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ORIGINAL ARTICLE

Outcomes of multiple salvage chemotherapy for advanced gastric cancer: implications for clinical practice and trial design

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Abstract
Purpose We analyzed the natural history of advanced gastric cancer with sequential salvage chemotherapy following first-line treatment.
Methods We studied 532 patients with unresectable gastric adenocarcinoma who were treated at Yonsei Cancer Center (2000–2008). The patients were managed with multiple sequential salvage chemotherapy as allowed by performance status and toxicity profiles. The tumor response was assessed every two cycles.
Results Four hundred sixty patients received palliative chemotherapy and 72 received supportive care only. The median overall survival was 12.0 months for all patients, 12.1 months for the chemotherapy group, and 2.5 months for the supportive care group ($P < 0.001$). In the chemotherapy group, 87% received first-line chemotherapy, 47% second-line, 23% third-line, 9% fourth-line, and 3% fifth-line. Response rates were 24.8, 12.6, 10.9, 2.6, and 0% and disease control rates were 76.3, 60.1, 54.2, 54.2, and 53.3% for first- to fifth-line treatment, respectively. The median progression-free survival was 5.5, 3.4, 2.5, 1.9, and 2.0 months and overall survival was 12.1, 7.9, 5.5, 5.0, and 6.8 months. Performance status and metastatic pattern were consistent prognostic factors throughout salvage treatment.
Conclusions Clinical trials may be feasible in second- or third-line salvage chemotherapy for gastric cancer. Future clinical trials in these settings should take into account the low response rate, short progression-free survival, and the prognostic factors for optimal trial design.

Keywords Gastric cancer · Sequential · Salvage chemotherapy · Progression-free survival

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Introduction

Gastric cancer remains the second most common cause of cancer deaths despite a declining incidence in many developed countries [1]. It is the most commonly diagnosed cancer and the leading cause of cancer deaths in Korea [2]. The most effective treatment strategy for gastric cancer is radical gastrectomy. However, gastric cancer is often undiagnosed until it reaches an unresectable stage, especially in areas other than Japan and Korea. Efforts for early detection are made in Japan and Korea. In addition,

the recurrence rate following curative surgery was reported to be 40–60%, and most relapsed patients die from the disease [3, 4]. Therefore, palliative chemotherapy may play a very important role in the treatment of advanced gastric cancer.

For patients with advanced gastric cancer, there is evidence that first-line palliative chemotherapy improves symptoms and prolongs survival [5, 6]. In general, fluoropyrimidine and platinum-containing regimens are widely accepted as standard first-line therapy with a response rate (RR) of 25–54% and a median overall survival (OS) of 8–13 months [7–10]. For some types of cancer, specific subsequent salvage therapy after failure of first-line treatment is recommended. For example, in advanced non-small cell lung cancer, second-line treatment with docetaxel, pemetrexed, or erlotinib after failure of platinum-based doublet chemotherapy has been proven effective [11]. For colorectal cancer, the three drugs fluoropyrimidine, oxaliplatin, and irinotecan should be used during the entire treatment course [12], although the optimal sequence is not known. For the anthracycline- and taxane-refractory breast cancer, capecitabine is a generally accepted salvage therapy and ixabepilone has recently been approved by the US Food and Drug Administration after triple failure [13]. However, little is known about the feasibility, clinical outcomes, and prognostic factors of subsequent salvage chemotherapy for gastric cancer following failed first-line chemotherapy. Studies in both Western and Asian countries have shown that a second-line approach is generally tolerated. In Asian countries, many phase II trials and retrospective analyses have been sporadically performed on second-line or subsequent chemotherapy as salvage settings of chemotherapy in gastric cancer [14–18]. When limited to second-line therapy, the RR was 5–25%, progression-free survival (PFS) was 2.5–4.4 months, and OS was 5.2–8.8 months. Only a few second-line trials have been performed in Western countries [19–21], and these showed RR (5–18%) was comparable to those from Asian studies but the PFS (2.0–2.4 months) and OS (3.5–5 months) seemed inferior to Asian data. It has been suggested that differences in tumor biology, tumor burden, or tolerability to treatment such as 5-FU [22], or the high proportions of patients who received subsequent chemotherapy after first-line failure in Asian trials may have contributed to the favorable outcome in Asian studies. However, firm conclusions on the benefits of subsequent salvage chemotherapy after first-line treatment in gastric cancer could not be drawn from these small trials.

