Review

The Role of Chemotherapy in Metastatic Gastric Cancer

FELICE PASINI[1], ANNA PAOLA FRACCON[2] and GIOVANNI DE MANZONI[3]

[1]*Oncology Department, S. Maria della Misericordia Public Hospital, ULSS 18 Rovigo, Italy;*
[2]*Medical Oncology Unit, Dr. Pederzoli Private Hospital, Peschiera del Garda, Verona, Italy;*
[3]*Upper Gastrointestinal Surgical Division, University of Verona, Verona, Italy*

Abstract. *In the setting of metastatic or inoperable gastric cancer, the current evidence shows that chemotherapy improves survival in comparison to best supportive care and that combination chemotherapy is superior to monotherapy in terms of survival, response rate and symptom control. Many randomized phase III trials tested different combinations of therapies showing better outcome for cisplatin-containing schedules. In recent years, new drugs, such as docetaxel, oxaliplatin, irinotecan, capecitabine and S1 have also been tested in phase III studies. Unfortunately, in all of these studies, but one, the median survival remained below one year. Although there are no internationally accepted standard regimens, in Europe, ECF (epirubicin, cisplatin, fluorouracil) has been considered the reference regimen; in the US cisplatin-fluoropyrimidine combinations are mainly used, while in Japan, cisplatin with S1 has become the standard. Currently, various targeted agents are being tested in clinical trials and promising data have been recently published for trastuzumab-containing therapy, with median survival exceeding one year. As regards progressive disease, about 20%-50% of patients receive second line chemotherapy and, although two phase III studies reported survival benefit with single-agent chemotherapy, the role of chemotherapy in this setting still needs to be defined. Despite the progress of recent decades, metastatic gastric cancer remains an incurable disease, and treatment options should primarily take into account the quality of life and quality-adjusted survival of patients. The hope for the future is that tailored interventions based on new cytotoxic drugs, targeted therapies and integration of molecular determinants may help to improve the current treatments.*

Correspondence to: Felice Pasini, MD, Struttura Operativa Complessa di Oncologia, Ospedale S. Maria della Misericordia, Viale Tre Martiri, 140, 45100 Rovigo, Italy. Tel: +39 0425394468, Fax: +39 0425394584, e-mail: pasini.felice@azisanrovigo.it

Key Words: Chemotherapy, metastatic gastric cancer, review.

Despite improvement in the diagnosis of gastric cancer, in the Western world, approximately two thirds of gastric cancer patients have inoperable locally advanced or metastatic disease at diagnosis or develop a recurrence after surgery. Patients with inoperable, recurrent or metastatic tumours are incurable and prognosis is of only few months with best supportive care (BSC). In this setting, systemic chemotherapy prolongs survival and improves symptom palliation, although these benefits are to be weighed against treatment-related toxicities.

The first-generation chemotherapy protocols were based on 5-fluorouracil (5-FU), the most extensively used single agent, cisplatin and anthracyclines. Recent phase III trials evaluated new drugs such as capecitabine, oxaliplatin, docetaxel, paclitaxel, irinotecan, S-1 and monoclonal antibodies (1-6); other new drugs are currently under evaluation in phase II and III clinical studies.

Although a large number of chemotherapy regimens have been tested in randomized studies, there is no internationally accepted standard of care and uncertainty remains regarding the most appropriate regimen.

In the setting of metastatic gastric cancer, the current evidence shows that: i) chemotherapy improves survival in comparison to BSC; ii) combination chemotherapy improves survival compared to single-agent 5-FU and produces a higher response rate, albeit, at the cost of higher toxicity.

First-line Treatment

Chemotherapy versus best supportive care. In the 1980s and 1990s, many trials demonstrated that 5-FU-based regimens provided superior survival in patients with advanced gastric cancer when compared with BSC (7-9). The median survival of BSC (4.3 months) was at least doubled in favour of chemotherapy, resulting in a hazard ratio (HR) of 0.37 (95% confidence interval, CI=0.24-0.55) and a response of 33%-50%. Since then, BSC is no longer considered as an appropriate control arm (10).

Table I. *Principal characteristics of the randomized studies.*

	No. of pts	% metastatic	% GEJ	Primary end point	Author, year (ref)
FAMTX	108	82	NR	OS* RR*	Wils *et al*., 1991 (14)
FAM	105	87.4	NR		
EAP	30	70	NR	RR	Kelsen *et al*., 1992 (15)
FAMTX	30	63	NR		
ECF	126	57.7	20	OS* RR*	Waters *et al*., 1999 (16)
FAMTX	130	57.7	24		
PF	134	86	NR	RR	Vanhoefer *et al*., 2000 (17)
ELF	132	83	NR		
FAMTX	133	83	NR		
PELF	100	84	NR	RR*	Cocconi *et al*., 2003 (18)
FAMTX	100	85	NR		
MCF	285	64	22.5	OS	Ross *et al*., 2002 (19)
ECF	289	55	21		
DCF	159	96	19	TTP*	Van Cutsem *et al*., 2006 (4)
PF	158	97	25		
FLO	112	97	NR	PFS	Al-Batran *et al*., 2008 (1)
FLP	108	91	NR		
IF	172	96	20	TTP	Dank *et al*., 2008 (3)
PF	165	95	19		
EOX	239	76	22.2	OS†	Cunningham *et al*., 2008 REAL 2 (2)
ECX	241	77	28.2		
EOF	235	77	23.4		
ECF	249	79.5	28.9		
XP	160	100	NR	PFS†	Kang *et al*., 2009 (25)
PF	156	100	NR		
S-1	160	NR	NR	OS*	Koizumi *et al*., 2008 SPIRITS (27)
P-S1	156		NR		
P-S1	521	95.6	15.7	OS	Ajani *et al*., 2010 FLAGS (28)
PF	508	96	17.3		
PF/PX-trastuzumab	298	97	19.7	OS*	Bang *et al*., 2010 ToGA (5)
PF/PX	296	97	16.6		
PF/PX-bevacizumab	387	95	14	OS	Kang *et al*., 2010 AVAGAST (6)
PF/PX	387	98	13		

GEJ: gastroesophageal junction tumor. *Statistically significant, †not inferior. NR: Not reported; RR: response rate; OS: overall survival, PFS: progression-free survival; TTP: time to progression. FAM (fluoruracil, doxorubicin and mitomycin), FAMTX (high-dose fluoruracil, adriamycin and methotrexate), EAP (etoposide, adriamycin, cisplatin), ECF (epirubicin, cisplatin, fluorouracil), PF (cisplatin and fluorouracil), ELF (etoposide, leucovorin, fluorouracil), PELF (cisplatin, epirubicin, leucovorin, fluorouracil), MCF (mitomycin, cisplatin, fluorouracil), DCF (docetaxel, cisplatin, fluorouracil), FLO (fluorouracil, leucovorin, oxaliplatin), FLP (fluorouracil, leucovorin, cisplatin), EOF (epirubicin, oxaliplatin, fluorouracil), EOX (epirubicin, oxaliplatin, capecitabine), XP (capecitabine, cisplatin), P-S1 (cisplatin, S1), PX (cisplatin, capecitabine).

Single-agent therapy versus combination therapy. A recent meta-analysis (10) demonstrated that combination chemotherapy had a statistically significant and consistent survival advantage compared with single-agent therapy (HR=0.80, 95% CI=0.72-0.89). Median survival was 8.3 *vs*. 6.7 months, median progression-free survival (PFS) 5.6 *vs*. 3.6 months and the pooled objective response rate 35% *vs*. 18% in the combination and single-agent arms, respectively. Overall, toxicity was higher with combination chemotherapy, but the difference was not statistically significant, probably because of dissimilarities in reporting. Death due to toxicity was different between treatment arms at 1.9% for combination and 0.9% for single-agent 5-FU (odds ratio, OR=1.69; 95% CI=0.58-4.94).

