without ascites; (2) patients with small or moderate ascites; and (3) patients with massive ascites.

P values for testing differences in baseline characteristics and response rates of each ascites group were calculated for homogeneity using chi-square tests and for trends using Fisher's exact test. The PFS and OS were compared among the ascites groups by the log-rank test; the hazard ratio (HR) was calculated by the Cox proportional hazards model, and presented as HRs and 95% confidence intervals (95% CIs). Statistical analyses were performed using STATA software (version 10; StataCorp LP, College Station, TX, USA). All tests were two sided, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 275 patients with AGC had received first-line chemotherapy with a fluoropyrimidine plus cisplatin regimen from January 2005 to March 2011. Of these patients, 120 patients met the inclusion criteria and were analyzed in this study. Patient characteristics are shown in Table 1. Most patients had PS 0 or 1; only 2 patients had PS 2. Peritoneal metastasis was diagnosed by laparotomy or laparoscopy in 45 patients. The other 75 patients were diagnosed by imaging data including CT scan or barium enema. Ascites was detected in 50 patients (42%) by CT scan: 27 patients (23%) had small ascites; 12 patients (10%) had moderate ascites; and 11 patients (9%) had massive ascites. Of the patients with massive ascites, 5 patients underwent paracentesis prior to chemotherapy. The estimated volume of ascites according to this classification was as follows: median of 190 mL in small ascites (range, <100–640 mL); median of 990 mL in moderate ascites (range, 600–1,600 mL); and median of 3,240 mL in massive ascites (range, 1,920–7,200 mL). The proportion of patients with lymph node metastasis or with two or more metastatic organs was higher in the patient group with small or moderate ascites than in the other two groups (Table 1, $P = 0.01$). Human epidermal growth factor receptor 2 (HER2) status was evaluated in 39 patients (22%); four of these patients (10%) were positive, which was defined as immunohistochemistry (IHC) 3+ or IHC 2+ plus amplification by fluorescence in situ hybridization (FISH). Of the 120 patients evaluated, 107 patients (89%) had been treated with SP and 13 patients (11%) with XP.

Treatment results and efficacy

The median TTF among all patients was 5.8 months, and cisplatin was administered a median of four times (range 0–13 times) during the median follow-up period of 34.9 months (Table 2). Three patients (2 patients without ascites and 1 patient with small ascites) started SP, but did not receive cisplatin on day 8 because of toxicity. After the initial dose, the dose of fluoropyrimidines was reduced in 23 patients (19%) and the dose of cisplatin was reduced in 33 patients (28%). One-hundred thirteen patients discontinued S-1 or capecitabine treatment for the following reasons: disease progression ($n = 97$; 81%), toxicity ($n = 6$; 5%), and other ($n = 10$; 8%).

The median numbers of times that cisplatin was administered within the ascites groups were as follows: 4 times in patients without ascites; 3 times in patients with small to moderate ascites; and 2 times in patients with massive ascites. The frequency of discontinuation due to toxicities and dose reduction was not higher in patients with massive ascites than in the other two groups (Table 2).

Of the 55 patients with measurable lesions, 23 patients achieved a CR ($n = 1$) or a PR ($n = 22$) for an overall response rate of 42.0% (95% CI, 28.7–55.9%; Table 3). Of the patients with ascites ($n = 50$), disappearance of ascites was observed in 8 patients (16%), and a decrease of ascites was observed in 12 patients (24%), for an overall response rate in terms of ascites of 40% (95% CI, 26.4–54.8%; Table 3). Response rates in terms of measurable lesions or ascites were relatively similar among the ascites groups (Table 3).

One hundred seven patients had already experienced disease progression at the time of analysis, with a median PFS of 6.1 months (95% CI, 5.3–7.3 months) (Fig. 1). Eighty-four patients (70%) were dead, with a median OS of 15.9 months (95% CI, 12.8–18.4 months) (Fig. 1). Median PFS was shorter in patients with massive ascites (3.7 months; 95% CI, 0.7–6.0 months) than in patients with small or moderate ascites (5.8 months; 95% CI, 4.0–8.8 months; HR 0.45; 95% CI, 0.22–0.93; $P = 0.03$) or patients without ascites (6.9 months; 95% CI, 5.5–9.0 months; HR 0.43; 95% CI, 0.22–0.85; $P = 0.02$) (Fig. 2). Median OS was also shorter in patients with massive ascites (9.5 months; 95% CI, 0.5–not reached) than in patients with small or moderate ascites (13.5 months; 95% CI, 9.4–17.0 months; HR 0.49; 95% CI; 0.21–1.15; $P = 0.1$) or patients without ascites (18.1 months; 95% CI, 14.5–20.0 months; HR 0.31; 95% CI, 0.13–0.71; $P = 0.006$) (Fig. 3).

Ninety-three patients (78%) received second-line chemotherapy, most commonly ($n = 69$) with taxanes (paclitaxel or docetaxel). The proportion of patients having second-line chemotherapy was relatively similar among the ascites groups: 53 patients without ascites (75.7%), 31 patients with small to moderate ascites (79.5%), and 9 patients with massive ascites (81.9%).

Table 1 Patient characteristics

Characteristics	All patients (n = 120%)	Patients without ascites (n = 70%)	Patients with small to moderate ascites (n = 39%)	Patients with massive ascites (n = 11%)
Age				
Median (range)	61 (27–79)	61 (34–79)	61 (27–74)	59 (28–66)
Gender				
Male	62 (52)	39 (56)	19 (49)	4 (36)
Female	58 (48)	31 (44)	20 (51)	7 (64)
ECOG PS				
0	26 (22)	20 (29)	6 (15)	2 (18)
1	92 (77)	50 (71)	31 (79)	9 (82)
2	2 (2)	0	2 (5)	0
Histological type				
Diffuse	96 (80)	61 (87)	28 (72)	7 (64)
Intestinal	24 (20)	9 (13)	11 (28)	4 (36)
Disease status				
Advanced	102 (85)	58 (83)	34 (87)	10 (91)
Recurrent	18 (15)	12 (17)	5 (13)	1 (9)
Previous gastrectomy				
No	86 (72)	45 (64)	31 (79)	10 (91)
Yes	34 (28)	25 (36)	8 (21)	1 (9)
Prior adjuvant chemotherapy				
No	110 (92)	62 (89)	37 (95)	11 (100)
Yes	10 (8)	8 (11)	2 (5)	0
Site of metastasis				
Lymph node	48 (40)	22 (31)	23 (59)	3 (27)
Liver	11 (9)	4 (6)	6 (15)	1 (9)
Ovary	11 (9)	4 (6)	5 (13)	2 (18)
Number of metastatic organs				
1	56 (47)	41 (59)	10 (26)	5 (45)
2 or more	64 (53)	29 (41)	29 (74)	6 (55)

PS performance status, *ECOG* Eastern Cooperative Oncology Group

Toxicity

Toxicity is shown in Table 4. The frequencies of any grade 3–4 hematological toxicity were 27% (19 of 70 patients) in patients without ascites, 41% (16 of 39 patients) in patients with small to moderate ascites, and 27% (3 of 11 patients) in patients with massive ascites; the frequency in patients with massive ascites was not significantly higher. The frequencies of any grade 3–4 nonhematological toxicity also did not differ significantly among patients without ascites (34%; n = 24), patients with small or moderate ascites (26%; n = 10), or patients with massive ascites (45%; n = 5). The frequency of grade 3 or higher anorexia tended to be higher in patients with massive ascites (36%; n = 4) than in patients without ascites (19%; n = 13) or patients with small or moderate ascites (15%; n = 6). No patients experienced grade 3 or higher renal toxicity.

Discussion

We retrospectively evaluated the efficacy and safety of a fluoropyrimidine plus cisplatin regimen for patients with AGC and peritoneal metastasis. Median PFS and OS were similar to that of the SPIRITS trial, in which about 30% of patients had peritoneal metastasis (34% in SP group, 24% in S-1 group) [2]. The frequencies of common toxicities in our analysis were also compatible with that in the SPIRITS trial; therefore, a fluoropyrimidine (S-1 or capecitabine) plus cisplatin regimen is considered to be effective and feasible for treatment of patients with peritoneal metastasis.

In our analysis, PFS and OS were worse in patients with massive ascites than in patients without ascites or patients with small or moderate ascites. Although the incidence of anorexia was higher in patients with massive ascites, the frequencies of discontinuation or dose reduction due to

Table 2 Treatment results

Variables	All patients (n = 120%)	Patients without ascites (n = 70%)	Patients with small or moderate ascites (n = 39%)	Patients with massive ascites (n = 11%)
Median TTF				
Median (months, range)	5.8 (0.3–33.8)	6.5 (0.3–33.8)	5.7 (0.3–28.4)	3.4 (0.4–10.6)
Cisplatin administration				
Median number of times	4 (0–13)	4 (0–13)	3 (0–12)	2 (1–6)
Dose reduction in fluoropyrimidine				
Yes	23 (19)	13 (19)	10 (26)	0 (0)
Dose reduction in cisplatin				
Yes	33 (28)	23 (33)	10 (26)	0 (0)
Cause of discontinuation of cisplatin				
Progressive disease	52 (43)	27 (39)	17 (44)	8 (73)
Toxicities	34 (28)	22 (31)	9 (23)	3 (27)
Other	31 (26)	18 (26)	13 (33)	0 (0)
Ongoing	3 (3)	3 (4)	0	0
Cause of S-1 or capecitabine discontinuation				
Progressive disease	97 (81)	52 (74)	35 (90)	10 (91)
Toxicities	6 (5)	4 (6)	2 (5)	0 (0)
Other	10 (8)	9 (13)	1 (3)	0
Ongoing	7 (6)	5 (4)	1 (3)	1 (9)

TTF time to treatment failure

Table 3 Objective response rates in measurable lesions and ascites

Groups	*N*	CR	PR	SD	PD	NE	ORR (%)	95% CI (%)	*P* value[a]
All patient with target lesions	55	1	22	23	5	4	42.0	28.7–55.9	0.87
No ascites	25	1	10	10	0	4	44.0	24.4–65.1	
Small to moderate ascites	26	0	10	12	4	0	38.5	20.2–59.4	
Massive ascites	4	0	2	1	1	0	50.0	6.8–93.2	
All patient with ascites	50	8	12	17	10	3	40.0	26.4–54.8	0.78
Small to moderate ascites	39	8	8	14	6	3	41.0	25.6–57.9	
Massive ascites	11	0	4	3	4	0	36.4	10.9–69.2	

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* objective response rate, *CI* confidence interval

[a] Comparison of ORR between 3 groups

toxicity were not higher. Therefore, this treatment may be feasible even for patients with massive ascites if they have good performance status, sufficient oral intake, and adequate organ function. However, median treatment duration and PFS are quite short in patients with massive ascites compared with other patients; therefore, more effective treatments may be necessary to improve the poor prognosis.

