ELSEVIER

EJC Supplements Vol 2 No. 7 (2004) 40–47

EJC Supplements

www.ejconline.com

State of the art treatment for gastric cancer: future directions

A. Cervantes [a,*], V. Georgoulias [b], A. Falcone [c]

[a] *Hospital Clinic, Department of Haematology and Oncology, University of Valencia, Blasco Ibáñez 17, Valencia, Spain*
[b] *University of Crete, Heraklion, Crete, Greece*
[c] *Division of Medical Oncology, University of Pisa, Livorno, Italy*

Received 29 March 2004; received in revised form 23 April 2004; accepted 25 April 2004

Abstract

Surgery remains the primary curative treatment for gastric cancer although the last 40 years has witnessed the increased utilisation of chemotherapy. 5-Fluorouracil (5-FU or F), then more recently cisplatin (C) and their derivatives, have laid the foundations for the use of chemotherapy and their activity has been modulated by combination with other anti-cancer drugs such as epirubicin (E) or leucovorin (folinic acid, LV) to improve the outcome for patients with advanced gastric cancer.

In the palliative setting, despite recent efforts to refine and develop cisplatin/5-FU-based combinations and explore their effectiveness in different settings and regimens, the response rate has remained at around 40% and the overall survival period has obstinately refused to rise above 7–8 months. However, the last few years have seen renewed impetus in the struggle against advanced gastric cancer, heralded by the introduction of a new wave of chemotherapy drugs, principally the taxanes and the topoisomerase inhibitor, irinotecan. Recent early phase studies of drug combinations that use these new agents are reporting objective response rates of about 70% and overall median survival periods in excess of 10 months. Importantly, these advances are being made without excessive toxicity.

In the adjuvant setting, recent meta-analyses of adjuvant chemotherapy have suggested that systemic treatment may achieve a small, statistically significant reduction in the risk of death. Preliminary data from an ongoing large, prospective phase III study of post-operative chemo-radiotherapy (US Intergroup 0116) shows significantly improved disease-free and 5-year survival. However, as 54% of patients appear to have had suboptimal surgery the observed benefit may arise from compensating for inadequate dissection. In the MAGIC trial perioperative chemotherapy with ECF demonstrated a significant improvement in progression-free survival (hazard ratio 0.70, $P = 0.002$) and a potential improvement in overall survival (hazard ratio 0.80, $P = 0.063$). Ongoing studies in the adjuvant setting are evaluating the potential role of new active agents such as docetaxel and irinotecan.

Despite the improvements in therapeutic outcome, there is still much work to do as complete response rates are disappointingly low, patients with poor performance scores do particularly badly and treatment-related toxicity remains an issue in what is a distressing disease.

Keywords: Adjuvant; Advanced gastric cancer; Irinotecan; Palliative; Taxanes

1. Introduction

Surgical resection remains the primary curative treatment for gastric cancer. In Western countries, between 50% and 70% of patients who undergo radical resection of their primary tumour will relapse and die within 5 years. Gains in surgical techniques, screening, epidemiology and preventative education, will no doubt impact on this situation. However, the use of chemotherapy (with or without radiotherapy) along with advances in our molecular understanding of the behaviour and genetics of cancer cells holds perhaps the greatest potential to increase survival for those affected by this condition.

Chemotherapy has been used for the treatment of gastric cancer since the 1960s but despite 40 years of clinical research, many unresolved issues surround its deployment. Most importantly, despite the costs and toxicity issues associated with treatment, chemotherapy has a justified role in the treatment of patients with advanced disease, where quality of life may be a critical

* Corresponding author. Tel.: +34-96-386-2625; fax: +34-96-362-2238.
E-mail address: Andres.cervantes@uv.es (A. Cervantes).

1359-6349/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejcsup.2004.04.014

