between the studies in terms of study size, patient selection, tumour sampling, use of archival versus fresh/frozen material, or laboratory methods and data analyses. More importantly, few studies have differentiated *KRAS* mutations at codon 12 from those at codon 13 with respect to clinicopathological features and survival (Bazan *et al*, 2002). Our analysis revealed that mutation at *KRAS12* had no effect on patient OS. In contrast, our Kaplan–Meier curves clearly demonstrated that OS for patients with *KRAS13* mutations were significantly worse than for those who had wt *KRAS* and *BRAF*. It has been reported that stage III patients with *KRAS* mutations displayed significantly worse disease-free survival, as compared with those with wt *KRAS* (Fariña-Sarasqueta *et al*, 2010). This finding may be partially explained by the impact of *KRAS13* mutations on prognosis. As both univariate and multivariate analysis failed to confirm *KRAS13* mutation as an independent prognostic factor, the prognostic value of mutations at *KRAS13* remains unclear in advanced and recurrent CRC. In non-small-cell lung cancer there are differences in transforming potential and EGFR tyrosine kinase inhibitor sensitivity associated with EGFR somatic mutations L858R and deletion mutant Del (746-750) (Carey *et al*, 2006). Therefore, it remains a possibility that the different *KRAS* mutations at codons 12 and 13 may have different biological consequences that could influence the prognosis for CRC.

With respect to technical issue on *KRAS* and *BRAF* genotyping, we evaluated the prognostic value of the mutations frequently found in *KRAS* and *BRAF* using specific PCR probes. In contrast, direct sequencing is able to detect all possible *KRAS* and *BRAF* mutations including some more rare mutations. In fact, it is reported that *KRAS* codon 146 mutation, which was identified by direct sequencing, was associated with resistance to cetuximab plus irinotecan therapy although this is a minor oncogenic *KRAS* mutation (Loupakis *et al*, 2009). Therefore, direct sequencing may be able to obtain further insights into predictive and prognostic impact of these mutations.

Our study found that the median OS of patients with wt *BRAF* was generally longer than that observed in other reports. It could be argued that the selection of patients with good prognosis could bias the results in this study. Indeed, more than half of our study population was screened for *KRAS/BRAF* genotype to determine the use of anti-EGFR antibody, and 42% of the patients were treated with cetuximab combined therapy mostly as a second- or third-line chemotherapy. Although treatment selection may be a major reason for the longer survival observed in the present study as compared with previous studies involving metastatic CRC patients, univariate analysis revealed no significant differences in survival between patients with and without anti-EGFR therapy (38.8 months *vs* 32.6 months, $P=0.277$) (Table 3). Furthermore, almost all recurrent and advanced CRC patients are routinely screened for *KRAS/BRAF* genotype at the initiation of the first line chemotherapy in our institution since the use of cetuximab was approved for the treatment of CRC patients in Japan.

Another key point of discussion is the potential treatment bias in this retrospective analysis. The focus of the present study is the patient group with advanced and recurrent CRC who received systemic chemotherapy. However, we need to take the difference in the specific treatment regimen among four genotypes into consideration. In particular, 63.7% (86 out of 135) of wt *KRAS* and *BRAF* patients have received anti-EGFR therapy whereas 33.3% (6 out of 15) and 2.5% (2 out of 79) of patients with *BRAF* and *KRAS12/13* mutations have received anti-EGFR therapy, respectively. Therefore, the prognostic advantage of wt *KRAS* and *BRAF* patients over *BRAF* or *KRAS13* mutation might be partially explained by the presence of anti-EGFR therapy. Nevertheless, it is noteworthy that the prognosis of wt *KRAS* and *BRAF* patients was similar to that of the patients with *KRAS12* mutation despite the frequent use of anti-EGFR therapy.

In conclusion, our retrospective analysis demonstrated that *BRAF* mutation was an independent prognostic factor in advanced and recurrent CRC. Although the presence of *KRAS12* mutation had no apparent effect on OS in advanced and recurrent disease, the prognostic value of *KRAS13* mutation remains uncertain. Our results are useful not only for predicting the efficacy of anti-EGFR therapy, but also for identifying patients with shorter OS in response to systemic chemotherapy, regardless of the use of anti-EGFR therapy. The exact effects of *KRAS12* and *KRAS13* mutations on survival require further study. The application of novel strategies targeting *BRAF* kinase is warranted for the treatment of CRC patients with *BRAF* mutation.

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ORIGINAL ARTICLE

Meta-analysis of neutropenia or leukopenia as a prognostic factor in patients with malignant disease undergoing chemotherapy

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Abstract
Purpose We performed a systematic review and meta-analysis to determine the impact of neutropenia or leukopenia experienced during chemotherapy on survival.
Methods Eligible studies included prospective or retrospective analyses that evaluated neutropenia or leukopenia as a prognostic factor for overall survival or disease-free survival. Statistical analyses were conducted to calculate a summary hazard ratio and 95% confidence interval (CI) using random-effects or fixed-effects models based on the heterogeneity of the included studies.
Results Thirteen trials were selected for the meta-analysis, with a total of 9,528 patients. The hazard ratio of death was 0.69 (95% CI, 0.64–0.75) for patients with higher-grade neutropenia or leukopenia compared to patients with lower-grade or lack of cytopenia. Our analysis was also stratified by statistical method (any statistical method to decrease lead-time bias; time-varying analysis or landmark analysis), but no differences were observed.
Conclusions Our results indicate that neutropenia or leukopenia experienced during chemotherapy is associated with improved survival in patients with advanced cancer or hematological malignancies undergoing chemotherapy. Future prospective analyses designed to investigate the potential impact of chemotherapy dose adjustment coupled with monitoring of neutropenia or leukopenia on survival are warranted.

