Anti-Cancer Drugs 1996, 7, pp. 137–149

Review paper

Chemotherapy of gastric cancer

DL Schipper[1,2] and DJT Wagener[1]

Departments of [1]Medical Oncology and [2]Gastroenterology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel: (+31) 80 615215; Fax: (+31) 80 540788.

Patients with gastric adenocarcinomas have a poor prognosis. Because curative surgery is often impossible (metastatic disease) or extremely difficult (locally advanced tumors), and the majority of patients undergoing curative resection relapse, chemotherapy has been actively studied in gastric cancer. Many drugs have shown activity; however, single-agent chemotherapy failed to demonstrate increased survival benefit. Several combination regimens have been developed with high activity in locally advanced and metastatic disease. Among them are 5-fluorouracil (5-FU) plus high dose methotrexate plus doxorubicin (FAMTX), etoposide plus doxorubicin plus cisplatin (EAP), etoposide plus leucovorin plus 5-FU (ELF), and epirubicin plus cisplatin plus 5-FU (ECF). Although the response rates of these schedules are encouraging, the toxicity is considerable. Randomized trials comparing chemotherapy with best supportive care showed an increase in overall survival and in quality-of-life. Up to now adjuvant chemotherapy in curatively resected gastric cancer patients has failed to improve survival as compared with surgical controls. Phase II trials with preoperative chemotherapy have shown very promising results, but results of randomized trials should be awaited to judge the real value of this approach. At this moment it cannot yet be estimated whether preoperative chemotherapy does positively influence the resection rate and survival of patients with clinically resectable tumors.

Key words: Adjuvant, chemotherapy, combination, gastric cancer, preoperative, single agent.

Introduction

Because surgery is the only treatment modality with curative intention, there is no doubt that surgery is the treatment of choice in localized gastric carcinoma. However, at diagnosis, 75% of all patients have disseminated disease.[1] Even among the subgroup of patients who are able to undergo potentially curative resection, relapse is common. Since 5 year survival ranges only from 10 to 15% of all patients with newly diagnosed disease, the use of chemotherapy in patients with gastric cancer has been a subject of great interest.

Until recently gastric cancer has been regarded as a tumor in which chemotherapy is only marginally active. However, recent advances have shown encouraging results.[2,3] This article reviews the most important results of phase II–III trials on chemotherapy of gastric cancer and of clinical trials on adjuvant and neoadjuvant chemotherapy published in the English literature from 1967 to April 1995, including those published in the English language in Japanese journals. The reports were obtained from a *MEDLINE* database search and from cross-reference from other published journals.

Single-agent chemotherapy

Over the last decade, much effort has been put into identification of active single agents in gastric cancer. Table 1 lists a number of agents and their observed response rates in gastric cancer. Direct comparisons of these responses are difficult because of different patient selection factors. Furthermore, evaluating chemotherapy in gastric cancer often involves some bias, as in many patients no bidimensionally measurable disease parameters are available.

At present, 5-fluorouracil (5-FU), doxorubicin (or its derivative epirubicin), mitomycin C and cisplatin have been identified as exhibiting modest or moderate single-agent activity in patients with advanced gastric cancer.[4,5] Recently activity has been described for the new chemotherapeutic agents taxotere[6] and irinotecan.[7]

5-FU is the most extensively studied drug in this disease. It was, until recently, used as an i.v. bolus administration, yielding a response rate of about

This work was supported by grant NUKC 92-64 from the Dutch Cancer Society.

Correspondence to DL Schipper

Table 1. Single-agent chemotherapy in advanced gastric cancer

Drug	No. of evaluable patients	Overall response rate (%)	References
Antimetabolites			
5-FU (protracted infusion)	13	31	12
5-FU (bolus)	392	21	8, 9
carmofur (oral)	31	19	5
hydroxyurea (oral)	31	19	5
methotrexate	28	11	41
triazinate	26	15	41
Antibiotics			
mitomycin C	211	30	4, 5, 13
epirubicin	80	19	5, 13
doxorubicin	141	17	5, 13
Heavy metals			
cisplatin	139	19	5
carboplatin	41	5	14
Alkylating agents			
BCNU	33	18	5
chlorambucil	18	17	42
methyl-CCNU	37	8	5
Miscellaneous			
etoposide	25	12	5
bisantrene	26	4	43
mitoguazone	31	3	44
gemcitabine	41	2	45, 46
taxotere	26	23	6
irinotecan	60	23	7

20%.[8,9] Because 5-FU is cell cycle specific and has a short plasma half-life, and because at any time approximately 3% of tumor cells are cycling, a protracted continuous i.v. infusion of this drug has been investigated.[10] This type of administration was piloted in colorectal cancer, yielding a significant improvement of response compared with an i.v. bolus schedule.[11] Although there has been no randomized trial in gastric cancer, there has been a small study of protracted infusion of 5-FU, demonstrating an interesting high response rate of 31%.[12] The adverse effects of 5-FU are in general mild. The major side-effects of 5-FU are mucositis, diarrhea, myelosuppression and, especially if infusional therapy is given, the hand–foot syndrome. 5-FU has been a common element in most combination chemotherapy regimens for gastric cancer.

Mitomycin C, an antitumor antibiotic that probably acts as an alkylating agent, also has been extensively used in the treatment of gastric cancer. The overall objective response rate for mitomycin C has been approximately 30%.[13] Its major toxic effect is delayed and cumulative myelosuppression.

Doxorubicin, an anthracycline antibiotic, is a potent drug in gastric cancer, yielding a response rate of 17%.[5,13] Its most critical toxicity is irreversible myocardial damage, after exceeding a dose of 550 mg/m^2. Epirubicin, a derivative of doxorubicin, thought to be less cardiotoxic, has also been shown to have significant activity in gastric cancer (response rate approximately 19%).[13]

Cisplatin, a heavy metal compound acting as an alkylating agent, has been studied as a single-agent, giving major responses in 19% of patients, including those previously treated.[5] Despite this activity, it has the disadvantages of nephrotoxicity, requiring hydration, and marked emesis, which in most of the cases can be alleviated by new antiemetic drugs. The less nephrotoxic and emetogenic analog of cisplatin, carboplatin, has not been found to be active in gastric cancer.[14]

Taxotere, a representative of the taxoids, is a new important antitumor compound, acting as a mitotic spindle poison and inducing a mitotic block.[15] A response rate of 23% was achieved in a small phase II trial.[6] Its dose-limiting toxicity is myelosuppression. Irinotecan, a topoisomerase inhibitor, is another new cytotoxic agent, also with a moderate activity in gastric cancer.[7] Its main toxicity is diarrhea. Both taxotere and irinotecan are interesting new anticancer agents, and deserve further investigation in combination chemotherapy regimens.

Other chemotherapeutic agents that have been studied in advanced gastric cancer with modest or

minimal activity are shown in Table 1. Complete responses are extraordinarily uncommon with single agents, even with those having the highest reported activity. Responses are generally of brief duration and without a significant impact on survival. No single-agent treatment in gastric cancer can be recommended as a clinical routine at present. The role of single-drug clinical trials therefore is to identify agents with activity that can subsequently be evaluated when incorporated into multidrug regimens.

Combination chemotherapy

Cytotoxic combinations in gastric cancer have been derived from single agents and scheduled to maximize the antitumor effect while minimizing the toxicity. Table 2 lists a number of more frequently used combination regimens, their observed response rates and median survival time. Until recently, the most extensively used combination in gastric cancer was 5-FU, doxorubicin and mitomycin C (FAM).[16] This schedule resulted in a response rate of approximately 30% and a median survival time of 5–9 months (Table 2). A number of similar combinations replacing mitomycin C in the FAM regimen with BCNU (FAB), methyl-CCNU (FAMe) or cisplatin (FAP) have been introduced, but without improvement of treatment results. The wide-scale use of FAM or other combinations like FAMe or FAP is a controversial issue, since in randomized studies, they have not shown a significant advantage over 5-FU alone.[17–19]

Klein *et al.* developed the FAMTX regimen, which includes the administration of high doses of methotrexate followed by 5-FU on day 1, and of doxorubicin on day 15, every 4 weeks. The methotrexate is given 1 h prior to 5-FU to modulate its action. They obtained a response rate of 58% in 116 patients, and a median survival of 9 months and for responders of 15 months.[20] Subsequent studies by other investigators yielded contradictory results (Table 2). However, in a randomized trial conducted by the EORTC, FAMTX induced a significantly higher remission rate (41 versus 9%) and a significantly longer median survival time (44 versus 29 weeks) than FAM.[21] Furthermore, hematological toxicity was lower in the FAMTX regimen. Although in this study the response rate seen with the FAM regimen is less than seen in previous studies, these results support the place of FAMTX as the best standard therapy for further randomized trials. Further attempts at refining the scheduling of FAMTX have been initiated, either with modulation of 5-FU or alterations in schedule and in substitution of adriamycin by epirubicin.