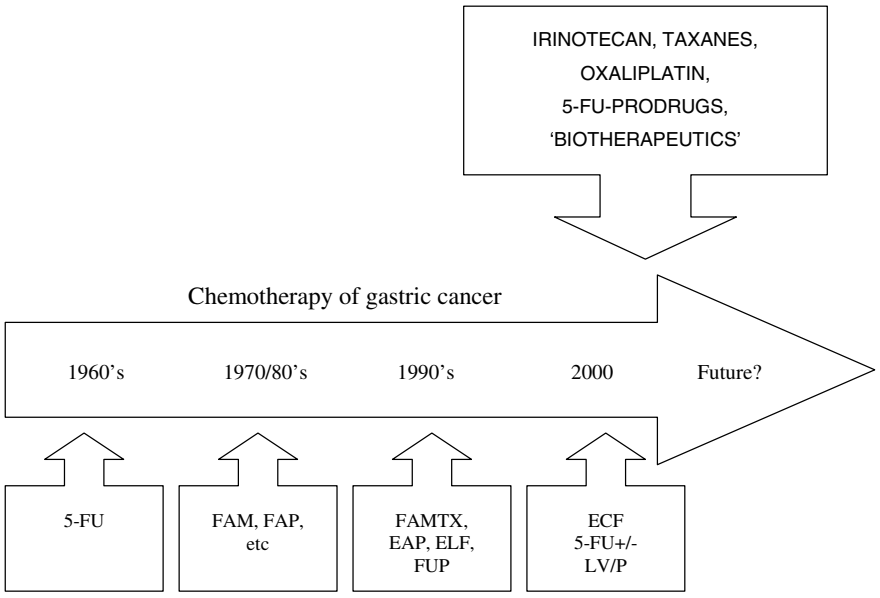

Fig. 1. An overview of the history of chemotherapy in the treatment of gastric cancer. 5-FU, fluorouracil; LV, leucovorin, FAM, fluorouracil/doxorubicin/mitomycin C; FAP, fluorouracil/doxorubicin/cisplatin; FAMTX, fluorouracil/doxorubicin/methotrexate; EAP, etoposide/doxorubicin/cisplatin; ELF, etoposide/leucovorin/fluorouracil; FUP, fluorouracil/cisplatin; ECF, epirubicin/cisplatin/fluorouracil; P, cisplatin.

issue [1,2]. However, although chemotherapy is able to prolong survival, several questions remain: does an optimum agent or combination exist? Is there an ideal setting or regimen that predicts whether chemotherapy should be provided before or after surgery in patients with localised disease? What is the contribution of radiotherapy to the adjuvant treatment of localised disease?

Although we may be some way from answering such questions many feel that we are entering a new phase of activity and vigour that is being driven by the advent of a new generation of chemotherapy agents such as irinotecan, the taxanes, oxaliplatin, 5-fluorouracil (5-FU)-prodrugs and 'biotherapeutics' (Fig. 1). If we are to derive the true potential of these and other new agents we must build on the lessons learnt from recent years. In this review we take stock of the current situation, assess the emerging data and evaluate what they can tell us about the application of the next generation of chemotherapeutic agents.

2. The early development of chemotherapeutic strategies

It is clear from several trials that when compared with best supportive care, chemotherapy alone provided improvements in response rates, progression-free survival and overall survival [3–6]. The timing of the initiation of chemotherapy relative to diagnosis and progression was also shown to have an effect on outcome. Treatment at diagnosis improved quality of life indicators (75% improved versus 25%) and time to survival (10 months versus 4 months) compared with treatment at progression for patients with advanced gastric cancer [7].

In the 1960s, 5-FU was introduced as the only active agent for the treatment of gastric cancer (Fig. 1). In the following decades combination regimens such as FAM (5-FU, doxorubicin, mitomycin C) were developed and considered as standard therapies as they provided responses in 30–50% of patients and extended median survival to 7 months compared with 3 months in untreated patients. These combinations were further developed during the 1990s with for example, the evolution of FAMTX where mitomycin C was replaced with the antimetabolite methotrexate. Other regimens also emerged during this period such as FUP (5-FU and cisplatin), EAP (etoposide, doxorubicin, cisplatin), and ELF (etoposide, leucovorin, 5-FU). Although such combinations, and especially those containing cisplatin, showed early promise and demonstrated improved response rates, randomised trials failed to show an increase over the earlier therapies in terms of overall survival (see Table 1 and [8–11]). Of these combinations FUP was considered to represent one of the standard contemporary therapies based on its favourable response rates (Table 1).