Keywords Chemotherapy · Neutropenia · Leukopenia · Prognostic factor · Meta-analysis

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Introduction

Neutropenia or leukopenia induced by cytotoxic chemotherapy is a common adverse event in patients with cancer. In general, the recommended doses of cytotoxic agents are determined in dose-finding phase I studies. However, sample sizes in phase I studies are not large enough to examine individual differences in drug metabolism; therefore, toxicity profiles are likely to be highly variable [1]. In other words, the determined standard dose may be conservatively low for some patients with faster drug elimination times [1]. In support of this hypothesis, toxicities such as neutropenia or leukopenia experienced during chemotherapy have been reported to be associated with favorable clinical outcomes in several cancer types. Recently, we analyzed the neutropenia that occurs during first-line FOLFOX (infusional 5-fluorouracil/leucovorin and oxaliplatin) chemotherapy in patients with advanced colorectal cancer [2] or during second-line chemotherapy with weekly paclitaxel in patients with advanced gastric cancer [3], using time-varying covariate (TVC) analysis. Since several studies, including ours, have primarily been retrospective analyses that lacked a statistically testable hypothesis, we conducted the present meta-analysis to evaluate the prognostic impact of neutropenia or leukopenia on patients with advanced cancer undergoing chemotherapy with a statistical power much higher than that of each individual trial.

Patients and methods

Selection of studies

This study was performed to assess whether neutropenia or leukopenia has an important effect upon survival in patients with cancer undergoing chemotherapy. A systematic review and meta-analysis of published articles were performed. Two authors (KS and KM) conducted a literature search for trials through computer-based searches of the Medline database (January 1966 and May 20, 2010) and of abstracts from conference proceedings of the American Society of Clinical Oncology (1995–2010) and European Society for Medical Oncology (1995–2009).

Search keywords included "neutropenia", "leukopenia", "prognostic", and "chemotherapy". The search was also guided by a thorough examination of reference lists of original and review articles. No limitation based on language was defined. We included abstracts or unpublished data if sufficient information on study design, characteristics of participants, interventions, and outcomes was available.

Procedures

Two investigators (KS and KM) abstracted data, according to Quality of Reporting of Meta-analyses (QUORUM) guidelines. Each study was assessed for quality and potential bias using a structured checklist based on the Method for Evaluating Research and Guideline Evidence criteria [4]. Studies that met the following criteria were analyzed: patients with malignant disease treated with chemotherapy; prospective and retrospective analyses in randomized study or cohort study that evaluated neutropenia or leukopenia as a prognostic factor; and attainment of hazard ratio (HR) with 95% confidence interval (CI). Adverse events were assessed and recorded according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC; version 2 or 3), which have been adopted widely in cancer clinical trials, in as many cases as possible. For each study, the following information was extracted: first author's name; year of publication; study design (prospective or retrospective); number of enrolled patients; underlying malignant disease; median age; treatment regimen(s); methods of analysis, including specific analysis to decrease lead-time bias (i.e., landmark analysis or TVC analysis); methods of comparison (i.e., grade 0 vs. grade 1–4, grade 0–2 vs. grade 3–4, or mild vs. moderate); and HR and 95% CI for clinical outcome (overall survival or disease-free survival).

Statistical methods

For each study, a HR (and 95% CI) was derived according to neutropenia or leukopenia. If HRs according to both univariate and multivariate analysis were reported, HR in multivariate analysis was used in this analysis. To estimate a summary HR for death for patients with neutropenia or leukopenia, patients with lower-grade (grade 0, grade 0–2, or lowest tertile) versus higher-grade neutropenia or leukopenia were compared, since the cut-off values used to divide neutropenia or leukopenia into low versus high grades differed between studies. Some trials used tertiles without using NCI-CTC grades. For meta-analyses, both the fixed-effects model (weighted with inverse variance) and the random-effects model were used. Statistical heterogeneity among studies with the Q statistic was assessed, and inconsistency was quantified with the I^2 statistic. The assumption of heterogeneity was judged as invalid if $P < 0.1$. To investigate possible reasons for heterogeneity, subgroup analyses were performed by disease type or specific methods such as landmark analysis or TVC analysis, and meta-regression analyses were performed to test for variation in risk estimates by those variables. A cumulative meta-analysis was also performed. Publication bias was assessed by a funnel plot. Statistical analyses were performed using STATA ver. 10 (StataCorp LP, College Station, TX, USA). All tests were 2-sided, and P values less than 0.05 were considered statistically significant.