5-FU is the most extensively studied single agent in gastric cancer. As in the laboratory the efficacy of 5-FU can be enhanced by modulation with leucovorin[22], Machover *et al.*[23] developed a schedule in which 5-FU was combined with high-dose leucovorin. He obtained a response rate of 48% in 27 patients with gastric cancer. Subsequent studies by

Table 2. Results of more frequently used combinations for the treatment of advanced gastric cancer

Combination	Evaluable Patients	Response rate (%) (range)	Median survival time (months)	References
FAM and modifications	941	29 (12–65)	5–9	16–19, 47–67
FAP	232	37 (20–56)	4–12	54, 68–75
FAB	303	44 (24–51)	6–8	76–80
FAMe	141	25 (15–47)	6–13	48, 56, 62, 68, 81, 82
FMe	224	19 (9–40)	3–5	48, 56, 83–86
FAMTX and modifications	637	32 (0–58)	3–11	20, 21, 25, 30, 87–94
E*AP and modifications	509	48 (13–73)	6–10	24, 25, 67, 95–103
E*LF and modifications	222	32 (15–53)	6–12	94, 97, 104–107
FEMTXP	41	34 (33–35)	NA	108–110
FEMTX	32	25	8	111
FLP	100	61 (48–69)	9–14	112–115
FLEP	318	41 (15–67)	8	55, 93, 115–119
FLE	37	38	NA	120
HLFP	40	58	12	121
FP and modifications	261	38 (24–45)	4–11	94, 122–126
ECF	235	59 (36–71)	8–9	27–29, 122
FL and modifications	101	20 (0–48)	5–6	23, 127–130

Abbreviations: A, adriamycin; B, BCNU; E, epirubicin, E*, etoposide; F, 5-fluorouracil; H, hydroxyurea; L, leucovorin; M, mitomycin C; Me, methyl-CCNU; MTX, methotrexate; P (or C), cisplatin; NA, not available

others yielded contradictory results (Table 2). However, recent studies with high-dose 5-FU and high-dose leucovorin are promising, and will be tested in a randomized trial in the EORTC.

In the late 1980s, Preusser *et al.* developed a cisplatin-containing regimen, combining etoposide and adriamycin with cisplatin (EAP).[24] The peculiarity of this protocol is that it is the only combination regimen in advanced gastric cancer that does not utilize 5-FU. They obtained a response rate of 64%, including 21% complete responses. The median survival of all patients was 9 months. The subsequent experience from different centers confirms the activity of this regimen (Table 2). This regimen, however, did appear to be very toxic. This was confirmed in a randomized trial comparing EAP with FAMTX. The trial was stopped early because of no apparent difference in response, but a significantly higher toxic death rate with EAP.[25]

Wilke *et al.* designed the etoposide/leucovorin/5-FU (ELF) combination[26] as a default study for patients with cardiac or other medical conditions or of advanced age, who were thought not likely to tolerate EAP. This combination achieved a response rate of 53%, including 8% complete responses. A median survival time of 11 months was observed. Because of the encouraging results and the low toxicity profile, the EORTC currently is comparing ELF, 5-FU combined with cisplatin and FAMTX in a randomized phase III trial.

The combination of 5-FU and cisplatin has been evaluated in six studies in 261 patients. Overall response rates of 24–45% with median survival times of 4–11 months have been reported (Table 2).

In a study in colorectal cancer patients,[11] 5-FU given as a continuous i.v. infusion yielded a higher tumor response (30 versus 7%) with less toxicity than an intermittent bolus schedule given daily for 5 days every month. In a small non-randomized trial in gastric cancer patients, continuous infusion of 5-FU yielded a response rate of 31%,[12] whereas 5-FU given as an i.v. bolus was known to give a response rate of about 20%.[8,9] These results have made it an attractive base for new combination chemotherapy regimens in gastric cancer. Two other drugs were added to the infusional 5-FU: cisplatin because of its activity in this disease[13] and potential synergy with 5-FU, and the anthracycline epirubicin. This combination has shown high antitumor activity (response rate 36–71%) with moderate toxicity.[27–29] Thus, ECF is an effective form of palliative treatment for patients with advanced gastric carcinoma. Because of the encouraging results, Findlay *et al.* are now testing the ECF regimen in a multicenter phase III study with FAMTX, using patient survival and quality-of-life as major end points.

Three studies compared chemotherapy with best supportive care. A study by Murad *et al.*[30] showed a survival benefit for chemotherapy in patients with advanced gastric cancer. Patients were randomized to a modified version of FAMTX or best supportive care. In the middle of the study the randomization was interrupted because of strong evidence of benefit in the treatment arm. Further patients were accrued to the treatment arm, and by the end of the study 30 evaluable patients had received chemotherapy and 10 supportive treatment only. The median overall survival of the treated group was 10 months and that of the control group only 3 months. A phase III study by Pyrhönen *et al.* comparing 5-FU, epirubicin and methotrexate (FEMTX) with best supportive care has also shown a significant prolongation of progression-free time ($p < 0.02$) as well as survival ($p < 0.007$) in the FEMTX group compared with the control group.[31] In a small Swedish pilot study, initial chemotherapy (ELF or leucovorin with 5-FU) was compared with best supportive care.[32] Overall survival was significantly better in the group of patients randomized to chemotherapy (median 10 months) than in those allocated to the best supportive care (median 4 months). In the overall assessment of quality-of-life, conducted to a structured questionnaire, more patients in the primary chemotherapy group than in the best supportive care group were improved or continued to have high quality-of-life for at least 4 months ($p = 0.06$).

In conclusion, the new chemotherapeutic developments have led to a step ahead in the systemic treatment of gastric cancer. Approximately half of the patients with metastasized disease may benefit from chemotherapy with the new combinations by amelioration of symptoms or prolongation of survival.

Adjuvant chemotherapy

The role of adjuvant chemotherapy in gastric cancer has been extensively studied over the last three decades, being the first attempt to improve the prognosis of resected gastric cancer patients. The most important studies of adjuvant chemotherapy that have used a surgery alone control arm are summarized in Table 3 and 4.

Up to now it could not be shown that adjuvant chemotherapy has a positive impact on survival as compared with surgery alone and a recently pub-

Table 3. Results of randomized trials of adjuvant single-agent chemotherapy following curative resection for advanced gastric cancer

Treatment	No. of patients randomized	Percent survival after no. of years	Median survival (months)	p	References
Surgery alone	315	19/5	NA	NS	131
Thiotepa	301	21/5	NA		
Surgery alone	212	34/3	NA	NS	132
FUDR	185	32/3	NA		
Surgery alone	34	24/5	16	NS	133
Cisplatin i.p.	33	21/5	17		
Surgery alone	66	26/5	NA	0.025	134
Mitomycin C	68	41/5	NA		
Surgery alone	37	62/5	NA	0.001	135
Mitomycin C	33	21/5	NA		
Surgery alone	223	43.5/5	NA	NS	136
Mitomycin C	207	52.5/5	NA		
Surgery alone	25	27/3	NA	<0.005	137
Carbon absorbed mitomycin C i.p.	24	69/3	NA		
Surgery alone	56	stage II: 31/3 stage III: 22/3	stage II: 34 stage III: 22	NS	138
Ftorafur	59	stage II: 69/3 stage III: 41/3	stage II: 60 stage III: 34		

Abbreviations: FUDR, 5-fluorodeoxyuridine; NA, not available; NS, not significant.

lished meta-analysis ruled out an only small survival benefit produced by the adjuvant treatment programmes used so far.[33,34] These negative results do not necessarily mean that the concept of adjuvant chemotherapy of gastric cancer is not working.[35–38] In the published trials chemotherapy consisted of only marginally active schedules and the patient numbers were in most of these trials too small to allow an appropriate statistical conclusion. Furthermore, in most trials, a homogeneous surgical approach and a surgical and pathological quality control was not mandatory. Therefore, well-designed trials with new and active chemotherapy regimens as well as precisely defined surgery and surgical quality controls are needed. At this moment adjuvant chemotherapy of gastric cancer remains an experimental approach and is not indicated outside clinical trials.