3. Current standards in chemotherapy

3.1. Agents of choice

The initial promise heralded by the early results with the platinum-based combinations like FUP (Table 1) was instrumental in the development during the mid-1990s of combination therapies such as ECF (epirubicin, cisplatin, infusional 5-FU), PELF (where bolus 5-FU

Table 1
Randomised trials of FAMTX versus CDDP combinations in the treatment of advanced gastric cancer

Author	Regimen	*N*	Response rate (%)	Analysis of RR (*P*)	OS (months)	Analysis of OS (*P*)
Kim [9]	FP	103	51	NA	8.5	ns
	FAM	98	25		6.7	
	5-FU	94	14		7.0	
Kelsen [8]	EAP	30	20	ns	6	ns
	FAMTX	30	33		7	
Wils [32]	FEMTX–CDDP	51	28	ns	7.0	ns
	FEMTX	50	26		7.0	
Vanhoefer [11]	FAMTX	132	12	ns	6.7	ns
	ELF	133	9		7.2	
	FUP	134	20		7.2	

N, number of patients; RR, response rate; *P*, probability; OS, overall survival; NA, not applicable; ns, not significant; FP, fluorouracil/cisplatin; FAM, fluorouracil/doxorubicin/mitomycin C; EAP, etoposide/doxorubicin/cisplatin; FAMTX, fluorouracil/doxorubicin/methotrexate; FEMTX–CDDP, fluorouracil/epirubicin/methotrexate/cisplatin; ELF, etoposide/leucovorin/fluorouracil; FUP, infusional fluorouracil/cisplatin.

plus leucovorin was added to epirubicin and cisplatin). A full evaluation of the effectiveness and usability of these combinations is only now becoming possible and as such they are representative of the standard regimens in use today.

Unlike many of the other platinum-based combination therapies, in addition to an increased response rate, ECF also demonstrated an apparent benefit over the established treatment regimens of the early 1990s, such as FAMTX, in terms of overall survival (Table 2). The superior activity of ECF was confirmed in the final analysis from the study of Waters *et al.* [12] where a response rate of 46% and a median survival of 8.7 months were achieved.

A comparison of three consecutive phase II studies carried out by the Spanish Group for Gastrointestinal Tumour Therapy (TTD) showed that high-dose continuous infusion with 5-FU could deliver a response rate of 18% (95% CI, 10–25%) whilst addition of cisplatin (i.e. FUP) increased the response rate to 44% (95% CI, 34–55%) [13]. The addition of epirubicin to the regimen (i.e. ECF) had little effect on the response rate (37%; 95% CI, 29–44%) but increased toxicity (notably vomiting and leucopoenia).

An evolution of the ECF regimen is PELF in which leucovorin is added and 5-FU is administered by intravenous bolus injection. However, this is associated with toxicity issues that require the administration of granulocyte-colony stimulating factor. An early phase II study indicated a response rate of 62% with median survival of 11 months [14] but when compared with FAMTX, PELF delivered significant improvements in terms of response rate but not overall survival (Table 2).

These results would indicate that ECF, once regarded as the great hope for the treatment of advanced gastric cancer, may not increase survival over that seen with other cisplatin plus 5-FU-based combinations. However, it is possible that by optimising the settings in

Table 2
Randomised trials comparing platinum-based combinations with non-platinum combinations

Author	Regimen	*N*	Response rate (%)	Analysis of RR (*P*)	OS (months)	Analysis of OS (*P*)
Massuti [33]	FLEP	75	26	0.008	7.2	ns
	FAMTX	73	9		5.4	
Waters [12]	ECF	126	46	0.0002	8.7	0.0005
	FAMTX	130	21		6.1	
Roth [34]	FEP	54	43	0.02	9.6	<0.05
	5-FU + EPI	56	29		7.1	
Cocconi [35]	PELF	98	38	0.003	7.7	ns
	FAMTX	97	21		6.9	
Ohtsu [10]	5-FU	105	11	0.001	7.1	ns
	5-FU-CDDP	105	34		7.3	
	5-FU-MMC	70	9		6.0	

N, number of patients; RR, response rate; *P*, probability; OS, overall survival; ns, not significant; FLEP, fluorouracil/leucovorin/epirubicin/cisplatin; ECF, epirubicin/cisplatin/fluorouracil; FEP, 5-fluorouracil/epirubicin/cisplatin; FU + EPI 5-fluorouracil/epirubicin; PELF, epirubicin/cisplatin/fluorouracil/leucovorin; FAMTX, fluorouracil/doxorubicin/methotrexate; 5-FU, 5-fluorouracil; CDDP, cisplatin; MMC, mitomycin C.

which such combinations are administered, particularly in the perioperative setting for localised disease, further gains may be made. Better selection of patients, further development of administration regimens, and combined use with radiotherapy may all yield better results for these contemporary therapies (see Section 4).

