable disease

[a] Good histologic grade includes well-differentiated and moderately differentiated adenocarcinoma, while poor histologic grade includes poorly differentiated adenocarcinoma and signet ring cell carcinoma

of the patients who fail first-line chemotherapy are candidates for further treatment.

We can suggest several reasons for supporting this clinical practice. As previously stated, the number of patients who maintain a good PS after the failure of first- or second-line chemotherapy has been increasing. In this situation, patients and physicians experience difficulty in accepting only supportive care without additional chemotherapy. One of the important aims of palliative chemotherapy is to improve quality of life (QoL). In a prospective report, improvement of QoL was demonstrated in patients with advanced gastric cancer who were treated with second-line chemotherapy [22]. In addition, although the reported response rate of second- or third-line chemotherapy was low, the disease control rate (DCR) ranged from 19 to 60%, and favorable toxicities were reported in several phase-II trials of second- and third-line chemotherapy [18, 21, 23–25].

Clearly, subsequent salvage chemotherapy after first-line treatment may not be beneficial for all patients. It is necessary to select the subgroup of patients who may benefit from salvage chemotherapy, because there is also potential for toxicity and adverse effects from the treatment.

Several studies have identified prognostic factors for patients with metastatic gastric cancer undergoing first-line chemotherapy [17, 26, 27]. These include PS; liver, bone or peritoneal metastasis; alkaline phosphatase level; albumin level; ascites; and the number of metastatic sites.

Table 5 Multivariate analysis of baseline clinicopathologic factors

Variable	HR	95% CI	*P* value
ECOG performance status (2–3)	1.46	1.06–2.02	0.022
Albumin (<4 g/dL)	1.82	1.32–2.53	<0.001
Histologic grade (poor[a])	1.77	1.27–2.47	0.001
Lauren classification (diffuse)	1.02	0.62–1.69	0.932
Disease control (CR + PR + SD) of first-line chemotherapy (No)	1.26	0.87–1.83	0.222
Disease control (CR + PR + SD) of second-line chemotherapy (No)	1.04	0.66–1.63	0.879
PFS of second-line chemotherapy (PFS < 2.7 months)	1.51	1.09–2.08	0.012

HR hazard ratio, *ECOG* Eastern Cooperative Oncology Group, *CR* complete response, *PR* partial response, *SD* stable disease, *PFS* progression-free survival

[a] Poor histologic grade includes poorly differentiated adenocarcinoma and signet ring cell carcinoma

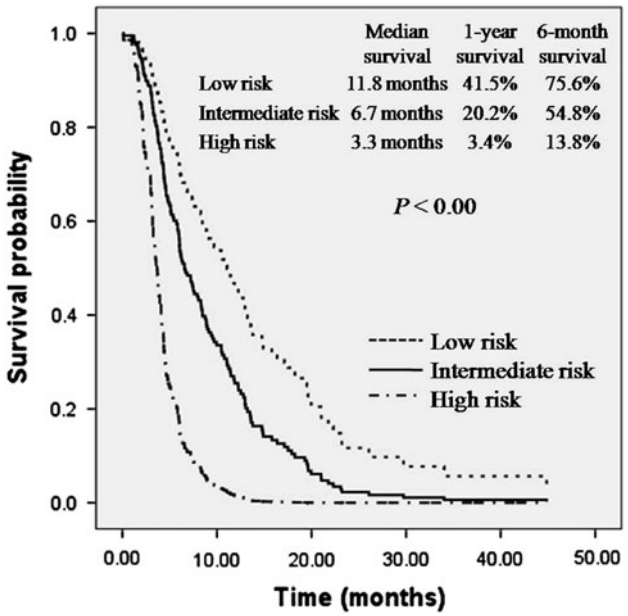

Fig. 1 Survival curves according to risk groups

Several prognostic factors have been suggested to affect survival in second-line chemotherapy [18–20]. ECOG PS; serum albumin; hemoglobin; C-reactive protein; CEA; duration of PFS under previous chemotherapy; liver, bone, or peritoneal metastasis; number of metastatic sites; and previous gastrectomy have been consistently reported as major prognostic factors with palliative chemotherapy from first- to second-line chemotherapy.

Only one report recently suggested histologic grade ($P = 0.07$) and chemotherapy ($P = 0.056$) as possible prognostic factors in third-line chemotherapy; however, they did not show statistical significance [21]. Therefore, the identification of prognostic factors allowing for the selection of patients who are likely to benefit from third-line chemotherapy remains to be determined.

