analysis [16] have demonstrated the efficacy of each of these agent classes as first-line chemotherapy, to our knowledge this is the first study to simultaneously evaluate exposure to each agent class in all lines of treatment. Based on the present results, we speculate that it is important to make these active agents available to all patients with AGC to prolong OS.

Because there was no exposure to any of these four classes of agents prior to the initiation of chemotherapy, a false association between exposure to each agent class and patient outcome, due to the tendency of more lines of chemotherapy and more agents to result in a better prognosis (lead-time bias) might have been expected, as shown in our results (6.5 months with one agent vs. 20.4 months with four agents). To address our a priori hypothesis, we therefore used Cox proportional hazards models to remove confounding factors and we used exposure to each agent as TVCs. This is one of the strengths of this study. In contrast to the four agent classes above, agents classified as "other" did not affect survival. This result also supports the assumption that the level of false-positive associations due to lead-time bias is low.

These results suggest the importance of making these active agents available to all patients with AGC. A similar strategy is warranted for metastatic colorectal cancer, for which exposure to three effective cytotoxic agents (5-FU, oxaliplatin, and irinotecan) has been shown to prolong survival [17]. The low proportion of patients eligible to receive third-line therapy (37.5%) in the present study suggests the importance of using effective agents in first- and second-line treatments. Although an early report of triplet combination chemotherapy for AGC showed a high frequency of toxicity [2], a more recent study of a modified regimen demonstrated more acceptable toxicity [18]. Future evaluation to determine optimal treatment strategies in patients with AGC is therefore warranted.

It is important to note the methodological strengths and limitations of the present study. First, while admittedly this was a retrospective cohort study, the conduct of a prospective study would have been hampered by the difficulty in gathering detailed information about all courses of treatment or disease progression with each line of chemotherapy, given that most studies to date have been conducted primarily to evaluate the efficacy of a single agent or regimen in a single treatment line. In contrast, the present study was designed to comprehensively evaluate the impact of each agent class regardless of treatment line, using TVC analysis, which is one of its strengths. On the other hand, TVC analysis was not necessarily perfect in the setting of our study, because this method may be valid under a strong assumption of an association between treatment selection at the time of events and the history up to the events [19]. Second, potential confounders such as PS, histological type, and metastatic site were considered in the multivariate analyses; therefore, although any associations observed were theoretically independent of confounders, the effect of residual confounding by factors not evaluated cannot be completely ruled out. Third, although current standard treatment for AGC is FU plus a platinum agent, fewer than half of the patients in the present analysis received such first-line combination chemotherapy, because FU monotherapy (5-FU or S-1) was the standard chemotherapy regimen during the earlier part of this study (prior to publication of the results of the SPIRITS trial [4]). However, we included the first-line chemotherapy regimen as a confounder in the multivariate analysis. Additionally, when we limited our analysis to patients who received FU plus a platinum agent as first-line chemotherapy, the impact of taxanes and irinotecan on survival in this cohort was similar to that in the overall patient population (data not shown). Finally, because the treatment regimens used in each line of therapy were quite variable due to the retrospective nature of this analysis, a variety of different treatment indications may also have been used by individual physicians, which may have affected the results. With regard to the strengths of this study, these include its relatively large sample size and the availability of detailed clinical information.

In conclusion, our findings indicate that each of the four agent classes (FU, platinum agents, taxanes, and irinotecan) evaluated in the present study is independently associated with improved OS in patients with AGC. This finding may indicate the importance of strategies to make all of these active agents available to all patients with AGC to prolong OS.

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

References

1. International Agency for Research on Cancer GLOBOCAN 2008. http://www-dep.iarc.fr/CancerMondial.htm.
2. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24:4991–7.
3. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36–46.
4. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9:215–21.
5. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol. 2009;20:666–73.

6. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/s-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28:1547–53.
7. NCCN Clinical Practice Guidelines in Oncology (2010) Gastric Cancer. NCCN practice guidelines in oncology, version 2.
8. Takiuchi H, Fukuda H, Boku N, Shimada Y, Nasu J, Hamamoto Y, et al. Randomized phase II study of best-available 5-fluorouracil (5-FU) versus weekly paclitaxel in gastric cancer (GC) with peritoneal metastasis (PM) refractory to 5-FU-containing regimens (JCOG0407). J Clin Oncol. 2010;28:18s. (suppl; LBA4513).
9. Takashima A, Boku N, Kato K, Mizusawa J, Nakamura K, Fukuda H, et al. Survival prolongation after treatment failure in patients with advanced gastric cancer (AGC): results from combined analysis of JCOG9205 and JCOG9912. J Clin Oncol. 2010;28:15s. (suppl; abstr 4061).
10. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, et al. Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10:1063–9.
11. Chin K, Iishi H, Imamura H, Kobayashi O, Imamoto H, Esaki T, et al. Irinotecan plus S-1 (IRIS) versus S-1 alone as first line treatment for advanced gastric cancer: preliminary results of a randomized phase III study (GC0301/TOP-002). J Clin Oncol. 2007;25:18 s. (suppl; abstr 4525).
12. Dank M, Zaluski J, Barone C, Valvere V, Yalcin S, Peschel C, et al. Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol. 2008;19:1450–7.
13. Thuss-Patience PC, Kretzschmar A, Deist T, Hinke A, Bichev D, Lebedinzew B, et al. Irinotecan versus best supportive care (BSC) as second-line therapy in gastric cancer: a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). J Clin Oncol. 2009;27:15 s. (suppl; abstr 4540).
14. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, et al. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol. 2003;21:54–9.
15. Shirao K, Boku N, Yamada Y, Yamaguchi K, Doi T, Takiuchi H, et al. Randomized phase III study of 5-fluorouracil continuous infusion (5FUci) versus methotrexate and 5-FU sequential therapy (MF) in gastric cancer with peritoneal metastasis (JCOG0106). J Clin Oncol. 2009;27:15 s. (suppl; abstr 4545).
16. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006;24:2903–9.
17. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol. 2004;22:1209–14.
18. Kelsen D, Jhawer M, Ilson D, Tse A, Randazzo J, Robinson E, et al. Analysis of survival with modified docetaxel, cisplatin, fluorouracil (mDCF), and bevacizumab (BEV) in patients with metastatic gastroesophageal (GE) adenocarcinoma: results of a phase II clinical trial (2009). J Clin Oncol. 2009;27:15s. (suppl; abstr 4512).
19. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the joint effect of non-randomized treatments. J Am Stat Assoc. 2001;96:440–8.

Invest New Drugs
DOI 10.1007/s10637-011-9648-y

PHASE III STUDIES

Progression-free survival and time to progression as surrogate markers of overall survival in patients with advanced gastric cancer: analysis of 36 randomized trials

Kohei Shitara · Junko Ikeda · Tomoya Yokota · Daisuke Takahari · Takashi Ura · Kei Muro · Keitaro Matsuo

Received: 5 January 2011 / Accepted: 14 February 2011
© Springer Science+Business Media, LLC 2011

Summary Progression-free survival (PFS) and time to progression (TTP) have been reported to correlate with overall survival (OS) in several types of cancers. To our knowledge, however, their use in the evaluation of new agents for AGC has not been investigated. We evaluated the potential of PFS and TTP to act as surrogates of OS in clinical trial settings. Randomized trials of systemic chemotherapy for advanced gastric cancer were identified by comprehensive electronic and manual search. Correlations between PFS/TTP and OS were evaluated. Thirty-six trials with a total of 83 treatment arms and 10,484 patients were selected for analysis. The nonparametric Spearman rank correlation coefficient (ρ) between median PFS/TTP and OS was 0.70 (95% CI, 0.59 to 0.82) and the correlation coefficient between hazard ratios in PFS/TTP and OS was 0.80 (95% CI, 0.68 to 0.92). Correlation tended to be higher in trials reporting PFS (ρ=0.85; 0.72–0.97) than in those reporting TTP (ρ=0.60; 0.24–0.97), trials in Non-Asian countries (ρ=0.80; 0.61–0.99) than Asia (ρ=0.67; 0.39–0.94), trials in patients with measurable lesions only (ρ=0.91; 0.77–1.00) than in those including non-measurable lesions (ρ=0.71; 0.50–0.93), albeit that none of these differences was significant. Our results indicate that improvements in PFS/TTP in advanced gastric cancer strongly correlate with improvements in OS. Further research is needed to clarify the surrogacy of PFS/TTP for OS or the role of PFS as the true end point in future randomized clinical trials of chemotherapy for AGC.