To date, several clinical trials have been conducted or are ongoing in patients with peritoneal metastasis. The JCOG 9603 trial showed the efficacy of 5-FU plus methotrexate in patients with AGC with ascites: a response rate in terms of ascites of 35.1% was noted [12]. The JCOG 0106 study was conducted to compare infused 5-FU versus 5-FU plus methotrexate in patients with AGC and peritoneal metastasis, but it did not show a superiority of 5-FU plus methotrexate [13]. Although the JCOG 0106 trial did not include patients with massive ascites and did not evaluate response in terms of ascites, improvement of oral intake was reported in 48% of patients who were unable to eat at the study outset [13]; this finding suggests substantial efficacy of the 5-FU-based therapy in patients with AGC and peritoneal metastasis.

In the SPIRITS trial, combination treatment with cisplatin (SP) showed favorable results compared with S-1 alone in the subset of patients with peritoneal metastasis [2]. Although patients with massive ascites were excluded and detailed information about ascites is not available in

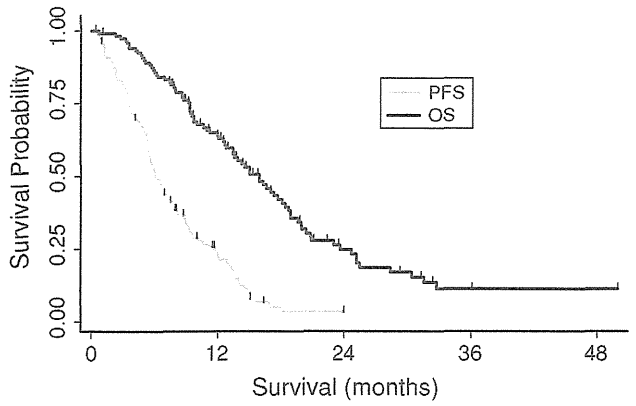

Fig. 1 Progression-free survival and overall survival. Median PFS was 6.1 months (95% CI, 5.3–7.3 months), and median OS was 15.9 months (95% CI, 12.8–18.4 months)

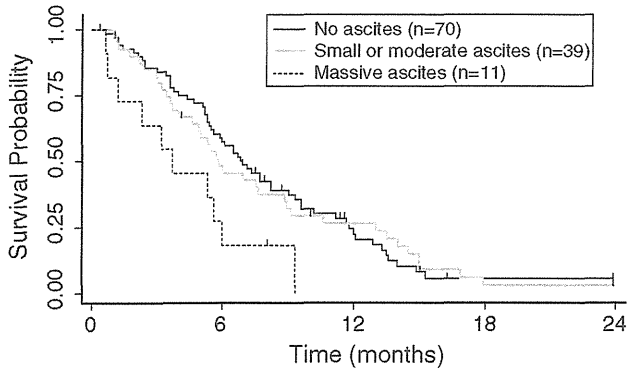

Fig. 2 Progression-free survival by ascites group. Median PFS was shorter in patients with massive ascites (3.7 months; 95% CI, 0.7–6.0 months) than in patients with small or moderate ascites (5.8 months; 95% CI, 4.0–8.8 months; HR 0.45; 95% CI, 0.22–0.93; $P = 0.03$) or patients without ascites (6.9 months; 95% CI, 5.5–9.0 months; HR 0.43; 95% CI, 0.22–0.85; $P = 0.02$)

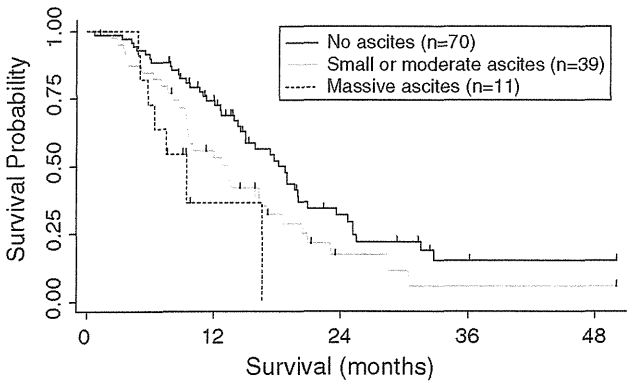

Fig. 3 Overall survival according to ascites group. Median OS was shorter in patients with massive ascites (9.5 months; 95% CI, 0.5–not reached) than in patients with small or moderate ascites (13.5 months; 95% CI, 9.4–17.0 months; HR 0.49; 95% CI, 0.21–1.15; $P = 0.1$) or patients without ascites (18.1 months; 95% CI, 14.5–20.0 months; HR 0.31; 95% CI, 0.13–0.71; $P = 0.006$)

the SPIRITS trial, this result suggests that cisplatin is also an important agent for patients with peritoneal metastasis. Oxaliplatin, another platinum agent, showed noninferior efficacy with significantly less renal toxicity [7] and gastrointestinal toxicity [21] in comparison with cisplatin. A 5-FU and oxaliplatin regimen was also evaluated in patients with AGC and ascites, with a response rate in terms of ascites of 33% with low toxicities [14].

Another effective drug type for patients with peritoneal metastasis is a taxane agent (paclitaxel or docetaxel). The JCOG 0407 trial is a randomized phase II study that compared second-line chemotherapy of weekly paclitaxel with 5-FU-based chemotherapy for patients with AGC and peritoneal metastasis [15]. The efficacy of paclitaxel was suggested by a longer PFS in the paclitaxel arm [15]. A phase II study of weekly paclitaxel for patients with malignant ascites, which included mostly patients with massive ascites (median 2,796 mL), showed a decrease in ascites and improvement of performance status in 39.1% of patients [16]. Combination treatment with 5-FU and paclitaxel also showed a high response rate (44%) in patients with massive ascites [17]. These results suggest the apparent efficacy of paclitaxel in patients with AGC and ascites. In our study, second-line chemotherapy, mainly with taxanes, was used in most patients, including those with massive ascites—possibly contributing to the relatively long survival after first-line chemotherapy. Additionally, a recent phase II study that evaluated S-1 combined with intravenous and intraperitoneal chemotherapy with paclitaxel included 40 patients with peritoneal metastasis in whom overall survival was as impressively long as 22.5 months [18]. Also, in the 30 patients with ascites in that study, the response in terms of ascites was reported to be as high as 60% [18]. These results compare favorably with those from our analysis. The efficacy of intraperitoneal administration of paclitaxel was suggested in a randomized study of patients with ovarian cancer and peritoneal metastasis [22]. Therefore, this treatment may be promising in AGC, especially for patients with peritoneal metastasis. Currently, a randomized study comparing S-1 plus intraperitoneal and intravenous paclitaxel versus S-1 plus cisplatin is ongoing.

It is important to note the limitations of the present study. First, it was a retrospective analysis in a single institution with patients that had sufficient oral intake and adequate organ function. None of the patients had symptoms or complications such as decreased oral intake or renal dysfunction due to hydronephrosis; the treatment regimen used in our study may not be feasible for such patients. Specifically, patients with peritoneal metastasis frequently have an inability to eat [23], making it impossible to use oral agents in such patients, and patients with renal dysfunction should not be given cisplatin. Therefore,

Table 4 Toxicities

	All (n = 120%)		Patients without ascites (n = 70%)		Patients with small or moderate ascites (n = 39%)		Patients with massive ascites (n = 11%)		P value[a]
	All (%)	G3–4 (%)	All (%)	G3–4 (%)	All (%)	G3–4 (%)	All (%)	G3–4 (%)	
Hematological toxicity									
Any	75 (62)	38 (32)	40 (57)	19 (27)	27 (69)	16 (41)	8 (73)	3 (27)	0.31
Leukopenia	58 (48)	15 (12)	29 (41)	9 (13)	22 (56)	5 (13)	7 (64)	1 (9)	0.94
Neutropenia	60 (50)	28 (23)	31 (44)	16 (23)	22 (56)	10 (26)	7 (64)	2 (18)	0.89
Anemia	51 (42)	12 (10)	27 (39)	6 (9)	19 (49)	5 (13)	5 (46)	1 (9)	0.77
Thrombocytopenia	25 (21)	4 (3)	14 (20)	3 (4)	9 (23)	1 (3)	2 (18)	0	0.72
Nonhematological toxicity									
Any	96 (80)	39 (33)	59 (84)	24 (34)	29 (74)	10 (26)	8 (73)	5 (45)	0.45
Nausea	73 (61)	17 (14)	44 (63)	12 (17)	22 (56)	5 (13)	7 (64)	2 (18)	0.71
Vomiting	30 (25)	4 (3)	18 (26)	3 (4)	7 (18)	0 (0)	5 (45)	1 (9)	0.26
Anorexia	80 (67)	23 (19)	45 (64)	13 (19)	28 (72)	6 (15)	7 (64)	4 (36)	0.29
Fatigue	55 (46)	8 (7)	32 (46)	6 (9)	19 (49)	2 (5)	4 (36)	1 (9)	0.51
Diarrhea	25 (20)	5 (4)	18 (26)	4 (6)	5 (13)	1 (3)	2 (18)	0	0.56
Increased creatinine	17 (14)	0	13 (19)	0	4 (10)	0	1 (9)	0	0.43[b]
Stomatitis	17 (14)	2 (2)	11 (16)	2 (3)	4 (10)	0	2 (18)	0	0.48
Rash	4 (3)	0	3 (4)	0	1 (3)	0	0	0	0.78[b]
Hand–foot syndrome	9 (8)	0	5 (7)	0	4 (10)	0	0	0	0.69[b]
Febrile neutropenia	2 (2)	2 (2)	0	2 (3)	0	0	0	0	0.48