Understanding the natural history of patients with stage IV gastric cancer receiving sequential salvage chemotherapy is critical for establishing proper management strategies for second- or third-line chemotherapy through future clinical trials. In addition, we evaluated survivals after multiple salvage chemotherapy in gastric cancer.

Patients and methods

Patients

Through retrospective review of medical records, we screened patients with unresectable gastric carcinoma who were treated with standard chemotherapy or in clinical trials from January 2000 to June 2008 at Yonsei Cancer Center. The inclusion criteria were as follows: (1) histologically confirmed diagnosis of gastric adenocarcinoma; (2) measurable or evaluable lesions; and (3) availability of medical records for palliative chemotherapy. Patients without macroscopic residual tumor after metastasectomy or with double primary cancers were excluded. Of the 572 patients screened, 532 fulfilled the inclusion criteria and were enrolled in the analysis (Fig. 1). This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, Seoul, Korea.

Chemotherapy

Patients with advanced gastric carcinoma were managed with a strategy of multiple salvage chemotherapy as performance status, organ function, and toxicity profiles allowed. That is, when patients were faced with progressive disease or adverse events, another salvage chemotherapy was given, irrespective of the number of previous chemotherapy regimens. In a clinical practice setting, based on the National Cancer Institute Common Toxicity Criteria, the dose administered was reduced by 25% if a grade 3/4 non-haematological toxicity occurred or if a grade 3/4 haematological toxicity was sustained for more than 2 weeks.

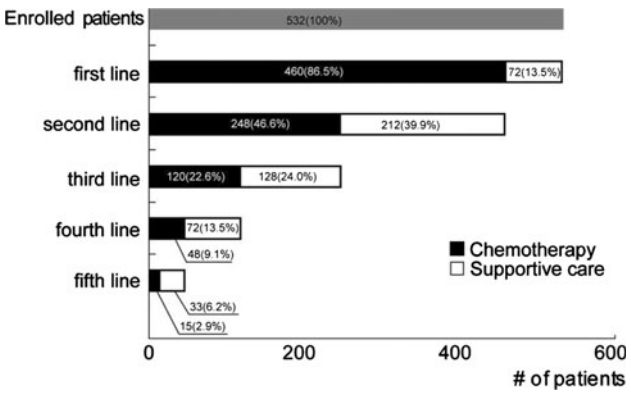

Fig. 1 Overview of patients receiving palliative chemotherapy in each line of treatment

Of the 532 patients included in the study, 460 received palliative chemotherapy (Fig. 1). The chemotherapeutic regimens administered are shown in Supplementary Fig. 1. The most commonly used regimen for the first-line treatment was a taxane-based regimen (51.7%, 238/460). Accordingly, all patients who received chemotherapy were divided into two groups based on first-line treatment: the taxane group ($n = 238$) and the non-taxane group ($n = 222$).

Evaluation of endpoints and statistical considerations

Tumor response was assessed every two cycles using the Response Evaluation Criteria in Solid Tumors (version 1.0) [23]. Response duration was defined as the time from response to each line of chemotherapy until progression of disease (PD). PFS was defined as the time from commencement of each line of chemotherapy until PD or death, and remnant survival was defined as the time from PD of the last chemotherapy to death with supportive care. OS was measured from the first date of each line of chemotherapy to death from any cause, irrespective of subsequent salvage treatment. In all cases, survival was modeled with the date of initiation of the given treatment as time zero. The relative dose intensity (RDI) of combined regimens indicates the mean of the RDIs calculated for each drug.

Chi-square or Fisher's exact test was used for comparison of categorical variables. Survival was calculated using the Kaplan–Meier method. Log-rank test was used to compare survival between groups. Multivariate analysis for prognostic factors was performed by Cox's proportional hazards regression model. All P values were two-sided, and the α-value was set at 0.05. All statistical calculations were carried out using SPSS for Windows version 12.0 (SPSS Inc., USA).