3.2. Chemotherapy for localised disease

When gastric cancer is unresectable, for example where there is evidence of locally advanced disease or distant metastasis, palliative chemotherapy may be the only treatment option. However, in the case of localised disease where surgery is indicated, three main strategies have been explored for adjuvant treatment; post-operative chemotherapy, post-operative chemoradiation and pre-operative or neoadjuvant chemotherapy.

3.2.1. Post-operative chemotherapy

The initial meta-analyses of post-operative adjuvant chemotherapy, published in 1993 [15], included 11 studies and 2096 patients but found no significant difference over surgery alone with an odds ratio for death of 0.88 (95% CI, 0.78–1.08). By comparison, more recent meta-analyses have indicated that post-operative chemotherapy provides a small but statistically significant absolute benefit in survival of between 3% and 5% (odds or hazard ratios for death ranging from 0.56 to 0.82 [1,16–18]). However, such meta-analyses have methodological limits: being literature-based introduces a selection-bias, some include early studies that used older chemotherapy regimens and had low statistical power, and heterogeneous criteria may be used for patient selection and analysis within studies.

Several studies published recently (and therefore not yet included in meta-analyses) compare regimens such as ELF ($n = 137$ [19]), EAP followed by 5-FU/leucovorin ($n = 274$ [20]), 5-FU + MMC (mitomycin C) + AraC (cytosine arabinoside) ($n = 252$ [21]) and PELF ($n = 258$ [22]) in the adjuvant setting versus surgery alone. The data for 5-year overall survival in these studies suggest moderate improvements of around 5% for the use of post-operative adjuvant therapy but only one showed a significant effect ($n = 137$, $P \leqslant 0.01$ [19]). However, the positive result of this study is questionable given that survival in the surgery only arm was 13% and the number of patients was low ($n = 137$).

Thus, these data suggest that adjuvant chemotherapy may provide a small survival benefit of around 3–5%, but such improvement has not yet been unequivocally demonstrated in any single, randomised, large phase III study. These findings support the future conduct of larger studies with greater statistical power and combinations containing the most active agents.

3.2.2. Post-operative chemoradiation

The current state of the art approach to combining chemotherapy with radiotherapy is represented by the SWOG 9008/INT 0116 trial. This study randomised 566 patients with resected stage IB to IV, M0 gastric carcinomas to either observation or to two cycles of 5-FU/leucovorin, then radiotherapy with two further doses of 5-FU/leucovorin at the start and end, followed by two further cycles of 5-FU/leucovorin [23]. The results demonstrated statistically significant differences for disease free-survival in favour of the addition of chemo-radiotherapy (median of 19 months versus 30 months, $P < 0.001$) and overall survival (median of 27 months versus 36 months, $P = 0.005$). Importantly, the overall benefit of the combined modality seemed to be derived predominantly from improved local control. Whereas the local relapse rate was 19% in the chemo-radiotherapy arm and 29% among control patients, there was no difference between groups for the risk of distant metastases. This observation may be explained by the nature of the surgical procedures where 54% of cases involved less than a D1 dissection, a level that is generally judged to be inadequate. It is therefore possible that the study found a benefit for chemo-radiotherapy only because it compensated for the effects of sub-optimal surgery.

3.2.3. Perioperative chemotherapy

The MAGIC trial is the only large randomised study of perioperative chemotherapy so far conducted that has an adequate follow-up period. It was initiated as a randomised study to compare surgery only (S arm) with perioperative chemotherapy where patients received three pre-operative and three post-operative cycles of ECF (CSC arm) [24]. In all, 503 patients were enrolled with operable gastric (74%) or lower oesophageal cancer (26%). Sixty-eight percent had a performance score of 0 and the median age was 62 years. More patients in the S arm actually received surgery (92% versus 85%), and the median time to surgery was shorter in the S arm (14 days versus 99 days). Despite this, the proportion of patients with curative resections was greater in the CSC arm (79% versus 69%, $P = 0.018$), and this is considered to be a direct result of the patients receiving pre-operative ECF.

After 5 years the data showed a highly significant effect in favour of the CSC arm over the S arm in terms of progression-free survival (hazard ratio 0.70, 95% CI, 0.56–0.88, $P = 0.002$) and a potential improvement in overall survival although this failed to reach conventional statistical significance (hazard ratio 0.80, 95% CI, 0.68–1.01, $P = 0.063$).