Keywords Chemotherapy · Gastric cancer · Surrogate endpoint · Progression-free survival · Time to progression

K. Shitara (✉) · J. Ikeda · T. Yokota · D. Takahari · T. Ura · K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, 1–1 Kanokoden, Chikusa-ku, Nagoya 464–8681 Aichi, 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]. The most effective treatment for localized disease is surgery, but approximately half of all patients with advanced-stage disease develop recurrence after curative resection. The prognosis of patients with advanced or recurrent gastric cancer (AGC) remains poor, with median survival times for commonly used combination chemotherapy regimens, consisting of a fluoropyrimidine plus a platinum agent with or without docetaxel or anthracyclines, of only 1 year [2–7]. Trastuzumab, a humanized monoclonal antibody that targets epidermal growth factor receptor 2 (HER2), has recently been shown to improve the prognosis of HER2-positive AGC[7], but these cases account for fewer than 20% of all AGCs. The development of novel anticancer agents for the treatment for AGC is thus urgently required.

The most important issue in the development of new agents for AGC is their ability to prolong survival with acceptable toxicity. This is conventionally evaluated in phase III trials, in which the primary endpoint is usually overall survival (OS). For practical reasons, however, the

Published online: 25 February 2011

use of OS as a primary endpoint may be problematic. In particular, several recent reports have suggested the efficacy of second-line chemotherapy for AGC [8–10], which would potentially lead to underestimation of the effect of new first-line treatment [11].The potential for other clinical endpoints to replace OS as the primary endpoint in randomized trials is therefore of interest: a validated shorter term surrogate endpoint would likely both reduce drug development costs and facilitate the assessment of efficacy.

Progression-free survival (PFS) and time to progression (TTP) have been evaluated as surrogate endpoint of OS in several types of cancers [12–16], and are considered acceptable surrogate endpoints for colorectal cancer and breast cancer [17]. To our knowledge, however, their use in the evaluation of new agents for AGC has not been investigated.

Here, we conducted a comprehensive analysis to determine whether PFS and TTP are correlated with OS in AGC, and whether improvements in PFS and TTP are associated with improvements in OS.

Materials and methods

Search for studies

We conducted a literature search for trials through computer-based searches of the Medline database (January 1966 and June 2010) and of abstracts from conference proceedings of the American Society of Clinical Oncology (1995–2010) and European Cancer Conference and European Society for Medical Oncology (1995–2009). To avoid publication bias, both published and unpublished trials were identified. Search keywords included: "gastric cancer," "randomized" "advanced or metastatic," 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 the data in accordance with the Quality of Reporting of Meta-analyses (QUORUM) guidelines [18]. Randomized trials of systemic chemotherapy for patients with histologically confirmed advanced or recurrent gastric cancer (metastatic disease or unresectable locally advanced disease) of the stomach or gastroesophageal junction were included in the analysis. Trials which compared chemotherapy with best supportive care were also included, as were those which included patients with adenocarcinoma of the distal esophagus. Eligibility was limited to trials which reported data on OS with either or both PFS and TTP.

Exclusion criteria included trials designed to assess combined modality treatments, including radiotherapy and surgery (neoadjuvant or adjuvant chemotherapy); those in which patients were pretreated with chemotherapy; and, to evaluate the risk reduction with chemotherapy for PFS/TTP or OS, those which did not report either hazard ratios (HRs) or Kaplan-Meier survival curves.

For each trial, the following information was extracted: first author's name; year of publication or report; trial design (randomized phase II or phase III); trial area; number of enrolled patients; and treatment regimens. The following was also extracted if reported: HR and 95% CI for clinical outcome (PFS/TTP and OS); proportion of patients with metastatic disease; proportion of patients with measurable lesions; and proportion of patients who received post-protocol chemotherapy.

All data were checked for internal consistency. Disagreements were resolved by discussions among the investigators. The reference arm in each trial was determined by consensus among three investigators (KS, DT, and TY) if not indicated; all other arms were considered investigational. For trials with more than two treatment arms, we constructed multiple pairs of each investigational arm and the reference arm.

Statistical methods

For each trial, median PFS, TTP, OS, and HR with 95% confidence intervals (CI) were abstracted. If the HR was not provided, we estimated HR and 95% CI as relevant effect measures directly or indirectly from the given data [19]. The nonparametric Spearman rank correlation coefficient (ρ) was used as a measure of correlation between the median PFS/TTP and OS and correlation between HR of PFS/TTP and HR of OS. As the number of subject studies was limited, we applied bootstrap resampling [20] using 10000 bootstrap samples to estimate 95% confidence intervals for correlation coefficients.

To investigate possible reasons for heterogeneity, subgroup analyses were conducted according to test variables (PFS or TTP), trial area (Asian or non-Asian), reported data (before 2006 or after 2006), number of patients (<200 or ≥ 200), registration trial with investigational agents (yes or not), number of chemotherapeutic agents in treatment arm (more agents vs. few agents or same number of agents), or proportion of measurable disease, and proportion of patients who received second-line chemotherapy. In the case of global trials, data were classified as both Asian and non-Asian unless suitable subset analysis results were provided.

Statistical analyses were performed using STATA ver. 10 (Stata Corp LP, College Station, TX, USA). All tests were

two-sided, and *P*-values less than .05 were considered statistically significant.

Results

Selection of studies

A total of 826 potentially relevant reports were identified, of which 717 were initially excluded (Fig. 1). After review of the remaining studies, 36 trials with sufficient data were identified as eligible for this meta-analysis, with a total of 83 treatment arms and 10,484 patients [2–7, 21–50].

Table 1 shows the characteristics of each trial. Eleven were randomized phase II trials and 25 were phase III. By region, 4 were conducted in North or South America, 13 in Europe, 2 in America and Europe, 13 in Asia, and 1 in Australia, while 3 were global. Six trials were registration trial [2, 5–7, 38, 46]. Seventeen trials compared combination chemotherapy with different number of agents (2 or more) and few agents (1 or 2).

Most trials were for metastatic disease, and the median proportion of patients with measurable lesions was 95% (47–100%). More studies reported PFS than TTP, while no trial reported both PFS and TTP. Information on second-line chemotherapy was available in 18 trials [2–7, 28, 30–33, 36, 37, 39, 42, 44, 46, 49]. Subset analysis according to area was reported in one global trial (AVAGAST) [46], and these subset data were accordingly included in analyses which focused on comparing Asian and non-Asian trials.

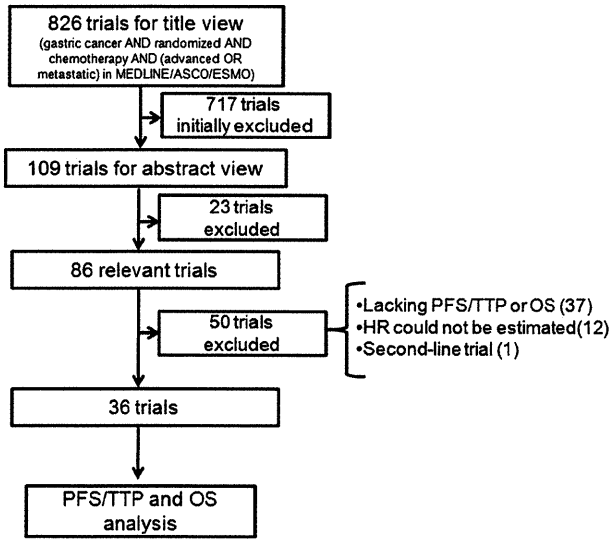


Fig. 1 Selection process for trials

Correlation between PFS/TTP and OS

A moderate correlation was seen between median PFS/TTP and OS, with a ρ value of 0.70 (95% CI, 0.59 to 0.82; $P<0.001$; Fig. 2). Correlations in non-Asian ($\rho=0.79$; 0.69–0.89) and Asian trials ($\rho=0.75$; 0.54–0.95; Fig. 3) were similar.