Results

Patient characteristics

Of the 532 patients included in this analysis (Table 1; Fig. 1), Eastern Cooperative Oncology Group performance status was 0–1 in 77.6% of patients, 2 in 14.3%, and 3–4 in 6.4%. The most common metastatic pattern at presentation was peritoneal carcinomatosis (42.5%) followed by hematogenous metastasis (23.9%). Measurable lesions were present in 71.4% of patients. Of the 532 patients, 460 (86.5%) received palliative chemotherapy and 72 (13.5%) had supportive care only due to poor performance ($n = 31$), patient refusal ($n = 23$), or comorbidity ($n = 18$). Patients in the chemotherapy group had a younger age than those in the supportive care group (median age 54 vs. 60; $P = 0.046$) and better performance status (0–1 in 84.8% of patients vs. 31.9%; $P < 0.001$). The initial metastatic pattern was more advanced (peritoneal carcinomatosis and hematogenous metastasis) in the supportive care group than in the chemotherapy group (8.1 vs. 5.9%; $P = 0.001$).

Treatment outcomes

The median follow-up duration was 11.0 months (range, 0.3–62.3). During follow-up, 71 of 72 patients (98.6%) in the supportive care group and 386 of 460 patients (83.9%) in the chemotherapy group died. Of the 71 patients who died in the supportive care group, 64 (90.1%) died from gastric cancer progression, four from infection, and three from other causes. Of the 386 patients who died in the chemotherapy group, 374 (96.9%) died from gastric cancer progression, seven from toxicity of chemotherapy (three taxane-based, one cisplatin-based, and one S-1 monotherapy in the first line; one taxane-based in the second line; one oxaliplatin-based in the third line), and five from other causes. The median OS was 12.0 months [95% confidence interval (CI),11.0–13.0] for all patients, 12.1 months (95% CI, 10.9–13.3) for the chemotherapy group, and 2.5 months (95% CI, 1.3–3.7) for the supportive care group ($P < 0.001$). In 460 patients who received chemotherapy, the median number of regimens delivered was 2 (range, 1–5). Of the enrolled patients, 86.5% received first-line therapy, 46.6% second-line, 22.6% third-line, 9.1% fourth-line, and 2.9% fifth-line chemotherapy (Fig. 1). One hundred and eighty (39.1%) of patients who received the first-line therapy, 23 (9.3%) of patients who received the second-line therapy, 10 (8.3%) of patients who received the third-line therapy, 10 (8.3%) of patients who received the fourth-line therapy, and 3 (20%) of patients who received the fifth-line therapy were treated in clinical trial settings. Targeted agents such as bevacizumab, trastuzumab, sunitinib, cetuximab, or CKD-732 (fumagillin analog) were tested in 14, 7, 1, 0, and 1 patient as the first, second, third, fourth, and fifth-line of systemic therapy. The median number of treatment cycles was 5, 2, 2, 2, and 2, and the RDIs of chemotherapy in each salvage treatment were 0.94, 0.95, 0.89, 0.88, and 0.87 from the first to the fifth line, respectively. The most common cause of discontinuation of chemotherapy was disease progression (68.2, 73.8, 70.0, 75.0, 73.3%), followed by patient refusal (5.2, 5.6, 8.3, 4.2, and 6.7% at the end of the first cycle and 10.0, 7.7, 3.4, 10.4, and 0% after the second cycle) and toxicity (5.9, 2.0, 4.2, 0, and 13.3%) from the first to fifth line, respectively.