[a] Comparison in grade 3 or more

[b] Comparison in all grades

in these types of patients, other treatments such as intravenous 5-FU or combination therapy with taxanes may be the preferred choice. Second, we included both SP and XP in this study, although most patients were treated with SP. Direct comparison of S-1 and capecitabine as well as indirect comparisons of several randomized studies using SP and XP suggest that these two treatments have similar efficacies [2, 3, 24]. Additionally, our retrospective analysis comparing these two treatment regimens showed that they have similar efficacies and safeties [25]. S-1 was suggested to be more efficacious than 5-FU in patients with diffuse-type AGC [26] or AGC associated with high dihydropyrimidine dehydrogenase (DPD), with diffuse-type tumors being more commonly associated with high DPD than intestinal-type tumors are [27]. Since diffuse-type cases are commonly associated with peritoneal metastasis, S-1 may be preferable for the treatment of AGC in this setting. In contrast, several small analyses have suggested that capecitabine is effective at treating high-thymidine phosphorylase (TP) gastric cancer [28, 29]; for such tumors, 5-FU and S-1 are reported to be relatively ineffective compared with their efficacy towards low-TP gastric cancer [30, 31]. The exact impact of using biomarkers or histology to select among 5-FU, S-1, and capecitabine should be evaluated in ongoing randomized studies.

In conclusion, although our findings are limited by the retrospective study design and small number of patients, a regimen consisting of a fluoropyrimidine plus cisplatin appears to be tolerated in selected patients with peritoneal metastasis.

Acknowledgments The manuscript has not been published nor submitted for publication elsewhere, except as a brief abstract in the proceedings of a scientific meeting or symposium (two topics were presented at the 49th Annual Meeting of Japanese Society of Clinical Oncology, October 27–29, 2011).

Conflict of interest None.

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Gastric Cancer
DOI 10.1007/s10120-011-0083-8

ORIGINAL ARTICLE

Reporting patient characteristics and stratification factors in randomized trials of systemic chemotherapy for advanced gastric cancer

Kohei Shitara · Junko Ikeda · Chihiro Kondo · Daisuke Takahari · Takashi Ura · Kei Muro · Keitaro Matsuo

Received: 14 May 2011 / Accepted: 24 July 2011

Abstract
Background There is no consensus on which patient characteristics are the most suitable to report or to be used as stratification factors in clinical trials for advanced gastric cancer (AGC), to our knowledge.
Methods We conducted a comprehensive review of published randomized trials for AGC to examine the patient characteristics that were reported.
Results Among the 67 analyzed trials, age, gender, performance status, proportion of patients with measurable disease, and previous gastrectomy were frequently reported (>69%). Histology, number of disease sites, and adjuvant treatment were reported in less than 50% of trials. Although the reporting of second-line chemotherapy has increased in recent trials, it remains at less than 50%. Notably, recent trials have tended to include patients with better performance status and less locally advanced disease, with Asian trials more frequently including patients with more diffuse histology and less locally advanced disease or liver metastasis than non-Asian trials. Stratification was conducted in approximately 60% of the trials, using quite variable stratifying factors.
Conclusion Inconsistency exists in the reporting of patient characteristics, the characteristics themselves, and the use of stratification factors in clinical trials for AGC. A consensus set of important patient characteristics and strata may be necessary to conduct and interpret quality randomized studies.

Keywords Chemotherapy · Gastric cancer · Prognostic factor · Randomized trial · Stratification

Electronic supplementary material The online version of this article (doi:10.1007/s10120-011-0083-8) contains supplementary material, which is available to authorized users.

K. Shitara (✉) · J. Ikeda · C. Kondo · D. Takahari · T. Ura · K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan
e-mail: Kouheis0824@yahoo.co.jp

K. Matsuo
Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan

Introduction

Gastric cancer remains one of the most common malignancies and leading causes of cancer death worldwide [1]. Although the most effective treatment for localized disease is surgery, approximately half of all patients with advanced-stage disease experience recurrence following curative resection. The prognosis of patients with advanced or recurrent gastric cancer (AGC) remains poor, with commonly used combination chemotherapy regimens, consisting of a fluoropyrimidine plus a platinum agent with or without docetaxel or anthracyclines, leading to a median survival of only 1 year [2–8]. Therefore, the development of novel anticancer agents or strategies for the treatment for AGC is urgently required; however, for the evaluation of such agents and treatments, it is critical to conduct effective randomized trials.

Reflecting the relatively high incidence of gastric cancer worldwide, numerous clinical trials have been conducted in multiple countries or as part of global studies [7, 8]. These clinical trials have displayed surprising heterogeneity in overall survival (OS) even if patients with similar stages of unresectable AGC are targeted. Although several identified prognostic factors in patient characteristics and practice

Published online: 13 August 2011

patterns, including surgery and chemotherapy, are thought to partially contribute to the observed heterogeneity [9], the exact reason for this heterogeneity is unknown.

A number of reports have evaluated prognostic factors in AGC patients who underwent chemotherapy [10–14]. For example, the recent Global Advanced/Adjuvant Stomach Tumor Research through International Collaboration (GASTRIC) project confirmed the impact of performance status (PS), disease status (metastatic vs. locally recurrence vs. locally advanced), number of metastatic organs, location of metastasis, and prior surgery on the survival of AGC based on individual patient data analysis of previous randomized studies [10]. In addition, Chau et al. [11] identified four independent prognostic factors for poor AGC survival: PS $\geq$ 2, liver metastasis, peritoneal metastasis, and increased serum alkaline phosphatase (ALP) levels, which were subsequently used to classify patients into three risk groups (Royal Marsden hospital prognostic index) that were validated in a large phase III trial [12]. The prognostic factors for AGC identified to date also serve as important stratification factors in randomized trials to exclude possible confounding variables. To our knowledge, however, there is no consensus as to the specific patient characteristics that are most suitable to report or to be used as stratification factors in clinical trials for AGC.

Here, we report the results of a comprehensive review of published randomized trials for AGC that we conducted to investigate the patient characteristics and stratification factors that have been evaluated and reported. We also examined differences in previous studies according to trial period and region.

Materials and methods

Search for studies

We conducted a literature search for randomized clinical trials of AGC through computer-based searches of the Medline database (January 1966 and December 2010) and searches of abstracts from conference proceedings of the American Society of Clinical Oncology (1995–2010), and the European Cancer Conference and European Society for Medical Oncology (1995–2010). Search key words included: "gastric cancer," "randomized", "advanced or metastatic", and "chemotherapy." The search was also guided by a thorough examination of reference lists from original and review articles.

Procedures

Two investigators (Kohei Shitara and Keitaro Matsuo) extracted data in accordance with the Quality of Reporting of Meta-analyses (QUORUM) guidelines [15]. Randomized trials of systemic chemotherapy for patients with histologically confirmed AGC (metastatic or unresectable locally advanced disease) of the stomach or gastroesophageal junction were included in the analyses. Trials that compared chemotherapy with best supportive care were also included, as were those which included patients with adenocarcinoma of the distal esophagus. Exclusion criteria included trials designed to assess combined modality treatments, including radiotherapy and surgery (neoadjuvant or adjuvant chemotherapies); and those in which patients were pretreated with systemic chemotherapy. Unpublished trials and trials published in non-English languages were also excluded from this analysis.

For each trial, the reporting of patient characteristics and stratification factors was extracted. As trial characteristics, the following information was extracted: first author's name, year of publication, trial design (randomized phase II or III, if reported), trial location, number of enrolled patients, and treatment regimens. As patient characteristics, the following information was extracted (if reported): age; gender; PS; histology (e.g., diffuse or intestinal type); disease status (e.g., advanced or recurrent disease); primary tumor location (e.g., stomach or gastroesophageal junction); extension of disease (e.g., locally advanced or metastatic); previous gastrectomy, adjuvant chemotherapy, and radiotherapy; sites of metastases (e.g., peritoneum, liver, and lymph node); number of metastatic organs; and proportion of patients with measurable disease. The proportion of patients who received second-line chemotherapy was also extracted. All data were checked for internal consistency.

Statistical methods

Differences in the reporting of patient characteristics according to trial period (before vs. after 2004) and trial region (Asian vs. non-Asian trials) were assessed by the χ^2 test or Fisher's exact test, as appropriate. Because there was no definitive cut-off time for performing trend analysis, we divided the period at 2004 as this led to the number of trials (36 vs. 31 trials) and number of patients being almost equally distributed in the two periods. Median values for patient characteristics were calculated for each trial and the combined patient population. Differences in patient characteristics according to region or trial period were evaluated using the Mann–Whitney test. Use of stratification factors according to trial period or region was evaluated with the χ^2 test or Fisher's exact test as appropriate. Statistical analyses were performed using STATA ver. 10 (StataCorp. LP; College Station, TX, USA). All tests were two-sided, and P values of less than 0.05 were considered statistically significant.