Results

Selection of studies

A total of 753 potentially relevant reports were identified, of which 688 were initially excluded (Fig. 1). After a review of the remaining publications, 13 trials with sufficient data were identified for this meta-analysis, with a total of 9,528 patients [2, 3, 5–15]. Table 1 shows the baseline characteristics of patients from each trial. Malignant diseases included non-small cell lung cancer in three reports, breast cancer in three reports, gastric cancer in two reports, and colorectal cancer, uterine cervical cancer, ovarian cancer, esophageal cancer, and Hodgkin's lymphoma in one report each. Seven studies enrolled chemo-naive patients, one included pretreated patients, two evaluated chemotherapy in the adjuvant setting, and two assessed chemoradiotherapy for locally advanced disease. All studies used multivariate analysis to calculate HRs, and pretreatment neutrophil counts or leukocyte counts were included in five studies. Five studies used specific analysis methodology (landmark analysis in two and TVC analysis in three). Ten studies evaluated neutropenia, and three evaluated leukopenia. Six studies compared prognosis of patients without neutropenia or leukopenia to that of patients that experienced these cytopenias. Four studies compared patients

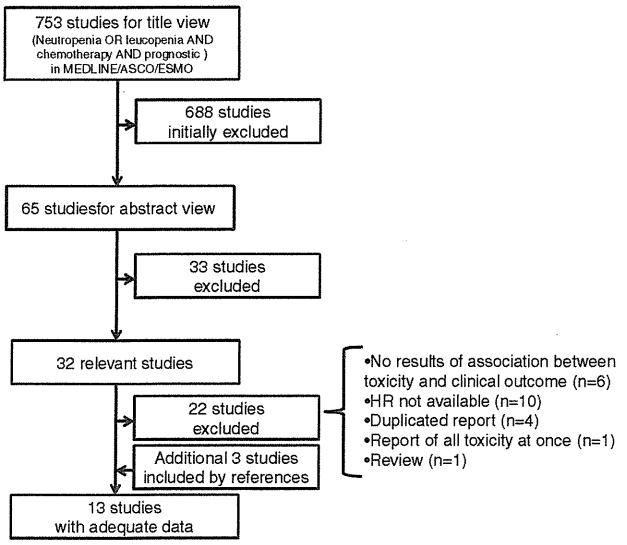

Fig. 1 Selection process for studies

with grade 0–2 versus grade 3–4 neutropenia. Two studies divided patients by tertile.

Survival analyses for neutropenia and leukopenia

The results of the meta-analysis revealed a combined estimate HR of 0.69 (95% CI, 0.64–0.75) (random-effects model) and 0.70 (95% CI, 0.65–0.75) (fixed-effects model). No apparent evidence for heterogeneity between these studies was detected ($P = 0.124$). A forest plot (Fig. 2) of the random-effects model analysis showed that eleven studies provided relatively similar HRs favoring higher-grade neutropenia or leukopenia, whereas the Kim et al. [11] and Miyoshi et al. [13] studies did not. The present analysis was also stratified by underlying disease (solid tumor in metastatic setting or solid tumor in adjuvant setting or hematologic malignancy; $P = 0.52$, Fig. 3), variable (neutropenia or leukopenia; $P = 0.55$), statistical method (landmark analysis or TVC analysis vs. without these methods; $P = 0.39$), and quality of report (low vs. high; $P = 0.46$); however, no differences were observed. Funnel plots showed that the possibility of bias is low (Fig. 4).

Discussion

We conducted the first meta-analysis to answer the question of whether patients with a higher grade of neutropenia or leukopenia during chemotherapy experienced superior survival compared to patients with lower-grade neutropenia or leukopenia. We found an approximately 30% risk reduction in mortality for patients with higher-grade cytopenias. Patients cannot be randomized to experience cytopenia or not, and so the only practical method of assessing the effect is by observational studies. These have a higher risk of bias than randomized trials, and so their results must be interpreted with caution, but well-conducted meta-analysis may reduce this risk. A lack of an obvious source of heterogeneity may support the consistency of our findings across heterogeneous methods of analysis, sites of malignancy, and clinical settings.

Based on our observation that patients who experience higher-grade neutropenia or leukopenia during chemotherapy have a better prognosis, we speculate that neutropenia, an indication of bone marrow suppression caused by a particular dose of a chemotherapeutic agent, may also be a surrogate marker that indicates that the same dose is adequate to provide an antitumor effect. Thus, lack of neutropenia or leukopenia may indicate a weak or absent biological effect by chemotherapy, which could possibly be caused by underdosing in an individual patient. Such underdosing may at least partly be the consequence of the methodology of phase I clinical trials in which the maximum tolerated dose (MTD) is selected according to body surface area (BSA) [7, 16]. Several studies have indicated that the pharmacokinetics of several cytotoxic drugs is poorly correlated with BSA due to inter-patient variability in metabolism (e.g., variability in enzymatic activity, genetic polymorphisms) [17–19]. If this inter-patient variability in pharmacokinetics is indeed a cause of underdosing, dose adjustment (increased or reduced) based on observed toxicity may be a possible solution. For example, dose increases of the epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab in the absence of skin toxicity have been shown to result in an improved objective response in patients with colorectal cancer [20].

Several other possible explanations in addition to chemotherapy dose may support the present findings. The first is the potential relationship between pretreatment neutrophil or leukocyte count and vulnerability to cytopenia during chemotherapy. Several reports have indicated that patients with high neutrophil or leukocyte counts prior to treatment might have a poor prognosis and be less likely to experience cytopenia during treatment [16, 21, 22]. However, our previous two studies [2, 3] and three other studies [8, 9, 12] included pretreatment neutrophil counts or leukocyte counts as adjusted factors, and these studies demonstrated that neutropenia or leukopenia experienced during chemotherapy was independently associated with prognosis. Therefore, this explanation is less likely to account for the findings of this meta-analysis.