Efficacy of chemotherapy

Response was not assessable in 30, 16, 12, 2, and 1 patient for first- to fifth-line treatment, respectively, due to early

Table 1 Patient characteristics

	Supportive care ($n = 72$) Number (%)	Chemotherapy ($n = 460$) Number (%)	P value
Median age (years)	60 (27–92)	54 (22–80)	0.046
Sex			
Male/female	48:24 (66.7:33.3)	276:184 (60.0:40.0)	0.281
ECOG PS			
0–1	23 (31.9)	390 (84.8)	<0.001
2	14 (19.4)	62 (13.4)	
3–4	31 (43.1)	3 (0.7)	
Unknown	4 (5.6)	5 (1.1)	
Histologic grade			
Adenocarcinoma, WD	4 (5.6)	10 (2.2)	0.551
Adenocarcinoma, MD	12 (17.7)	83 (18.0)	
Adenocarcinoma, PD	31 (43.1)	195 (42.4)	
Signet ring cell carcinoma	15 (20.8)	95 (20.7)	
Undifferentiated carcinoma	1 (1.4)	5 (1.1)	
Mucinous carcinoma	0 (0)	8 (1.7)	
Unknown	9 (12.5)	64 (13.9)	
Disease status			
Initially unresectable	41 (56.9)	275 (59.8)	0.648
Recurrence after gastrectomy	31 (43.1)	185 (40.2)	
Prior chemotherapy exposure			
Yes (adjuvant)	22 (30.6)	144 (31.3)	0.899
No	50 (69.4)	316 (68.7)	
Initial metastatic pattern			
LN only or locoregional	10 (13.9)	129 (28.1)	0.001
Hematogenous	15 (20.8)	112 (24.3)	
Peritoneal carcinomatosis	34 (47.2)	192 (41.7)	
Peritoneal + hematogenous	13 (18.1)	27 (5.9)	

ECOG PS Eastern Cooperative Oncology Group performance status, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *LN* lymph node

* *P* values were calculated by Chi-square test or Fisher's exact test except for age (Mann–Whitney test)

termination of chemotherapy, mainly from patient refusal (24, 14, 10, 2, and 1 patients). Overall, 72.8, 77.0, 76.7, 79.2, and 73.3% of patients in the first, second, third, fourth, and fifth line had measurable lesions. RRs were 24.8, 12.6, 10.9, 2.6, and 0% in first, second, third, fourth, and fifth-line chemotherapy. The median response duration was 4.2, 3.7, 2.8 months in the first, second, and third line, respectively, and was not calculable in the fourth (only 1 responder) or fifth line (no responder). Disease control rates (DCRs) were 76.3, 60.1, 54.2, 54.2, and 53.3%; and the median PFS durations were 5.5, 3.4, 2.5, 1.9, and 2.0 months in first- to fifth-line chemotherapy, respectively (Fig. 2a). PFS was longer in the first and second line than in the third to fifth line ($P < 0.001$; Fig. 2a), whereas there was no difference in PFS among the third, fourth, and fifth lines ($P = 0.512$; Fig. 2a). The median PFS of patients with measurable vs. nonmeasurable lesions was 5.5 months (95% CI, 5.0–6.0) vs. 5.5 months (95% CI, 4.3–6.7) in the first line ($P = 0.732$), 3.8 months (95% CI, 3.0–4.6) vs. 2.5 months (95% CI, 1.6–3.4) in the second line ($P = 0.062$), and 2.5 months (95% CI, 2.1–2.9) vs. 2.2 months (95% CI, 1.4–3.0) in the third line ($P = 0.703$), respectively. The median OS durations were 12.1, 7.9, 5.5, 5.0, and 6.8 months in first- to fifth-line treatment, respectively (Fig. 2b). There was no difference in OS between patients with measurable and without measurable lesions (Supplementary Table 1).

The median OS duration was not different between the taxane [12.1 months (95% CI, 10.3–13.9)] and non-taxane groups [12.1 months (95% CI, 10.7–13.5)] ($P = 0.935$). For the first- to third-line treatment, there were no differences in PFS and OS between monotherapy and