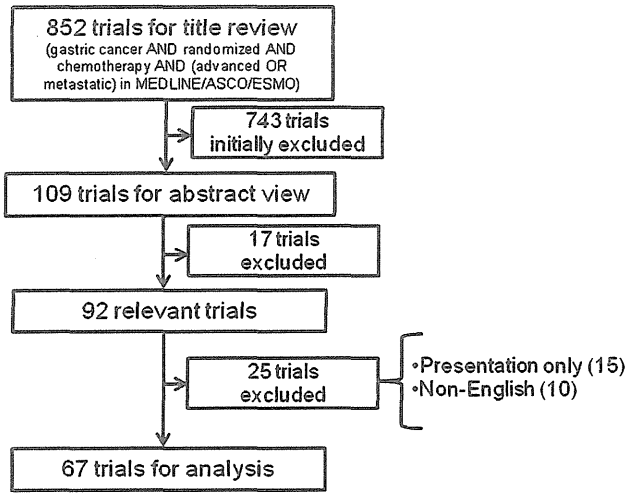

Fig. 1 Selection process for trials. An initial literature search for randomized clinical trials of advanced gastric cancer (AGC) identified a total of 852 potentially relevant reports, of which 743 were excluded on examination of titles. After review of the abstracts of the remaining studies, 67 randomized trials, with a total of 153 treatment arms and 12,656 patients were identified as eligible for analysis. *ASCO* American Society of Clinical Oncology, *ESMO* European Society for Medical Oncology

Results

Study selection

Our extensive literature search yielded a total of 852 potentially relevant reports, of which 743 were initially excluded on examination of titles (Fig. 1). After review of the abstracts of the remaining studies, 67 randomized trials, with a total of 153 treatment arms and 12,656 patients were identified as eligible for analysis (Supplement 1). Table 1 summarizes the characteristics of the 67 selected clinical trials, which consisted of 23 and 30 randomized phase II and III trials, respectively, and 14 trials that did not report the trial phase.

Patient characteristics reported in trials

Table 2 summarizes the patient characteristics reported in the 67 clinical trials included in the analysis. Two global studies that included Asian countries were excluded when comparing trials in Asia and non-Asian countries.

Age, gender, and PS

All 67 clinical trials provided information of patient age, with nearly all (94%) providing a median value, and four trials providing categorized values. One trial targeted elderly patients (>70 years). Gender information was reported by all but one trial. Sixty-four trials (96%) provided information regarding PS, with 46 reporting Eastern Cooperative Oncology Group (ECOG)/WHO PS classifications and the other 17 using the Karnofsky Performance Scale (KPS). Considerable PS variability was detected among the trial patients, as follows: PS 0–1, 4 trials; PS 0–2, 25 trials; and PS 0–3, 17 trials; and KPS 100–80, 1 trial; KPS 100–70, 5 trials; KPS 100–60, 7 trials; and KPS 100–50, 4 trials. Among the trials that used ECOG PS, 22 reported ECOG PS 0 versus 1 versus 2, whereas the other studies reported PS 0 and 1 without discrimination. No significant differences in reporting were detected in the trial period or region for PS, age, and gender.

Table 1 Characteristics of the 67 clinical trials analyzed in the present study

Characteristic	*N*	%
Reported year		
Before 2004	36	54
2004–2010	31	46
Trial setting		
Phase II	23	34
Phase III	30	45
Not indicated	14	21
Number of patients		
<100	28	42
100–300	28	42
>300	11	16
Trial area		
Asia	14	21
North America	12	18
Europe	31	46
Other	6	9
North America and Europe	2	3
Global, including Asia	2	3

Disease characteristics

The proportion of patients with measurable disease was reported in 69% of trials, with half including only patients with at least one measurable disease. Extension of disease and disease status were reported in 57 and 27% of trials, respectively. The location of metastases was reported in 64% of trials; the liver was the most commonly reported site, followed by the peritoneum. Histology and the number of metastatic organs were not reported in more than half of the trials. The Lauren classification (intestinal or diffuse type) was used in 12 trials, while classifications such as the American Joint Committee on Cancer grading system (well- or poorly differentiated adenocarcinoma, etc.) were used in 18 trials. The location of primary tumors was reported in 26 trials (39%), with 17 trials including not only gastric cancer, but also esophagogastric junction or

Table 2 Reported patient characteristics in the 67 clinical trials analyzed in the present study

Characteristic	Reported studies (%)	Reported year			Area of trial[a]		
		Before 2004 ($n = 36$)	After 2004 ($n = 31$)	P value[†]	Non-Asian ($n = 51$)	Asian ($n = 14$)	P value[†]
Age	67 (100)	36 (100)	31 (100)	ns	51 (100)	14 (100)	ns
Gender	66 (99)	35 (97)	31 (100)	ns	50 (98)	14 (100)	ns
PS	64 (96)	34 (94)	30 (97)	ns	48 (94)	14 (100)	ns
Measurable disease	46 (69)	21 (58)	25 (81)	0.05	35 (69)	9 (64)	ns
Metastatic site	43 (64)	22 (61)	21 (68)	ns	33 (65)	9 (64)	ns
Disease extension (local or metastatic)	38 (57)	19 (53)	19 (61)	ns	33 (65)	5 (36)	ns
Histology	30 (45)	12 (33)	18 (58)	0.04	20 (39)	9 (64)	ns
Location of primary tumor	26 (39)	8 (22)	18 (58)	≤0.01	24 (47)	1 (7)	≤0.01
Number of metastatic organs	25 (37)	5 (14)	20 (65)	≤0.01	18 (35)	5 (36)	ns
Disease status (advanced or recurrent)	18 (27)	5 (14)	13 (42)	ns	13 (25)	5 (36)	ns
Previous gastrectomy	46 (69)	21 (58)	25 (81)	0.05	32 (63)	12 (86)	ns
Previous adjuvant chemotherapy	16 (24)	0 (0)	16 (52)	≤0.01	6 (12)	9 (64)	≤0.01
Previous radiotherapy	11 (16)	3 (8)	8 (26)	ns	9 (17)	1 (7)	ns
Second-line chemotherapy	18 (27)	3 (8)	15 (48)	≤0.01	10 (20)	6 (43)	ns

ns not significant, *PS* performance status

[a] Excluded two global studies

[†] Statistical analyses were performed using the χ^2 test or Fisher's exact test, with the level of significance set at $P < 0.05$ (underlined)

esophageal cancer. The frequency of reporting these characteristics appeared to be increasing in more recent trials, although most examined characteristics were reported in less than 60% of the trials (Table 2). Only primary tumor location was more frequently reported in non-Asian than Asian trials, and no other significant differences in reporting of disease characteristics were observed based on trial area.

The other reported patient characteristics were as follows: weight loss ($n = 12$; 18%); any symptoms (anorexia, dysphasia, etc., $n = 7$; 10%); body surface area ($n = 3$; 4%); ethnic groups ($n = 2$; 3%); hemoglobin level ($n = 4$; 6%); serum ALP level ($n = 3$; 4%); comorbidities ($n = 3$; 4%), and Royal Marsden hospital prognostic index ($n = 1$; 1%).

Previous treatment and second-line chemotherapy

An indication of the proportion of patients with previous gastrectomy was reported in 69% of trials, with the curability of gastrectomy (curative or palliative with residual disease) specified in approximately 50% of trials. Previous adjuvant chemotherapy and radiotherapy were infrequently reported (24 and 16% of trials, respectively). Second-line chemotherapy was also reported with low frequency (27% of trials), and was typically indicated in the text, rather than being included in patient characteristic tables. The reporting of previous treatment and second-line chemotherapies was found to be increasing in recent trials, although more than half did not include information related to second-line chemotherapy. In addition, Asian trials more commonly reported the use of adjuvant chemotherapy than non-Asian trials.

Patient characteristics of the combined trial population

The characteristics of the 12,656 AGC patients were calculated based on the reported values in each of the 67 clinical trials (Table 3). Recent trials included more patients with better PS (ECOG PS 0–1; 94 vs. 64%; $P < 0.01$) and less locally advanced disease (4 vs. 27%) than older trials. Asian trials included more patients with diffuse histology than non-Asian trials (53 vs. 34%; $P < 0.01$), while patients with liver metastasis (43 vs. 31%; $P = 0.01$) or locally advanced disease (15 vs. 3%; $P = 0.04$) were more common in non-Asian trials. Second-line chemotherapy was more commonly used in Asian and recent trials.

Stratification factors

Among the 67 trials, 40 (60%) used stratification factors (Table 4). The median number of factors was 3, with an observed range of 1–5. The most common stratification factor was PS, followed by institution and previous gastrectomy. More recent trials used one or more stratification factors than older trials (47 vs. 75%, $P = 0.03$, Table 4).