Another possible explanation is that the association between cytopenia and prognosis is the result of bias introduced by the different analytical methods used in different studies. Since neutropenia does not exist prior to the initiation of chemotherapy, a false association between neutropenia and patient outcome might have been observed due to a

Table 1 Baseline characteristics of patients of the 13 included trials

Primary author	Year	Study type	Analysis	Disease	*n*	Setting	Treatment	Variable	Endpoint
Saarto [5]	1997	Prospective	MA	Breast	193	Adjuvant	AC, 5-FU	Leukopenia	DFS
Poikonen [6]	1999	Retrospective	MA	Breast	368	Adjuvant	CMF	Leukopenia	DFS
Di Maio [7]	2005	Prospective	MA with landmark[b]	NSCLC	1,265	Metastatic (1st-line)	GEM or VNR combinations	Neutropenia	OS
Klimm [8]	2005	Prospective	MA[a]	Hodgkin's lymphoma	4,626	1st-line	COPP/ABVD, BEACOPP ± RT	Leukopenia	FFTF
Yamanaka [9]	2007	Retrospective	MA[a] with TVC	Gastric	1,055	Metastatic (1st-line)	S-1	Neutropenia	OS
Pallis [10]	2008	Prospective	MA	NSCLC	858	Metastatic (1st-line)	GEM + DOC	Neutropenia	OS
Kim [11]	2009	Retrospective	MA	Cervical	107	Adjuvant	PTX + CBDCA + RT	Neutropenia	DFS
Kishida [12]	2009	Prospective	MA[a] with landmark	NSCLC	337	Metastatic (1st-line)	VNR + GEM followed by DOC vs. PTX + CBDCA	Neutropenia	OS
Miyoshi [13]	2009	Retrospective	MA	Esophageal	42	Preoperative	FP/FAP + RT	Leukopenia	OS
Shitara [2]	2009	Retrospective	MA[a] with TVC	Colorectal	153	Metastatic (1st-line)	FOLFOX ± BV	Neutropenia	OS
Kim [14]	2010	Retrospective	MA	Ovarian	179	Metastatic (1st-line)	PTX + CBDCA	Neutropenia	OS
Ishitobi [15]	2010	Retrospective	MA	Breast	103	Neoadjuvant	Epirubicin combination	Neutropenia	DFS
Shitara [3]	2010	Retrospective	MA[a] with TVC[c]	Gastric	242	Metastatic (2nd-line)	Weekly PTX	Neutropenia	OS

MA multivariate analysis, *TVC* time-varying covariate analysis, *NSCLC* non-small cell lung cancer, *AC* doxorubicin + cyclophosphamide, *5-FU* 5-fluorouracil, *CMF* cyclophosphamide + methotrexate + 5-fluorouracil, *C-MOPP* cyclophosphamide + vincristine + procarbazine + prednisone, *ABVD* adriamycin + bleomycin + vinblastine + dacarbazine, *BEACOPP* bleomycin + etoposide + doxorubicin + cyclophosphamide + vincristine + procarbazine + prednisolone, *RT* radiotherapy, *VNR* vinorelbine, *GEM* gemcitabine, *DOC* docetaxel, *PTX* paclitaxel, *CBDCA* carboplatin, *DFS* disease-free survival, *OS* overall survival, *FFTF* freedom from treatment failure

[a] Pretreatment neutrophil counts or leukocyte counts were included

[b] Landmark analysis in 436 patients and out of landmark analysis in 829 patients