Preoperative chemotherapy

To date, preoperative or neoadjuvant chemotherapy seems the most promising approach to increase the rate of curative resections in patients with gastric cancer by eradication of micrometastases early after diagnosis. In addition, reduction in tumor size could have an impact on resection rates (down-staging). A number of phase II trials have been performed investigating the ability of preoperative chemotherapy to influence outcome in patients with gastric cancer. In assessing these trials, one should be careful to separate studies in which patients who had potentially resectable gastric cancer at diagnosis underwent surgery after receiving chemotherapy, from studies in which patients with unresectable locally advanced gastric cancer received similar treatment.

Table 5 summarizes trials in which it was shown that locally advanced and not resectable tumors as defined by explorative laparotomy could be rendered resectable by preoperative chemotherapy. In a trial of Wilke *et al.*,[39] who used preoperative EAP in 33 evaluable patients with irresectable gastric cancer, 20 of 23 patients who had an objective response to chemotherapy underwent a second look operation. In 15 patients the tumor had become resectable. In this study a median survival time for all patients of 18 months and for disease-free patients of 24 months was achieved, whereas in untreated patients a median survival of 3–5 months can be expected.

A positive impact on prognosis was also claimed in studies where preoperative chemotherapy was given to patients with clinically staged locally advanced disease (Table 6). However, the difficulty with this approach is the lack of reliable criteria for clinically defining locally advanced disease. The other difficulty is that in these studies no randomi-

Table 4. Results of randomized trials of adjuvant combination chemotherapy following curative resection for advanced gastric cancer

Treatment	No. of patients randomized	Percent survival after no. of years	Median survival (months)	p	References
Surgery alone	71	31/5	33	0.003	139
FMe	71	44/5	not reached		
Surgery alone	54	42/5	NA	NS	140
FB	49	57/5	not reached		
Surgery alone	34	10/5	15	NS	141
C/MTX/F/VCR	29	11/5	15		
Surgery alone	130	NA		NS	142
F/VCR/MTX/C	140	NA			
induction + F/M			16		
F/M	141	NA			
Surgery alone	145	13/5	14	NS	143
FAM	138	9/5	18		
Radiotherapy	153	18/5	12		
Surgery alone	69	50/5	NA	NS	144
FMe	75	50/5	NA		
FMe/levamisole	69	50/5	NA		
Surgery alone	47	38/4	33	0.03	145
FMe	41	55/4	not reached		
Surgery alone	68	NA	NA	NS	146
FMe	66	NA	NA		
Surgery alone	89	57/2	33	NS	147
FMe	91	57/2	37		
Surgery alone	79	51/5	NA	NS	148
M/F/Cyt + F	81	68/5	NA		
M/Ftorafur/Cyt +	83	63/5	NA		
Ftorafur					
Surgery alone	145	20/5	15	NS	149
Radiotherapy	153	12/5	13		
FAM	138	19/5	17		
Surgery alone	64	33/5	31	NS	150
FA	61	32/5	36		
Surgery alone	118	46/15	NA	0.03	151
M/Tegafur/PSK	137	57/15	NA		
Surgery alone	148	35/5	NA	NS	152
FAM (1 year)	133	46/5	NA		
Surgery alone	93	NA	28	NS	153
FAM	83	NA	32		
Surgery alone	26	18/5	27	NS	154
F/Vinblastine/C	27	16/5	24		
Surgery alone	38	56/5	NA		155
M	42	64/5	NA		
M/F/Cyt	40	67/5	NA	0.05	
Surgery alone	34	29/5	17	NS	156
M/F/Cyt	53	45/5	46		

Abbreviations: A, adriamycin; B, BCNU; C, cyclophosphamide; Cyt, cytarabine; E*, etoposide; F, 5-fluorouracil; I, ifosfamide; L, leucovorin; M, mitomycin C; Me, methyl-CCNU; MTX, methotrexate; Tri, triazinate; VCR, vincristine; NA, not available; NS, not significant.

zation to a no-treatment arm was performed, thus interpretation of results would rely only on historical controls.

In an interim report, Kang *et al.*[40] presented the preliminary results of a study comparing preoperative chemotherapy (cisplatin plus etoposide plus continuous infusion of 5-FU) followed by surgery with surgery alone in clinically staged locally advanced gastric cancer. At the time of their preliminary report, 51 patients had entered the study. Curative resections were possible in 75% of patients in the neoadjuvant arm and 56% in the surgery arm. Twenty-five percent of patients had stage IB or less in the neoadjuvant arm, while no early stage tumors were seen in the surgery only arm. Based on these results the authors continue patient accrual.

Table 5. Results of preoperative chemotherapy in unresectable gastric cancer at prior laparotomy

Treatment	Timing of chemotherapy	No. of evaluable patients	Responses (CR + PR)	No. of patients having surgery	Complete resection achieved	Pathologic complete response	Median survival (months)	References
E*AP	pre + post	33	23	20	15	5	18	39
E*EP	pre	19	8	10	7	0	NA	157
FMTX	pre	17	8	14	8	0	NA	158
F*AP	pre	41	NA	37	32	0	NA	159

Abbreviations: A, adriamycin; E*, etoposide; E, epirubicin; F, 5-fluorouracil; MTX, methotrexate; P, cisplatin; NA, not available; NS, not significant.

Table 6. Results of preoperative chemotherapy in potentially resectable gastric cancer

Treatment	Timing of chemotherapy	No. of evaluable patients	Responses (CR + PR)	No. of patients having surgery	Complete resection achieved	Pathologic complete response	Median survival (months)	References
E*FP	pre + post	25	6	25	18	0	15	160
FLP + floxuridine + P i.p.	pre + post	38	17	35	29	1	17+	161
E*AP	pre + post	48	15	41	37	0	16	162
FP	pre + post	27	15	27	17	0	16	163
E*FP	pre	24	NA	20	15	3	NA	40
E*AP + G-CSF	pre	30	NA	30	24	NA	16	164
FAMTX + P i.p. + F i.v.	pre + post	46	NA	37	23	NA	NA	165

Abbreviations: A, doxorubicin; E, epirubicin; E*, etoposide; F, 5-fluorouracil; G-CSF, filgastrim; MTX, methotrexate; P, cisplatin; NA, not available.

In summary, in assessing results of trials of neoadjuvant chemotherapy in gastric cancer, one has to take in mind that patients with potentially resectable tumors at the time of study entry are different from those with advanced unresectable disease, who only undergo exploration if they have response. The currently available data indicate that neoadjuvant chemotherapy is feasible and that the results are encouraging. Therefore it may be proposed to patients with locally advanced gastric carcinomas, if they have an unresectable gastric cancer at prior laparotomy. For patients with potentially resectable locally advanced cancer only randomized studies comparing preoperative chemotherapy versus initial surgery can be recommended.

Conclusion

Gastric cancer is a chemotherapy-sensitive neoplasm. With the new combination cytotoxic regimens approximately half of the patients with metastasized disease may benefit from chemotherapy by reduction of tumor-related symptoms and/or prolongation of survival.

The results of trials with adjuvant chemotherapy of gastric cancer are disappointing. Further well designed trials with new and more active chemotherapy regimens are needed. At this moment adjuvant chemotherapy is not indicated outside of clinical trials.