Table 3 Patient characteristics (n = 12,656) in AGC trials included in this analysis

Patient characteristic	Entire patient population (median)	Median per trial	Range	Reported year			Area of trial[a]		
				Before 2004 (median)	After 2004 (median)	P value[†]	Non-Asian (median)	Asian (median)	P value[†]
Median age (years)	–	59	52–72	58	59	ns	59	58	Ns
Male gender (%)	73	72	58–83	70	74	ns	72	69	ns
PS0–1 (%)	84	83	18–100	69	94	≤0.01	78	89	ns
PS2 or more (%)	16	17	0–82	31	6	≤0.01	22	11	ns
Diffuse histology (%)	42	38	1–66	44	34	ns	34	53	≤0.01
One metastatic organ (%)	33	30	9–51	26	32	ns	27	35	ns
Locally advanced disease (%)	15	14	0–43	27	4	≤0.01	15	3	0.04
Liver metastasis (%)	44	42	18–79	42	42	ns	43	31	0.02
Peritoneal metastasis (%)	23	24	3–62	23	29	ns	20	29	ns
With measurable disease (%)	88	99	33–100	96	100	ns	100	96	ns
Previous gastrectomy (%)	33	39	8–83	38	40	ns	41	33	ns
Previous adjuvant chemotherapy (%)	5	5	1–31	–	5	–	4	9	0.02
Previous radiotherapy (%)	1	1	0–3	2	1	ns	1	1	ns
Second-line chemotherapy (%)	40	41	14–83	18	40	≤0.01	36	57	0.01

ns not significant, *PS* performance status

[a] Excluded two global studies

[†] Statistical analyses were performed using the Mann–Whitney test, with the level of significance set at $P < 0.05$ (underlined)

Table 4 Stratification factors in the 67 clinical trials analyzed in the present study

Stratification factor	N of studies (%)	Reported year			Area of trial[a]		
		Before 2004 (%)	After 2004 (%)	P value[†]	Non-Asian (%)	Asian (%)	P value[†]
No factor	27 (47)	19 (53)	8 (26)	0.03	22 (43)	5 (36)	ns
1 or 2 factors	12 (21)	5 (14)	7 (23)		7 (14)	4 (29)	
3 or more factors	28 (49)	12 (33)	16 (52)		22 (43)	5 (36)	
PS	24 (42)	9 (25)	15 (48)	ns	16 (31)	7 (50)	ns
Previous gastrectomy	18 (32)	9 (25)	9 (29)	ns	14 (27)	4 (29)	ns
Institution	18 (32)	5 (14)	7 (23)	0.35	16 (31)	2 (14)	ns
Measurable disease	12 (21)	6 (17)	6 (19)	ns	10 (20)	1 (7)	ns
Metastatic sites	8 (14)	2 (6)	6 (19)	0.08	8 (16)	0 (0)	ns
Disease extension	8 (14)	4 (11)	4 (13)	ns	7 (14)	1 (7)	ns
Age	6 (11)	5 (14)	1 (3)	ns	5 (10)	1 (7)	ns
Gender	5 (9)	5 (14)	0 (0)	0.03	5 (10)	0 (0)	ns
Adjuvant chemotherapy	5 (9)	1 (3)	4 (13)	ns	3 (6)	2 (14)	ns
Disease status	3 (5)	0 (0)	3 (10)	ns	0 (0)	2 (14)	≤0.01
Location of primary tumor	3 (5)	1 (3)	2 (6)	ns	2 (4)	0 (0)	ns

ns not significant, *PS* performance status

[a] Excluded two global studies

[†] Statistical analyses were performed using the χ^2 test or Fisher's exact test, with the level of significance set at $P < 0.05$ (underlined)

Gender was more commonly used in older trials (14 vs. 0%). No significant difference of stratification factors was observed between Asian and non-Asian trials, other than the frequency of use of disease status (0 vs. 14%).

Discussion

To our knowledge, this represents the first study to review the reporting of patient characteristics in published

randomized trials for AGC. Our results showed considerable inconsistency in the reporting of patient characteristics and the use of stratification factors in clinical trials for AGC. A similar finding was reported by Sorbye et al. [16], who analyzed metastatic colorectal cancer (MCRC) clinical trials and advocated that an urgent need exists for an international consensus on the reporting of patient characteristics and stratification in MCRC trials. Our data also revealed several differences in patient characteristics between trials conducted before and after 2004, and between Asian and non-Asian trials. It is possible that these differences may have contributed to the observed heterogeneity in the survival outcomes of each trial.

Several prognostic factors have been identified for patients with AGC who have undergone chemotherapy [10–14]. As described in the "Introduction", the GASTRIC project confirmed the impact of ECOG PS, disease status, number of metastatic organs, location of metastasis, and prior surgery on the survival of AGC patients, as determined by individual patient data analysis of previous randomized studies [10]. Notably, this project, which may have included the largest AGC patient set to date, identified that PS1 and PS2 were significantly associated with poor survival, with hazard ratios (HRs) of death of 1.36 and 2.17, respectively [10]. In the GASTRIC analysis, although most trials included PS among the reported patient characteristics, a number of studies classified PS0 and PS1 separately, and several studies used KPS rather than the ECOG scale. In addition, local recurrence and metastatic disease were reported to be associated with worse outcomes than locally advanced disease [10]. In our present analysis, approximately 50% of trials reported disease extension (locally advanced or metastatic disease), and only 30% of trials indicated disease status (advanced or recurrent disease).

Although the GASTRIC analysis did not evaluate the importance of specific metastatic organs on outcomes, another large prognostic analysis, by Chau et al. [11, 12], reported the impact of liver and peritoneal metastasis on AGC patient survival. Affected metastatic organs were reported in 64% of the trials in our analysis, but the number of metastatic organs, which has significant impact on survival according to the GASTRIC analysis, was only reported with a frequency of 39%. Although histology was not identified as prognostic in the GASTRIC analysis, several recent trials suggest that an interaction exists between histology and drug response [6, 7, 17, 18]. For example, a subset analysis of the First-line Advanced Gastric Cancer Study (FLAGS) trial has indicated that the oral fluoropyrimidine S-1 appears to be superior to fluorouracil in the treatment of diffuse-type gastric cancer [6]. This finding is consistent with the results of a subset analysis of the Japan Clinical Oncology Group (JCOG) 9912 study that also indicated S-1 is better than fluorouracil in patients with diffuse-type AGC or gastric cancer associated with high dihydropyrimidine dehydrogenase (DPD) activity, which is more commonly associated with diffuse-type than intestinal-type tumors [17]. This result was not unexpected, because S-1 is a potent competitive inhibitor of DPD. In contrast to DPD, human epidermal growth factor receptor 2 (HER2)-positive AGC, for which the anti-HER2 agent trastuzumab is effective [7], is reported to be higher among intestinal-type tumors [18]. The prognostic factors and tumor characteristics identified in these studies should be reported in all clinical trials of AGC, as they are necessary to adequately interpret trial data and treatment outcomes.

Our analysis also revealed that the types of second-line chemotherapy and proportions of patients who received such treatment were not routinely reported in AGC trials. As several recent reports have suggested that second-line chemotherapy has a significant impact on OS [19–21], we propose that second-line therapies should be diligently reported in future clinical trials of first-line AGC treatment, because second-line chemotherapy might influence the OS as the primary endpoint, as suggested by our previous analysis [22].

Additionally, the numerous prognostic factors identified for AGC may be important for the stratification of patients with respect to risk and treatment arms in randomized trials. To adequately analyze treatment effects on clinical outcomes, efforts should be undertaken to maximally decrease imbalance of prognostic factors between treatment arms in a clinical trial [23]. Although there is no definite consensus on the optimal method for stratification, stratification is recommended for superiority trials with fewer than 400 patients [24] and for non-inferiority trials with any number of patients [25]. In our analysis, stratification was conducted in only 60% of the examined trials, and was performed with quite variable stratifying factors. Based only on the present analysis, it is difficult to suggest a standardization approach for stratification factors in AGC trials, and further analysis and discussion are necessary.

In recent years, a trend of increased median OS in AGC patients has been observed concurrent with the development of new chemotherapeutic agents [2, 4, 7, 26]. It is also possible that second-line chemotherapy may have contributed to the improvement in OS [19–21]; however, our crude comparison of trials conducted prior to and after 2004 also showed significant differences in PS and disease extension. These differences may have also contributed to the improved survival reported in more recent trials, as well as survival differences between Asian and non-Asian trials. The exact impact of chemotherapy and patient characteristics on survival would be best addressed in well-designed randomized studies and meta-analyses of individual patient data.

In conclusion, our analyses of published clinical trials for AGC revealed inconsistencies in the reporting of

patient characteristics and use of stratification factors. An international consensus on the reported characteristics and stratification in AGC trials is necessary to improve the analysis of future clinical trials.

Conflict of interest None.

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Chemotherapy for Patients With Advanced Gastric Cancer With Performance Status 2

Kohei Shitara, Kei Muro, Keitaro Matsuo, Takashi Ura, Daisuke Takahari, Tomoya Yokota, Akira Sawaki, Hiroki Kawai, Seiji Ito, Masaki Munakata, Yuh Sakata

ABSTRACT

Methods: We retrospectively analyzed 657 patients with advanced gastric cancer who received first-line chemotherapy. Baseline patient characteristics and treatment results were compared between Eastern Cooperative Oncology Group performance status (PS) 0–1 and PS 2 patients.

Results: Prior to beginning first-line chemotherapy, 513, 112, and 32 patients were PS 0–1, PS 2, and PS 3–4, respectively. Patients with massive ascites (42% vs. 3%; $P < .001$) or inability to eat (39% vs. 4%; $P < .001$) were more likely to be PS 2 than PS 0–1. Significantly fewer PS 2 patients received first-line chemotherapy regimens containing oral agents (40% vs. 77%; $P < .001$) or combination chemotherapy (19% vs. 40%; $P < .001$) compared to PS 0–1 patients. Median survival time was significantly shorter in PS 2 patients (5.8 vs. 13.9 months; $P < .001$). Multivariate survival analysis revealed that use of oral agents was associated with a better prognosis in PS 0–1 patients (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.59–0.97, $P = .03$), while it was associated with poorer survival in PS 2 patients (HR 1.52, 95% CI 1.0–2.3, $P = .046$).

Conclusion: Advanced gastric cancer patients with PS 2 not only had a poorer prognosis but also differed in several baseline characteristics compared to PS 0–1 patients. These results indicate that additional clinical trials that specifically target gastric cancer patients with PS 2 may be required to evaluate optimal treatment regimens for this patient population.