Combination regimens. Regimens not including cisplatin. The FAM regimen (5-FU, doxorubicin and mitomycin) was the first reference combination; preliminary studies reported

Table II. *Results of the randomized studies*.

	% response	Median PFS/TTP	Survival			Author, year (ref)
			Median†	1-year	2-year	
FAM	9	NR	29 weeks	22	0	Wils *et al*., 1991 (14)
FAMTX	41*		42 weeks*	41	9	
EAP	20	NR	6.1	7	0	Kelsen *et al*., 1992 (15)
FAMTX	33	NR	7.3	17	10‡	
FAMTX	21	3.3	6.1	22	5	Waters *et al*., 1999 (16)
ECF	46*	7.4*	8.7*	37	14	
PF	20	4.1	7.2	27	10‡	Vanhoefer *et al*., 2000 (17)
ELF	9	3.1	7.2	25	10‡	
FAMTX	12	3.3	6.7	28	10‡	
PELF	39*	5.9	7.7	30.8	15.7	Cocconi *et al*., 2003 (18)
FAMTX	22	3.5	6.9	22.4	9.5	
MCF	44	7	8.7	32.7	14.2	Ross *et al*., 2002 (19)
ECF	42	7	9.4	40.2	15.8	
PF	25	3.7	8.6	32	9	Van Cutsem *et al*., 2006 (4)
DCF	37	5.6*	9.2*	40	18	
FLO	35	5.8	10.7	45	14	Al-Batran *et al*., 2008 (1)
FLP	24.5	3.9	8.8	40	16	
IF	32	5	9	37	<10‡	Dank *et al*., 2008 (3)
PF	26	4.2	8.7	31	<10‡	
ECF	40.7	6.2	9.9	37.7	15-20‡	Cunningham *et al*., 2008 REAL 2 (2)
ECX	46.6	6.7	9.9	40.8	15-20‡	
EOF	42	6.5	9.3	40.4	15-20‡	
EOX	47.9	7	11.2	46.8	15-20‡	
XP	46*	5.6	10.4	37	10‡	Kang *et al*., 2009 (25)
PF	32	5	9.3	37	10‡	
S-1	31	4	11	46.7	15	Koizumi *et al*., 2008 SPIRITS (27)
P-S1	54*	6*	13*	54	23.6	
PF	32	5.5	7.9	30	10‡	Ajani *et al*., 2010 FLAGS (28)
P-S1	29	4.8	8.6	30	10‡	
PF/PX	34.5	5.5	11.1	45‡	15‡	Bang *et al*., 2010 ToGA (5)
PF/PX-trastuzumab	47.3*	6.7*	13.8*	57‡	25	
PF/PX	29.5/37	5.3	10.1	42‡	17‡	Kang *et al*., 2010 AVAGAST (6)
PF/PX-bevacizumab	38*/46	6.7*	12.1	52‡	17‡	

*Statistically significant; †months, unless specified differently; ‡derived from the curve; NR: Not reported; RR: response rate, PFS: progression-free survival; TTP: time to progression. For abbreviations see Table I.

a response rate of more than 40%, with a favourable toxicity profile (11-12). However, a randomized three-arm trial performed by the North Central Cancer Treatment Group (NCCTG) including 305 patients with advanced gastric and pancreatic cancer, compared 5-FU single-agent, 5-FU plus doxorubicin, and FAM; however, response rates and survival were not statistically different (13).

The European Organization for Research and Treatment of Cancer (EORTC) then compared the FAM and FAMTX (high-dose 5-FU, adriamycin and methotrexate) regimens; FAMTX conferred a significantly superior response rate and improved overall survival (14). In turn, FAMTX was compared with other regimens (Tables I and II) (15-18).

Regimens including cisplatin. In a small U.S. study (15), FAMTX provided similar results to EAP (etoposide, adriamycin, cisplatin) but was significantly less toxic. In a UK trial (16) ECF (epirubicin, cisplatin, 5-FU) was superior both in terms of response rate (45% *vs*. 21%) and median survival (8.9 *vs*. 5.7 months); the authors concluded that the ECF regimen should be regarded as the standard treatment in advanced esophagogastric cancer.

In the EORTC trial (17), there were no statistical differences in response rate and survival between FAMTX, PF (cisplatin and 5-FU) and ELF (etoposide, leucovorin, 5-FU). An Italian trial (18) showed that PELF (cisplatin, epirubicin, leucovorin, 5-FU) was statistically superior in terms of response rate, but not survival.

A further UK study (19) compared ECF with the similar MCF regimen in which the doses of 5-FU were increased and epirubicin was substituted for mitomycin. Survival and response rate were not statistically different, but quality of life (QoL) was better with ECF. The study concluded that ECF should remain the reference regimen. In this study, one third of the patients had inoperable locally advanced disease; in this subset, median survival was 11.8 months with ECF and 12.6 months with MCF (p=0.4), one-year survival was 47.7% and 50.4% with ECF and MCF, respectively. This is the study with the highest percentage of patients with non-metastatic disease and the only one in which separate data for this subset have been reported; in general, the other series included fewer than 20% of patients with locally advanced disease.

As a whole, the meta-analysis (10), comparing the three-drug (FU/cisplatin/anthracycline) with the two-drug regimens (5-FU/cisplatin or 5-FU/anthracycline) demonstrated a small, but statistically significant benefit in overall survival in favour of the three-drug combinations (2 months and 1 month, respectively).

Regimens including new chemotherapy agents. New agents, such as docetaxel, oxaliplatin, irinotecan, capecitabine, S-1 have been tested in randomized trials in the recent years. Many phase II studies have shown that taxanes (paclitaxel and docetaxel) produce response rates in the range of 22% to 65%. To date, no randomized phase III trials have been published with paclitaxel, while three phase II randomized studies demonstrated that docetaxel-based regimens had a response rate of approximately 40% and gave a median survival of 10 months (20-22).

Following these findings, docetaxel in combination with cisplatin and 5-FU (DCF) was tested in the V325 phase III trial against the US reference PF (4). The DCF arm demonstrated statistically superior time to progression (6.6 *vs*. 3.7 months), response rate (37% *vs*. 25%) and overall survival (9.2 *vs*. 8.6 months). DCF was also associated with a better preservation of QoL and maintenance of clinical benefit compared with PF (23, 24). Based on these results, the DCF regimen was approved for use by the US Food and Drugs Administration. However, it is of note that the DCF arm experienced a higher rate of complicated neutropenia (29% *vs*. 12%) necessitating granulocyte colony-stimulating factor prophylaxis. Moreover, the median patient age of 55 years was well below the median age of the patients included in other trials and needs to be considered when applying these findings to the general population.

The meta-analysis (10), pooling the results of three docetaxel-based protocols, reported that the HR for overall survival favoured the docetaxel-containing regimens; however, without reaching statistical significance (HR=0.93, 95% CI=0.75-1.15). PFS was, on the whole, not statistically different, but the results were flawed by the differences between the schedules. The objective response rate was 36% in the docetaxel-containing arms *vs*. 31% in the control arms, corresponding to an OR of 1.30 (95% CI=0.98-1.72), with a non-significant advantage for the docetaxel-containing regimens.

Al-Batran *et al*. (1) compared the FLO regimen (5-FU, leucovorin, oxaliplatin) *vs*. the FLP regimen (5-FU, leucovorin, cisplatin). There was only a trend in favour of FLO in PFS (the primary end point), but no difference in overall survival (OS). However, in the subset of patients older than 65 years, FLO resulted in significantly superior response rates (41.3% *vs*. 16.7%; p=0.012), time to treatment failure (5.4 *vs*. 2.3 months; p=0.001), PFS (6.0 *vs*. 3.1 months; p=0.029) and an improved OS (13.9 *vs*. 7.2 months) as compared with FLP. Overall, FLO was associated with reduced toxicity and seemed to be associated with improved efficacy in the elderly.