[c] TVC with landmark analysis in 202 patients

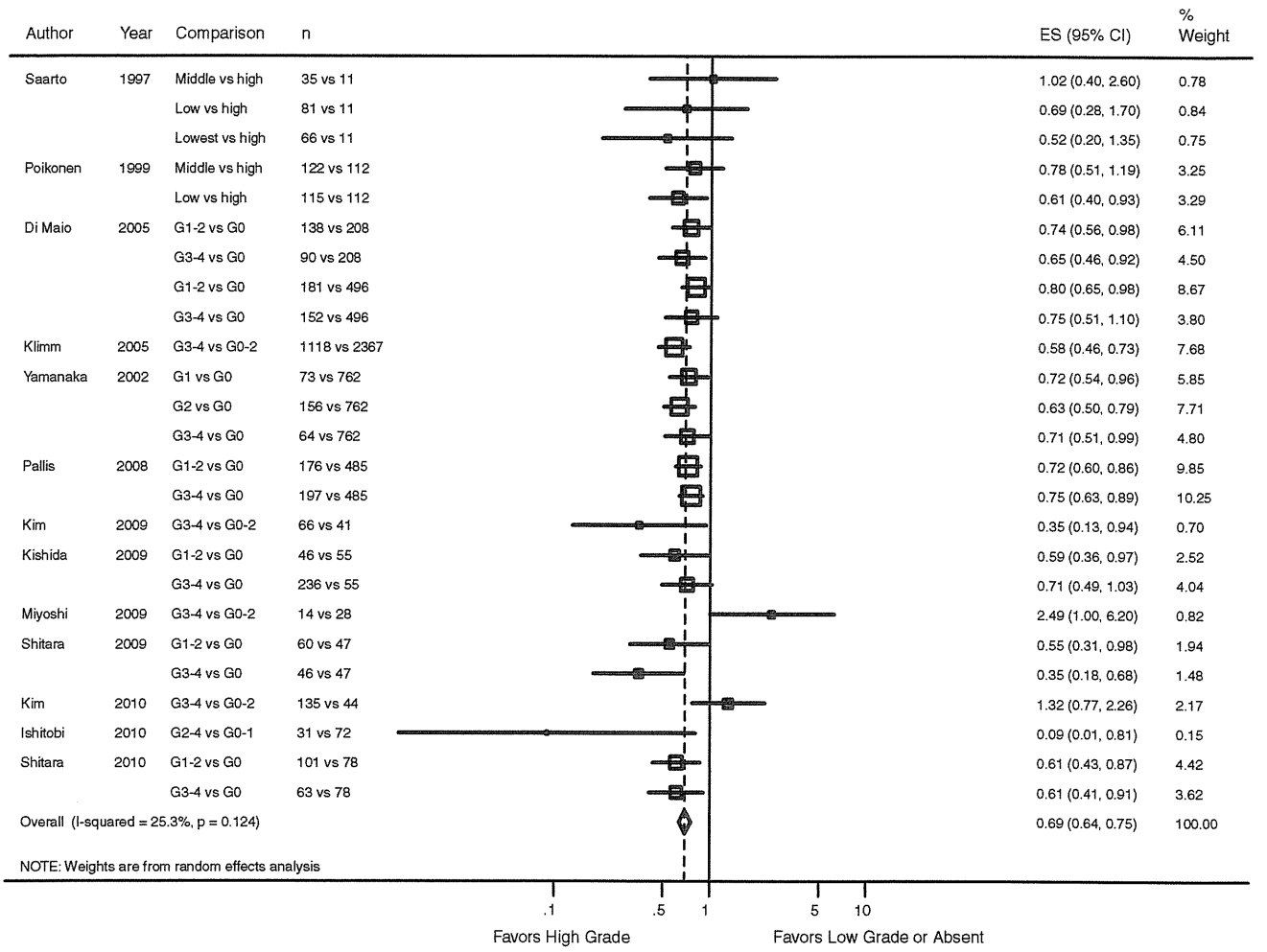

Fig. 2 Forest plots of hazard ratios. The size of the *gray markers* (*squares*) corresponds to the weight of the study in the meta-analysis. Combined hazard ratio was calculated using the random-effects model

higher incidence of neutropenia with increasing cycles of chemotherapy in patients with a better prognosis (lead-time bias). Therefore, some studies, including our previous studies, used landmark analysis and/or TVC analysis to decrease lead-time bias as much as possible. However, the present meta-analysis revealed the limited impact of survival analysis methods as shown by lack of significant heterogeneity. In our two previous studies in colorectal cancer [2] and gastric cancer [3], the majority of patients with neutropenia experienced their highest grade within 4 weeks of initiating treatment, and those who did not experience neutropenia during the first 4 weeks rarely experienced severe late-onset neutropenia. These observations support the possibility that false-positive association by lead-time bias is low and indicate that the impact of landmark analysis and/or TVC analysis is not high, as shown in this meta-analysis. The impact of neutropenia was shown in this study despite the treatment bias by severe neutropenia, which might reduce the effect of treatment by dose reduction or delay. Although the use of G-CSF was not evaluated in detail in each study, the possibility that G-CSF itself prolonged the survival of patients with neutropenia might be low.

This study has several methodological issues. Although the sample size was considered to be sufficient, the disease types and study settings were variable. Therefore, it is difficult to completely rule out potential heterogeneity across disease types. Second, the evaluation of neutropenia or leukopenia was performed differently in different studies; however, a lack of obvious heterogeneity among the results of different studies suggests this had little, if any, impact. Third, although most studies calculated HR using multivariate analysis, the variables used in multivariate analysis could have been insufficient. Fourth, although the funnel plot of our study suggested publication bias was low, there might be we did comprehensive literature search, the studies that failed to show an association between lack of neutropenia and outcome are less likely to have been published; therefore, this might have led to an exaggeration