Neoadjuvant chemotherapy has been studied in an attempt to improve relapse-free survival and cure rate in patients with locally advanced disease. There have been promising results, but large-scale confirmatory studies and prospective randomized trials are needed in order to establish the role of this treatment modality. Furthermore, new developed drugs such as taxotere and irinotecan have to be incorporated in new chemotherapy regimens.

References

1. Dupont JB, Lee JR, Burton GR, *et al.* Adenocarcinoma of the stomach: review of 1497 cases. *Cancer* 1987; **41**: 941–53.
2. Cocconi G. Chemotherapy of advanced gastric carcinoma: to be completely rewritten? *Ann Oncol* 1194; **5**: 8–11.

3. Wils JA. Perspectives in chemotherapy of advanced gastric cancer. *Anti-Cancer Drugs* 1991; **2**: 133–7.
4. Findlay M, Cunningham D. Chemotherapy of carcinoma of the stomach. *Cancer Treat Rev* 1993; **19**: 29–44.
5. Kelsen D. The use of chemotherapy in the treatment of advanced gastric and pancreatic cancer. *Semin Oncol* 1994; **21** (Suppl 7): 58–66.
6. Sulkes A, Cavalli F, van Oosterom A, *et al.* Taxotere is active in advanced gastric carcinoma: results of a phase II clinical trial. *Eur J Cancer* 1993; **23A**: S101 (Abstr 539) (Suppl 6).
7. Kambe M. Wakui A, Nakao I, *et al.* A late phase II study of irinotecan (CPT-11) in patients with advanced gastric cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 198 (Abstr 584).
8. Comis R. Integration of chemotherapy into combined modality treatment of solid tumors. *Cancer Treat Rev* 1974; **1**: 22–33.
9. Cocconi G, DeLisi V, Di Blasio B. Randomized comparison of 5-FU alone or combined with mitomycin and cytarabine (MCF) in the treatment of advanced gastric cancer. *Cancer Treat Rev* 1982; **66**: 1263–6.
10. Fraile RJ, Baker LH, Buroker TR, *et al.* Pharmacokinetics of 5-fluorouracil administered orally, by rapid intravenous and by slow infusion. *Cancer Res* 1980; **40**: 2223–8.
11. Lokich J, Ahlgren J, Gullo J, *et al.* A prospective randomised comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma. A mid-Atlantic Oncology Program Study. *J Clin Oncol* 1989; **7**: 425–32.
12. Moynihan T, Hansen R, Anderson T, *et al.* Continuous 5-fluorouracil infusion in advanced gastric carcinoma. *Am J Clin Oncol* 1988; **11**: 461–4.
13. Preusser P, Achterrath W, Wilke H, *et al.* Chemotherapy of gastric cancer. *Cancer Treat Rev* 1988; **15**: 257–77.
14. Einzig A, Kelsen DP, Cheng E. Phase II trial of carboplatin in patients with adenocarcinomas of the upper gastrointestinal tract. *Cancer Treat Rep* 1985; **69**: 1453–4.
15. Gueritte-Voegelein F. Relationships between the structure of taxol analogues and their antimitotic activity. *J Med Chem* 1991; **83**: 288–91.
16. MacDonald JS, Wooley PV, Smythe T, *et al.* 5-Fluorouracil, adriamycin and mitomycin-C (FAM) combination chemotherapy in the treatment of advanced gastric cancer. *Cancer* 1979; **44**: 42–7.
17. Cullinan SA, Moertel CG, Fleming TR, *et al.* A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma: fluorouracil versus fluorouracil and doxorubicin versus fluorouracil, doxorubicin and mitomycin. *J Am Med Ass* 1985; **253**: 2061–7.
18. Cullinan SA, Moertel CG, Wieand HS, *et al.* Controlled evaluation of three drug combination regimens versus fluorouracil alone for the therapy of advanced gastric cancer.*J Clin Oncol* 1994; **12**: 412–6.
19. Beretta G, Arnoldi E, Beretta GD, *et al.* A randomized study of fluorouracil versus FAM polychemotherapy in gastric carcinoma. In: *Proc EORTC Symp* in *Advances in gastrointestinal tract cancer research and treatment*, Strasbourg, 1989; Abstr 48.
20. Klein HO. Long-term results with FAMTX (5-fluorouracil, adriamycin, methotrexate) in advanced gastric cancer. *Anticancer Res* 1989; **9**: 1025–6.
21. Wils J, Klein HO, Wagener DJTh, *et al.* Sequential high-dose methotrexate and fluorouracil combined with doxorubicin—a step ahead in the treatment of advanced gastric cancer: a trial of the European Organisation for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 1991; **9**: 827–31.
22. Evans RM, Laskin JD, Hakala MT. Effect of excess folates and deoxyinosine on the activity and site of action of 5-fluorouracil. *Cancer Res* 1981; **41**: 3288–95.
23. Machover D, Goldschmidt E, Chollet P, *et al.* Treatment of advanced colorectal and gastric adenocarcinomas with 5-FU and high-dose folonic acid. *J Clin Oncol* 1986; **4**: 685–90.
24. Preusser P, Wilke H, Achterrath W, *et al.* Phase II study with the combination etoposide, doxorubicin, and cisplatin in advanced measurable gastric cancer. *J Clin Oncol* 1989; **7**: 1310–7.
25. 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**: 541–8.
26. Stahl M, Wilke H, Preusser P, *et al.* Etoposide leucovorin and 5-fluorouracil (ELF) in advanced gastric carcinoma—final results of a phase II study in elderly patients or patients with cardial risk. *Onkologie* 1991; **14**: 314–8.
27. Findlay M, Cunningham D, Norman A, *et al.* A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). *Ann Oncol* 1994; **5**: 609–16.
28. Delfino C, Caccia C, Fein L, *et al.* for the Argentine Cooperative Group. Cisplatin, epirubicin and 5-fluorouracil in patients with advanced gastric cancer. *Eur J Cancer* 1991; **S81** (Suppl 2).
29. Zaniboni A, Labianca R, Martignoni G, *et al.* ECF is an active feasible regimen for advanced gastric cancer. A Giscad confirmatory study. *Ann Oncol* 1994; **5** (Suppl 8): 79 (Abstr P395).
30. Murad AM, Santiago FF, Petroianu A, *et al.* Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993; **72**: 37–41.
31. Pyrhönen S, Kuitunen T, Kouri M. A randomized, phase III trial comparing fluorouracil, epidoxorubicin and methotrexate (FEMTX) with best supportive care in non resectable gastric cancer. *Ann Oncol* 1992; **3** (Suppl 5): 12 (Abstr).
32. Glimelius B, Hoffman K, Haglund U, *et al.* Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol* 1994; **5**: 189–90.
33. 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**: 1441–7.
34. Pignon JP, Ducreux M, Rougier P, *et al.* Meta-analysis of adjuvant chemotherapy in gastric cancer: a critical reappraisal. Meta-analyses need time, collaboration and funding. *J Clin Oncol* 1994; **12**: 877–80.
35. Douglass HO Jr. Adjuvant therapy of gastric cancer: have we made any progress? *Ann Oncol* 1994; **5** (Suppl 3): 69–72.
36. Wils J, Meyer H-J, Wilke H. Current status and future directions in the treatment of localized gastric cancer. *Ann Oncol* 1994; **5** (Suppl 3): 69–72.