The REAL-2 (2), a UK non-inferiority phase III trial, compared ECF, ECX (X: capecitabine), EOF (O: oxaliplatin), and EOX (O: oxaliplatin; X: capecitabine). Median survival in the ECF, ECX, EOF and EOX groups was 9.9, 9.9, 9.3 and 11.2 months, respectively; one-year survival rates were 37.7%, 40.8%, 40.4% and 46.8%, respectively; response rate (41%-48%) and non-haematological toxicity were not statistically different. In the secondary analysis, OS was superior with EOX compared with ECF (HR=0.80, 95% CI=0.66-0.97; p=0.02). There were significantly lower incidences of grade 3 or 4 neutropenia, thromboembolism, grade 2 alopecia, and elevation of serum creatinine levels in the oxaliplatin groups than in the ECF group.

In the ML17032 trial with a prevalent Asian population, capecitabine with cisplatin showed significant non-inferiority for PFS *vs*. PF; the OS favoured the oral regimen (HR=0.85, 95% CI=0.65-1.11) with median survival times of 10.4 and 9.3 months in favour of capecitabine, without reaching, however, statistical significance (25).

These two trials (2, 25) consistently demonstrated the non-inferiority of capecitabine in comparison to 5-FU and also suggested better outcome in patients receiving capecitabine. This finding was confirmed by a recent meta-analysis (26) of individual patients data from the ML17032 and REAL-2 trials. The median OS was 285 days for patients treated with 5-FU and 322 days for patients treated with capecitabine, giving an unadjusted HR of 0.87 (95% CI=0.77–0.98) in favour of capecitabine (p=0.027). Besides the problem of whether one month gain in median OS is clinically relevant, additional advantages of capecitabine over continuous infusion of 5-FU include the convenience of oral chemotherapy, which is generally more acceptable to

patients, lack of potential morbidity associated with central venous access and the opportunity to make dose adjustments in order to manage toxicity.

Another novel oral fluoropyrimidine (S-1), providing a response rate exceeding 40% in phase II studies, has been tested in two randomized trials (27, 28).

The Japanese SPIRITS trial (27) compared S-1 plus cisplatin with S-1 alone. Median PFS (6.0 *vs*. 4.0 months; $p<0.0001$) and OS (13.0 *vs*. 11.0 months; $p=0.04$) were significantly longer in the combination group. Response was also significantly improved in patients with target tumors and assigned to S-1 plus cisplatin (54% *vs*. 31%). On the basis of these findings, the S-1 plus cisplatin has become the standard of care in Japan. A possible criticism of this study is the lack of information about the advantage of S-1 over 5-FU when each drug is combined with cisplatin.

In Western populations, the First-Line Advanced Gastric Cancer Study (FLAGS) compared S-1 with 5-FU, both when combined with cisplatin (28). Median OS was 8.6 months in the cisplatin/S-1 arm and 7.9 months in the PF arm ($p=0.2$). On the other hand, the study showed statistically significant safety advantages for the S-1-based combination, regarding the rates of G3-4 neutropenia (32% *vs*. 63.6%), stomatitis (1.3% *vs*. 13.6%), renal function (5.2% *vs*. 9.3%) and treatment related deaths (2.5% *vs*. 4.9%).

Although the SPIRITS trial was the first randomized trial to break the apparently insuperable wall of 12 months, this result was not repeated in FLAGS. This inconsistency in survival may be explained by some relevant differences between the two studies. In the SPIRITS trial, only 65% of patients had metastatic disease compared with 96% of those in FLAGS; 74% and 31% of patients, respectively, received second-line therapy; Japanese investigators are highly experienced with excellent facilities, while FLAGS was a non-Asian global trial; despite dose adjustment, different pharmacokinetics due to ethnic variations cannot be excluded.

Thus, the future role of S-1 in gastric cancer is still unclear, but its use in three-drug regimens in order to improve tolerability of DCF or ECF is worthy of study.

Recent data were reported on the use of weekly irinotecan in combination with 5-FU and leucovorin (IF protocol) *vs*. PF. Time to progression (TTP) and OS were similar in both arms and the results on the non-inferiority of IF were borderline. However, the toxicity profile favoured the irinotecan arm over the PF arm in terms of discontinuation due to toxicity (10.0% *vs*. 21.5%), febrile neutropenia (4.8% *vs*. 10.2%) and stomatitis (2% *vs*. 16.9%). The authors suggested that IF may provide a viable platinum-free treatment alternative (3).

As for irinotecan, the meta-analysis reported that the irinotecan-containing combinations resulted in improved, although not statistically superior, median survival times (9.8 *vs*. 8.3 months, HR=0.86, 95% CI=0.73-1.02), objective response rates (40% *vs*. 30%, OR=1.77, 95% CI=0.85-3.69) and a lower rate of treatment discontinuation and deaths due to toxicity. Therefore, irinotecan-containing regimens should be considered as suitable alternatives to platinum combinations in consideration of the results and of the different toxicity profile (*i.e*. absence of neurotoxicity, no significant renal toxicity, less nausea and vomiting, no need for hyperhydration).

In conclusion, cisplatin is the basis for combination regimens all over the world, with geographical variations for the partner drugs. In Europe, ECF has long been considered the reference regimen; in the US cisplatin-fluoropyrimidine is mainly used, while in Japan, cisplatin-S1 has become widely accepted.

Regimens including targeted agents. Phase III studies. In recent years, different classes of targeted agents, such as monoclonal antibodies directed against the epidermal growth factor receptor 1 (EGFR) and 2 (HER-2), tyrosine kinase inhibitors (TKIs) and angiogenesis inhibitors have been tested in clinical trials.

To date, the Trastuzumab for gastric cancer (ToGA) trial (5) is the only phase III study already published which enrolled 594 patients with immunohistochemical overexpression of *HER2* or gene amplification by fluorescence *in situ* hybridization (FISH). HER2 overexpression was positive in 21% of gastric carcinomas and in 33.2% of gastroesophageal junction carcinomas. The two treatment arms compared a chemotherapy regimen consisting of capecitabine or fluorouracil plus cisplatin with and without trastuzumab. The primary endpoint was OS. Median OS was 13.8 months (95% CI=12-16) in the trastuzumab arm compared with 11.1 months in the chemotherapy alone arm (HR=0.74; 95% CI=0.60-0.91; $p=0.0046$). There was no difference in the rate of grade 3 or 4 adverse events and the percentage of cardiac events was identical in the two arms (<1%). The response rate was 47.3% and 34.5% ($p=0.0017$) in the trastuzumab arm and control arm, respectively. An explorative analysis showed that in the subgroup of tumors with high HER2 expression, the HR was 0.65 (95% CI=0.51-0.83) and median survival was 16.0 months (95% CI=15-19) in patients receiving trastuzumab, compared with 11.8 months (95% CI=10-13) for the controls. It has been proposed that trastuzumab be considered in combination with chemotherapy as a new standard option for patients with HER2-positive advanced gastric or gastroesophageal junction cancer.

The anti-VEGF (vascular endothelial growth factor) monoclonal antibody bevacizumab was tested in the AVAGAST phase III trial (6) that enrolled 774 patients and compared the combination of cisplatin capecitabine (or fluorouracil) with and without bevacizumab. The primary end point was OS. The difference was not statistically significant and therefore the trial failed to met the primary endpoint; median OS was 10.1 and 12.1 months in the control and bevacizumab arms, respectively (HR=0.87; $p=0.1$); however, there was a significant improvement in PFS (5.3 *vs*. 6.7 months) and ORR (37% *vs*. 46%) with an

acceptable safety profile for bevacizumab treated patients, except for hypertension 6.2% *vs*. 0.5% and gastrointestinal (GI) perforation 2.3% *vs*. 0.3%.

Lapatinib (TKI of EGFR and HER-2), apatinib (TKI inhibitor of VEGFR), catumaxomab (anti-CD3 and anti-EpCAM monoclonal antibody), ramucirumab (anti-VEGFR-2 monoclonal antibody) are at present under evaluation in phase III trials for metastatic gastric cancer (29).