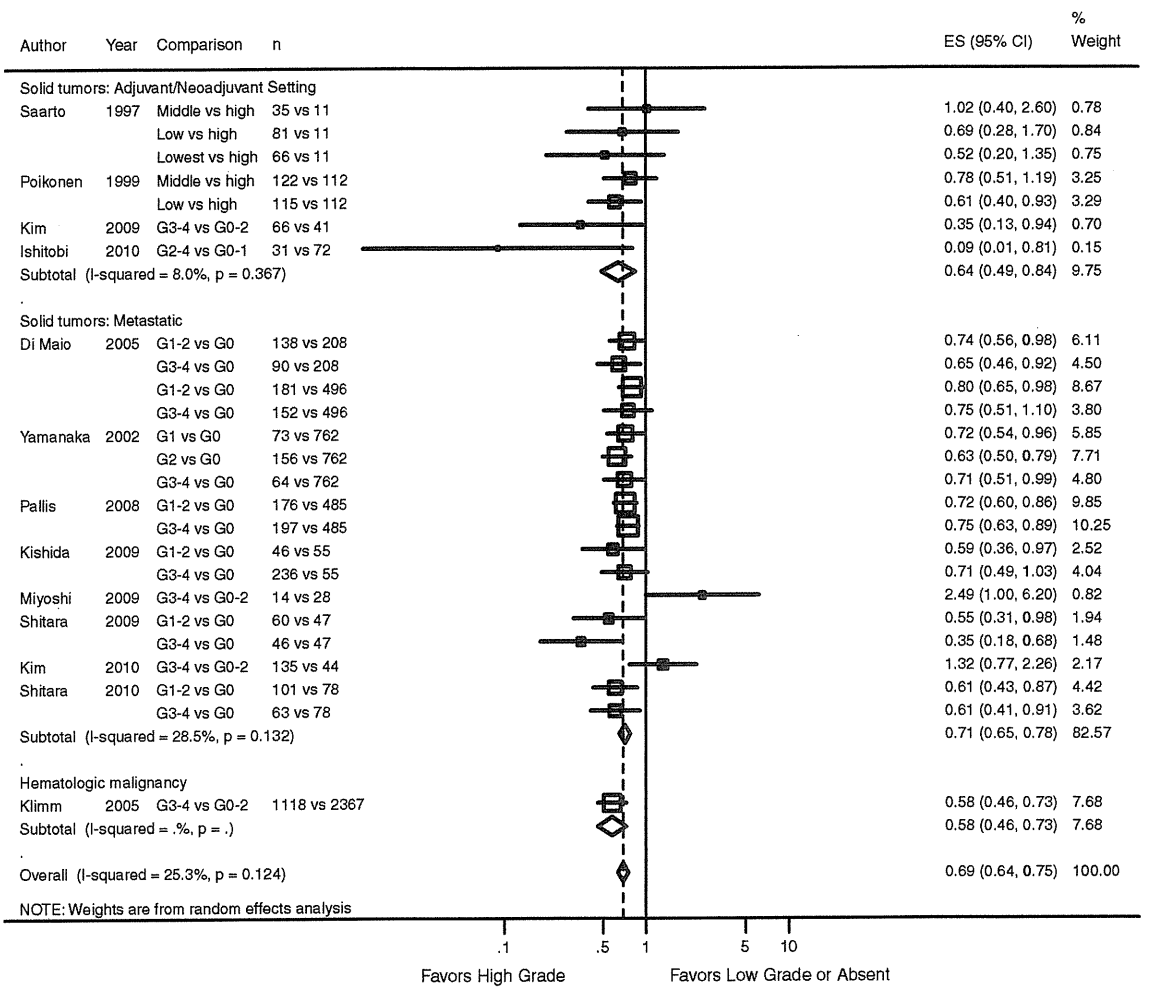

Fig. 3 Subset-analysis according to disease type

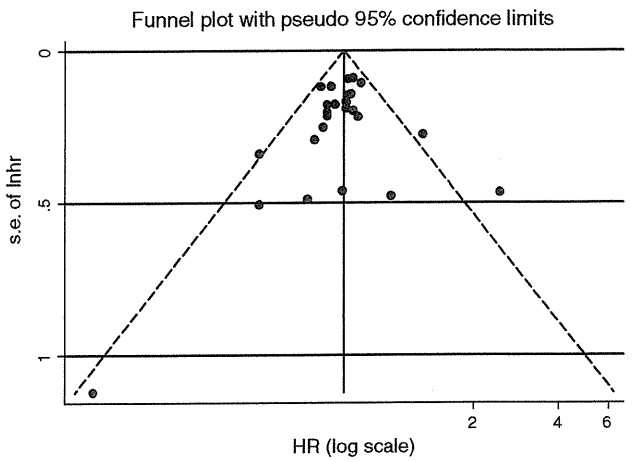

Fig. 4 Funnel plot of included studies

of the purported benefit in this meta-analysis. Ideally, an individual data-based meta-analysis might clarify this issue. Further study is warranted.

In conclusion, this meta-analysis indicated that neutropenia or leukopenia occurring during chemotherapy in patients with solid tumors or hematological malignancies is strongly associated with better prognosis. This suggests that neutropenia or leukopenia could be utilized as a surrogate marker to determine adequate antitumor doses of chemotherapeutic agents. An additional well-defined prospective trial designed to evaluate dose escalation in patients without neutropenia or leukopenia during the early course of treatment is warranted. We are currently planning a dose-escalation study of weekly paclitaxel in patients with advanced gastric cancer based on incidence of neutropenia.

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

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ORIGINAL ARTICLE

Fluoropyrimidine plus cisplatin for patients with advanced or recurrent gastric cancer with peritoneal metastasis

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Abstract
Background There are few data on the efficacy of combination chemotherapy with a fluoropyrimidine plus cisplatin for patients with advanced or recurrent gastric cancer (AGC) complicated by peritoneal metastasis, especially massive ascites.
Methods We retrospectively evaluated the efficacy and safety of a fluoropyrimidine (S-1 or capecitabine) plus cisplatin as first-line chemotherapy in 120 patients with AGC and peritoneal metastasis.
Results Ascites was detected in 50 patients, with 11 patients having massive ascites. Median progression-free survival (PFS) and overall survival (OS) of all patients was 6.1 and 15.9 months, respectively. The PFS and OS were shorter in patients with massive ascites ($n = 11$; 3.7 and 9.5 months) compared with patients with small or moderate ascites ($n = 39$; 5.8 and 13.5 months) or patients without ascites ($n = 70$; 6.9 and 18.1 months). The objective response in terms of ascites was similar whether ascites was massive (4 of 11 patients; 36.4%) or small or moderate (16 of 39 patients; 41%). The frequencies of grade 3 or higher toxicity or treatment discontinuation due to toxicity are relatively similar across ascites groups.
Conclusions Fluoropyrimidine plus cisplatin appears to be tolerated in selected patients with peritoneal metastasis.