Correlation between HR for PFS/TTP and OS

A total of 50 pairs of HRs for PFS/TTP and OS between treatment arms were available from the 36 trials, being reported in 19 trials and estimated in 17. A close correlation between HRs for PFS/TTF and OS was seen, with a ρ value of 0.80 (95% CI, 0.68 to 0.92; $P<0.0001$; Fig. 4). No difference in correlation was observed between reported ($\rho=0.80$; 0.60–1.00) and estimated HRs ($\rho=0.82$; 0.67–0.99). Correlation tended to be higher in Non Asian ($\rho=0.80$; 0.61–0.98) than Asian trials ($\rho=0.67$; 0.39–0.94; Fig. 5), higher with registration trials ($\rho=0.94$; 0.60–1.00) and no-registration trial ($\rho=0.79$; 0.64–0.93), higher with comparison of treatment with same number of agents ($\rho=0.89$; 0.76–1.00) than comparison of different number of agents ($\rho=0.75$; 0.54–0.95), higher in trials reporting PFS ($\rho=0.85$; 0.72–0.97) than in those reporting TTP ($\rho=0.60$; 0.24–0.97), and higher in trials in patients with measurable lesions only ($\rho=0.91$; 0.77–1.00) than in those including non-measurable lesions ($\rho=0.71$; 0.50–0.93), albeit that none of these differences was significant. In also, no differences were observed between trials before 2006 ($\rho=0.73$; 0.45–1.00) and after 2006 ($\rho=0.83$; 0.68–0.98), or trials with less than 200 patients ($\rho=0.85$; 0.67–1.00) and with more than 200 patients ($\rho=0.70$; 0.50–0.90).

Discrepancy in HRs for PFS/TTP and second-line chemotherapy

Among the 18 studies with information on second-line chemotherapy, the ratio of the HR of PFS/TTP to that of OS deviated from 1 as the proportion of patients who received second-line chemotherapy increased ($\rho=-0.40$; $P=0.04$; Fig. 6).

Discussion

To our knowledge, this is the first study to evaluate whether PFS and TTP can be used as surrogate endpoints for randomized studies of first-line chemotherapy for AGC. Our results showed that an improvement in PFS/TTP was closely associated with an improvement in OS. Although no consensus on what defines a valid surrogate endpoint has yet been reached, any candidate must correlate to the

Table 1 Baseline characteristics of patients in the 36 included trials

Author	Year	Phase	Region	Treatment arms	No. of patients	Origin	Metastatic disease (%)	Measurable disease (%)	Endpoint (TTP/PFS)	Information on second-line treatment
Cullinan [21]	1985	III	Am	FU vs FU+ADM vs FU+ADM+MMC	151	G	NR	47	TTP	NR
Kim [22]	1993	III	A	FU vs FAM vs FU	324	G	NR	56	TTP	NR
Cullinan [23]	1994	III	Am	FU vs FAP vs FAMe vs FEMe+TZT	252	G	NR	84	TTP	NR
Loehrer [24]	1994	III	Am	FU vs epirubicin vs FU+epirubicin	165	G	63	69	TTP	NR
Pyrhonen [25]	1995	III	E	BSC vs FAMTX	41	G	71	NR	TTP	NR
Kondo [26]	2000	III	A	FU vs Doxifluridine	86	G	NR	NR	TTP	NR
Vanhoefe [27]	2000	III	E	ELF vs CF vs FAMTX	399	G	84	63	PFS	NR
Ohtsu [28]	2002	III	A	FU vs CF vs UFTM	280	G	86	96	PFS	Yes
Ross [29]	2002	III	E	ECF vs MCF	574	E,GEJ,G	57	95	PFS	NR
Tebbutt [30]	2002	III	E	FU vs FU+MMC	254	E,GEJ,G	57	94	PFS	Yes
Bouché [31]	2004	II	E	FU+FA vs CF+FA vs FU+FA+irinotecan	134	G	100	100	PFS	Yes
Pozzo [32]	2004	II	E	FU+FA+irinotecan vs irinotecan+CDDP	146	GEJ, G	94	90	TTP	Yes
Ajani [33]	2005	II	Am	DC vs DCF	155	GEJ, G	95	79	PFS	Yes
Moehler [34]	2005	II	E	ILF vs ELF	114	GEJ,G	100	100	PFS	NR
Thuss-Patience [35]	2005	II	E	DF vs ECF	90	G	98	96	TTP	NR
Van custem [2]	2006	III	E, Am	CF vs DCF	445	GEJ, G	97	100	TTP	Yes
Chin [36]	2007	III	A	S1 vs S1+irinotecan	315	G	NR	57	PFS	Yes
Cunnningham [3]	2008	III	E	ECF vs ECX vs EOF vs EOX	1002	E,GEJ,G	74	100	PFS	Yes
Al-Batra [37]	2008	III	E	FLP vs FLO	220	GEJ,G	94	89	PFS	Yes
Dank [38]	2008	III	E	CF+FA vs ILF	333	GEJ,G	96	NR	TTP	NR
Ikeda [39]	2008	II	A	CF vs S1+DOC	49	G	100	100	PFS	Yes
Jeung [40]	2008	II	A	DOC+CDDP vs S1+DOC	80	G	79	100	PFS	NR
Koizumi [4]	2008	III	A	S1 vs S1+CDDP	305	G	100	63	PFS	Yes
Lee [41]	2008	II	A	S1 vs Capecitabine	91	G	100	100	TTP	NR
Park [42]	2008	II	A	ILF vs PILF	91	G	100	100	PFS	Yes
Ridwelski [43]	2008	III	E	DOC+CDDP vs FLC	270	G	90	100	TTP	NR
Boku [44]	2009	III	A	FU vs S1 vs irinotecan+CDDP	704	G	NR	75	PFS	Yes
Kang [5]	2009	III	A, E, Am	FP vs XP	316	G	100	100	PFS	Yes
Lee [45]	2009	III	A	FP vs Haptoplatin+FU	174	G	94	90	TTP	NR
Ajani [6]	2010	III	E, Am	FP vs S1+CDDP	1053	GEJ,G	96	96	PFS	Yes
Bang [7]	2010	III	A, E, Am	XP vs XP+trastuzumab	584	GEJ,G	96	90	PFS	Yes
Kang [46]	2010	III	A, E, Am	XP vs XP+bevacizumab	774	GEJ,G	96	79	PFS	Yes
Kishimoto [47]	2010	II	A	S1+paclitaxel vs S1+irinotecan	102	G	100	100	PFS	NR
Sawaki [48]	2010	III	A	S1 vs FU+FA	177	G	100	100	PFS	NR
Moehler [49]	2010	II	E	XP vs XI	118	E,GEJ,G	100	NR	PFS	Yes
Tebbutt [50]	2010	II	Australia	wTCF vs wTX	116	E,GEJ,G	93	98	PFS	NR