The preliminary results from this large phase III study demonstrate that pre-operative ECF has a qualitative effect on the tumour that increases the curative resection rate as shown by downsizing and a histopathologic down-staging effect in operable gastric cancer. As with other adjuvant approaches, perioperative

chemotherapy improves progression-free survival. It is hoped that continued follow-up of the MAGIC phase III trial will allow a more definitive conclusion to be drawn with regards to the effect of perioperative chemotherapy on survival in advanced gastric cancer.

4. New studies, new compounds

Recent developments can be divided broadly into three classifications:

- continued evolution of the existing standard regimens,
- new approaches to the settings and administration of existing chemotherapy combinations,
- the introduction of new compounds or novel analogues of existing compounds.

Some investigations are combining novel agents with new approaches and settings.

4.1. Ongoing studies in the adjuvant setting

A number of new trials are examining existing cisplatin-based combinations in the adjuvant setting as well as new chemo-radiotherapy combinations such as radiotherapy and continuous infusion of 5-FU preceded and followed by ECF (Table 3). There are also several studies that are evaluating pre-operative chemotherapy, randomising patients to pre-operative versus post-operative chemotherapy or to pre-operative chemotherapy versus surgery only. Finally, studies exploring the potential role of new active agents such as docetaxel and irinotecan are also ongoing (Table 3).

4.2. New compounds

The last few years has seen the introduction of several new drugs into the clinical research setting: docetaxel (Taxotere®), oxaliplatin (Eloxatin®), paclitaxel (Taxol®), and irinotecan (CPT-11, Campto®).

4.2.1. Docetaxel

Initial reports from a phase III study in 460 chemotherapy-naive patients with unresectable metastatic gastric cancer, where one randomised arm received docetaxel in addition to the standard cisplatin–5-FU combination, were extremely favourable [25]. Time to progression was superior (5.2 months versus 3.7 months for DCF and CF, respectively, $P = 0.0036$), as was the response rate (39% versus 23% for DCF and CF, respectively, $P = 0.012$) and overall survival (10.2 months versus 8.5 months for DCF and CF, respectively, $P = 0.0053$). Toxicity, as indicated by the proportion of National Cancer Institute Common Toxicity Criteria (NCICTC) grade 3–4 adverse events was similar for the two arms.

A phase I/II study is currently aiming to recruit and randomise 240 patients to four cycles of docetaxel, cisplatinum, 5-FU (TCF) as either pre- or post-operative adjuvant therapy (see Table 3).

4.2.2. Oxaliplatin

Oxaliplatin is a third-generation platinum compound that has shown some activity against pre-clinical tumour lines, including some that are resistant to other platinum compounds. A non-randomised phase II study in patients with metastatic or advanced gastric cancer combined oxaliplatin with 5-FU and leucovorin [26]. Forty-nine patients were assessable and the overall response rate was a promising 44.9%, time to progression was 6.2 months and overall survival was 8.6 months. Seven patients withdrew because of treatment-related toxicity. Early data from a randomised phase III trial where oxaliplatin was compared with cisplatinum in combinations with epirubicin and 5-FU and capecitabine showed that the two compounds had similar activity

Table 3
Ongoing adjuvant studies in advanced gastric cancer

Group	Study design	Planned accrual
GISCAD (Italy)	Surgery → 5-FU/LV (Machover) × 6 Surgery → w PELF × 8	400 patients (closed)
EORTC (Europe)	Surgery CDDP/5-FU/LV × 2 → surgery	360 patients
FRE-FNCLCC (France)	Surgery CDDP/5-FU × 2–3 → surgery	250 patients
SAKK/IEO (Swiss/Italy)	TCF × 4 → surgery Surgery → TCF × 4	240 patients
CALGB (USA)	Surgery → 5-FU/LV → 5-FU c.i./RT → 5-FU/LV Surgery → ECF → 5-FU c.i./ → ECF	824 patients
ITMO (Italy)	Surgery → MMC × 6 Surgery → FOLFIRI × 3 → TXT/CDDP × 3	820 patients

5-FU, 5-fluorouracil; LV, leucovorin; PELF, epirubicin/cisplatin/fluorouracil/leucovorin; CDDP, cisplatin; TCF, docetaxel/cisplatin/5-fluorouracil; 5-FU c.i. continuous infusion 5-fluorouracil; RT, radiotherapy; ECF, epirubicin/cisplatin/fluorouracil; MMC, mitomycin C; FOLFIRI, irinotecan/5-FU/FA modified de Gramont; TXT, docetaxel (Taxotere®).