Gastrointest Cancer Res 3:220–224.

K. Shitara, MD; K. Muro, MD; T. Ura, MD; D. Takahari, MD; T. Yokota, MD:
Department of Clinical Oncology

K. Matsuo MD, PhD, MSc:
Division of Epidemiology and Prevention

A. Sawaki, MD; H. Kawai, MD:
Department of Gastroenterology

S. Ito, MD:
Department of Surgery
Aichi Cancer Center Hospital
Aichi, Japan

M. Munakata, MD; Y. Sakata, MD:
Department of Internal Medicine
Misawa City Hospital
Aomori, Japan

Submitted: April 28, 2009
Accepted: August 6, 2009

Performance status (PS) is an independent prognostic factor for survival in patients with advanced gastric cancer.[1,2] As a result of disease progression, patients with gastric cancer are subject to several debilitating complications, including anorexia, fatigue, and abdominal distension, that can lead to deterioration of general patient status. Overall, inclusion criteria for the majority of clinical trials have specified an Eastern Cooperative Oncology Group (ECOG) PS ≤ 2. According to multivariate survival analysis of three phase-III studies conducted between 1992 and 2001, PS 2 patients represented 22.8% of the patient population, and these patients experienced significantly poorer survival compared to patients with a more favorable PS.[2] However, because recent pivotal phase-III studies performed in Japan[3–5] and Western countries[6–8] included very few PS 2 patients (2% in three Japanese trials and 0%–10% in Western trials), standard treatment of PS 2 patients has not yet clearly been established. Furthermore, the characteristics of advanced gastric cancer patients with PS 2 have not yet been reported in detail.

To address this issue, we conducted a retrospective analysis comparing baseline characteristics and treatment results in advanced gastric cancer patients with PS 0–1 vs. PS 2.

PATIENTS AND METHODS

This study was a retrospective analysis of patients with advanced or recurrent gastric cancer who received chemotherapy. Principal inclusion criteria were the presence of histologically or cytologically proven, inoperable gastric cancer. Written informed consent was obtained from all patients prior to chemotherapy. Performance status was evaluated prior to initiation of first-line chemotherapy according to ECOG criteria.[9]

Between April 2001 and June 2008, 657 patients with gastric cancer underwent first-line chemotherapy at Aichi Cancer Center and Misawa City Hospital. Baseline characteristics and treatment results were compared between patients with PS 0–1 and PS 2. Patients with PS 3 or 4 were excluded from this analysis. The following baseline characteristics were assessed: age (<65 years or ≥65 years), gender, disease status (advanced or recurrent), previous gastrectomy (yes or no), previous adjuvant chemotherapy (yes or

Address correspondence to: Dr. Kohei Shitara, Department of Clinical Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Aichi, Japan. Phone: 81-52-762-6111; Fax: 81-52-752-8390; E-mail: Kouheis0824@yahoo.co.jp

no), pathologic classification (diffuse or intestinal), metastasis to peritoneum (yes or no), metastasis to liver (yes or no), presence of massive ascites (yes or no), number of metastatic sites (one or multiple), and inability to eat (yes or no).

"Multiple metastatic sites" was defined as the presence of metastases in more than one organ. "Massive ascites" was defined as the presence of ascites from the pelvic cavity to the liver surface or upper abdominal cavity, or ascites that required drainage. "Inability to eat" was defined as requirement for daily intravenous fluids or hyperalimentation. Chemotherapeutic regimens were selected individually by physicians or within the context of a clinical trial. Dosing and scheduling of most chemotherapy regimens were performed as reported in the literature.[3–5,10–15]

First-line chemotherapeutic regimens were directly compared, with particular attention focused on oral vs. infusional drugs and monotherapy vs. combination chemotherapy regimens. Toxicities grade ≥ 3, according to the National Cancer Institute Common Toxicity Criteria version 3.0, were also compared between PS 0–1 and PS 2 patients.

Statistical Methods

Overall survival (OS) was estimated starting from the date of initial chemotherapy to the date of death or last follow-up visit using the Kaplan-Meier method. Time-to-treatment failure (TTF) was measured from the date of treatment initiation to the last day of first-line treatment. OS and TTF in PS 0–1 and PS 2 patients were compared using the log-rank test. Distribution of baseline characteristics was assessed by chi-square test or Fisher exact test, as appropriate.

To evaluate the effect of types of treatment (oral vs. infusional; combination therapy vs. monotherapy) on OS in PS 0–1 vs. PS 2 patients, univariate and multivariate Cox proportional hazards modeling was applied. Therefore, a measure of association in this study was the hazard ratio (HR) along with the 95% confidence interval (95% CI). Forward and backward stepwise methods were used for model building. Threshold *P* values for inclusion or exclusion in the model were defined as .10 and .20, respectively. Statistical analyses were performed using STATA ver. 10 (StataCorp LP, College Station, TX, USA). All tests were two-sided, and *P* values less than .05 were considered statistically significant.

Table 1. Patient characteristics (PS 0–1 vs. PS 2)

Characteristics		PS 0–1 (n=513) n (%)	PS 2 (n=112) n (%)	*P* value
Median age (range)		63 (28–85)	64 (29–81)	.8
Gender	Male	353 (69)	63 (56)	.01
	Female	160 (31)	49 (44)	
Pathologic type	Intestinal	166 (32)	15 (13)	< .001
	Diffuse	347 (68)	97 (87)	
Disease status	Advanced	340 (66)	75 (67)	.9
	Recurrent	173 (34)	37 (33)	
Prior gastrectomy	Yes	283 (55)	42 (38)	< .001
	No	230 (45)	70 (62)	
Adjuvant chemotherapy	Yes	77 (15)	10 (9)	.08
	No	435 (85)	102 (91)	
Disease site	Peritoneum	240 (47)	83 (74)	< .001
	Ascites (massive)	17 (3)	47 (42)	< .001
	Liver	163 (32)	21 (19)	.02
	Multiple sites	228 (44)	72 (64)	< .001
Inability to eat	Yes	23 (4)	44 (39)	< .001

Table 2. First-line treatment in PS 0–1 vs. PS 2 patients

		PS 0–1 (n=513) n (%)	PS 2 (n=112) n (%)
First-line regimens	5-FU*–based†	277 (54)	66 (59)
	5-FU* + cisplatin	130 (25)	12 (12)
	5-FU* + taxane	22 (4)	5 (6)
	5-FU* + irinotecan	14 (3)	0 (0)
	Irinotecan ± cisplatin	33 (6)	2 (2)
	Taxane ± cisplatin	37 (7)	21 (20)
First-line agents	5-FU	444 (86)	83 (78)
	Cisplatin	171 (34)	17 (16)
	Taxane	59 (11)	26 (23)
	Irinotecan	47 (9)	2 (2)

* Including S-1 or capecitabine.
† Including 5-FU plus methotrexate.
Abbreviations: 5-FU = 5-fluorouracil

RESULTS

Patient Characteristics

Among the 657 patients, PS at initiation of first-line chemotherapy was as follows: PS 0, 172 patients (26.1%); PS 1, 341 patients (51.9%); PS 2, 112 patients (17.0%); and PS 3–4, 32 patients (4.9%). The characteristics of patients with PS 0–1 or PS 2 are shown in Table 1. A larger proportion of PS 2 patients had peritoneal dissemination, massive ascites, and/or multiple metastatic sites compared to PS 0–1 patients. A larger number of PS 2 patients suffered an "inability to eat" (39% vs. 4%; $P < .001$), primarily due to the presence of gastrointestinal stenosis/obstruction and/or massive ascites. In contrast, liver metastasis was less common in PS 2 patients than in PS 0–1 patients.

Treatment Results

Table 2 shows the results of first-line treatment in PS 0–1 and PS 2 patients. Significantly fewer PS 2 patients (n = 1, 0.9%) were registered in clinical trials compared

to PS 0–1 patients (n = 148, 29%; P < .001). Overall, first-line chemotherapy containing oral agents (S-1/capecitabine) was less frequently used in PS 2 patients (n = 45, 40%) than in PS 0–1 patients (n = 394, 77%; P < .001). Furthermore, fewer PS 2 patients received combination regimens as first-line chemotherapy (n = 22, 19%) than PS 0–1 patients (n = 210, 41%; P < .001).

With respect to chemotherapeutic agents, taxanes (paclitaxel or docetaxel) were more frequently used in PS 2 patients than in PS 0–1 patients. In contrast, cisplatin and irinotecan were less frequently given to PS 2 patients compared to PS 0–1 patients, with reduced doses used in most PS 2 patients. Median TTF for first-line chemotherapy was significantly shorter in PS 2 patients compared to PS 0–1 patients (2.4 months vs. 4.8 months; P < .001; Figure 1). Significantly fewer PS 2 patients received second-line chemotherapy (n = 56, 50%) compared to PS 0–1 patients (n = 400, 78%; P < .001). In addition, significantly fewer PS 2 patients received third-line chemotherapy (n = 16, 14%) compared to PS 0–1 patients (n = 210, 41%; P < .001).

Toxicity

Grade 3/4 hematologic toxicity was more frequently observed in PS 2 patients compared to PS 0–1 patients (Table 3). Febrile neutropenia also occurred significantly more frequently in PS 2 patients (6.3% vs. 1.2%). The incidence of chemotherapy-related grade 3/4 diarrhea and stomatitis did not significantly differ between PS 0–1 and PS 2 patients. Anorexia and nausea/vomiting were more frequently observed in PS 2 patients, though in some cases it was difficult to determine whether anorexia and nausea/vomiting were related to treatment, as the majority of PS 2 patients experienced these symptoms prior to chemotherapy. The frequency of treatment withdrawal due to toxicity or treatment-related death did not significantly differ between PS 0–1 and PS 2 patients (Table 3).