Am America; *A* Asia; *E* Europe; *FU* 5-fluorouracil; *ADM* doxorubicin; *MMC* mitomycin C; *CDDP* cisplatin; *FAM* FU+ADM+MMC; *FAP* FU+ADM+CDDP; *FAMe* FU+ADM+methyl lomustine; *TZT* triazinate; *Epi* epirubicin; *BSC* best supportive care; *FAMTX* FU+ADM+methotrexate; *ELF* etoposide+leucovorin+FU; *CF* CDDP+FU; *UFTM* uracil/tegafur+MMC; *ECF* epirubicin+CDDP+FU; *MCF* MMC+CDDP+FU; *FA* folinic acid; *DC* docetaxel+CDDP; *DCF* docetaxel+CDDP+FU; *ILF* irinotecan+leucovorin+FU; *ELF* epirubicin+leucovorin+FU; *DF* docetaxel+FU; *ECX* epirubicin+CDDP+capecitabine; *EOF* epirubicin+oxaliplatin+FU; *EOX* epirubicin+oxaliplatin+capecitabine; *FLP* FU+LV+CDDP; *FLP* FU+LV+oxaliplatin: *DOC* docetaxel; PILF,CDDP+ILF; *FLC* FU+LV+CDDP; *FP* CDDP+FU; *XP* capecitabine+CDDP; *PTX* XI, capecitabine+irinotecan; *wTCF* weekly docetaxel+CDDP+FU; *wTX* weekly docetaxel+capecitabine, *G* gastric; *GEJ* gastroesophageal junction; *E* esophagus; *NR* not reported; *TTP* time to progression; *PFS* progression-free survival

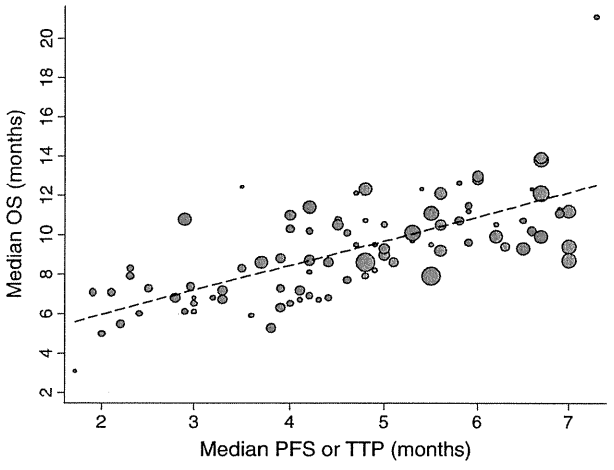


Fig. 2 Median PFS/TTP and OS in 36 trials. The size of the gray markers (*circles*) corresponds to the number of randomized patients in the trial in this analysis. A moderate relationship was seen between median PFS/TTP and OS, with a ρ value of 0.70 (95% CI, 0.59 to 0.82; $P<0.001$)

true endpoint, and effects on the surrogate must correlate to those on the true endpoint [51, 52]. In our analysis, the HR for PFS/TTP showed a significant correlation with that for OS, indicating that the effect of treatment on PFS likely predicts the effect of treatment on OS. In this regard, the coefficient of 0.80 was compatible with that for advanced colorectal cancer, for which PFS is considered an adequate surrogate endpoint in clinical trials [12, 13, 17].

In this analysis we included studies which evaluated either or both PFS or TTP. In their study in patients with advanced colorectal cancer receiving systemic chemotherapy, Tang et al. reported that PFS was more closely correlated with OS than TTP [13]. Although we saw no significant difference between the ρ value of PFS and TTP in our analysis, it nevertheless tended to be higher for PFS, consistent with Tang et al. PFS differs from TTP in that it incorporates death as a result of any cause, in addition to progression. On this basis, PFS might be the better surrogate for OS, as suggested by our results.

Reflecting the relatively high incidence of gastric cancer worldwide, several studies have been performed or are ongoing in various countries or as global studies. A number of differences in AGC between Western and Eastern countries have been identified in tumor characteristics and practice patterns, including surgery or chemotherapy [53]. In Asian trials, the percentage of patients with measurable disease are usually lower than in non-Asian study, which may cause relatively longer survival due to less tumor burden. In also, the proportion of patients who receive second-line chemotherapy is reported to be higher in Asian than western trials. This difference was clearly revealed in the AVAGAST study, where 66% of Asian patients received second-line chemotherapy compared with 31% in Europe and 21% in America [46]. If this difference in second-line chemotherapy contributed to the differences in survival after progression in the various areas, PFS/TTP might be a more sensitive endpoint for future global studies since it might directly reflect the anti-tumor effect of first-line chemotherapy.

In also, our results suggest that the second-line therapy has the potential to underestimate the efficacy of an experimental agent in patients when compared with control patients who receive multiple subsequent therapies. Influence of second-line treatment as crossover might contribute to the non-significant survival differences especially with non-registered trials with approved agents. Additionally, given our finding

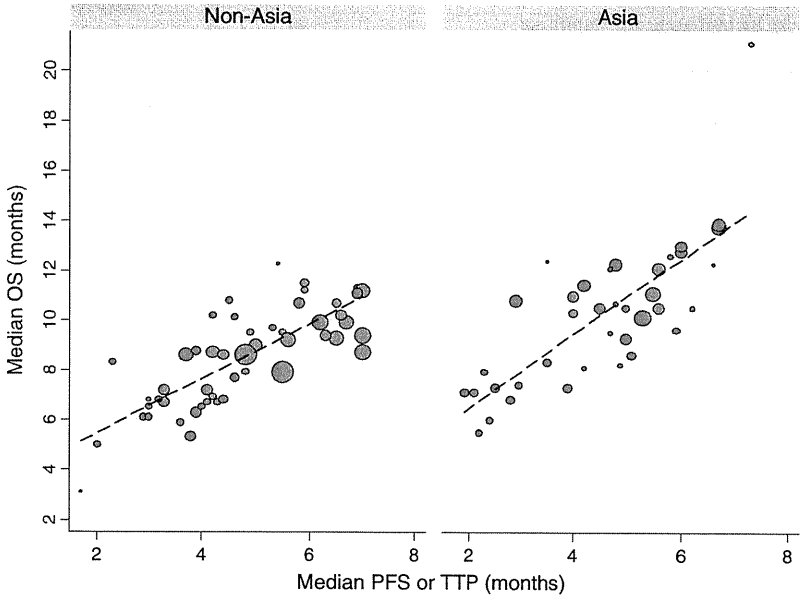


Fig. 3 Median PFS/TTP and OS by trial area. Correlation in non-Asian (ρ=0.79; 0.69–0.89) and Asian studies (ρ=0.75; 0.54–0.95; Fig. 3) was similar

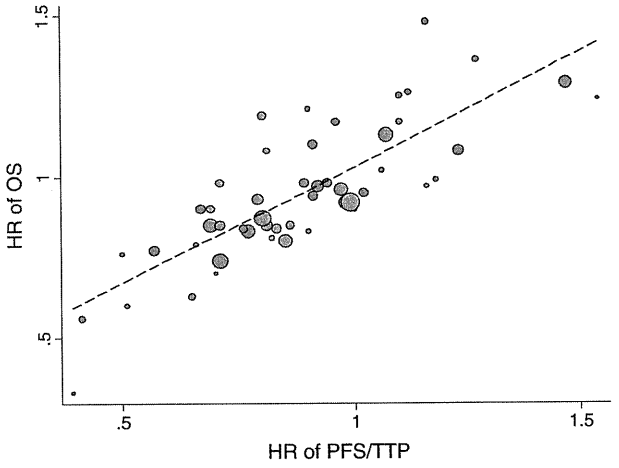


Fig. 4 HR of PFS/TTP and OS in 36 trials. A significant relationship is seen between HRs for PFS/TTF and OS, with the ρ value of 0.80 (95% CI, 0.68 to 0.92; $P<0.0001$)