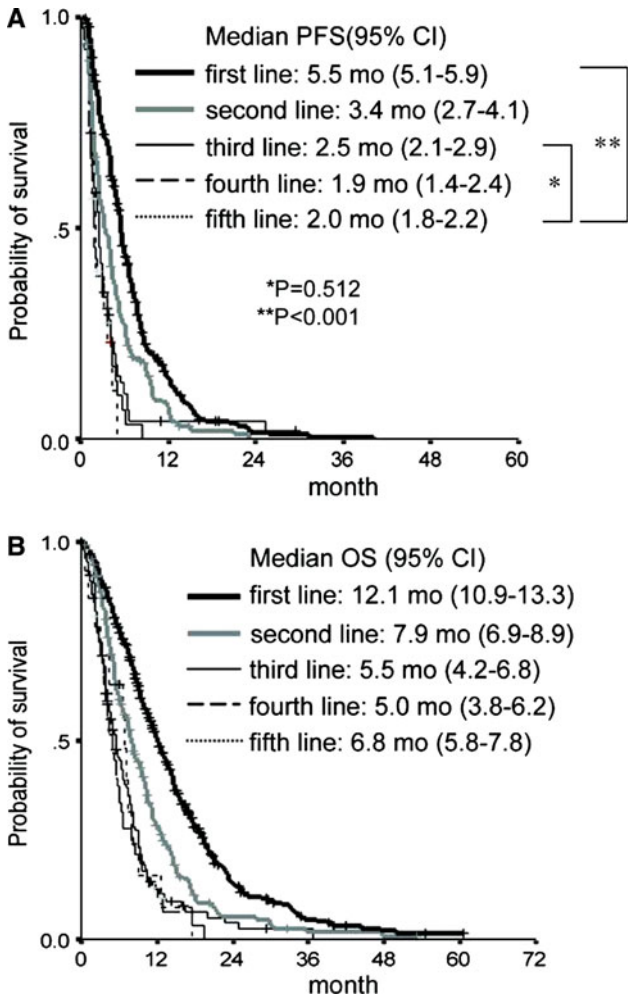

Fig. 2 Progression-free survival (**a**; PFS) and overall survival (**b**; OS) in salvage chemotherapy. *CI* confidence interval, *mo* month. The log-rank test was not applied to compare OS because the OS durations for each line could be overlapped

combination chemotherapy, except that second-line combination chemotherapy showed longer PFS than single agent ($P = 0.004$; Supplementary Table 2).

After PD with each salvage treatment, the subsequent salvage chemotherapy group had longer OS than the supportive care group in each treatment line (data not shown; $P < 0.001$). We compared OS between patients with supportive care and subsequent salvage chemotherapy by simple subtraction to support visual comparability (Fig. 3a). Differences in survival between the two groups were 7.1, 4.9, 4.6, and 2.7 months for the first, second, third, and fourth line, respectively. When remnant survival was calculated by the Kaplan–Meier method (Fig. 3b), remnant survival after the first-line treatment was longer than that after subsequent salvage treatment ($P = 0.010$), but there was no difference in remnant survival after the second-, third-, and fourth-line of salvage treatment ($P = 0.152$). Analysis of the fifth line was not performed due to the small number of patients ($n = 15$).

Prognostic factors at the start of each line of chemotherapy

Clinical factors were analyzed as prognostic factors before the first line and each subsequent salvage treatment (Table 2). Significant factors in univariate analysis were submitted to multivariate analysis. Before the first line of chemotherapy, prognostic factors for OS were performance status, histology, metastatic pattern, and chemotherapy. The prognostic factors before the second- or third-line treatment were generally the same as those before the first-line therapy (data not shown), although histology ($P = 0.070$) and chemotherapy ($P = 0.056$) only showed borderline significance in the third line.

Discussion

In the current study, most patients (87%) diagnosed with stage IV gastric cancer received palliative chemotherapy. Moreover, a considerable number of patients could receive second-line (47%) or third-line (23%) treatment, a slightly