Phase II trials. Bevacizumab was tested in combination with irinotecan-cisplatin (30) or with docetaxel-oxaliplatin (31), demonstrating a PFS and OS of 7-8 and of 11-12 months, respectively. The response rate was in the range of 65%-79%; the most relevant toxicities consisted of neutropenia (34%) and GI perforation (6%-8%).

Cetuximab (anti-EGFR monoclonal antibody) was tested in different schedules (fluorouracil/capecitabine plus oxaliplatin or irinotecan, docetaxel plus oxaliplatin) (32-35). The response rate was about 50% (range 41%-65%) and the TTP 6 months (range 5-8 months). The principal toxicities were neutropenia (40%) and acne-like rash (20%). A phase III trial of capecitabine and cisplatin with or without cetuximab is now recruiting patients (29).

Panitumumab (anti-EGFR monoclonal antibody) is currently being tested in combination with EOX in the REAL-3 phase III trial in which OS is the primary end point (29, 36).

Sunitinib (TKI) as a single agent was evaluated in ≥second line setting achieving mainly a disease stabilization in 33% of the patients (range 31%-34.7%) and a PFS of 1.4-2.3 months. However the clinical value of these results was deemed insufficient and the studies considered negative (37-38).

Sorafenib (TKI) in combination with docetaxel and cisplatin in first line achieved a response rate of 41%, a PFS of 5.8 months and an OS of 13.6 months; the toxicity was haematological, with 64% of severe neutropenia (39).

Everolimus (mTOR inhibitor) in second and third line settings (40) produced only disease stabilization in 56% of the patients without unexpected toxicities. PFS and OS were 2.7 and 10.1 months, respectively. Two phase III trials in pretreated patients are ongoing (29).

In summary, many randomized studies reported the inclusion also of adenocarcinoma of the gastroesophageal junction which represented a median of 20% of the patients (range 13%-28.9%) (1-6, 15, 16, 19, 28); two old studies also included esophageal cancer (16, 19). Since the 7th TNM Cancer Staging edition classified gastroesophageal junction tumours as esophageal cancer, in future trials it will be worthwhile having separate data in order to avoid possible confounding factors.

Despite the positive impact of chemotherapy, response was achieved in only about one third of the cases (median 31.5%, range 9%-54%).

The 15 studies had different end points: OS in 6, TTP/PFS in 4, RR in 3, OS and RR in 2. The results are shown in Table III. Whichever the primary end point, median survival was statistically superior in 5 studies (4, 5, 14, 16, 27) and showed non inferiority in 2 (2, 25). Regrettably, survival remained below 12 months in all but two trials (5, 27), and 1-year survival ranged from 7% to 57% (median 37%) (Table II). However the survival curves show no plateau and at 2 years, survival was only about 10% (range 0%-25%). It is still an open question whether the survival benefit achieved by three-drug *vs*. two-drug combinations compensates for the additional toxicity suffered by the patients.

Table III. *Primary end points and outcome of the randomized trials (n 15).*

	OS	TTP/PFS	RR	OS and RR
Statistically significant	2	1	1	2
Statistically not significant	3	2	2	
Statistically not inferior	1	1		

RR: Response rate; TTP: time to progression; PFS: progression-free survival; OS: overall survival.

Second-line Treatment

After disease progression, the role of second-line chemotherapy is even less defined than that of first-line, both in terms of efficacy and toxicity profile. However, this information is meaningful because 20%–50% of patients with advanced gastric cancer receive second-line chemotherapy (41-43). A pooled analysis of 1080 patients from phase III studies testing first-line fluorouracil-based regimens suggested that about 20% of patients with progressive disease received second-line treatment, with a response rate of 13.3% and median OS of 5.6 months since starting the second-line chemotherapy (44). It is important to note that most trials on second-line therapy have been conducted in Japan, Korea, and Italy, where the practice of offering second-line treatment to patients with advanced gastric cancer is common.

Phase III trials. The critical point is that only two phase III trials (45, 46) have been reported so far, while the remaining studies were phase II and did not provide direct comparison with BSC. A small study (45) compared irinotecan with BSC, but was prematurely closed due to poor accrual, with only 40 of an expected 120 patients enrolled. There was stabilization in 58% of patients, but no objective responses; on the other hand, there was a 44% improvement in symptoms in the active arm, compared to 5% in the control arm. OS, which was the primary end point, was 123 *vs*. 72 days in the treatment and control arm, respectively (p=0.003). Despite the small size of the study, the authors concluded that second-line chemotherapy could be considered as a proven option in gastric cancer.

Table IV. *Results of the phase II studies*.

Drug/combination (references)	Number of studies	Median number of patients (range)	RR, % (range)	DCR, % (range)	TTP, months (range)	OS, months (range)
Irinotecan (48-51, 58, 60-63)	9	29 (8-87)	25.5 (0-52)	55 (0-64.2)	3.5 (2.6-5.3)	8 (5-10.6)
FOLFIRI/CAPIRI (47, 52-57, 59, 76)	9	38 (29-131)	18 (10-29)	46 (31-71)	3.2 (2.2-4.1)	6.5 (5-10.9)
Paclitaxel (65, 79-89)	12	38.5 (4-85)	20.6 (0-26)	57.5 (25-77)	3.5 (2.1-6.4)	7.8 (5-13)
Docetaxel (64-78)	15	34 (20-154)	17 (9.4-38)	55 (22-80)	3.95 (2.5-5.2)	6.5 (5-8.3)
S-1 (93-95)	3	32 (21-43)	16.5 (0-26.5)	48 (47-56)	3 (2.7-3.3)	8.1 (7.2-9)
FOLFOX/FLOX (90-92)	3	52 (26-59)	23 (4-26)	4 (35-58)	3 (2.5-4.3)	7.3 (6.6-8)

FOLFIRI: Fluorouracil, leucovorin, irinotecan; CAPIRI: capecitabine, irinotecan; FOLFOX: fluorouracil, leucovorin, oxaliplatin; FLOX: fluorouracil, leucovorin, oxaliplatin; RR: response rate; DCR: disease control rate; TTP: time to progression; OS: overall survival after starting second-line therapy.

Very recently, a Korean study (46) including 193 patients reported survival improvement in patients with progressive disease receiving chemotherapy (docetaxel or irinotecan) compared to those with BSC (5.1 and 3.8 months, respectively, p=0.009). However, no data regarding response rate, QoL or symptom control were reported.

These two studies showed that second-line chemotherapy has proven benefit and should be offered to medically fit patients willing to receive further treatment.

Phase II trials. Irinotecan has been tested mostly in combination with cisplatin and fluoropyrimidines (FOLFIRI/CAPIRI or similar schedules). The studies included a median of 33 patients each (range 8-131); on the whole the results were consistent over the studies showing a median response rate of about 21% (from 0% to 52%) and a disease control rate ranging from 0% to 77% (median 47%). Median TTP and survival were reported to be approximately 3.3 (range 2.2-5.3) and 7.5 (range 5-10.9) months, respectively. Neutropenia was the most common relevant toxicity (11%-45%), followed by anaemia (3%-57%), diarrhoea (3% to 19%) and anorexia (12%-17%) (47-63, 76).

Docetaxel was mostly used in combination with other drugs (fluorouracil/capecitabine, cisplatin, epirubicin, oxaliplatin) achieving response rates ranging from 9% to 38% (median 17%), disease control rates of 50% (22%-80%), TTP of 3.9 (from 2.4 to 5.2) months and survival of 6.6 (from 6 to 8.9) months. The most frequent G3-4 toxicities consisted of neutropenia in about 27% (12%-71%) of the patients, febrile neutropenia in 11.5% and fatigue-asthenia in 32% (64-78).