Survival

At a median follow-up time of 38 months, OS of PS 0–1 patients was 13.9 months (95% CI 12.7–15.3) and that of PS 2 patients was 5.8 months (range 4.7–6.9 months; HR for death 3.5, 95% CI 2.7–4.5, P < .001; Figure 2).

Use of Oral Agents and Combination Chemotherapy in PS 0–1 and PS 2 Patients

Table 4 shows the results of univariate and multivariate analyses comparing types of treatment (use of oral vs. infusional agents; combination therapy vs. monotherapy) and survival in PS 0–1 and PS 2 patients. In PS 0–1 patients, use of oral agents was significantly associated with better prognosis (HR 0.76, 95% CI 0.59–0.97, P = .03), while it was associated with poorer survival in PS 2 patients (HR 1.52, 95% CI 1.0–2.3, P = .046) after adjustment of other baseline characteristics. The interaction between PS and oral agents was statistically significant (P = .02). Combination chemotherapy tended to be associated with a better prognosis in PS 0–1 patients, though this difference was not statistically significant.

DISCUSSION

In this study, we retrospectively compared several baseline characteristics and treatment results of PS 0–1 and PS 2 patients with advanced gastric cancer who underwent chemotherapy. To our knowledge, this is the first report to show several differences between PS 0–1

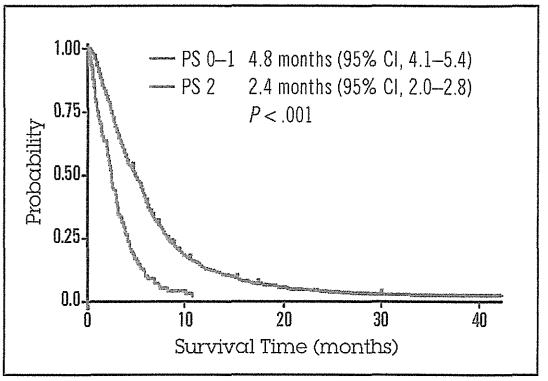

Figure 1. Kaplan-Meier survival curves of time to treatment failure (TTF). Median TTF for first-line chemotherapy was significantly shorter in PS 2 patients compared to PS 0–1 patients (2.4 months vs. 4.8 months; P < .001).

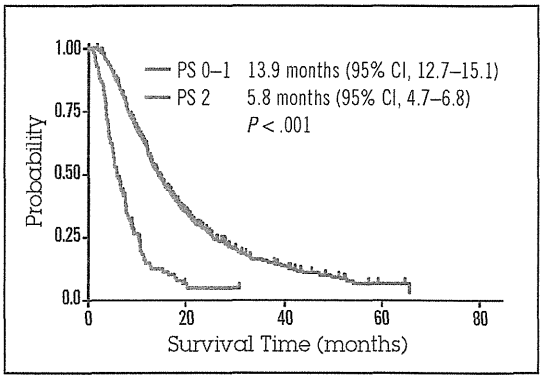

Figure 2. Kaplan-Meier survival curves of overall survival (OS). Median OS for first-line chemotherapy was significantly shorter in PS 2 patients compared to PS 0–1 patients (5.8 months vs. 13.9 months; P < .001).

Table 3. Toxicity during first-line treatment in PS 0–1 vs. PS 2 patients

Adverse event (≥ grade 3)	PS 0–1 (%) (n=513)	PS 2 (%) (n=112)	*P* value
Leukopenia	5.7	17.8	< .001
Neutropenia	14.3	26.7	< .001
Febrile neutropenia	1.2	6.3	< .001
Anemia	5.8	25.0	< .001
Thrombocytopenia	0.4	4.5	< .001
Increased transaminases	2.3	7.1	< .001
Increased creatinine	0.4	1.8	NS
Anorexia	9.4	17.8	< .001
Nausea/vomiting	5.6	11.6	.02
Diarrhea	3.9	4.5	NS
Stomatitis	2.1	4.5	NS
Treatment withdrawal due to toxicity	5.6	6.3	NS
Treatment-related death	1.0	1.8	NS

Abbreviations: NS = not significant

Table 4. Use of oral agents and combination chemotherapy in PS 0–1 vs. PS 2 patients

		Univariate analysis			Multivariate analysis		
Treatment		HR	95% CI	*P* value	HR	95% CI	*P* value
PS 0–1	Oral agents: Yes (n=394) vs. No (n=119)	0.75	0.59–0.94	.014	0.76	0.59–0.97	.03
(n=513)	Combination CTx: Yes (n=210) vs. No (n=303)	1	0.82–1.2	.92	0.85	0.70–1.07	.19
PS 2	Oral agents: Yes (n=45) vs. No (n=67)	1.51	0.99–2.2	.051	1.52	1.0–2.3	.046
(n=112)	Combination CTx: Yes (n=22) vs. No (n=90)	0.97	0.60–1.5	.91	1	0.62–1.7	.94

*Adjusted by age, gender, pathologic type, disease status, prior gastrectomy, adjuvant chemotherapy, peritoneal metastasis, liver metastasis, massive ascites, multiple metastatic sites, and inability to eat. *P* for interaction between PS and oral agents = .02.
Abbreviations: HR = hazard ratio; 95% CI = 95% confidence interval; CTx = chemotherapy

and PS 2 patients with gastric cancer in Japan. Our results demonstrate that PS 2 patients not only have a poorer prognosis compared with PS 0–1 patients but they also differ in several baseline characteristics.

Although the cause and type of PS deterioration may differ between individual advanced gastric cancer patients, the results of our study clearly showed that patients with a poor PS more frequently suffered inability to eat and massive ascites. These complications may specifically reflect the characteristics of Japanese gastric cancer patients, among whom pathologically diffuse-type disease and peritoneal metastasis are more common than in gastric cancer patients in Western countries.[2,6,7] As a result of these complications, administration of oral agents is difficult in many PS 2 patients and is therefore less commonly used. Recent clinical trials[3–5] have frequently excluded patients with inability to eat or massive ascites due to the increasing use of oral agents such as S-1 and capecitabine; this may explain the relatively low entry rate of PS 2 patients into clinical trials conducted at our institutions.

Additionally, our multivariate survival analysis revealed that use of oral agents was associated with poorer prognosis only in PS 2 patients (HR 0.76), while it is associated with better survival in PS 0–1 patients (HR 1.52). Although the cause of unfavorable results with oral agents in PS 2 patients is not known, it may be due in part to decreased absorption or motility in the gastrointestinal tract in patients with gastrointestinal stenosis or massive ascites, which is frequently observed in PS 2 patients in this analysis. Recent combined analysis of phase-III studies (REAL-2 and ML17032) showed that capecitabine tended to be associated with better survival than infusional 5-fluorouracil (5-FU) in PS 2 patients.[16] However, less than 20% of patients had peritoneal metastasis,[16,17] which is quite different from patients in this analysis (peritoneal carcinomatosis, 74%; massive ascites, 42%). Jeung et al reported the feasibility of S-1 monotherapy in patients with advanced gastric cancer with a poor PS.[18] However, their study also included a relatively small proportion of patients with peritoneal carcinomatosis (29%). It would seem, therefore, that a study that specifically targets patients with peritoneal metastases might be warranted.

The results of a phase-III study in Japan, which compared 5-FU vs. methotrexate plus 5-FU in patients with advanced gastric cancer with peritoneal metastasis, were recently reported (JCOG0106).[19] However few PS 2 patients (3.3%) were included in this study, because patients with massive ascites or gastrointestinal obstruction were excluded; thus, data in PS 2 patients are limited. Therefore, additional studies may be required to identify optimal regimens in PS 2 gastric cancer patients.

Since the chemotherapeutic regimens used for PS 2 patients in this analysis varied considerably, the optimal regimen for this patient population remains unclear. The incidence of treatment discontinuation due to toxicity or treatment-related death did not differ significantly between PS 0–1 and PS 2 patients, which indicates that systemic chemotherapy could be feasible and indeed warranted in PS 2 patients. Hematologic toxicity such as neutropenia, however, was significantly more common in PS 2 patients, despite a low rate of combination chemotherapy administration, suggesting that caution should be used when giving combination chemotherapy to PS 2 patients. Since current clinical trials frequently use combination chemotherapy regimens, including those containing standard doses of platinum agents, it might be necessary to exclude PS 2 patients from future trials that employ more toxic combination chemotherapy regimens.

Our study has several limitations. First, PS is not an absolute criterion for evaluating the general status of gastric cancer patients. However, no alternative criteria for classifying general status are currently available. Second, comorbidities and age were not considered. Both comorbidities and advanced age can contribute to PS deterioration and should be considered as a matter of course in the clinical decision-making process. We should develop more comprehensive criteria—including general status, nutrition status, age, and comorbidity—to make better informed decisions in the best interest of our patients. However, it should be noted that none of the patients in our analysis had poor PS due only to age or comorbidity.

In conclusion, advanced gastric cancer patients with PS 2 not only had a poorer prognosis but also differed in several baseline characteristics, including frequency of ascites and eating status, compared to PS 0–1 patients. These results suggest that clinical trials that specifically target gastric cancer patients with PS 2 may be required to evaluate optimal chemotherapeutic regimens for this patient population.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Prognostic Factors for Metastatic Colorectal Cancer Patients Undergoing Irinotecan-Based Second-Line Chemotherapy

Kohei Shitara,[1] Keitaro Matsuo,[2] Tomoya Yokota,[1] Daisuke Takahari,[1] Takashi Shibata,[1] Takashi Ura,[1] Yoshitaka Inaba,[3] Hidekazu Yamaura,[3] Yozo Sato,[3] Mina Najima,[3] Kei Muro[1]

[1] *Department of Clinical Oncology*

[3] *Department of Diagnostic and Interventional Radiology*
Aichi Cancer Center Hospital
Aichi, Japan

[2] *Division of Epidemiology and Prevention*
Aichi Cancer Center Research Institute
Aichi, Japan

ABSTRACT

Background: No reports about factors that predict prognosis after second-line chemotherapy for metastatic colorectal cancer have been published.