The present analysis, which was based on the individual data of 174 patients treated with third-line chemotherapy, identified 4 independent prognostic factors: ECOG PS, serum albumin level, histologic grade, and PFS of second-line chemotherapy. We also showed that our prognostic index allowed for the stratification of three distinct risk groups. In previous studies, similar forms of prognostic indices were used to define risk groups. The results of the present study were rather similar to those reported in other series, including patients treated with first- and second-line chemotherapy [17, 18, 26].

It is a well-known fact that ECOG PS is an important prognostic factor in advanced gastric and other cancers [12, 18]. Regarding palliative treatment, it is very important that salvage chemotherapy is limited to patients with good PS.

In the present study, patients with longer PFS under second-line chemotherapy had longer survival times from the start of the third-line chemotherapy. PFS or time to progression (TTP) under first-line chemotherapy was reported as a prognostic factor of second-line chemotherapy [18, 19, 28]. Gastric cancer is a group of heterogeneous diseases that differ in the expression of cell-signaling molecules and have a varying degree of metaplasia [29]. Therefore, the growth, response rate, and duration of response to chemotherapy of each kind of tumor have great diversity [29]. Patients with a longer PFS under previous chemotherapy either have a chemosensitive tumor or a slow tumor growth rate; as a result, patients in this heterogeneous group may have a longer survival duration when undergoing additional chemotherapy.

The present study also indicates that a significant prognostic factor in palliative chemotherapy is PFS or DCR, not the response rate itself. In advanced gastric cancer, many patients have non-measurable lesions such as peritoneal metastases, ascites, and bone metastases. For this reason, PFS might reflect the presence of chemosensitivity better than the response rate, especially in second- or third-line chemotherapy. Even if patients do not show a good response to chemotherapy, if their disease remains

stable and they have a longer time to progression, we consider that these patients may have a survival benefit from subsequent salvage chemotherapy.

Serum albumin level has been reported as a prognostic factor in advanced gastric cancer [17, 19]. Patients with advanced gastric cancer with gastric outlet obstruction or peritoneal dissemination experience inadequate nutritional intake. The serum albumin level reflects the patient's nutritional condition. Furthermore, the prognostic value of albumin may be secondary to an ongoing systemic inflammatory response [30].

In our study, the group with poor histologic grade showed a short survival benefit from third-line chemotherapy. When interpreting this result, we considered that signet ring cell carcinoma was a major and independent factor of poor prognosis due to its specific characteristics, including more infiltrative tumors showing affinity for lymphatic tissue with higher rates of peritoneal carcinomatosis, regardless of the tumoral clinical presentation [31].

A potential weakness of the present study was its retrospective nature ; thus, some considerations must be taken into account when interpreting our results. First, a variety of chemotherapeutic regimens was used. Although taxane-containing regimens were the most commonly used in first-line chemotherapy, many heterogeneous regimens were used in second- and third-line chemotherapy. This is a consequence of the absence of well-established first-line chemotherapy and subsequent salvage chemotherapy for gastric cancer.

Second, due to the lack of randomized, blinded comparisons with placebo, it is unclear whether any of the subsequent salvage chemotherapies used in the study are actually better than best supportive care alone. However, many obstacles, including poor patient enrollment, are expected when conducting large-scale, randomized prospective trials in practice [16].

QoL analysis was not included in the present study. Park et al. [22] suggested that second-line chemotherapy could improve the QoL of gastric cancer patients. Pretreatment QoL has been shown to have prognostic value in patients with esophagogastric cancer who receive palliative chemotherapy [26]. Analysis of improvement in QoL, in addition to survival analysis, needs to be performed in further trials.

Targeted agents previously tested in advanced gastric cancer, such as trastuzumab, cetuximab, bevacizumab, and sunitinib, were not used in our study. Therefore, suggested prognostic factors from our analysis cannot be generalized for the addition of targeted agents to chemotherapy.

Nevertheless, the results of our analysis have importance. To our knowledge, this is the first report that has suggested significant clinicopathologic prognostic factors for patients who received third-line chemotherapy for advanced gastric cancer. Because no prospective study has been performed in this specific setting, our findings can help to determine which patients might be appropriate candidates for additional chemotherapy. Moreover, it would be better to treat high-risk groups of patients with best supportive care instead of cytotoxic chemotherapy.

Conclusion

Selected patients with advanced gastric cancer who are in good general condition could be considered for third-line chemotherapy after the failure of second-line chemotherapy. We have demonstrated that ECOG PS, serum albumin, histologic type, and PFS under second-line chemotherapy are independent prognostic factors for survival in patients receiving third-line chemotherapy for advanced gastric cancer. The prognostic index based on these four prognostic factors showed distinct differences in survival rates among the different risk groups. Information from this analysis could facilitate individual patient risk assessments and the administration of more appropriate therapies for each patient. We should also consider toxicities from additional chemotherapy and the QoL of patients.