(overall response rates of 37% for cisplatinum and 38% for oxaliplatin) and similar toxicity [27].

4.2.3. Paclitaxel

Paclitaxel has exhibited promising activity as a single agent and has been used as a combination therapy with carboplatin in the treatment of gastric cancer where response rates of 33% have been reported with median survival of 7.5 months [28].

4.2.4. Irinotecan

The alkaloid irinotecan is a potent topoisomerase I inhibitor and has shown potent anti-tumour activity as a single agent in the treatment of gastric cancer (see article by Wilke *et al.* in this issue).

The data from a recent, randomised phase II study indicates that irinotecan in combination with 5-FU provides an overall response rate of 42% [29]. This figure was significantly better than the corresponding data for the combination of irinotecan with cisplatin (26%) in the same study.

Another recent phase II study, performed in France (FFCD 9803 [30]), compared LV5FU2 (leucovorin, 5-FU bolus and 5-FU c.i. [de Gramont]), alone ($n = 45$) or in combination with either cisplatinum ($n = 44$) or irinotecan ($n = 45$) in patients with metastatic gastric cancer. LV5FU2 alone provided an overall response rate of 13% compared with 27% in the LV5FU2 + platinum arm and 40% in the LV5FU2 + irinotecan arm. The 1-year survival rates for each of the arms were 31% (LV5FU2), 43% (LV5FU2 + platinum), and 43% (LV5FU2 + irinotecan). However, whilst the addition of either cisplatinum or irinotecan to the LV5FU2 regimen increased the survival by similar magnitude, the irinotecan arm showed less toxicity. In the platinum arm, the incidences of WHO grade 3–4 adverse events were; neutropenia (61%), anaemia (30%), nausea/vomiting (23%), and febrile neutropenia and infection (16%). In the irinotecan arm these were neutropenia (40%), diarrhoea (22%), anaemia (16%), febrile neutropenia and infection (11%), and alopecia (11%). In the platinum arm there was one toxic death and treatment was stopped by 14% of patients due to toxicity. There were no toxic deaths in the irinotecan arm and only 4% of the patients stopped treatment due to toxicity.

5. Where we are and where we are going

Since the first meta-analysis was published showing little role for adjuvant chemotherapy in advanced gastric cancer [14] there have been numerous studies with greater numbers of patients, better designs, and improved agents and treatment regimens. This sizeable body of evidence indicates that there is real potential for the adjuvant use of chemotherapy in improving the prognosis for patients. The realisation of this potential will depend on several factors including the development of the most appropriate delivery of adjuvant treatment, its applicability to the various patient and/or disease subtypes and the continued exploration of the role for the new agents that are showing promise in this setting.

There is little doubt that gastric cancer represents a chemosensitive tumour and it is possible to achieve response rates in the region of 40% if not greater [31]. ECF, PLF, FOLFIRI, AIO + irinotecan and DCF are all effective but currently the duration of the responses is short. The ongoing development of new regimens and agents, such as docetaxel and irinotecan, has improved the prognosis for patients such that median survival is starting to extend beyond 10 months (Table 4). There are further issues that still need to be addressed. The complete response rate remains disappointingly low, and patients with a better performance status have a higher probability of a beneficial effect than those with a performance score of two or more.

Many of the studies that are currently being performed will add valuable new information in the pursuit of an improved prognosis for patients with advanced gastric cancer (see Table 3). However, the data that these studies generate will need to be assimilated into those being designed today that will utilise the next generation of chemotherapy agents such as irinotecan and docetaxel. One such study, which combined irinotecan with 5-FU/LV and biweekly cisplatinum, has delivered a promising response rate of 74% (of which 4 of the 14 responses were complete) in phase I/II and this is confirmed in the early analysis of the subsequent full phase II component [31].

Thus, there is a huge unmet medical need for improved chemotherapy options in the treatment of gastric cancer. Encouraging data from randomised trials of new regimens containing for example, docetaxel and irinotecan may set new standards. Large randomised trials are needed to assess the role of these new agents in the adjuvant setting. Contiguous with this is the need for

Table 4
Overview of the current status for combination therapy in the treatment of gastric cancer

Combination	Phase	Approximate response rate (%)	Median survival (months)
ECF	III	40	9
Inf.5-FU/LV/cis	II[a]	40	10
DCF	III[b]	40	10.2
Irinotecan/5-FU/LV	II[a]	40	11.3

ECF, epirubicin/cisplatin/fluorouracil; inf.5-FU, infusional fluorouracil; LV, leucovorin; cis, cisplatin; DCF; doxorubicin/cisplatin/fluorouracil.