Methods: We retrospectively analyzed 124 patients with metastatic colorectal cancer who received irinotecan-based second-line chemotherapy after first-line folinic acid/5-fluorouracil (5-FU)/oxaliplatin (FOLFOX) with or without bevacizumab.

Results: A multivariate Cox model revealed 5 prognostic factors for worse survival: ECOG performance status 2, pathologically poorly differentiated adenocarcinoma, peritoneal metastasis, progression-free survival of first-line FOLFOX < 6 months, and lactate dehydrogenase ≥ 400 IU/L. When patients were categorized into 3 risk groups—patients without any prognostic factors (low-risk, n = 55), patients with one prognostic factor (intermediate-risk, n = 32), and patients with 2 or more prognostic factors (high-risk, n = 37)—overall survival from initiation of second-line chemotherapy was 23.5, 14.6, and 5.5 months, respectively. The proportion of patients who were eligible to receive further chemotherapy after disease progression was significantly lower in the high-risk group (41%) than in the intermediate- (67%) and low-risk (95%) groups.

Conclusion: Several prognostic factors for survival after second-line therapy and probability of receiving third-line chemotherapy were identified. This risk classification system might be useful for determining which patients should receive cetuximab in the second-line setting rather than the third-line setting.

Gastrointest Cancer Res 4:168–172.

Submitted: September 18, 2009
Accepted: January 10, 2010

Folinic acid/5-fluorouracil (5-FU)/oxaliplatin (FOLFOX) plus bevacizumab is the most widely used first-line chemotherapy regimen for metastatic colorectal cancer (MCRC).[1,2] After failure of FOLFOX, FOLFIRI [folinic acid/ (5-FU)/irinotecan] or irinotecan monotherapy is usually administered in the second-line setting.[3,4] The results of a large observational study have also suggested that continued use of bevacizumab during second-line therapy may provide additional benefit.[1]

Cetuximab, a recombinant, human-mouse chimeric monoclonal IgG1 antibody that specifically targets epidermal growth factor receptor (EGFR) has been shown to improve the prognosis of MCRC significantly compared to best supportive care alone in the third-line setting.[5] Furthermore, combining cetuximab with irinotecan results in a higher response rate than cetuximab alone, even in patients with irinotecan-refractory disease, suggesting that cetuximab may restore chemosensitivity in these patients.[6]

The EPIC trial was a large phase III study that compared irinotecan plus cetuximab to irinotecan monotherapy as second-line treatment in patients with MCRC following failure of oxaliplatin-based therapy.[7] Although the primary end point of improved survival was not achieved (10.7 vs 10.0 months, $p = .71$), patients in the combination arm experienced a superior response rate and progression-free survival (PFS). Approximately half of the patients in the irinotecan monotherapy arm received cetuximab after irinotecan failure, which may have contributed to the similar overall survival rates in the 2 arms. However, 35% of patients in the irinotecan group were unable to receive any third-line chemotherapy, most likely due to rapid tumor progression.[7] Thus, it was suggested that cetuximab with irinotecan may be better than irinotecan as second-line therapy for patients with rapidly progressing disease. So far, no reports about factors that predict the prognosis after second-line irinotecan or

Address correspondence to: Kohei Shitara, MD, Department of Clinical Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Aichi, Japan. Phone: 81-52-762-611; E-mail: Kouheis0824@yahoo.co.jp

probability of receiving third-line therapy have been published. To address this issue, we conducted the following retrospective analysis of MCRC patients who received irinotecan-based chemotherapy as second-line treatment after first-line FOLFOX.

PATIENTS AND METHODS

This was a retrospective cohort study of MCRC patients who received irinotecan-based chemotherapy as second-line treatment after first-line FOLFOX. Irinotecan-based chemotherapy consisted of FOLFIRI (2-hr infusion of leucovorin isomers at 200 mg/m^2 followed by bolus 5-FU 400 mg/m^2 plus a 46-hr infusion of 5-FU 2,400 mg/m^2 every 2 weeks, with irinotecan 150 mg/m^2 as a 1.5-hr infusion on day 1) with or without bevacizumab (5 mg/m^2 every 2 weeks), irinotecan monotherapy (irinotecan 150 mg/m^2 every 2 weeks), or S-1 plus irinotecan (S-1 40 mg/m^2 twice daily for 14 consecutive days followed by a 2-week rest, with irinotecan 100 mg/m^2 every 2 weeks). Individual regimens were selected at the discretion the physicians or as called for in clinical trials.

Principal inclusion criteria were presence of histologically proven, inoperable colorectal cancer, age < 80 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, sufficient bone marrow function, and normal liver and renal function. Treatment failure (defined as disease progression/discontinuation due to toxicity) within 6 months of the last dose of first-line fluoropyrimidine and oxaliplatin treatment for metastatic disease was required. Prior bevacizumab was allowed. These criteria were very similar to those of the EPIC study. Written informed consent was obtained from all patients prior to chemotherapy.

Among patients with MCRC treated at our institution between October 2005 and December 2008, 124 patients who fulfilled the inclusion criteria were identified. Detailed patient characteristics prior to initiation of second-line chemotherapy were acquired from hospital patient records. Objective tumor response of first-line FOLFOX was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST).[8] PFS associated with first-line FOLFOX was measured from the beginning of treatment to the date of progression.

Statistical Methods

The primary end point of this study was evaluation of the association between several prognostic factors and overall survival, which was defined as the interval between the date of initiation of second-line treatment and the date of death or last follow-up using the Kaplan-Meier method. Progression-free survival was also measured from the beginning of second-line treatment to the date of disease progression.

To evaluate the prognostic factors associated with overall survival, univariate and multivariate Cox proportional hazards modeling was applied. The hazard ratio (HR) along with the 95% confidence interval (95% CI) was used as a measure of association in this study. Forward and backward stepwise methods were used for model building. Threshold p values for inclusion or exclusion in the model were defined as .10 and .20, respectively.

Factors included in the uni- and multivariate analyses were age (< 65 vs ≥ 65 years), gender (male vs female), ECOG PS (0–1 vs 2), peritoneal metastasis (yes vs no), liver metastasis (yes vs no), number of metastatic sites (1–2 vs ≥ 3), pathologic type (moderately or well-differentiated adenocarcinoma vs poorly differentiated adenocarcinoma), serum alkaline phosphatase (ALP) level (< 400 vs ≥ 400 IU/L), serum lactate dehydrogenase (LDH) level (< 400 vs ≥ 400 IU/L), serum carcinoembryonic antigen (CEA) level (< 500 vs ≥ 500 ng/mL), leukocyte count (< 8.0 × 10^9/L vs ≥ 8.0 × 10^9/L), response to first-line FOLFOX (responder vs nonresponder), and PFS associated with first-line FOLFOX (< 6 months vs ≥ 6 months). "Responders" were defined as patients who achieved a complete response or partial response, while "nonresponders" were patients with stable disease or progressive disease.

Distribution of subject characteristics was assessed by the chi-square test or the Fisher exact test, as appropriate. Statistical analyses were performed using STATA ver. 10 (StataCorp LP, College Station, TX). All tests were 2-sided, and p values < .05 were considered to be statistically significant.

RESULTS

Detailed patient characteristics are shown in Table 1. All 124 patients experienced disease progression prior to second-line chemotherapy. Oxaliplatin was discontinued due to neuropathy or allergy prior to disease progression in 59 patients; most of these patients continued 5-FU/leucovorin with or without bevacizumab until disease progression. First-line FOLFOX resulted in a partial response in 54 patients (43.5%), stable disease in 47 patients (37.9%), and progressive disease in 23 patients (18.5%). Median PFS associated with first-line FOLFOX was 7.3 months (95% CI, 6.2–8.0).

Second-line chemotherapy was administered as follows: FOLFIRI, 71 patients; irinotecan, 39 patients; and S-1 plus irinotecan, 14 patients. Bevacizumab was also used in 21 patients. The median treatment duration of second-line chemotherapy was 3.8 months (95% CI, 3–4.8).

At the time of analysis, 74 (59.6%) patients had died, with a median follow-up of 24.1 months since initiation of second-line chemotherapy. Median overall survival for all patients was 14.6 months (95% CI, 10.8–18.8). Median PFS was 3.8 months (95% CI, 2.9–5.2).

Salvage Chemotherapy

Among the 124 patients, 115 patients experienced disease progression despite second-line irinotecan-based chemotherapy; 82 of these patients (71%) received salvage chemotherapy as follows: anti-EGFR antibody (including cetuximab and panitumumab; n = 33), mitomycin-C plus irinotecan (n = 11), FOLFOX reintroduction with bevacizumab (n = 15), hepatic arterial infusion chemotherapy mainly using 5-FU (n = 10), and other regimens (n = 13). *KRAS* status was evaluated in 40 patients; 25 of these patients were determined to have cancers with a wild-type *KRAS* genotype.

Survival Analyses and Probability of Receiving Salvage Chemotherapy

Tables 2 and 3 show the results of univariate and multivariate analyses of baseline and clinical characteristics as prognostic factors for survival, including objective response and PFS associated with first-line FOLFOX. According to a multivariate Cox model, 5 prognostic factors for worse survival were identified: PS 2, pathologically poorly differentiated adenocarcinoma, peritoneal metastasis, PFS associated with first-line FOLFOX < 6 months, and LDH ≥ 400 IU/L.