References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006;24:2137–50.
2. Macdonald JS. Gastric cancer—new therapeutic options. N Engl J Med. 2006;355:76–7.
3. D'Angelica M, Gonen M, Brennan MF, Turnbull AD, Bains M, Karpeh MS. Patterns of initial recurrence in completely resected gastric adenocarcinoma. Ann Surg. 2004;240:808–16.
4. Kim S, Lim DH, Lee J, Kang WK, MacDonald JS, Park CH, et al. An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys. 2005;63:1279–85.
5. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer. 1993;72:37–41.
6. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer. 1995;71:587–91.
7. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol. 1997;8:163–8.

8. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006;24:2903–9.
9. Catalano V, Labianca R, Beretta GD, Gatta G, de Braud F, Van Cutsem E. Gastric cancer. Crit Rev Oncol Hematol. 2009; 71:127–64.
10. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24:4991–7.
11. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009;20:666–73.
12. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
13. Ajani JA, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, et al. Irinotecan/cisplatin in advanced, treated gastric or gastro-esophageal junction carcinoma. Oncology (Williston Park). 2002;16:16–8.
14. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36–46.
15. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97.
16. Thuss-Patience P, Kretzschmar A, Deist T, Hinke A, Bichev D, Lebedinzew B, et al. Irinotecan versus best supportive care (BSC) as second-line therapy in gastric cancer: a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). J Clin Oncol. 2009;27(15S):abstract 4540.
17. Lee J, Lim T, Uhm JE, Park KW, Park SH, Lee SC, et al. Prognostic model to predict survival following first-line chemotherapy in patients with metastatic gastric adenocarcinoma. Ann Oncol. 2007;18:886–91.
18. Catalano V, Graziano F, Santini D, D'Emidio S, Baldelli AM, Rossi D, et al. Second-line chemotherapy for patients with advanced gastric cancer: who may benefit? Br J Cancer. 2008;99:1402–7.
19. Hashimoto K, Takashima A, Nagashima K, Okazaki SS, Nakajima TE, Kato K, et al. Progression-free survival in first-line chemotherapy is a prognostic factor in second-line chemotherapy in patients with advanced gastric cancer. J Cancer Res Clin Oncol. 2010;136:1059–64.
20. Ji SH, Lim do H, Yi SY, Kim HS, Jun HJ, Kim KH, et al. A retrospective analysis of second-line chemotherapy in patients with advanced gastric cancer. BMC Cancer. 2009;9:110.
21. Moon YW, Rha SY, Jeung HC, Kim C, Hong MH, Chang H, et al. Outcomes of multiple salvage chemotherapy for advanced gastric cancer: implications for clinical practice and trial design. Cancer Chemother Pharmacol. 2010;66:797–805.
22. Park SH, Lee WK, Chung M, Bang SM, Cho EK, Lee JH, et al. Quality of life in patients with advanced gastric cancer treated with second-line chemotherapy. Cancer Chemother Pharmacol. 2006;57:289–94.
23. Satoh S, Kawashima K, Matsumoto S, Hasegawa S, Okabe H, Nomura A, et al. Retrospective evaluation of sequential outpatient chemotherapy for advanced gastric cancer. Chemotherapy. 2007;53:226–32.
24. Shimoyama R, Yasui H, Boku N, Onozawa Y, Hironaka S, Fukutomi A, et al. Weekly paclitaxel for heavily treated advanced or recurrent gastric cancer refractory to fluorouracil, irinotecan, and cisplatin. Gastric Cancer. 2009;12:206–11.
25. Wesolowski R, Lee C, Kim R. Is there a role for second-line chemotherapy in advanced gastric cancer? Lancet Oncol. 2009;10:903–12.
26. Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer—pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol. 2004;22:2395–403.
27. Yoshida M, Ohtsu A, Boku N, Miyata Y, Shirao K, Shimada Y, et al. Long-term survival and prognostic factors in patients with metastatic gastric cancers treated with chemotherapy in the Japan Clinical Oncology Group (JCOG) study. Jpn J Clin Oncol. 2004;34:654–9.
28. Stahl M, Muller C, Koster W, Wilke H. Second-line chemotherapy of advanced disseminated gastric cancer after cisplatin, infusional 5-fluorouracil, folinic acid (PLF): benefit dependent on progression-free interval after first-line therapy. Onkologie. 2005;28:499–502.
29. Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg. 1998;85:1457–9.
30. Crumley AB, Stuart RC, McKernan M, McMillan DC. Is hypoalbuminemia an independent prognostic factor in patients with gastric cancer? World J Surg. 2010;34:2393–8.
31. Piessen G, Messager M, Leteurtre E, Jean-Pierre T, Mariette C. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. Ann Surg. 2009;250:878–87.