37. Bleiberg H, Gerard B, Deguiral P. Adjuvant therapy in resectable gastric cancer *Br J Cancer* 1992; **66**: 987–91.
38. Agboola O. Adjuvant treatment in gastric cancer. *Cancer Treat Rev* 1994; **20**: 217–40.
39. Wilke H, Preusser P, Fink U, *et al.* Preoperative chemotherapy in locally advanced and nonresectable gastric cancer: a phase II study with etoposide, doxorubicin, and cisplatin. *J Clin Oncol* 1989; **7**: 1318–26.
40. Kang YK, Choi DW, Kim CM, *et al.* The effect of neoadjuvant chemotherapy on the surgical outcome of locally advanced gastric adenocarcinoma: interim report of a randomized controlled trial. *Proc Am Soc Clin Oncol* 1992; **11**: 173 (Abstr 505).
41. Bruckner HW, Lokich JJ, Stablein DM. Studies of Baker's antifol, methotrexate, and razozane in advanced gastric cancer: a gastrointestinal tumor study group report. *Cancer Treat Rep* 1982; **66**: 1713–7.
42. Moore G, Bross I, Ausman R, *et al.* Effects of chlorambucil (NSC 3088) in 374 patients with advanced cancer. *Cancer Chemother Rep* 1968; **52**: 661–6.
43. Pannettiere F, Jones S, Oishi N, *et al.* Bisantrene hydrochloride in gastric adenocarcinoma: a Southwest Oncology Group Study. *Med Pediatr Oncol* 1986; **14**: 78–80.
44. Ravry M, Omura G, Hill G, *et al.* Phase II evaluation of mitoguazone in cancers of the esophagus, stomach and pancreas: a Southeastern Cancer Study Group trial. *Cancer Treat Rep* 1986; **70**: 533–4.
45. Sessa C, Aamdal S, Wolff I, *et al.* Gemcitabine in patients with advanced malignant melanoma or gastric cancer: phase II studies of the EORTC Early Clinical Trials Group. *Ann Oncol* 1994; **5**: 471–2.
46. Christman K,Kelsen D, Saltz L, *et al.* Phase II trial of gemcitabine in patients with advanced gastric cancer. *Cancer* 1994; **73**: 5–7.
47. Bitran J, Desser R, Kozloff M, *et al.* Treatment of metastatic pancreatic and gastric adenocarcinomas with 5-fluorouracil, adriamycin, and mitomycin-C (FAM). *Cancer Treat Rep* 1979; **63**: 2049–51.
48. The Gastrointestinal Tumor Study Group. A comparative clinical assessment of combination chemotherapy in the management of advanced gastric carcinoma. *Cancer* 1982; **49**: 1362–6.
49. MacDonald JS, Schein PS, Woolley BV, *et al.* 5-Fluorouracil, doxorubicin, and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med* 1980; **93**: 533–6.
50. Faedi M, Amadori M, Gentilini P, *et al.* Chemotherapy of advanced gastric cancer: a study of 43 consecutive cases treated with fluorouracil, adriamycin and mitomycin C (FAM). *Chemiotherapia* 1986; **5**: 240–3.
51. Ridolfi R, Casadei-Giunchi D, Cortesi C, *et al.* A retrospective study of FAM regimen in 38 patients with advanced gastric cancer. *Tumori* 1984; **70**: 375–9.
52. Fornasiero A, Cartei G, Daniele O, *et al.* FAM2 regimen in disseminated gastric cancer. *Tumori* 1984; **70**: 77–80.
53. Gill PG, Jones AM, Abbott R. Chemotherapy of advanced gastric cancer. *Austr NZ J Surg* 1983; **53**: 237–40.
54. Figoli F, Galligioni E, Crivellari D, *et al.* Evaluation of 2 consecutive regimens in advanced gastric cancer. *Cancer Invest* 1991; **9**: 257–62.
55. Cocconi G, Bella M, Zironi S, *et al.* Fluorouracil, doxorubicin, and mitomycin combination versus PELF chemotherapy in advanced gastric cancer: a prospective randomized trial of the Italian Oncology Group for Clinical Research. *J Clin Oncol* 1994; **12**: 2687–93.
56. Douglass HO Jr, Lavin PT, Goudsmid A, *et al.* 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* 1984; **2**: 1372-81.
57. Beretta G, Fraschini P, Labianca R, *et al.* The value of FAM polychemotherapy in advanced gastric carcinoma. *Proc Am Soc Clin Oncol* 1982; **5**: 103 (Abstr C-400).
58. The Southwest Oncology Group. 5-Fluorouracil, adriamycin, and mitomycin-C ± vincristine (FAM vs. V-FAM) compared to chlorozotocin, M-AMSA and dihydroxyanthracenedione with unimpressive differences. *Proc Am Soc Clin Oncol* 1983; **2**: 122.
59. Cummingham D, Soukop M, McArdle C, *et al.* Advanced gastric cancer: experience in Scotland using 5-fluorouracil, adriamycin, and mitomycin-C. *Br J Surg* 1984; **71**: 673–6.
60. Haim N, Cohen Y, Honigman J, *et al.* Treatment of advanced gastric carcinoma with 5-fluorouracil, adriamycin, and mitomycin-C (FAM). *Cancer Chemother Pharmacol* 1982; **8**: 277–80.
61. Pannettiere FJ, Haas Ch, McDonald B, *et al.* Drug combinations in the treatment of gastric adenocarcinoma. *J Clin Oncol* 1984; **2**: 420–4.
62. The Gastrointestinal Tumor Study Group. Randomized study of combination chemotherapy in unresectable gastric cancer. *Cancer* 1984; **53**: 13–7.
63. Biran H, Sulkes A. A possible dose–response relationship in 'FAM' chemotherapy for advanced gastric cancer. *Proc Am Soc Clin Oncol* 1984; **132** (Abstr C-515).
64. De Lisi V, Bella M, Soldani M, *et al.* The FAM combination versus the combination of Cisplatin, Adriamycin and Mitomycin (PAM) in advanced gastric cancer. A phase III study of the Italian oncology group for clinical research (GOIRC). *Proc ECCO* 1987; **4**: 37 (Abstr 141).
65. Haas C, Oishi N, McDonald B, *et al.* Southwest Oncology Group phase II–III gastric cancer study: 5-Fluorouracil, Adriamycin, and Mitomycin-C + Vincristine (FAM vs. V-FAM) compared to Chlorozotocin (CZT), M-AMSA, and Dihydroxyanthracenedione (DHAD) with unimpressive differences. *Proc Am Soc Clin Oncol* 1983; **2**: 122 (Abstr C-478).
66. Beretta G, Fraschini P, Labianca R, *et al.* Weekly 5-fluorouracil (F) versus combination chemotherapy for advanced gastrointestinal carcinomas. A prospective study program. *Proc Am Soc Clin Oncol* 1986; **5**: 94 (Abstr C-367).
67. Icli F, Karaoguz H, Dicol D, *et al.* Comparison of EAP and FAM combination chemotherapies in advanced gastric cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 207 (Abstr 619).
68. The Gastrointestinal Tumor Study Group. Triazinate and platinum efficacy in combination with 5-fluorouracil and doxorubicin: results of a three arm randomized trial in metastatic gastric cancer. *J Natl Cancer Inst* 1988; **80**: 1011–5.
69. Epelbaum R, Haim M, Stein M, *et al.* Treatment of advanced gastric cancer with DDP (cisplatin), adriamycin, and 5-fluorouracil (DAF). *Oncology* 1987; **44**: 201–6.