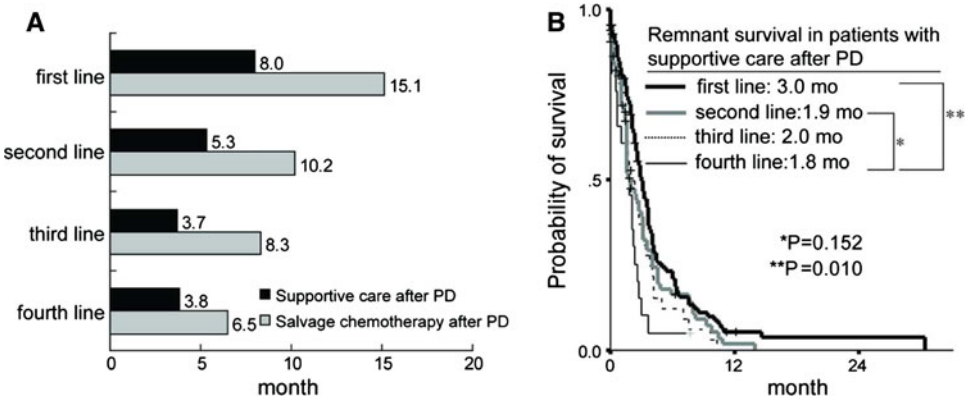

Fig. 3 **a** Comparison of median overall survival duration between patients with supportive care and subsequent salvage chemotherapy after progression of disease (*PD*). **b** Remnant survival in patients receiving supportive care after *PD*. *mo* month

Table 2 Prognostic factors for overall survival

Univariate analysis			*P* value
Age (<65 years vs. ≥65 years)			0.122
Sex (male vs. female)			0.635
ECOG performance status (0–1 vs. 2 vs. 3–4)			<0.001
Histology (good vs. poor)[a]			0.052
Disease status (initially unresectable vs. recurrent)			
Initial metastatic patterns (LN or locoregional vs. hemato. vs. peritoneal vs. hemato. + peritoneal)			<0.001
Measurable lesion (yes vs. no)			0.088
Adjuvant chemotherapy (yes vs. no)			0.368
Prior recurrence-free duration (≤6 vs. >6 months)			0.721
First-line chemotherapy (yes vs. no)			<0.001
Multivariate analysis	**HR**	**95% CI**	***P* value**
ECOG performance status			
0–1	1	–	–
2	1.23	0.91–1.66	0.176
3–4	1.71	1.05–2.80	0.031
Histology[a]			
Good	1	–	–
Poor	1.36	1.06–1.73	0.014
Initial metastatic patterns			
LN or locoregional	1	–	–
Hemato.	1.88	1.39–2.54	<0.001
Peritoneal	1.51	1.17–1.95	0.002
Hemato. + peritoneal	3.29	2.18–4.95	<0.001
First-line chemotherapy			
Yes	1	–	–
No	3.63	2.51–5.24	<0.001

ECOG Eastern Cooperative Oncology Group, *HR* hazard ratio, *CI* confidence interval, *LN* lymph node, *hemato.* hematogenous metastasis, *peritoneal* peritoneal carcinomatosis

[a] Good histology includes well-, moderately differentiated adenocarcinoma, while poor histology includes poorly differentiated adenocarcinoma, undifferentiated carcinoma, or signet ring cell carcinoma

higher rate than that previously reported for second-line treatment (14–40%) [9, 24, 25] Patients receiving chemotherapy survived five times longer than those with supportive care only (12.1 vs. 2.5 months). This difference in survival may be determined by differences in performance status, tumor burden, tumor biology, or chemotherapy.

Recently, in a German prospective trial, second-line chemotherapy with irinotecan for gastric cancer prolonged OS, comparing to the best supportive care alone [26]. However, only 40 patients were randomized into the study due to poor accrual, which is too small to provide convincing evidence. Accordingly, whether second- or third-line chemotherapy provides survival benefit should be evaluated further. In Asian countries, including Korea and Japan, second- or third-line chemotherapy issues are of great concern given the high incidence of gastric cancer [1] and relatively long survival with metastatic disease [8, 10]. This issue has been less important in Western countries, due to the low incidence of gastric cancer [1] and typical short survival with advanced disease. However, recently published phase III trials in Western areas [7, 9, 27, 28] indicate that the OS for gastric cancer has become as long as that in Asian patients; therefore, salvage chemotherapy for metastatic gastric cancer has become an important issue in both regions.