Paclitaxel was prevalently used as weekly single agent and in a few studies it was combined with fluoropyrimidines. The studies included a median of 38 patients (from 4 to 85); the response rate was reported to be about 21% (0%-35%), disease control rate between 25% and 77% (median 63.5%), median TTP 3.6 (range 2.6-6.4) months and survival 7.8 (range 5-13.9) months. G3-4 toxicities were usually haematological, such as neutropenia in about 23% (2%-62%) and anaemia in 12% (1%-41%) of the cases; peripheral neuropathy was generally reported to be below 10% (65, 79-89).

Oxaliplatin-fluorouracil combinations have also been tested as a second- and third-line regimens for advanced gastric cancer with response rates from 4% to 26%, disease control rates of about 50%, TTP of 3 to 4 months and survival of about 7 months. Severe neutropenia was reported to be about 15% (90-92).

Some reports have been published with single agent S-1 (93-94), S-1 plus mitomycin (95) and fluorouracil plus mitomycin (96). The disease control rate was about 50% and the TTP 3 months.

In summary, two randomised phase III studies support the use of single agent chemotherapy (irinotecan or docetaxel) in progressing patients with good performance status; however, since the survival gain is only of 4 to 6 weeks, further research should also focus on QoL items in order to ensure that treated patients do not suffer from unnecessary toxicities. In the clinical setting, the decision about treating patients with progressive disease should rely on careful selection based on performance status, history of agents used, degree of response to the first-line therapy and amount of metastatic disease.

In conclusion, despite the progress of recent decades, metastatic gastric cancer remains an incurable disease; although small subsets of patients may benefit from survival prolongation, the overall survival benefit achieved is small and does not exceed a couple of months in first-

and even less in second-line therapy. Because of the toxicity suffered by the patients, it remains an open question, whether these results are clinically relevant. The hope for the future is that tailored interventions based on new cytotoxic drugs, targeted therapies, identification of predictive or prognostic markers and integration of molecular determinants may help to select patients likely to benefit from treatment.

References

1 Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, Rethwisch V, Seipelt G, Homann N, Wilhelm G, Schuch G, Stoehlmacher J, Derigs HG, Hegewisch-Becker S, Grossmann J, Pauligk C, Atmaca A, Bokemeyer C, Knuth A, Jäger E; Arbeitsgemeinschaft Internistische Onkologie: 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(9)*: 1435-1442, 2008.

2 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J and Norman AR: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med *358(1)*: 36-46, 2008.

3 Dank M, Zaluski J, Barone C, Valvere V, Yalcin S, Peschel C, Wenczl M, Goker E, Cisar L, Wang K and Bugat R: 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(8)*: 1450-1457, 2008.

4 Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodriguez A, Fodor M, Chao Y, Voznyi E, Risse ML and Ajani JA: 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(31)*: 4991-4997, 2006.

5 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J and Kang YK, for the ToGA Trial Investigators: 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, 2010.

6 Kang Y, Ohtsu A, Van Cutsem E, Rha SY, Sawaki A, Park S, Lim H, Wu J, Langer B and Shah JMA: 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). Proc ASCO *28(15S) (Part II)*: Abstr 4007, 2010.

7 Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA and Rausch M: Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer *72*: 37-41, 1993.

8 Glimelius B, Hoffman K, Haglund U, Nyrén O and Sjödén PO: Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. Ann Oncol *5*: 189-190, 1994.

9 Pyrhonen S, Kuitumen T, Nyandoto P and Kouri M: Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus best supportive care alone in patients with non-resectable gastric cancer. Br J Cancer *71*: 587-591, 1995.

10 Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J and Fleig WE: Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev Mar *17(3)*: CD004064. Review, 2010.

11 MacDonald JS, Schein PS, Woolley PV, Smythe T, Ueno W, Hoth D, Smith F, Boiron M, Gisselbrecht C, Brunet R and Lagarde C: 5-Fluorouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. Ann Intern Med *93*: 533-536, 1980.

12 Douglass HO Jr, Lavin PT, Goudsmit A, Klaassen DJ and Paul AR: An Eastern Cooperative Oncology Group evaluation of combinations of methyl-CCNU, mitomycin C, adriamycin, and 5-fluorouracil in advanced measurable gastric cancer (EST 2277). J Clin Oncol *2*: 1372-1381, 1984.

13 Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, Windschitl HE, Twito DI, Marschke RF and Foley JF: 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, 1985.

14 Wils JA, Klein HO, Wagener DJ, Bleiberg H, Reis H, Korsten F, Conroy Th, Fickers M, Leyvraz S, Buyse M and Duez N for the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group: Sequential high-dose methotrexate and fluorouracil combined with doxorubicin-A step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. J Clin Oncol *9(5)*: 827-831, 1991.

15 Kelsen D, Atiq OT, Saltz L, Niedzwiecki D, Ginn D, Chapman D, Heelan R, Lightdale C, Vinciguerra V and Brennan M: FAMTX *versus* etoposide, doxorubicin, and cisplatin: a random assignment trial in gastric cancer. J Clin Oncol *10(4)*: 541-548, 1992.

16 Waters JS, Norman A, Cunningham D, Scarffe JH, Webb A, Harper P, Joffe JK, Mackean M, Mansi J, Leahy M, Hill A, Oates J, Rao S, Nicolson M and Hickish T: Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. Br J Cancer *80(1/2)*: 269-272, 1999.

17 Vanhoefer U, Philippe R, Hansjochen W, Ducreux MP, Lacave AJ, Van Cutsem E, Planker M, Guimaraes Dos Santos J, Piedbois Pa, Paillot B, Bodenstein H, Schmoll HJ, Bleiberg H, Nordlinger B, Couvreur ML, Baron B and Wils JA: Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin *versus* etoposide, leucovorin, and fluorouracil *versus* infusional 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(14)*: 2648-2657, 2000.

18 Cocconi G, Carlini P, Gamboni A, Gasperoni S, Rodinò C, Zironi S, Bisagni G, Porrozzi S, Cognetti F, Di Costanzo F, Canaletti R, Ruggeri EM, Camisa R and Pucci F on behalf of the Italian Oncology Group for Clinical Research: Cisplatin, epirubicin, leucovorin and 5-fluorouracil (PELF) is more active than 5-fluorouracil, doxorubicin and methotrexate (FAMTX) in advanced gastric carcinoma. Ann Oncol *14*: 1258-1263, 2003.

19 Ross P, Nicolson M, Cunningham D, Valle J, Seymour M, Harper P, Price T, Anderson H, Iveson T, Hickish T, Lofts F and Norman A: 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(8)*: 1996-2004, 2002.

20 Roth AD, Fazio N, Stupp R, Falk S, Bernhard J, Saletti P, Köberle D, Borner MM, Rufibach K, Maibach R, Wernli M, Leslie M, Glynne-Jones R, Widmer L, Seymour M and de Braud F; Swiss Group for Clinical Cancer Research: Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol *25*: 3217-23, 2007.

21 Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S, Majlis A, Assadourian S and Van Cutsem E: 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(24)*: 5660-5667, 2005.

22 Thuss–Patience PC, Kretzschmar A, Repp M, Kingreen D, Hennesser D, Micheel S, Pink D, Scholz C, Dörken B and Reichardt P: Docetaxel and continuous-infusion fluorouracil *versus* epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: a randomized phase II study. J Clin Oncol *23(3)*: 494-501, 2005.

23 Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Awad L and Van Cutsem E, V-325 Study Group: Quality of life with docetaxel plus cisplatin and fluorouracil compared with cisplatin and fluorouracil from a phase III trial for advanced gastric or gastroesophageal adenocarcinoma: the V-325 Study Group. J Clin Oncol *25(22)*: 3210-3216, 2007.

24 Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Marabotti C, Van Cutsem E, V-325 Study Group: Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. J Clin Oncol *25(22)*: 3205-3209, 2007.

25 Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Guan Z, Khasanov R, Zheng L, Philco-Salas M, Suarez T, Santamaria J, Forster G, McCloud PI: Capecitabine/cisplatin *versus* 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III non inferiority trial. Ann Oncol *20*: 666-673, 2009.