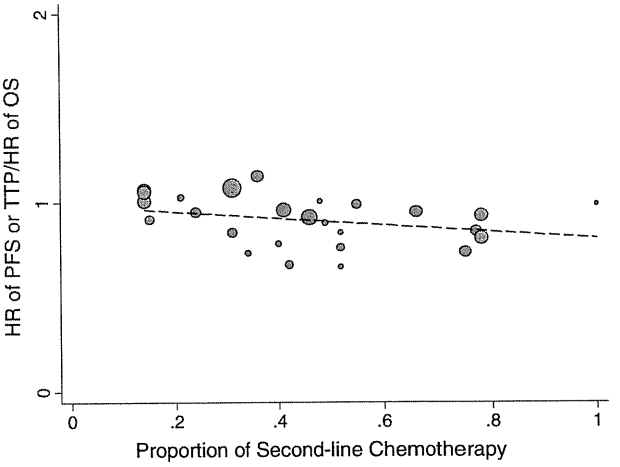


Fig. 6 Discrepancy in HRs for PFS/TTP and second-line chemotherapy. HR of PFS/TTP and HR of OS deviated from 1 in positive proportion to the number of patients who received second-line chemotherapy ($\rho=-0.40$; $P=0.04$)

that studies which included non-measurable lesions tended to have lower ρ values, it might be desirable to restrict entry in studies which use PFS is a primary endpoint to patients with measurable disease, to allow accurate and independent evaluation using standard definitions, such as those by the Response Evaluation Criteria in Solid Tumors Group.

This study has several methodological limitations. First, it was not based on analysis of data from individual patients, which is a better means of evaluating individual-level measures of agreement between the two endpoints (PFS/TTP and OS) [54]. Additional individual data analysis might therefore necessary to confirm the correlation between PFS/TTP and OS. Second, as we did not include trials which did not report HRs or survival curves, a degree of selection bias might be present, albeit that most recent trials did in fact report HR. Third, since not all trials reported information on subset analysis, such as the proportion of measurable lesions or of cases receiving second-line chemotherapy, our results which derive from or refer to these variables were likely insufficient. Accordingly, future trials should ensure that these data are reported. Finally, because most trials provided little information on disease progression, it was impossible to confirm whether the evaluation of this variable had been consistent in each trial arm. Future clinical trials using PFS as a primary endpoint for AGC should ensure that the definition and evaluation of progression be strictly determined.

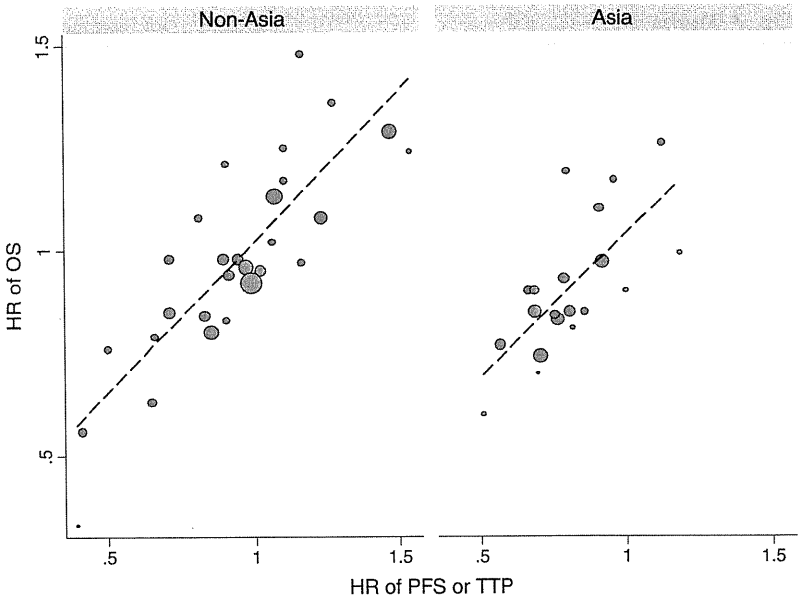


Fig. 5 HR of PFS/TTP and OS by trial area. No significant difference in correlation was observed between Asian ($\rho=0.67$; 0.39–0.94) and non-Asian studies ($\rho=0.80$; 0.61–0.98)

In conclusion, this study shows that improvements in PFS/TTP in AGC are closely associated with improvements in OS. Further research is needed to clarify the surrogacy of PFS/TTP for OS or the role of PFS as the true end point in future randomized clinical trials of chemotherapy for AGC.

Acknowledgements None.

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

Financial disclosure None.

References

1. Kamangar F, Dores GM, Anderson WF (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24:2137–2150
2. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C et al (2006) Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 24:4991–4997
3. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F et al (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36–46
4. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
5. Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J et al (2009) Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 20:666–673
6. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V et al (2010) Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol 28:1547–1553
7. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A et al (2010) Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376:687–697
8. Thuss-Patience PC, Kretzschmar A, Deist T, Hinke A, Bichev D, Lebedinzew B et al (2009) Irinotecan versus best supportive care (BSC) as second-line therapy in gastric cancer: a randomized phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). J Clin Oncol 27:15s (suppl; abstr 4540)
9. Takiuchi H, Fukuda H, Boku N, Shimada Y, Nasu J, Hamamoto Y et al (2010) Randomized phase II study of best-available 5-fluorouracil (5-FU) versus weekly paclitaxel in gastric cancer (GC) with peritoneal metastasis (PM) refractory to 5-FU-containing regimens (JCOG0407). J Clin Oncol 28:15s (suppl; abstr 4052)
10. Takashima A, Boku N, Kato K, Mizusawa J, Nakamura K, Fukuda H et al (2010) Survival prolongation after treatment failure in patients with advanced gastric cancer (AGC): results from combined analysis of JCOG9205 and JCOG9912. J Clin Oncol 28:15s (suppl; abstr 4061)
11. Broglio KR, Berry DA (2009) Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 101:1642–1649
12. Johnson KR, Ringland C, Stokes BJ, Anthony DM, Freemantle N, Irs A et al (2006) Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol 7:741–746
13. Tang PA, Bentzen SM, Chen EX, Siu LL (2007) Surrogate end points for median overall survival in metastatic colorectal cancer: literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. J Clin Oncol 25:4562–4568
14. Hotta K, Fujiwara Y, Matsuo K, Kiura K, Takigawa N, Tabata M et al (2009) Time to progression as a surrogate marker for overall survival in patients with advanced non-small cell lung cancer. J Thorac Oncol 4:311–317
15. Hackshaw A, Knight A, Barrett-Lee P, Leonard R (2005) Surrogate markers and survival in women receiving first-line combination anthracycline chemotherapy for advanced breast cancer. Br J Cancer 93:1215–1221
16. Burzykowski T, Buyse M, Piccart-Gebhart MJ, Sledge G, Carmichael J, Lück HJ et al (2008) Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. J Clin Oncol 26:1987–1992
17. Saad ED, Katz A, Hoff PM, Buyse M (2010) Progression-free survival as surrogate and as true end point: insights from the breast and colorectal cancer literature. Ann Oncol 21:7–12
18. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG (2008) CONSORT for reporting randomised trials in journal and conference abstracts. Lancet 371:281–283
19. Parmar MB, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17:2815–2834
20. Efron B (1979) Bootstrap methods: another look at the jackknife. Ann Stat 7:1–26
21. Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK et al (1985) A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma: fluorouracil vs fluorouracil and doxorubicin vs fluorouracil, doxorubicin, and mitomycin. JAMA 253:2061–2067
22. Kim NK, Park YS, Heo DS, Suh C, Kim SY, Park KC et al (1993) A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. Cancer 71:3813–3818
23. Cullinan SA, Moertel CG, Wieand HS, O'Connell MJ, Poon MA, Krook JE et al (1994) Controlled evaluation of three drug combination regimens versus fluorouracil alone for the therapy of advanced gastric cancer. North Central Cancer Treatment Group. J Clin Oncol 12:412–416
24. Loehrer PJ Sr, Harry D, Chlebowski RT (1994) 5-fluorouracil vs. epirubicin vs. 5-fluorouracil plus epirubicin in advanced gastric carcinoma. Invest New Drugs 12:57–63
25. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M (1995) Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 71:587–591
26. Kondo K, Sakamoto J, Nakazato H, Koike A, Kitoh T, Hachisuka K et al (2000) A phase III randomized study comparing doxifluridine and 5-fluorouracil as supportive chemotherapy in advanced and recurrent gastric cancer. Oncol Rep 7:485–490
27. Vanhoefer U, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Cutsem E et al (2000) Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infu-