Keywords Chemotherapy · Cisplatin · Fluoropyrimidine · Gastric cancer · Peritoneal metastasis

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Introduction

Gastric cancer is the fourth most common malignancy in the world (988,602 cases in 2008, 7.8% of all malignancies) and the second leading cause of cancer death (737,419 deaths, 9.7% of all cancer deaths) [1]. The prognosis for patients with advanced or recurrent gastric cancer (AGC) remains poor; chemotherapy confers only a minimal survival advantage, with a median overall survival (OS) of approximately 1 year. In a pivotal phase III trial (SPIRITS trial) in Japan that compared S-1 alone with S-1 plus cisplatin (combination = SP), patients treated with SP showed a significantly higher response rate (54 vs. 31%), longer progression-free survival (PFS; 6.0 vs. 4.0 months), and longer OS (13 vs. 11 months) than patients receiving S-1 alone [2]. Therefore, SP is now considered to be one of the standard regimens for AGC in Japan. Capecitabine, another oral fluoropyrimidine, when combined with cisplatin (combination = XP), is also reported to have an effectiveness that is statistically indistinguishable from that of 5-fluorouracil (5-FU) plus cisplatin (ML17032 trial [3]), which was used as a reference regimen in recent global studies, including those in Japan [4, 5]. Thus, the most commonly used treatments for AGC are combination

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chemotherapy regimens consisting of a fluoropyrimidine (5-FU or an oral fluoropyrimidine) plus a platinum agent, although docetaxel or anthracyclines are sometimes combined in Western countries [6, 7].

Peritoneal metastasis, a common type of metastasis in AGC, causes several complications such as ascites, bowel obstruction, and hydronephrosis—all leading to a deterioration of the patient's general condition. Several reports have suggested that the presence of peritoneal metastasis or ascites is associated with poor survival in patients with AGC [8–11]. To improve the prognosis for patients with AGC and peritoneal metastasis, several clinical trials have been conducted [12–18]. However, there are few data on the efficacy of a fluoropyrimidine plus cisplatin for peritoneal metastasis as the current standard treatment for patients with AGC. Moreover, since patients with massive ascites have usually been excluded in previous pivotal randomized studies, the efficacy and feasibility in this patient population is also unclear. Therefore, we retrospectively evaluated the efficacy and safety of a fluoropyrimidine plus cisplatin regimen in patients with AGC and peritoneal metastasis.

Patients and methods

Patients

This retrospective study was designed to evaluate the efficacy and safety of first-line chemotherapy with a fluoropyrimidine plus cisplatin (SP and XP) in patients with AGC from January 2005 to March 2011. Since capecitabine was not available in Japan until February 2011, most patients had been treated by SP, although we included patients who had been treated with XP in the context of two global studies [3, 4]. Patients who had received XP plus experimental agents (i.e., trastuzumab or bevacizumab) were excluded from our analysis.

Eligibility criteria were as follows: (1) presence of histologically proven, inoperable AGC; (2) Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; (3) sufficient oral intake to take oral agents; (4) adequate bone marrow, hepatic, and renal function; (5) diagnosis of peritoneal metastasis, which could be confirmed either by macroscopic evaluation (upon laparotomy or laparoscopy) with cytology or by imaging data [computed tomography (CT) scan or barium enema] with relevant signs such as ascites, hydronephrosis, and intestinal stenosis; (6) no previous chemotherapy other than adjuvant chemotherapy, which was required to have been finished more than 6 months before enrollment. Written informed consent for chemotherapy was obtained from each patient prior to treatment initiation.

Treatment plan

Patients were treated with either: (1) a standard regimen of SP [S-1 (80 mg/m^2) for 21 consecutive days followed by a 14-day rest; cisplatin (60 mg/m^2) intravenous infusion on day 8] with repetition of the 35-day cycle [2]; or (2) XP [capecitabine (1,000 mg/m^2) for 14 days followed by a 7-day rest; cisplatin (80 mg/m^2) intravenous infusion on day 1] with repetition of the 21-day cycle [4, 5]. Intravenous hydration (1,500 mL) was performed on the day of cisplatin administration and on the next 2 days. Dose modification and scheduling of the two regimens were performed as reported in the literature [2, 4, 5]. Patients could continue with the fluoropyrimidine alone if they experienced severe toxicity with cisplatin. Treatment was discontinued if the tumor progressed, severe toxicity occurred, or at the patient's request.