26 Okines AF, Norman AR, McCloud P, Kang YK and Cunningham D: Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol *20(9)*: 1529-1534, 2009.

27 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H and Takeuchi M: 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, 2008.

28 Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, Vynnychenko I, Garin A, Lang I and Falcon S: 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 *8(9)*: 1547-1553, 2010.

29 Available at: http://www.cancer.gov/clinicaltrials/search. (searched at 31/05/2011).

30 Manish AS, Ramanathan RK, Ilson DH, Levnor A, D'Adamo D, O'Reilly E, Tse A, Trocola R, Schwartz L, Capanu M, Schwartz GK and Kelsen DP: Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol *24(33)*: 5001-5006, 2006.

31 El-Rayes BF, Zalupski M, Bekai-Saab T, Heilbrun LK, Hammad N, Patel B, Urba S, Shields AF, Vaishampayan U, Dawson S, Almhanna K, Smith D and Philip PA: A phase II study of bevacizumab, oxaliplatin, and docetaxel in locally advanced and metastatic gastric and gastroesophageal junction cancers. Ann Oncol *21(10)*: 1999-2004, 2010.

32 Kim C, Lee JL, Ryu MH, Chang HM, Kim TW, Lim HY, Kang HJ, Park YS, Ryoo BY and Kang YK: A prospective phase II study of cetuximab in combination with XELOX (capecitabine and oxaliplatin) in patients with metastatic and/or recurrent advanced gastric cancer. Invest New Drugs *29(2)*: 366-373, 2011.

33 Lordick F, Luber B, Lorenzen S, Hegewisch-Becker S, Folprecht G, Wöll E, Decker T, Endlicher E, Röthling N, Schuster T, Keller G, Fend F and Peschel C: Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Br J Cancer *102(3)*: 500-505, 2010.

34 Pinto C, Di Fabio F, Siena S, Cascinu S, Rojas Llimpe FL, Ceccarelli C, Mutri V, Giannetta L, Giaquinta S, Funaioli C, Berardi R, Longobardi C, Piana E and Martoni AA: Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). Ann Oncol *18*: 510-517, 2007.

35 Pinto C, Di Fabio F, Barone C, Siena S, Falcone A, Cascinu S, Rojas Llimpe FL, Stella G, Schinzari G, Artale S, Mutri V, Giaquinta S, Giannetta L, Bardelli A and Martoni AA: Phase II study of cetuximab in combination with cisplatin and docetaxel in patients with untreated advanced gastric or gastro-oesophageal junction adenocarcinoma (DOCETUX study). Br J Cancer *101*: 1261-1268, 2009.

36 Okines A, Ashley SE, Cunningham D, Oates J, Turner A, Webb J, Saffery C, Chua YJ and Chau I: Epirubicin, Oxaliplatin, and Capecitabine With or Without Panitumumab for Advanced Esophagogastric Cancer: Dose-finding study for the prospective multicenter, randomized, phase II/III REAL-3 Trial. J Clin Oncol *28(25)*: 3945-3950, 2010.

37 Bang YJ, Kang YK, Kang WK, Boku N, Chung HC, Chen JS, Doi T, Sun Y, Shen L, Qin S, Ng WT, Tursi JM, Lechuga MJ, Lu DR, Ruiz-Garcia A and Sobrero A: Phase II study of sunitinib as second-line treatment for advanced gastric cancer. Invest New Drugs May 12 [Epub ahead of print] 2010.

38 Moehler MH, Hartmann JT, Lordick F, Al-Batran S, Reimer P, Trarbach T, Ebert MP, Daum S, Weihrauch M and Galleet PR: An open-label, multicenter phase II trial of sunitinib for patients with chemorefractory metastatic gastric cancer. Proc ASCO *28:15S(Part I)*: Abstr e14503, 2010.

39 Sun W, Powell M, O'Dwyer PJ, Catalano P, Ansari RH and Benson AB 3rd. Phase II study of sorafenib in combination with docetaxel and cisplatin in the treatment of metastatic or advanced gastric and gastroesophageal junction adenocarcinoma: ECOG 5203. J Clin Oncol *28(18)*: 2947-2951, 2010.

40 Doi T, Muro K, Boku N, Yamada Y, Nishina T, Takiuchi H, Komatsu Y, Hamamoto Y, Ohno N, Fujita Y, Robson M and Ohtsu A: A Multicenter phase II study of everolimus in patients with previously treated metastatic gastric cancer. J Clin Oncol *28(11)*: 1904-1910, 2010.

41 Wesolowski R, Lee C and Kim R: Is there a role for second-line chemotherapy in advanced gastric cancer? Lancet Oncol *10(9)*: 903-912, 2009.

42 Catalano V, Graziano F, Santini D, D'Emidio S, Baldelli AM, Rossi D, Vincenzi B, Giordani P,Alessandroni P, Testa E, Tonini G and Catalano G: Second-line chemotherapy for patients with advanced gastric cancer: Who may benefit? Br J Cancer *99*: 1402-1407, 2008.

43 Ji SH, Lim do H, Yi SY, Kim HS, Jun HJ, Kim KH, Chang MH, Park MJ, Uhm JE, Lee J, Park SH, Park JO, Park YS, Lim HY and Kang WK: A retrospective analysis of second-line chemotherapy in patients with advanced gastric cancer. BMC Cancer *9*: 110, 2009.

44 Chau I, Norman AR and Ross PJ: Multivariate prognostic factor analysis and second-line treatment in locally advanced and metastatic oesophago-gastric cancer, pooled analysis of 1080 patients from three multicentre randomised controlled trials using individual patient data. Proc Gastrointestinal cancer symposium, Abstr 5, 2004.

45 Thuss-Patience PC, Kretzschmar A, Deist T, Hinke A, Bichev D, Lebedinzew B, Schumacher G, Gebauer B, Maier V and Reichardt P: 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, Abstr 4540, 2009.

46 Park SH, Lim DH, Park K, Lee S, Oh SY, Kwon H, Kang JH, Hwang IG, Lee J, Park JO, Park YS, Lim HY and Kang WK: A multicenter, randomized phase III trial comparing second-line chemotherapy (SLC) plus best supportive care (BSC) with BSC alone for pretreated advanced gastric cancer (AGC), Proc ASCO *29(18S) (Part I)*: Abstr 4004, 2011.

47 Assersohn L, Brown G, Cunningham D, Ward C, Oates J, Waters JS, Hill ME and Norman AR: Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. Ann Oncol *15(1)*: 64-69, 2004.

48 Baek JH, Kim JG, Sohn SK, Kim DH, Lee KB, Song HS, Kwon KY, Do YR, Ryoo HM, Bae SH, Park KU, Kim MK, Lee KH, Hyun MS, Chung HY and Yu W: Biweekly irinotecan and cisplatin as second-line chemotherapy in pretreated patients with advanced gastric cancer: a multicenter phase II study. J Korean Med Sci *20(6)*: 966-970, 2005.

49 Chun JH, Kim HK, Lee JS, Choi JY, Lee HG, Yoon SM, Choi IJ, Ryu KW, Kim YW and Bae JM: Weekly irinotecan in patients with metastatic gastric cancer failing cisplatin-based chemotherapy. Jpn J Clin Oncol *34(1)*: 8-13, 2004.

50 Giuliani F, Molica S, Maiello E, Battaglia C, Gebbia V, Di Bisceglie M, Vinciarelli G, Gebbia N and Colucci G: Irinotecan (CPT-11) and mitomycin-C (MMC) as second-line therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico dell' Italia Meridionale (prot. 2106). Am J Clin Oncol *28(6)*: 581-585, 2005.

51 Kanat O, Evrensel T, Manavoglu O, Demiray M, Kurt E, Gonullu G, Kiyici M and Arslan M: Single-agent irinotecan as second-line treatment for advanced gastric cancer. Tumori *89(4)*: 405-407, 2003.