sional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 18:2648–2657
28. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H et al (2003) Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol 21:54–59
29. Ross P, Nicolson M, Cunningham D, Valle J, Seymour M, Harper P et al (2002) Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 20:1996–2004
30. Tebbutt NC, Norman A, Cunningham D, Iveson T, Seymour M, Hickish T et al (2002) A multicentre, randomised phase III trial comparing protracted venous infusion (PVI) 5-fluorouracil (5-FU) with PVI 5-FU plus mitomycin C in patients with inoperable oesophago-gastric cancer. Ann Oncol 13:1568–1575
31. Bouché O, Raoul JL, Bonnetain F, Giovannini M, Etienne PL, Lledo G et al (2004) Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study—FFCD 980. J Clin Oncol 22:4319–4328
32. Pozzo C, Barone C, Szanto J, Padi E, Peschel C, Bükki J et al (2004) Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study. Ann Oncol 15:1773–1781
33. Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S et al (2005) Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol 23:5660–5667
34. Moehler M, Eimermacher A, Siebler J, Hohler T, Wein A, Menges M et al (2005) Randomised phase II evaluation of irinotecan plus high-dose 5-fluorouracil and leucovorin (ILF) vs 5-fluorouracil, leucovorin, and etoposide (ELF) in untreated metastatic gastric cancer. Br J Cancer 92:2122–2128
35. Thuss-Patience PC, Kretzschmar A, Repp M, Kingreen D, Hennesser D, Micheel S et al (2005) Docetaxel and continuous-infusion fluorouracil versus epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: a randomized phase II study. J Clin Oncol 23:494–501
36. Chin K, Iishi H, Imamura H, Kobayashi O, Imamoto H, Esaki T et al (2007) Irinotecan plus S-1 (IRIS) versus S-1 alone as first line treatment for advanced gastric cancer: preliminary results of a randomized phase III study (GC0301/TOP-002). J Clin Oncol 25:15s, suppl; abstr 4525
37. Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R et al (2008) Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol 26:1435–1442
38. Dank M, Zaluski J, Barone C, Valvere V, Yalcin S, Peschel C et al (2008) Randomized phase III study comparing irinotecan combined with 5-fluorouracil and folinic acid to cisplatin combined with 5-fluorouracil in chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 19:1450–1457
39. Ikeda R, Yoshida K, Satou Y, Takahashi M, Une Y, Yamamoto W et al (2009) Randomized phase II/III study of docetaxel/S-1 (DS-1) versus CDDP/5FU (FUP) in advanced or recurrent gastric cancer: updated phase II results. J Clin Oncol 27:15s (suppl; abstr 4595)
40. Jeung H, Im C, Rha S, Ahn J, Shin S, Noh S et al (2008) A randomized phase II trial of docetaxel plus S-1 versus docetaxel plus cisplatin in advanced gastric cancer as a first-line treatment. J Clin Oncol 26 (suppl; abstr 4534)
41. Lee JL, Kang YK, Kang HJ, Lee KH, Zang DY, Ryoo BY et al (2008) A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer 99:584–590
42. Park SH, Nam E, Park J, Cho EK, Shin DB, Lee JH et al (2008) Randomized phase II study of irinotecan, leucovorin and 5-fluorouracil (ILF) versus cisplatin plus ILF (PILF) combination chemotherapy for advanced gastric cancer. Ann Oncol 19:729–733
43. Ridwelski K, Fahlke J, Kettner E, Schmidt C, Keilholz U, Quietzsch D et al (2008) Docetaxel-cisplatin (DC) versus 5-fluorouracil-leucovorin-cisplatin (FLC) as first-line treatment for locally advanced or metastatic gastric cancer: Preliminary results of a phase III study. J Clin Oncol 26 (suppl; abstr 4512)
44. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A et al (2009) Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol 10:1063–1069
45. Lee KH, Hyun MS, Kim HK, Jin HM, Yang J, Song HS et al (2009) Randomized, multicenter, phase III trial of heptaplatin 1-hour infusion and 5-fluorouracil combination chemotherapy comparing with cisplatin and 5-fluorouracil combination chemotherapy in patients with advanced gastric cancer. Cancer Res Treat 41:12–18
46. Kang Y, Ohtsu A, Van Cutsem E, Rha SY, Sawaki A, Park S et al (2010) AVAGAST: A randomized, double-blind, placebo-controlled, phase III study of first-line capecitabine and cisplatin plus bevacizumab or placebo in patients with advanced gastric cancer (AGC). J Clin Oncol 28:18s (suppl; abstr LBA4007)
47. Kishimoto T, Imamura H, Uedou F, Fujitani K, Iijima S, Takiuchi H et al (2010) Randomized phase II trial of S-1 plus irinotecan versus S-1 plus paclitaxel as first-line treatment for advanced gastric cancer (OGSG0402): final report. J Clin Oncol 28:15s (suppl; abstr 4015)
48. Sawaki A, Yamaguchi K, Nabeya Y, Sakai Y, Osanai H, Denda T et al (2009) 5-FU/l-LV (RPMI) versus S1 as first-line therapy in patients with advanced gastric cancer: a randomized phase III non-inferiority trial. (ISO-5FU10 Study Group trial). Eur J Cancer (Supplements 7)363
49. Moehler M, Kanzler S, Geissler M, Raedle J, Ebert MP, Daum S et al (2010) A randomized multicenter phase II study comparing capecitabine with irinotecan or cisplatin in metastatic adenocarcinoma of the stomach or esophagogastric junction. Ann Oncol 21:71–77
50. Tebbutt NC, Cummins MM, Sourjina T, Strickland A, Van Hazel G, Ganju V et al (2010) Randomised, non-comparative phase II study of weekly docetaxel with cisplatin and 5-fluorouracil or with capecitabine in oesophagogastric cancer: the AGITG ATTAX trial. Br J Cancer 102:475–481
51. Fleming TR (2005) Surrogate endpoints and FDA's accelerated approval process. Health Aff (Millwood) 24:67–68
52. Baker SG (2006) Surrogate endpoints: wishful thinking or reality? J Natl Cancer Inst 98:502–503
53. Ohtsu A (2007) Diverse eastern and Western approaches to the management of gastric cancer. Gastrointest Cancer Res 1(2 Suppl): S10–S15
54. Buyse M, Molenberghs G, Burzykowski T, Renard D, Geys H (2000) The validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics 1:49–67

外来化学療法と化学療法の副作用マネージメント

安井 久晃

ポイント

★外来で安全に化学療法を行うためには，支持療法(副作用対策)が必須である．
★骨髄抑制自体は通常無症状だが，合併症の予防が重要である．G-CSFはガイドラインに沿った適切な使用が必要である．
★抗がん剤やレジメンの催吐性に応じた制吐療法を行う必要がある．

外来へシフトする化学療法

短時間で有効な治療の開発，支持療法の進歩などにより，多くの化学療法は外来でも安全に行うことが可能となってきている．制度的な背景として，外来化学療法加算の算定(500点/1日)と，DPC(診療群別包括払い制度)の普及が挙げられる．インフォームド・コンセントに基づいて患者が納得して治療を受け，これまで通りの社会生活を続けられる環境が整いつつあるなかで，標準化学療法を外来で安全かつ快適に行うことが求められている．