70. Cazap EL, Gisselbrecht C, Smith FP, *et al.* Phase II trials of 5-FU, doxorubicin and cisplatin in advanced, measurable adenocarcinoma of the lung and stomach. *Cancer Treat Rep* 1986; **70**: 781–3.
71. Wagener DJ, Yap SH, Wobbes T, *et al.* Phase II trial of 5-fluorouracil, adriamycin and cisplatin (FAP) in advanced gastric cancer. *Cancer Chemother Pharmacol* 1985; **15**: 86–7.
72. Moertel CG, Rubin J, O'Connell MJ, *et al.* A phase II study of combined 5-fluorouracil, doxorubicin and cisplatin in the treatment of advanced upper gastrointestinal adenocarcinomas. *J Clin Oncol* 1986; **4**: 1053–7.
73. Rougier P, Droz JP, Theodore C, *et al.* Phase II trial of combined 5-fluorouracil plus doxorubicin plus cisplatin (FAP regimen) in advanced gastric carcinoma. *Cancer Treat Rep* 1987; **71**: 1301–2.
74. Woolley P, Smith F, Estevez R, *et al.* A phase II trial of 5-FU, Adriamycin and Cisplatin (FAP) in advanced gastric cancer. *Proc Am Soc Clin Oncol* 1981; **455**: (Abstr C-481).
75. Figoli F, Calligioni E, Crivellari D, *et al.* Cisplatin (DDP) in combination with Adriamycin (A), and Fluorouracil (F) (DAF) in advanced gastric cancer—a phase II study. *Proc Am Soc Clin Oncol* 1986; **95**: (Abstr C-369).
76. Levi JA, Fox RM, Tattersall MH, *et al.* Analysis of a prospectively randomized comparison of doxorubicin versus 5-fluorouracil, doxorubicin, and BCNU in advanced gastric cancer: implications for future studies. *J Clin Oncol* 1986; **4**: 1348–55.
77. Lopez M, Perno CF, Di-Lauro L, *et al.* 5-Fluorouracil, adriamycin, and BCNU (FAB) combination chemotherapy for advanced gastric cancer. *Cancer Chemother Pharmacol* 1984; **12**: 194–7.
78. Schnitzler G, Queisser W, Heim ME, *et al.* Phase III study of 5-FU and carmustine versus 5-FU, carmustine and doxorubicin in advanced gastric cancer. *Cancer Treat Rep* 1986; **70**: 477–9.
79. Levi JA, Dalley DN, Aroney RS. Improved combination chemotherapy in advanced gastric cancer. *Br Med J* 1979; **2**: 1471–3.
80. Lopez M, Di Lauro L, Papaldo P, *et al.* Treatment of advanced measurable gastric carcinoma with 5-Fluorouracil, Adriamycin, and BCNU. *Oncology* 1986; **43**: 288–91.
81. The Gastrointestinal Tumor Study Group. Phase II–III chemotherapy studies in advanced gastric cancer. *Cancer Treat Rep* 1979; **63**: 1871–6.
82. Lacave A, Wils J, Bleiberg H, *et al.* An EORTC gastrointestinal group phase III evaluation of combinations of Methyl-CCNU, 5-Fluorouracil, and Adriamycin in advanced gastric cancer. *J Clin Oncol* 1987; **5**: 1387–93.
83. Buroker T, Kim P, Grappe C, *et al.* 5-FU infusion with mitomycin-C versus 5-FU infusion with methyl-CCNU in the treatment of advanced upper gastrointestinal cancer. *Cancer* 1979; **44**: 1215–21.
84. Moertel CG, Lavin PT. Phase II–III chemotherapy studies in advanced gastric cancer. Eastern Cooperative Oncology Group. *Cancer Treat Rep* 1979; **63**: 1863–9.
85. Baker LH, Talley RW, Matter R, *et al.* A Southwest Oncology Group Study. Phase III comparison of the treatment of advanced gastrointestinal cancer with bolus weekly 5-FU VS. methyl-CCNU plus bolus weekly 5-FU. *Cancer* 1976; **38**: 1–7.
86. Moertel CG, Mittleman JA, Bakemeier RF, *et al.* Sequential and combination chemotherapy of advanced gastric cancer. *Cancer* 1976; **38**: 678–82.
87. Wils J, Bleiberg H, Dalesio O, *et al.* An EORTC gastrointestinal group evaluation of the combination of sequential methotrexate and 5-fluorouracil, combined with adriamycin in advanced measurable gastric cancer. *J Clin Oncol* 1986; **4**: 1799–803.
88. Ajani JA, Goudeau P, Levin B, *et al.* Phase II study of adriamycin with sequential methotrexate and 5-fluorouracil (AMF) in gastric carcinoma. *Cancer Chemother Pharmacol* 1989; **24**: 41–4.
89. Herrmann R, Fritze D, Queisser W, *et al.* Chemotherapie des Magenkarzinoms. *Dtsch Med Wschr* 1984; **109**: 1704.
90. Scherdin G, Garbrecht M, Muellerleile U, *et al.* Polychemotherapy with methotrexate in medium doses range, 5-fluorouracil and adriamycin in advanced gastric carcinoma. *J Cancer Res Clin Oncol* 1986; **111**: 85 (Suppl) (Abstr Sto 14).
91. Muro H, Romero Acuna K, Castagnari A, *et al.* Sequential methotrexate, 5-fluorouracil (high-dose) and doxorubicin for advanced gastric cancer. *Cancer Treat Rep* 1986; **70**: 1333–4.
92. Weh HJ, Platz D, Garbrecht M, *et al.* Ergebnisse eines modifizierten FAMethchemotherapieprotokolls beim metastasierten magenkarzinom. *Dtsch Med Wschr* 1989; **114**: 1391–6.
93. Massuti B, Cervantes A, Aranda E, *et al.* A phase III multicenter randomized study in advanced gastric cancer (GC): fluorouracil + leucovorin + epirubicin + cisplatin (FLEP) versus fluorouracil + adriamycin + methotrexate + Leucovorin (FAMTX). In: *Proc 2nd Int Conf on Biology, Prevention and Treatment of Gastrointestinal Malignancies*, Koln, 1995; 50.
94. Vanhoefer U, Wilke H, Wils J, *et al.* Preliminary analysis of a randomized phase III trial of FAMTX versus ELF versus Cisplatin/FU in advanced gastric cancer (GC). A trial of the EORTC Gastrointestinal Tract Cancer Cooperative Group and the AIO (Arbeitsgemeinschaft Internistische Onkologie). In: *Proc 2nd Int Conf on Biology, Prevention and Treatment of Gastrointestinal Malignancies*, Koln, 1995; 71.
95. Gebbia V, Valenza R, Testa A, *et al.* Etoposide, doxorubicin (adriamycin) and cisplatin regimen in advanced gastric adenocarcinoma: experience with a lower dose schedule. *J Cancer Res Clin Oncol* 1994; **120**: 550–2.
96. Rath U, Flechtner H, Selbach J, *et al.* Etoposide, adriamycin, and cisplatin (EAP) combination chemotherapy for advanced gastric cancer. A phase II trial by the 'Chemotherapiegruppe Gastrointestinaler Tumoren (CGT)'. *Onkologie* 1990; **13**: 194–7.
97. Wilke H, Preusser P, Fink U, *et al.* New developments in the treatment of gastric carcinoma. *Semin Oncol* 1990; **17** (Suppl 2): 61–70.
98. Lerner A, Gonin R, Steele GD Jr, *et al.* Etoposide, doxorubicin, and cisplatin chemotherapy for advanced gastric adenocarcinoma: Results of a phase II trial. *J Clin Oncol* 1992; **4**: 536–40.
99. Sparano JA, Schwartz EL, Salva KM, *et al.* Phase II trial of etoposide, doxorubicin (adriamycin), and cisplatin (EAP regimen) in advanced gastric cancer. *Am J Clin Oncol* 1990; **13**: 374–8.
100. Katz A, Gansi RC, Simon SD, *et al.* Phase II trial of

etoposide (V), adriamycin (A) and cisplatinum (P) in patients with advanced gastric cancer. *Am J Clin Oncol* 1991; **14**: 357–8.