52 Kim SG, Oh SY, Kwon HC, Lee S, Kim JH, Kim SH and Kim HJ: A phase II study of irinotecan with bi-weekly, low-dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFIRI) as salvage therapy for patients with advanced or metastatic gastric cancer. Jpn J Clin Oncol *37*: 744-749, 2007.

53 Kim SH, Lee GW, Il Go S, Cho SH, Kim HJ, Kim HG and Kang JH: A Phase II Study of Irinotecan, Continuous 5-lluorouracil, and leucovorin (FOLFIRI) combination chemotherapy for patients with recurrent or metastatic gastric cancer previously treated with a fluoropyrimidine-based regimen. Am J Clin Oncol *33(6)*: 572-576, 2010.

54 Kim ST, Kang WK, Kang JH, Park KW, Lee J, Lee SH, Park JO, Kim K, Kim WS, Jung CW, Park YS, Im YH and Park K: Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer. Br J Cancer *92(10)*: 1850-1854, 2005.

55 Leary A, Assersohn L, Cunningham D, Norman AR, Chong G, Brown G, Ross PJ, Costello C, Higgins L and Oates J: A phase II trial evaluating capecitabine and irinotecan as second line treatment in patients with oesophago-gastric cancer who have progressed on, or within 3 months of platinum-based chemotherapy. Cancer Chemother Pharmacol *64(3)*: 455-462, 2009.

56 Lorizzo K, Fazio N, Radice D, Boselli S, Ariu L, Zampino MG, Nolè F, Magni E, Ardito R, Minchella I, Rocca A, Di Meglio G, Squadroni M and de Braud F: Simplified FOLFIRI in pre-treated patients with metastatic gastric cancer. Cancer Chemother Pharmacol *64(2)*: 301-306, 2009.

57 Seo MD, Lee KW, Lim JH, Yi HG, Kim DY, Oh DY, Kim JH, Im SA, Kim TY, Lee JS and Bang YJ: Irinotecan combined with 5-fluorouracil and leucovorin as second-line chemotherapy for metastatic or relapsed gastric cancer. Jpn J Clin Oncol *38(9)*: 589-595, 2008.

58 Shimada S, Yagi Y, Kuramoto M, Aoki N and Ogawa M: Second-line chemotherapy with combined irinotecan and low-dose cisplatin for patients with metastatic gastric carcinoma resistant to 5-fluorouracil. Oncol Rep *10(3)*: 687-691, 2003.

59 Sun Q, Hang M, Xu W, Mao W, Hang X, Li M and Zhang J: Irinotecan plus capecitabine as a second-line treatment after failure of 5-fluorouracil and platinum in patients with advanced gastric cancer. Jpn J Clin Oncol *39(12)*: 791-796, 2009.

60 Suzuki S, Harada N, Takeo Y, Tanaka S, Hayashi T, Suzuki M and Hanyu F: Bi-weekly irinotecan hydrochloride and cisplatin as a second-line chemotherapy for patients with advanced gastric cancer. Gan To Kagaku Ryoho *34(13)*: 2245-2248, 2007 (in Japanese).

61 Takahari D, Shimada Y, Takeshita S, Nishitani H, Takashima A, Okita N, Hirashima Y, Kato K, Hamaguchi T, Yamada Y and Shirao K: Second-line chemotherapy with irinotecan plus cisplatin after the failure of S-1 monotherapy for advanced gastric cancer. Gastric Cancer *13(3)*: 186-119, 2010.

62 Ueda S, Hironaka S, Boku N, Fukutomi A, Yoshino T and Onozawa Y: Combination chemotherapy with irinotecan and cisplatin in pretreated patients with unresectable or recurrent gastric cancer. Gastric Cancer *9(3)*: 203-207, 2006.

63 Yoshida T, Yoshikawa T, Tsuburaya A, Kobayashi O, Hasegawa S, Osaragi T and Sairenji M: Feasibility study of biweekly CPT-11 plus CDDP for S-1- and paclitaxel-refractory, metastatic gastric cancer. Anticancer Res *26(2B)*: 1595-1598, 2006.

64 Barone C, Basso M, Schinzari G, Pozzo C, Trigila N, D'Argento E, Quirino M, Astone A, Cassano A: Docetaxel and oxaliplatin combination in second-line treatment of patients with advanced gastric cancer. Gastric Cancer *10(2)*: 104-111, 2007.

65 Chon HJ, Rha SY, Im CK, Kim C, Hong MH, Kim HR, An JR, Noh SH, Chung HC and Jeung HC: Docetaxel *versus* paclitaxel combined with 5-FU and leucovorin in advanced gastric cancer: combined analysis of two phase II trials. Cancer Res Treat *41(4)*: 196-204, 2009.

66 Giuliani F, Gebbia V, De Vita F, Maiello E, Di Bisceglie M, Catalano G, Gebbia N and Colucci G: Docetaxel as salvage therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico Italia Meridionale (G.O.I.M.). Anticancer Res *23(5B)*: 4219-4222, 2003.

67 Jo JC, Lee JL, Ryu MH, Sym SJ, Lee SS, Chang HM, Kim TW, Lee JS and Kang YK: Docetaxel monotherapy as a second-line treatment after failure of fluoropyrimidine and platinum in advanced gastric cancer: experience of 154 patients with prognostic factor analysis. Jpn J Clin Oncol *37(12)*: 936-941, 2007.

68 Kunisaki C, Imada T, Yamada R, Hatori S, Ono H, Otsuka Y, Matsuda G, Nomura M, Akiyama H, Kubo A and Shimada H: Phase II study of docetaxel plus cisplatin as a second-line combined therapy in patients with advanced gastric carcinoma. Anticancer Res *25*: 2973-2977, 2005.

69 Lee JL, Ryu MH, Chang HM, Kim TW, Yook JH, Oh ST, Kim BS, Kim M, Chun YJ, Lee JS and Kang YK: A phase II study of docetaxel as salvage chemotherapy in advanced gastric cancer after failure of fluoropyrimidine and platinum combination chemotherapy. Cancer Chemother Pharmacol *61(4)*: 631-637, 2008.

70 Nakajima Y, Suzuki T, Haruki S, Ogiya K, Kawada K, Nishikage T, Nagai K and Kawano T: A pilot trial of docetaxel and nedaplatin in cisplatin-pretreated relapsed or refractory esophageal squamous cell cancer. Hepatogastroenterology *55(86-87)*: 1631-1635, 2008.

71 Nguyen S, Rebischung C, Van Ongeval J, Flesch M, Bennamoun M, André T, Ychou M, Gamelin E, Carola E and Louvet C: Epirubicin-docetaxel in advanced gastric cancer: two phase II studies as second and first line treatment. Bull Cancer *93(1)*: E1-6, 2006.

72 Park SH, Kang WK, Lee HR, Park J, Lee KE, Lee SH, Park JO, Kim K, Kim WS, Chung CW, Im YH, Lee MH, Park CH and Park K: Docetaxel plus cisplatin as second-line therapy in metastatic or recurrent advanced gastric cancer progressing on 5-fluorouracil-based regimen. Am J Clin Oncol *27(5)*: 477-480, 2004.

73 Polyzos A, Tsavaris N, Kosmas C, Polyzos K, Giannopoulos A, Felekouras E, Nikiteas N, Kouraklis G, Griniatsos J, Safioleas M, Stamatakos MPikoulis E, Papachristodoulou A and Gogas H: Subsets of patients with advanced gastric cancer responding to second-line chemotherapy with docetaxel-cisplatin. Anticancer Res *26*: 3749-3753, 2006.

74 Rosati G, Bilancia D, Germano D, Dinota A, Romano R, Reggiardo G and Manzione L: Reduced dose intensity of docetaxel plus capecitabine as second-line palliative chemotherapy in patients with metastatic gastric cancer: a phase II study. Ann Oncol *18(Suppl 6)*: 128-132, 2007.