副作用の評価と支持療法

副作用(side effect)とは，有害事象(adverse event：治療や処置に際してみられるあらゆる好ましくない徴候・症状・疾患・検査値異常)のうち，薬物との因果関係が否定できないものを指す．薬物有害反応(adverse drug reaction)，毒性(toxicity)ともいう．

化学療法の有用性は抗腫瘍効果と安全性によって決定される．副作用を適切に評価し治療すること(支持療法)が，安全で有効な化学療法を行ううえで必須である．

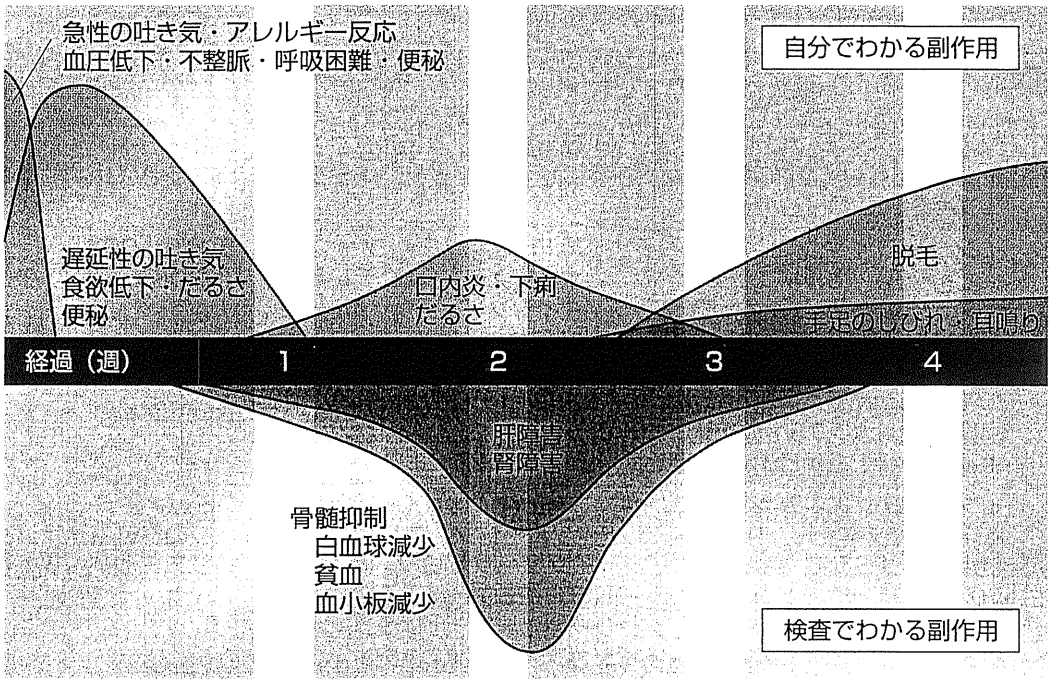
CTCAE(common terminology criteria for adverse events)は，化学療法だけでなくすべての有害事象の記録や報告を標準化したものである．もともと臨床試験での使用を目的に米国国立がん研究所(NCI)により作成されたが，実地臨床で治療を行う際も有害事象を把握し，治療継続や中止，投与量減量などの判断を行うために有用なツールである．多職種のチーム医療として行われる化学療法において，スタッフ間で有害事象の評価を共通化することは診療の効率化にも寄与する．現在ver.4.0が一般に用いられており，日本語訳JCOG版がwebで公開されている(http://www.jcog.jp/doctor/tool/ctcaev4.html)．

副作用の出るタイミング

副作用の出現時期は，抗がん剤の種類によっても異なるが，だいたいの時期(急性期，亜急期，

やすい ひさてる：国立病院機構京都医療センター腫瘍内科 〒612-8555 京都市伏見区深草向畑町1-1

0025-7699/11/¥500/論文/JCOPY



【図 1】副作用の発現時期(文献 1 より引用)

晩期など)が決まっている(**図 1**). 副作用は非常に多岐にわたるが, 抗がん剤やレジメンによって副作用のプロファイルが決まっている. 本稿では, 頻度が高く是非熟知しておきたい副作用に絞って解説する.

骨髄抑制

ほとんどの抗がん剤・レジメンの投与量規制因子(dose limiting factor：DLT)となっているが, 合併症を起こさなければ, 骨髄抑制は無症状である. 感染や出血, 貧血症状といった合併症のために治療の継続が困難になることは, 治療成績の悪化につながる.

好中球減少

顆粒球コロニー刺激因子(G-CSF)の投与について, 化学療法後に好中球減少(500/μl 未満)を確認してから開始する治療的投与と, 好中球減少が起きる前から開始する予防的投与がある. G-CSF の適切な使用のために, ASCO (American Society of Clinical Oncology)のガイドラインに目を通しておく必要がある[2]. 治療後の好中球減少について, 発熱のない患者に対してルーチンに G-CSF を投与すべきではない. 発熱患者においても, 高リスク患者(好中球 100/μl 未満, 原疾患のコントロール不良, 肺炎, 低血圧, 多臓器不全, 敗血症, 真菌感染, 65 歳以上, 入院中の発熱など)においては G-CSF 投与を考慮してもよいが, それ以外ではルーチンに G-CSF の投与を行うべきではない.

貧血

化学療法や放射線治療のほか, がんの骨髄浸潤や出血, DIC, 鉄利用障害, ビタミン欠乏, エリスロポエチン産生低下などさまざまな要因によって起こる. 赤血球造血刺激因子(ESAs)の投与は, わが国においては現時点で保険適用外であり, 輸血が唯一の治療である.

【表 1】注射抗がん剤の催吐性リスク分類(文献 3 より改変して引用)

催吐性リスク分類	薬剤・レジメン	制吐療法
高度リスク(催吐頻度>90%)	シスプラチン，シクロホスファミド(1.5>g/m²)，ダカルバジン，ドキソルビシン+シクロホスファミド(AC)，エピルビシン+シクロホスファミド(EC)	APR+5-HT₃+DEX ±ロラゼパム，H_2 ブロッカー or PPI
中等度リスク(催吐頻度30～90%)	インターロイキン 2(>12～15×10⁶U/m²)，ブスルファン(>4 mg/m²/日)，カルボプラチン，シクロホスファミド(<1.5 g/m²)，シタラビン(>200 mg/m²)，アクチノマイシン-D，ダウノルビシン，ドキソルビシン，エピルビシン，イダルビシン，イホスファミド，インターフェロン α(>10,000 U/m²)，イリノテカン，メルファラン(>50 mg/m²)，メトトレキサート(250～1,000 mg/m²)，オキサリプラチン(>75 mg/m²)，ネダプラチン*，エノシタビン*，テラルビシン*，アムルビシン*，亜ヒ酸，テモゾロミド	5-HT₃+DEX (CBDCA，CPT，IFO などには +APR を推奨)
軽度リスク(催吐頻度10～30%)	インターロイキン 2(≦12 MU/m²)，シタラビン(100～200 mg/m²)，ドセタキセル，リポゾーマルドキソルビシン，エトポシド，5-フルオロウラシル，ゲムシタビン，インターフェロン α(5,000～10,000 U/m²)，メトトレキサート(50～250 mg/m²)，マイトマイシン C，ミトキサントロン，パクリタキセル，アルブミン結合パクリタキセル，ペメトレキセド，トポテカン，ペントスタチン，ニムスチン*，ラニムスチン*	DEX ±プロクロルペラジン or メトクロプラミド±ロラゼパム，H_2 ブロッカー or PPI
最小度リスク(催吐頻度<10%)	L-アスパラギナーゼ，ベバシズマブ，ブレオマイシン，ボルテゾミブ，セツキシマブ，クラドリビン，シタラビン(<100 mg/m²)，フルダラビン，ゲムツズマブオゾガマイシン，メトトレキサート(<50 mg/m²)，リツキシマブ，トラスツヅマブ，ネララビン，ビンブラスチン，ビンクリスチン，ビノレルビン，ビンデシン*，ペプロマイシン*	基本的に不要