[a] Randomised phase II.

[b] Interim analysis.

reduced toxicity that will allow better treatment of the elderly and those patients with a poor performance status.

References

1. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. *Eur J Cancer* 1999, **35**(7), 1059–1064.
2. Kohne CH, Wils JA, Wilke HJ. Developments in the treatment of gastric cancer in Europe. *Oncology* 2000, **14**(12 suppl 14), 22–25.
3. Pyrhönen S, Kuitunen T, Nyanodoto P, Kouri M. 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* 1995, **71**(3), 587–591.
4. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993, **72**(3), 37–41.
5. Scheithauer W, Kornek G, Zeh B, *et al*. Palliative chemotherapy versus supportive care in patients with metastatic gastric cancer: A randomized trial (abstract). *Second International Conference on Biology, Prevention and Treatment of GI Malignancies*, 1995. Köln, 1995:**68**.
6. Glimelius B, Ekstrom K, Hoffman K, *et al*. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997, **8**, 163–168.
7. Glimelius B, Hoftmann K, Haglund U, *et al*. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol* 1994, **5**, 189–190.
8. Kelsen D, Atiq OT, Saltz L, *et al*. FAMTX versus etoposide, doxorubicin, and cisplatin: a random assignment trial in gastric cancer. *J Clin Oncol* 1992, **10**(4), 515–516.
9. Kim NK, Park YS, Heo DS, *et al*. A phase III randomised 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* 1993, **71**(3), 3818–3818.
10. Ohtsu A, Shimada Y, Shirao K, *et al*. Randomised phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japanese Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003, **21**(3), 54–59.
11. Vanhoefer U, Rougier P, Wilke H, *et al*. Final results of a randomised 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 Organisation for Research and Treatment of Gastrointestinal Tract Cancer Cooperative Group. *J Clin Oncol* 2000, **18**(14), 2648–2657.
12. Waters JS, Norman A, Cunningham D, *et al*. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomized trial. *Br J Cancer* 1999, **80**, 269–272.
13. Cervantes A, Navarro M, Carrato A, *et al*. The addition of cisplatin to continuous infusion 5-fluorouracil for the treatment of advanced gastric cancer. Results of two consecutive phase II trials of the Spanish Group for Gastrointestinal Tumor Therapy (TTD). *Proc Am Soc Clin Oncol* 1999, **18** (Abstract 980).
14. Cascinu S, Labianca R, Alessandroni P, *et al*. Intensive weekly chemotherapy for advanced gastric cancer using fluorouracil, cisplatin, epi-deoxirubicin, 6S-leucovorin, glutathione and filgrastim: a report from the Italian Group for the Study of Digestive Tract Cancer. *J Clin Oncol* 1997, **15**, 3313–3319.
15. Hermans J, Bonenkamp JJ, Boon MC, *et al*. Adjuvant therapy after curative resection for gastric cancer: meta-analysis of randomized trials. *J Clin Oncol* 1993, **11**, 1441–1447.
16. Mari E, Floriani I, Tinazzi A, *et al*. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. A study of the GISCAD (Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente). *Ann Oncol* 2000, **11**, 837–843.
17. Panzini I, Gianni L, Fattori PP, *et al*. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomised trials and comparison with previous meta-analyses. *Tumori* 2002, **88**, 21–27.
18. Hu JK, Chen ZX, Zhou ZG, *et al*. Intravenous chemotherapy for resected gastric cancer: meta-analysis of randomized controlled trials. *World J Gastroenterol* 2002, **8**(3), 1023–1028.
19. Neri B, Cini G, Andreoli F, *et al*. Randomized trial of adjuvant chemotherapy versus control after curative resection for gastric cancer: 5-year follow-up. *Br J Cancer* 2001, **84**(3), 875–877.
20. Bajetta E, Buzzoni R, Mariani L, *et al*. Adjuvant chemotherapy in gastric cancer: 5 year results of a randomized study by the Italian Trials in Medical Oncology (ITMO) Group. *Ann Oncol* 2002, **13**(3), 299–307.
21. Nashimoto A, Nakajima T, Furukawa H, *et al*. Randomised trial of adjuvant chemotherapy with mitomycin, fluorouracil, and cytosine arabinoside followed by oral fluorouracil in serosa-negative gastric cancer: Japan Clinical Oncology Group 9206-1. *J Clin Oncol* 2003, **21**(3), 2234–2236.
22. Di Constanzo F, Gasperoni S, Manzione L, *et al*. Post-operative chemotherapy (CT) in resected gastric cancer (GC): follow-up (FUP) vs pelf. Results of an Italian intergroup (GOIRC & GISCAD) study. *Proc Am Soc Clin Oncol* 2003, **22**, 296 (Abstract 1189).
23. Macdonald JS, Smalley SR, Benedetti J, *et al*. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001, **345**(3), 725–730.
24. Allum W, Cunningham D, Weeden S, *et al*. Perioperative chemotherapy in operable gastric cancer and lower oesophageal cancer: a randomised, controlled trial (the MAGIC trial, ISRCTN 93793971). *Proc Am Soc Clin Oncol* 2003, **22** (Abstract 998).
25. Ajani JA, Van Cutsem E, Moiseyenko S, *et al*. Docetaxel (D), cisplatin, 5-fluorouracil compared to cisplatin (C) and 5-fluorouracil (F) for chemotherapy-naive patients with metastatic or locally recurrent, unresectable gastric carcinoma (MGC): interim results of a randomised phase III trial (V325). *Proc Am Soc Clin Oncol* 2003, **22**, 249 (Abstract 999).
26. Louvet C, Andrē T, Tigaud JM, *et al*. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. *J Clin Oncol* 2002, **20**(23), 4543–4548.
27. Tebbutt N, Norman A, Cunningham D, *et al*. Randomised, multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophago-gastric cancer: interim analysis. *Proc Am Soc Clin Oncol* 2002, **21** (Abstract 1031).
28. Gadgeel SM, Shields AF, Heilbrun LK, *et al*. Phase II study of paclitaxel and carboplatin in patients with advanced gastric cancer. *Am J Clin Oncol* 2003, **26**(3), 37–41.
29. Pozzo C, Bugat R, Peschel C, *et al*. Irinotecan in combination with CDDP or 5-FU and folinic acid is active in patients with advanced gastric or gastric-oesophageal junction adenocarcinoma; final results of a randomized phase II study. *Proc Am Soc Clin Oncol* 2001, **20** (Abstract 531).
30. Bouche O, Raoul JL, Giovaninini M, *et al*. Randomized phase II trial of LV5FU2, LV5FU2-cisplatinum or LV5FU2-irinotecan in patients (pts) with metastatic gastric or cardial adenocarcinoma (MGA): final results of study FFCD 9803. *Proc Am Soc Clin Oncol* 2003, **22** (Abstract 1033).