101. Haim N, Tsalik M, Robinson E. Treatment of advanced gastric carcinoma with VP-16, adriamycin and cisplatin (EAP). *Eur J Cancer* 1993; **29A**: S102 (Abstr 549) (Suppl 6).
102. Roth AD, Herrmann R, Thuerlimann B, *et al.* Cisplatin, adriamycin and VP-16 (PAV) in advanced gastric carcinoma (AGC): the Sakk experience. *Ann Oncol* 1994; **5** (Suppl 8): 85 (Abstr 426).
103. Jovanovic DM, Muzikravic Lj, Antonic M, *et al.* Evaluation of the combination of chemotherapy with etoposide, adriamycin and cisplatin (EAP) in advanced or recurrent gastric cancer. *Ann Oncol* 1994; **5** (Suppl 8): 85 (Abstr 427).
104. Taal BG, Teller FGM, Ten Bokkel Huinink WW, *et al.* Etoposide leucovorin, 5-fluorouracil (ELF) combination chemotherapy for advanced gastric cancer: experience with two treatment schedules incorporating intravenous or oral etoposide. *Ann Oncol* 1994; **5**: 90–2.
105. Di Bartolomeo M, Bajetta E, de Braud F, *et al.* Phase II study of the etoposide, leucovorin and fluorouracil combination for patients with advanced gastric cancer unsuitable for aggressive chemotherapy. *Oncology* 1995; **52**: 41–4.
106. Suspiro A, Oliveira J, Lage P, *et al.* Low activity of etoposide + folinic acid + 5fluorouracil (ELF) in advanced gastric cancer. *Ann Oncol* 1994; **5** (Suppl 8): 88 (Abstr 441).
107. De Braud F, Bajetta E, Di Bartolomeo M, *et al.* Etoposide, leucovorin and fluorouracil (ELF) regimen in the treatment of advanced gastric cancer (AGC). An Italian Trials in Medical Oncology (I.T.M.O.) study. *Proc Am Soc Clin Oncol* 1993; **12**: 210 (Abstr 632).
108. McDonald A, Harding M, McNulty L, *et al.* A pilot study of cisplatin based combination chemotherapy in gastric cancer. *Clin Oncol R Coll Radiol* 1993; **5**: 284–5.
109. Taal BG, Ten Bokkel Huinink WW, Simonetti G, *et al.* A phase II trial of sequential MTX and 5-FU alternated with 4'-epidoxorubicin and cisplatin in advanced gastric cancer. *Cancer Invest* 1990; **8**: 501–4.
110. Roelofs EJ, Wagener DJTh, Conroy T, *et al.* Phase II study of sequential high-dose methotrexate (MTX) and 5-fluorouracil (F) alternated with epirubicin (E) and cisplatin (P) (FEMTX-P) in advanced gastric cancer. *Ann Oncol* 1993; **4**: 426–8.
111. Wils JA, Coombes RC, Bliss JM, *et al.* Phase I–II study of sequential high dose methotrexate and 5-fluorouracil combined with epirubicin (FEMTX) at different dose levels in advanced gastric cancer. *GI Cancer* 1995; **1**: 55–9.
112. Ychou M, Fedkovic Y, Saint Aubert B, *et al.* A phase II study with 5-FU, leucovorin and cisplatin in metastatic gastric cancer. *Eur J Cancer* 1993; **29A**: S106 (Abstr 573) (Suppl 6).
113. Im YH, Kang YK, Kim CM, *et al.* A phase II trial of low dose leucovorin, 5-fluorouracil and cisplatin (LV-FP) combination chemotherapy in patients with advanced gastric adenocarcinoma. *Proc Am Soc Clin Oncol* 1994; **13**: 207 (Abstr 616).
114. Wilke H, Vanhoefer U, Fink U, *et al.* Weekly high-dose FU/folinic acid (HD-FU/FA) and cisplatin (C): a safe and active combination for advanced gastric cancer (GC). In: *Proc 2nd Int Conf on Biology, Prevention and Treatment of Gastrointestinal Malignancies*, Koln, 1995; 72.
115. Wilke H, Vanhoefer U, Fink U, *et al.* Weekly high-dose FU/folinic acid (HD-FU/FA) plus biweekly cisplatin (C) = (Group A) or HD-FU/FA plus alternating C/epidoxorubicin (E) = (Group B) for gastric cancer (GC). *Ann Oncol* 1994; **5**: (Suppl 8): 80 (Abstr P397).
116. Cervantes A, Villar-Grimalt A, Abad A, *et al.* 5-Fluorouracil, folinic acid, epidoxorubicin and cisplatin (FLEP) combination chemotherapy in advanced measurable gastric cancer. A phase II trial of the Spanish Cooperative Group for Gastrointestinal Tumor Therapy (TTD). *Ann Oncol* 1993; **4**: 753–7.
117. Wilke H, Vanhoefer U, Fink U, *et al.* Pilot study with a weekly 24h-infusion of 5-FU/folinic acid (HD-FU/FA) plus weekly alternating cisplatin (C) and epidoxorubicin (E) for advanced gastric cancer (GC). In: *Proc 2nd Int Conf on Biology, Prevention and Treatment of Gastrointestinal Malignancies*, Koln, 1995; 53.
118. Crivellari D, Buonadonna A, Sorio R, *et al.* Feasibility and activity of a 3-day PELF like regimen in advanced gastric cancer, preliminary data. In: *Proc 2nd Int Conf on Biology, Prevention and Treatment of Gastrointestinal Malignancies*, Koln, 1995; 59.
119. Ducreux M, Yakendji K, Rougier Ph, *et al.* First line combined chemotherapy with 5-fluorouracil (5-FU), folinic acid, epirubicin and cisplatin (FLEP) in advanced gastric cancer: the Gustave Roussy Institute experience. *Ann Oncol* 1994; **5** (Suppl 8): 79 (Abstr P394).
120. Kornek G, Schulz F, Depisch D, *et al.* A phase I–II study of epirubicin, 5-fluorouracil, and leucovorin in advanced adenocarcinoma of the stomach. *Cancer* 1993; **71**: 2177–80.
121. Louvet C, De Gramont A, Beerblock K, *et al.* Hydroxyurea, leucovorin, 5FU and cisplatin (HLFP regimen) in advanced gastric cancer. In: *Proc 2nd Int Conf on Biology, Prevention and Treatment of Gastrointestinal Malignancies*, Koln, 1995.
122. Kyoto Research Group for Chemotherapy of Gastric Cancer (KRGCGC). A randomized, comparative study of combination chemotherapies in advanced gastric cancer: 5-fluorouracil and cisplatin (FP) versus 5-fluorouracil, cisplatin, and 4'-epidoxorubicin (FPEPIR). *Anticancer Res* 1992; **12**: 1983–8.
123. Lacave AJ, Baron FJ, Anton LM, *et al.* Combination chemotherapy with cisplatin and 5-fluorouracil 5-day infusion in the therapy of advanced gastric cancer: a phase II trial. *Ann Oncol* 1991; **2**: 751–4.
124. Ohtsu A, Yoshida S, Saito D, *et al.* An early phase II study of 5-fluorouracil combined with cisplatin as a second line chemotherapy against metastatic gastric cancer. *Jpn J Clin Oncol* 1991; **21**: 120–4.
125. Rougier P, Ducreux M, Mahjoubi M, *et al.* Efficacy of combined 5-fluorouracil and cisplatinum in advanced gastric carcinomas. A phase II trial with prognostic factor analysis. *Eur J Cancer* 1994; **30A**: 1263–9.
126. Weitzen R, Ghodsizadeh A, Brenner H, *et al.* Gastric carcinoma: continuous infusion 5-fluorouracil plus cisplatinum: dose intensification study. *Eur J Cancer* 1993; **29A**: S104 (Abstr 560) (Suppl 6).
127. Schmitz SH, Voliotis DL, Schimke J, *et al.* Continuous 5-fluorouracil and leucovorin as a second-line therapy for advanced gastric carcinoma. *Oncology* 1994; **51**: 502–6.