*：海外のガイドラインには記載がないが，わが国で使用可能な薬剤
APR：アプレピタント，5-HT₃：5-HT₃ 受容体拮抗薬，DEX：デキサメタゾン

血小板減少症

血小板減少が DLT となっている抗がん剤は，カルボプラチン，ネダプラチン，ゲムシタビン，マイトマイシン C などである．血小板減少による出血リスクの閾値は 1 万/μl とされるが，膀胱腫瘍で積極的治療を受ける場合や壊死性の腫瘍が認められる場合では，局所の出血リスクがあるため，閾値は 2 万/μl とされる．血小板輸血が唯一の治療である．

出血予防の対応として，駆血帯や血圧計の圧迫は最小限にする，注射やカテーテル挿入は極力避ける，咳が頻発する場合は鎮咳を心がける，便秘は緩下薬で排便コントロールする，血小板減少を起こす NSAIDs などの薬剤の使用を避ける，坐薬・浣腸は使用しない，転倒・打撲に注意し患者に応じた日常生活制限を行う，などに配慮する．

消化器毒性

悪心・嘔吐

悪心・嘔吐は延髄の嘔吐中枢(VC)が刺激されて出現する．①抗がん剤投与後 24 時間以内に出現する急性悪心・嘔吐，②24 時間以上経過してから出現する遅発性悪心・嘔吐，③過去に経験した悪心・嘔吐の記憶により抗がん剤投与前から条件反射的に出現する予期性悪心・嘔吐に分類される．

リスク因子は，若年者(50 歳未満)，女性，アルコール常用なし，乗り物酔い，つわりの経験，前治療にて悪心・嘔吐，副作用への不安，が挙げられる．

制吐薬の使用については多くのエビデンスがあり，投与する抗がん剤の種類あるいはレジメンにより催吐性が分類され，それぞれに対する適切な制吐療法がガイドラインで示されている(表1)[3]．

急性期の悪心・嘔吐にはセロトニンが関与しており，5-HT_3受容体拮抗薬が頻用されてきたが，遅発性の悪心・嘔吐のコントロールは難しかった．最近作用時間の長い第2世代の5-HT_3受容体拮抗薬であるパロノセトロンや，サブスタンスPを阻害するNK1(ニューロキニン1)受容体拮抗薬であるアプレピタントが登場し，高度リスクの抗がん剤による嘔吐を高度に抑制するだけでなく，遅発性の悪心・嘔吐にも効果が期待できるようになった．アプレピタントはCYP3A4の基質で軽度～中等度の阻害と誘導作用，CYP2C9の誘導作用があるため，デキサメタゾンは半量に減量するなど併用薬に注意が必要である．

口内炎

口内炎の発生機序として，抗がん剤により粘膜が直接破壊され，生理的な粘膜再生が阻害されるもの(直接作用)と，白血球・好中球減少に伴う口腔内感染によるもの(二次的)が考えられている．前者は投与2～10日後に発生する．5-FU，メトトレキサート，シタラビン，ドキソルビシン，シクロホスファミド，パクリタキセル，ドセタキセルなどの投与で起きやすい．

口内炎は一度できてしまうと有効な治療法が確立されておらず，治癒に時間がかかることが多いため，予防が非常に大切である．ポイントは口腔内の清潔と感染防止である．治療としては，スクラルファートによる粘膜保護や，コルチコステロイドの局所塗布などが行われるが，疼痛が強ければ，キシロカイン入りの含嗽液でのうがいや，積極的な鎮痛薬の使用を行う．

下痢

抗がん剤投与直後に出現するコリン作動性による早発性下痢と，抗がん剤により消化管粘膜が傷害され腸管粘膜傷害によって起こる遅発性下痢がある．前者は当日発症し，硫酸アトロピンの投与が有効である．後者は抗がん剤投与後数日～2週間経ってから発症し，粘膜傷害のため感染が起きやすく，骨髄抑制の時期と重なるため注意が必要である．

軽い下痢が始まった時点で乳糖を含む食品の制限や十分な水分摂取などを指導し，それでも改善しない場合は薬物療法の適応となる．重篤化を示唆する症状を伴わない場合は，ロペラミドを投与する．下痢が24時間以上持続する場合はロペラミド2 mgを2時間ごとに投与し，経口抗菌薬(ニューキノロンなど)を開始する．下痢が48時間以上持続する場合は，オクトレオチドの投与を考慮する．

多くの抗がん剤で下痢が起こりうるが，特にイリノテカン(CPT-11)では重要な副作用である．CPT-11の活性代謝物SN-38の代謝酵素であるUDP-グルクロン酸転移酵素の遺伝子多型(UGT1A1*6/*28)を事前に検査し，副作用を予測することが望ましい．

皮膚障害

手足皮膚反応(手足症候群)

四肢末端の皮膚炎で，手掌・足底の紅斑，疼痛性発赤，知覚過敏，ほてり，色素沈着などを生じ，高度なものでは水疱，びらん形成などを認める．

手足の角化，落屑が著しくなって亀裂を生じ，物をつかめないなどの症状を訴えることがある．カペシタビンなどフッ化ピリミジン系抗が

ん剤の投与において発症率が高いが，ソラフェニブやスニチニブなどの分子標的薬(チロシンキナーゼ阻害薬)でも頻度が高い．

抗EGFR治療薬による皮膚障害

ゲフィチニブやエルロチニブ(EGFRチロシンキナーゼ阻害薬)，セツキシマブやパニチムマブ(抗EGFR抗体)では，特徴的な「ざ瘡様皮疹」が出現する．見た目はニキビ(ざ瘡)に類似するが，無菌性の炎症であるため，ステロイド外用を適切に行うことが大切である．長期的には皮膚乾燥や爪囲炎なども問題となる．

皮疹は治療効果予測因子でもあるが，患者のQOLを損ねるため，ステロイドや保湿剤の塗布などのスキンケアがきわめて重要である．

神経障害

比較的よくみられるのは手足のしびれなど末梢神経障害であるが，中枢神経障害や自律神経障害を生じることもある．

プラチナ系抗がん剤(シスプラチン・オキサリプラチンなど)や，タキサン系抗がん剤(パクリタキセル)，ビンカアルカロイド系抗がん剤(ビンクリスチンなど)，ボルテゾミブなどで頻度が高い．

神経障害の予防法は確立されておらず，確実な治療法もないため，患者教育や，症状や徴候の早期発見・早期対応が重要となる．患者からの訴えは必ずしも多くないため，医療者側から症状や徴候を聞き出す工夫が必要である．

肺障害

抗がん剤投与後2カ月以内に出現する早発性の肺障害として，間質性肺炎，肺浮腫，胸水貯留などがあり，2カ月以降に出現する遅発性のものは肺線維症が主である．

ブレオマイシン，マイトマイシンC，シクロホスファミド，ゲムシタビンなどが知られているが，分子標的治療薬であるゲフィチニブやエルロチニブにおいても重篤な肺障害が問題となる．

使用する抗がん剤について肺障害の起こる時期と頻度，危険因子を把握し，治療中は早期診断に努める．発症したら薬剤中止とステロイド投与などを行う．

おわりに

本稿では紹介していないが，循環器障害(心毒性，高血圧，血栓塞栓症)，腎障害，晩期障害としての二次発がんなども重要な項目であり，成書を参照されたい．

文献

1) がん情報サービスホームページ
http://ganjoho.jp/public/dia_tre/attention/chemotherapy/about_chemotherapy.html
2) 日本癌治療学会：制吐薬適正使用ガイドライン，金原出版，2010
3) Smith TJ, et al：2006 update of recommendations for the use of white blood cell growth factors；An evidence-based clinical practice guideline. J Clin Oncol 24：3187-3205, 2006