Evaluation of treatment and statistical analysis

In patients with measurable lesions, the tumor response was assessed objectively according to the guidelines of the Response Evaluation Criteria In Solid Tumors (RECIST, ver. 1.0), and the best overall response was recorded as the antitumor effect for that patient. The objective response rate in these patients was presented as the percentage of patients with a complete response (CR) or partial response (PR). According to the Japanese Classification of Gastric Carcinoma [19], the amount of ascites was assessed by a radiologist using CT. Response rate for ascites represented the percentage of patients with complete disappearance (CR) or a dramatic decrease in ascites (PR). Time to treatment failure (TTF) was measured from the date of initiation of chemotherapy to the date of the last administration of fluoropyrimidine or cisplatin. The PFS was measured from the date of chemotherapy to the date of progressive disease or death from any cause. The OS was estimated from the date of initiation of chemotherapy to the date of death or last follow-up visit. Median PFS and median OS were estimated by the Kaplan–Meier method. Toxicities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Our primary interest was in comparing the clinical outcomes among patient groups that had different amounts of ascites. The amount of ascites was defined as follows: small (limited to pelvic cavity or around liver); moderate (not small or massive); or massive (continuous ascites from surface of liver to pelvic cavity). This definition of massive ascites was the same as that used in the JCOG 0106 study [13]. The volume of ascites was also estimated by the five-point method, as previously reported [16, 20]. We divided patients into the following three groups: (1) patients

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

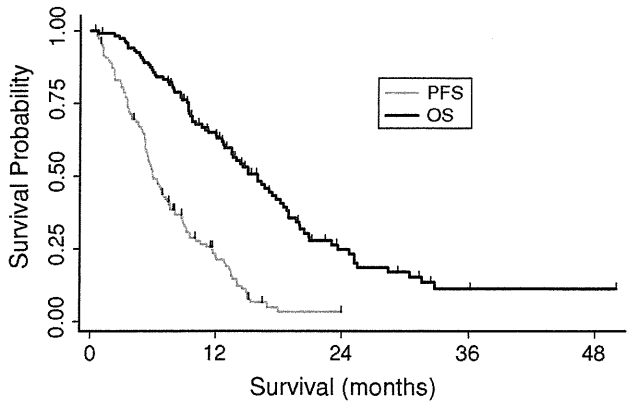

Fig. 1 Progression-free survival and overall survival. Median PFS was 6.1 months (95% CI, 5.3–7.3 months), and median OS was 15.9 months (95% CI, 12.8–18.4 months)

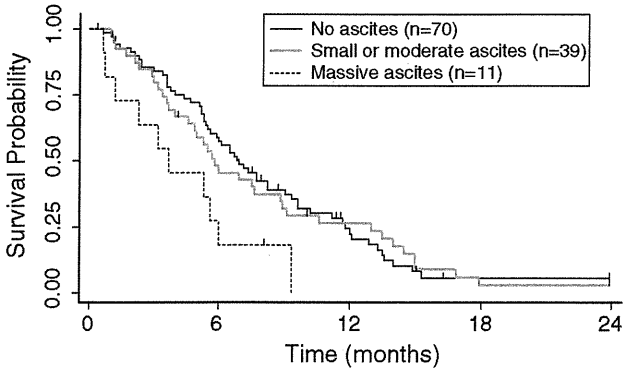

Fig. 2 Progression-free survival by ascites group. Median PFS was shorter in patients with massive ascites (3.7 months; 95% CI, 0.7–6.0 months) than in patients with small or moderate ascites (5.8 months; 95% CI, 4.0–8.8 months; HR 0.45; 95% CI, 0.22–0.93; $P = 0.03$) or patients without ascites (6.9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

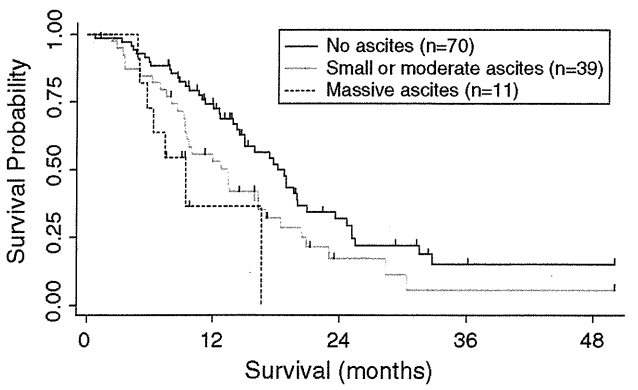

Fig. 3 Overall survival according to ascites group. Median OS was shorter in patients with massive ascites (9.5 months; 95% CI, 0.5–not reached) than in patients with small or moderate ascites (13.5 months; 95% CI, 9.4–17.0 months; HR 0.49; 95% CI, 0.21–1.15; $P = 0.1$) or patients without ascites (18.1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

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

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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

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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

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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.

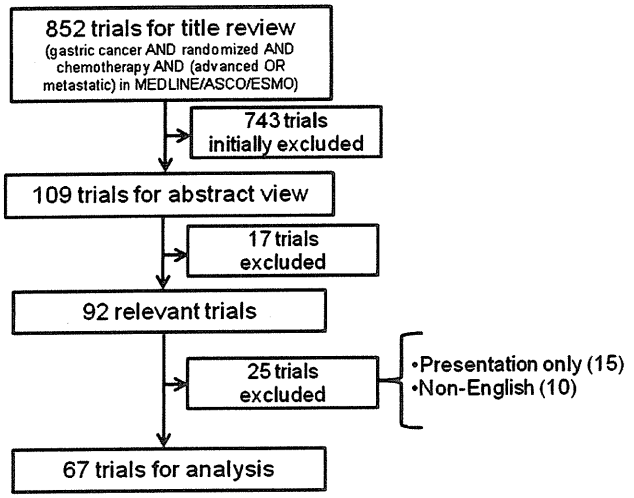

Fig. 1 Selection process for trials. An initial literature search for randomized clinical trials of advanced gastric cancer (AGC) identified a total of 852 potentially relevant reports, of which 743 were excluded on examination of titles. After review of the abstracts of the remaining studies, 67 randomized 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