In our analysis, survival duration from PD after the first-line treatment to death reached 6.6 months, longer than the 3–5 months reported for Western studies in which second or subsequent lines of salvage chemotherapy were not usually given [7, 9, 28]. This suggests that multiple salvage chemotherapy might have provided the survival benefit that was previously explained by differences in tumor biology. When patients were managed with the strategy of multiple salvage chemotherapy, remnant survival after failure of each salvage treatment was not clinically different (2–3 months). To explain this fixed remnant survival duration after each salvage chemotherapy, we hypothesize that remnant survival in advanced gastric cancer may be biologically determined. The fact that the OS of the supportive care group without chemotherapy paralleled the

remnant survival supports our hypothesis. In other words, when patients reach a full-blown cancer status where chemotherapy cannot be given any more, remnant survival may be 2–3 months with supportive care, regardless of the number of previous salvage regimens. In first- to third-line salvage treatment, differences in survival (4.6–7.1 months) between the supportive care group and the salvage chemotherapy group after PD from previous treatment surpassed the biologically determined remnant survival. Sequential salvage chemotherapy may suppress tumor growth and prolong survival until a full-blown cancer status, when tumor stasis can no longer be attained. However, this possible prolongation of survival with sequential salvage chemotherapy may result from multiple factors, including the biology of slow-growing tumors.

In our study, although the RR of second- or third-line salvage chemotherapy was low, DCRs ranged from 54 to 76%, even after third-line salvage treatment. Tumor response and disease control predicted a survival advantage from the first to the third line (data not shown). Ichikawa et al. [29] reported that tumor response has a potential role as a surrogate endpoint in first-line chemotherapy trials of unresectable gastric cancer; however, disease control has never been studied as a surrogate in gastric cancer. Considering the low RR with short response duration, the high proportion of patients with nonmeasurable disease, and similar PFS between patients with measurable and nonmeasurable lesions, the potential role of disease control as a surrogate endpoint in the second- or third-line setting of gastric cancer treatment warrants further investigation. If PFS is used as an endpoint for efficacy in clinical trials, the short PFS of second-line (3.4 months) or third-line (2.5 months) chemotherapy reported in our study could be a guideline for further assumption of survival benefit with new salvage treatment regimens.

Newer agents such as taxanes, irinotecan, oxaliplatin, S-1, and capecitabine have been frequently investigated in salvage treatment and are considered active agents [7–10, 15–17, 28, 30]. Taxanes are some of the most active therapeutic agents in gastric cancer [7, 30] and were used most commonly in first-line treatment of our patients. However, when patients were divided into taxane and non-taxane groups with respect to first-line chemotherapy, there was no difference in survival between the two groups; this may reflect the crossover of various drugs used in subsequent salvage treatment. There was also no difference between the taxane and non-taxane groups with respect to the proportion of patients who discontinued the first- to third-line treatments due to toxicity (Supplementary Fig. 2). Although a recent metaanalysis showed combination therapy was better than monotherapy in terms of RR and OS [31], in our study, prolongation of PFS with the second-line combination over monotherapy was not translated into OS. Efficacy was not different for the third-line treatment, either. However, the rate of chemotherapy discontinuation due to toxicity seemed to increase in combination therapy.

Performance status and tumor burden (or metastatic patterns) have been consistently reported as major factors that predict a survival benefit of palliative chemotherapy in both first- and second-line treatment [17, 25, 32]. Furthermore, in our study, these two factors were confirmed as prognostic factors in the third line, as well as in the first and second lines. Interestingly, multivariate analysis identified second- or third-line chemotherapy itself as an independent good prognostic factor. This potential survival benefit of second- or third-line chemotherapy needs further investigation to exclude the bias such as patient selection.

Although a potential weakness may lie in the retrospective nature of the current study and the variety of chemotherapeutic regimens, our patient population was clinically homogenous. That is, a large number of patients (>500) were managed with the same strategy of multiple salvage chemotherapy and complied well with subsequent salvage chemotherapy with a refusal rate of 7–15% at each salvage treatment. In this respect, our data may represent the natural history of stage IV gastric cancer treated with sequential salvage chemotherapy.

In conclusion, clinical trials may be feasible in the second- or third-line setting. Future clinical trials in these settings should take into account the low RR of chemotherapy and prognostic factors for optimal trial design. The use of disease control as a surrogate outcome in the second- or third-line setting of gastric cancer needs to be addressed through further studies.

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