31. Schleucher N, Tewes M, Wilke HJ, *et al*. Phase I/II study with weekly infusional high-dose 5-fluorouracil/leucovorin/irinotecan in combination with biweekly cisplatin as first-line chemotherapy for metastatic gastric carcinoma. *Proc Am Soc Clin Oncol* 2003, **22** (Abstract 1378).
32. Wils J. The treatment of advanced gastric cancer. *Semin Oncol* 1996, **23**(3), 397–406.
33. Massuti B, Cervantes A, Aranda E, *et al*. A phase II multicentric randomized trial in advanced gastric cancer (GC): fluorouracil + leucovorin + epirubicin + cisplatin (FLEP) vs fluorouracil + adriamycin + methotrexate + leucovorin (FAMTX): response and survival report. Proceedings of the Sixth International Congress on Anti-cancer Treatment, Paris, France, February 6–9, 1996. *Paris, Service d'Oncologie, Médical Hospital Pitié-Salpetrière* 1996, **120** (Abstract UI:97614417).
34. Roth A, Kolaric K, Zupanc D, Oresic V, Roth A, Ebling Z. High doses of 5-fluorouracil and epirubicin with or without cisplatin in advanced gastric cancer: a randomized study. *Tumori* 1999, **85**, 234–238.
35. Cocconi G, Carlini P, Gamboni A, *et al*. Cisplatin, epirubicin, leucovorin and 5-fluorouracil (PELF) is more active than 5-fluorouracil, doxorubicin, and methotrexate (FAMTX) in advanced gastric carcinoma. *Ann Oncol* 2003, **14**, 1258–1263.