75 Shin SJ, Kim MK, Lee KH, Hyun MS, Kim SW, Song SK, Bae SH and Ryoo HM: The Efficacy of Docetaxel and Cisplatin Combination Chemotherapy for the treatment of advanced gastric cancer after failing 5-fluorouracil-based chemotherapy. Cancer Res Treat *36(6)*: 367-371, 2004.

76 Sym SJ, Chang HM, Kang HJ, Lee SS, Ryu MH, Lee JL, Kim TW, Yook JH, Oh ST, Kim BS and Kang YK: A phase II study of irinotecan and docetaxel combination chemotherapy for patients with previously treated metastatic or recurrent advanced gastric cancer. Cancer Chemother Pharmacol *63(1)*: 1-8, 2008.

77 Yildiz R, Kalender ME, Dane F, Sevinc A, Gumus M, Camci C, Alici S, Kaya AO, Yaman E, Ozturk B, Coskun U, Benekli M, Uncu D and Buyukberber S: Docetaxel combined with oral etoposide as second-line treatment for advanced gastric carcinoma after failure of platinum- and fluoropyrimidine-based regimens. J Oncol Pharm Pract *16(3)*: 173-182, 2010.

78 Zhong H, Zhang Y, Ma S, Ying JE, Yang Y, Yong D, Hang X, Sun Q, Zhong B and Wang D: Docetaxel plus oxaliplatin (DOCOX) as a second-line treatment after failure of fluoropyrimidine and platinum in Chinese patients with advanced gastric cancer. Anticancer Drugs *19(10)*: 1013-1018, 2008.

79 Arai W, Hosoya Y, Hyodo M, Haruta H, Kurashina K, Saito S, Hirashima Y, Yokoyama T, Zuiki T, Sakuma K, Yasuda Y and Nagai H: Doxifluridine combined with weekly paclitaxel for second-line treatment in patients with gastric cancer resistant to TS-1. Int J Clin Oncol *12(2)*: 146-149, 2007.

80 Baize N, Abakar-Mahamat A, Mounier N, Berthier F and Caroli-Bosc FX: Phase II study of paclitaxel combined with capecitabine as second-line treatment for advanced gastric carcinoma after failure of cisplatin-based regimens. Cancer Chemother Pharmacol *64(3)*: 549-555, 2009.

81 Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T and Onozawa Y: Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer *9(1)*: 14-18, 2006.

82 Im CK, Rha SY, Jeung HC, Jeong J, Lee SH, Noh SH, Roh JK and Chung HC: A phase II feasibility study of weekly paclitaxel in heavily pretreated advanced gastric cancer patients with poor performance status. Oncology *77(6)*: 349-357, 2009.

83 Kodera Y, Ito S, Mochizuki Y, Fujitake S, Koshikawa K, Kanyama Y, Matsui T, Kojima H, Takase T, Ohashi N, Fujiwara M, Sakamoto J and Akimasa N; Chubu Clinical Cancer Group: A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). Anticancer Res *27(4C)*: 2667-2671, 2007.

84 Koizumi W, Akiya T, Sato A, Yamaguchi K, Sakuyama T, Nakayama N, Tanabe S, Higuchi K, Sasaki T and Sekikawa T: Second-line chemotherapy with biweekly paclitaxel after failure of fluoropyrimidine-based treatment in patients with advanced or recurrent gastric cancer: a report from the gastrointestinal oncology group of the Tokyo Cooperative Oncology Group, TCOG GC-0501 trial. Jpn J Clin Oncol *39(11)*: 713-719, 2009.

85 Matsuda G, Kunisaki C, Makino H, Fukahori M, Kimura J, Sato T, Oshima T, Nagano Y, Fuii S, Takagawa R, Kosaka T, Ono HA, Akiyama H and Ichikawa Y: Phase II study of weekly paclitaxel as a second-line treatment for S-1-refractory advanced gastric cancer. Anticancer Res *29(7)*: 2863-2867, 2009.

86 Rino Y, Yukawa N, Murakami H, Wada N, Yamada R, Hayashi T, Sato T, Ohshima T, Masuda M and Imada T: Phase II study of S-1 monotherapy as a first-line combination therapy of S-1 plus cisplatin as a second-line therapy, and weekly paclitaxel monotherapy as a third-line therapy in patients with advanced gastric carcinoma: A Second Report. Clin Med Insights Oncol *4*: 1-10, 2010.

87 Shimoyama R, Yasui H, Boku N, Onozawa Y, Hironaka S, Fukutomi A, Yamazaki K, Taku K, Kojima T, Machida N, Todaka A, Tomita H, Sakamoto T and Tsushima T: Weekly paclitaxel for heavily treated advanced or recurrent gastric cancer refractory to fluorouracil, irinotecan, and cisplatin. Gastric Cancer *12(4)*: 206-211, 2009.

88 Takiuchi H, Goto M, Imamura H, Furukawa H, Imano M, Imamoto H, Kimura Y, Ishida H, Fujitani K, Narahara H and Shimokawa T: Multi-center phase II study for combination therapy with paclitaxel/doxifluridine to treat advanced/recurrent gastric cancer showing resistance to S-1 (OGSG 0302). Jpn J Clin Oncol *38(3)*: 176-181, 2008.

89 Yamaguchi K, Nakagawa S, Yabusaki H and Nashimoto A: Combination chemotherapy with 5-fluorouracil, cisplatin and paclitaxel for pretreated patients with advanced gastric cancer. Anticancer Res *27(5B)*: 3535-3539, 2007.

90 Kim DY, Kim JH, Lee S, Kim TY, Heo DS, Bang YJ and Kim NK: Phase II study of oxaliplatin, 5-fluorouracil and leucovorin in previously platinum-treated patients with advanced gastric cancer. Ann Oncol *14*: 383-387, 2003.

91 Seo HY, Kim DS, Choi YS, Sung HJ, Park KH, Choi IK, Kim SJ, Oh SC, Seo JH, Choi CW, Kim BS, Shin SW, Kim YH and Kim JS: Treatment outcomes of oxaliplatin, 5-FU, and leucovorin as salvage therapy for patients with advanced or metastatic gastric cancer: a retrospective analysis. Cancer Chemother Pharmacol *63*: 433-739, 2008.

92 Jeong J, Jeung HC, Rha SY, Im CK, Shin SJ, Ahn JB, Noh SH, Roh JK and Chung HC: Phase II study of combination chemotherapy of 5-fluorouracil, low-dose leucovorin, and oxaliplatin (FLOX regimen) in pretreated advanced gastric cancer. Ann Oncol *19*: 1135-1140, 2008.

93 Jeung HC, Rha SY, Shin SJ, Ahn JB, Noh SH, Roh JK and Chung HC: A phase II study of S-1 monotherapy administered for 2 weeks of a 3-week cycle in advanced gastric cancer patients with poor performance status. Br J Cancer *97(4)*: 458-463, 2007.

94 Ono A, Boku N, Onozawa Y, Hironaka S, Fukutomi A, Yasui H, Yamazaki K, Yoshino T, Taku K and Kojima T: Activity of S-1 in advanced or recurrent gastric cancer patients after failure of prior chemotherapy, including irinotecan + cisplatin or fluorouracil (except S-1). Jpn J Clin Oncol *39(5)*: 332-335, 2009.

95 Park SH, Kim YS, Hong J, Park J, Nam E, Cho EK, Shin DB, Lee JH, Lee WK and Chung M: Mitomycin C plus S-1 as second-line therapy in patients with advanced gastric cancer: a noncomparative phase II study. Anticancer Drugs *19(3)*: 303-307, 2008.

96 Hartmann JT, Pintoffl JP, Al-Batran SE, Quietzsch D, Meisinger I, Horger M, Nehls O, Bokemeyer C, Königsrainer A, Jäger E and Kanz L: Mitomycin C plus infusional 5-fluorouracil in platinum-refractory gastric adenocarcinoma: an extended multicenter phase II study. Onkologie *30(5)*: 235-240, 2007.

Received June 13, 2011
Revised August 10, 2011
Accepted August 11, 2011