128. Cascinu S, Fedeli A, Luzi Fedeli S, *et al.* Treatment of elderly advanced gastric cancer patients with 5-fluorouracil and leucovorin combination. *J Chemother* 1992; **4**: 185–8.
129. Arbuck SG, Douglass HO, Trave F, *et al.* A phase II trial of 5-fluorouracil and high-dose intravenous leucovorin in gastric carcinoma. *J Clin Oncol* 1987; **5**: 1150–6.
130. Vanhoefer U, Wilke H, Weh H, *et al.* Weekly high-dose 5-FU/Folic acid is active in chemotherapeutically pretreated gastric cancer. *Ann Oncol* 1994; **5** (Suppl 8): 80 (Abstr P398).
131. Longmire WP Jr, Kuzma JW, Dixon WJ. The use of triethylenethiophosphoramide as an adjuvant to the surgical treatment gastric carcinoma. *Ann Surg* 1968; **167**: 293–312.
132. Serlin O, Wolkoff JS, Amadeo JM, *et al.* The use of 5-fluorodeoxiuridine (FUDR) as an adjuvant to the surgical management of carcinoma of the stomach. *Cancer* 1969; **24**: 223–8.
133. Sautner T, Hofbauer F, Depisch D, *et al.* Adjuvant intraperitoneal cisplatin chemotherapy does not improve long-term survival after surgery for advanced gastric cancer. *J Clin Oncol* 1994; **12**: 970–4.
134. Grau JJ, Estape J, Alcobendas F, *et al.* Positive results of adjuvant mitomycin C in resected gastric cancer: a randomised trial on 134 patients. *Eur J Cancer* 1993; **29A**: 340–2.
135. Estape J, Grau JJ, Lcobendas F, *et al.* Mitomycin C as an adjuvant treatment to resected gastric cancer. A 10-year follow-up. *Ann Surg* 1991; **213**: 219–21.
136. Nakajima T, Fukami A, Ohashi I, *et al.* Long-term follow up study of gastric cancer patients treated with surgery and adjuvant chemotherapy with mitomycin C. *Int J Clin Pharmacol* 1978; **16**: 209-16.
137. Hagiwara A, Takahashi T, Kojima O, *et al.* Prophylaxis with carbon-absorbed mitomycin against peritoneal recurrence of gastric cancer. *Lancet* 1992; **339**: 629–31.
138. Chou FF, Sheen-Chen SM, Liu PP, *et al.* Adjuvant chemotherapy for resectable gastric cancer: a preliminary report. *J Surg Oncol* 1994; **57**: 239–42.
139. Douglas HO, Stablein DM, Bruckner HM, *et al.* Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. The Gastrointestinal Tumor Study Group. *Cancer* 1982; **49**: 1116–22.
140. Schlag P. Adjuvant chemotherapy in gastric cancer. *World J Surg* 1987; **11**: 473–7.
141. Blake JR, Hardcastle JD, Wilson RG. Gastric cancer: a controlled trial of adjuvant chemotherapy following gastrectomy. *J Clin Oncol* 1981; **7**: 13–21.
142. Allum WH, Hallissey MT, Kelly KA. Adjuvant chemotherapy in operable gastric cancer. 5 year follow-up of first British Stomach Cancer Group Trial. *Lancet* 1989; **1**: 571–4.
143. Allum WH, Hallissey MT, Ward LC, *et al.* A controlled prospective, randomised trial of adjuvant chemotherapy or radiotherapy in resectable gastric cancer: interim report. British Stomach Cancer Group. *Br J Cancer* 1989; **60**: 739–44.
144. The Italian Gastrointestinal Tumor Study Group. Adjuvant treatments following curative resection for gastric cancer. *Br J Surg* 1988; **75**: 1100–4.
145. The Gastrointestinal Tumor Study Group. Controlled trial of adjuvant chemotherapy following curative resection for gastric cancer. *Cancer* 1982; **49**: 1116–22.
146. Higgins GA, Amadeo JH, Smith DE, *et al.* Efficacy of prolonged intermittent therapy with combined 5-FU and methyl-CCNU following resection for gastric carcinoma. A Veterans Administration Surgical Oncology Group Report. *Cancer* 1983; **52**: 1105–12.
147. Engstrom PF, Lavin PT, Douglass HO Jr, *et al.* Postoperative adjuvant 5-fluorouracil plus methyl-CCNU therapy for gastric cancer patients. Eastern Cooperative Oncology Group Study (EST 3275). *Cancer* 1985; **55**: 1868–73.
148. Nakajima T, Takahashi T, Takagi K, *et al.* Comparison of 5-fluorouracil with ftorafur in adjuvant chemotherapies with combined inductive and maintenance therapies for gastric cancer. *J Clin Oncol* 1984; **2**: 1366–71.
149. Hallissey MT, Dunn JA, Ward LC, *et al.* The second British Stomach Cancer group trial of adjuvant radiotherapy or chemotherapy in resectable gastric cancer: five-year follow up. *Lancet* 1994; **343**: 1309–12.
150. Krook JE, O'Connell MJ, Wieand HS, *et al.* A prospective, randomized evaluation of intensive course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. *Cancer* 1991; **67**: 2454–8.
151. Maehara Y, Moriguchi S, Sakaguchi Y, *et al.* Adjuvant chemotherapy enhances long-term survival of patients with advanced gastric cancer following curative resection. *J Surg Oncol* 1990; **45**: 169–72.
152. Coombes RC, Schein PS, Chilvers CE, *et al.* A randomized trial comparing adjuvant fluorouracil, doxorubicin, and mitomycin with no treatment in operable gastric cancer. International Collaborative Cancer Group. *J Clin Oncol* 1990; **8**: 1362–9.
153. Macdonald JS, Gagliano R, Fleming T, *et al.* A phase II trial of FAM (5-fluorouracil, adriamycin, mitomycin-C) chemotherapy vs control as adjuvant treatment for resected gastric cancer (A Southwest Oncology Group Trial—SWOG 7804). *Proc Am Soc Clin Oncol* 1992; **11**: 168.
154. Hugier M, Destroyes JP, Baschet C, *et al.* Gastric carcinoma treated by chemotherapy after resection. *Am J Surg* 1980; **139**: 1105–12.
155. Nakajima T, Fukami A, Tagaki K, *et al.* Adjuvant chemotherapy with mitomycin C and with a multi-drug combination of mitomycin C, 5-fluorouracil and cytosine arabinoside after curative resection of gastric cancer. *Jpn J Clin Oncol* 1980; **10**: 187–94.
156. Jakesz R, Dittrich C, Funovics J, *et al.* The effect of adjuvant chemotherapy in gastric carcinoma is dependent on tumor histology: 5-year results of a prospective randomized trial. *Recent Res Cancer Res* 1988; **110**: 44–51.
157. Rosen HR, Scheithauer W, Jakesz R, *et al.* Epirubicin, Etoposide and Cisplatin in the treatment of locally advanced, nonresectable gastric carcinoma—results of a multicentric pilot study. *GI Cancer* 1995; **1**: 49–53.
158. Plukker JTh, Mulder NH, Sleijfer DTh, *et al.* Chemotherapy and surgery for locally advanced cancer of the cardia and fundus: phase II study with methotrexate and 5-fluorouracil. *Br J Surg* 1991; **78**: 955–8.
159. Schuhmacher CH, Fink U, Boettcher K, *et al.* Neoadjuvant chemotherapy for locally advanced gastric cancer: a phase II study with etoposide, adriamycin and cisplatin (EAP). *Ann Oncol* 1994; **5** (Suppl 8): 76 (Abstr O380).

160. Ajani JA, Ota DM, Jessup JM, *et al.* Resectable gastric carcinoma. An evaluation of preoperative and postoperative chemotherapy. *Cancer* 1991; **68**: 1501–6.
161. Leichman L, Silberman H, Leichman CG, *et al.* Preoperative systemic chemotherapy followed by adjuvant postoperative intraperitoneal therapy for gastric cancer: a University of Southern California pilot program. *J Clin Oncol* 1992; **10**: 1933–42.
162. Ajani JA, Mayer RJ, Ota DM, *et al.* Preoperative and postoperative combination chemotherapy for potentially resectable gastric carcinoma. *J Nat Cancer Inst* 1993; **85**: 1839–44.
163. Rougier Ph, Lasser Ph, Ducreux M, *et al.* Preoperative chemotherapy of locally advanced gastric cancer. *Ann Oncol* 1994; **5** (Suppl 3): 59–68.
164. Fink U, Schuhmacher CH, Bottcher K, *et al.* Neoadjuvant chemotherapy (EAP) with r-metHuG-CSF (Filgastrim) for patients with locally advanced gastric cancer. *Eur J Cancer* 1993; **29A**: S55 (Abstr 272) (Suppl 6).
165. Kelsen D, Karpeh M, Schwartz G, *et al.* Neoadjuvant and postoperative chemotherapy for high-risk gastric cancer. *Proc Am Soc Clin Oncol* 1994; **13**: 195 (Abstr 566).

(Received 10 August 1995; accepted 25 September 1995)