Original article

Docetaxel (Taxotere®)–cisplatin (TC): An effective drug combination in gastric carcinoma

A. D. Roth,[1] R. Maibach,[2] G. Martinelli,[3] N. Fazio,[3] M. S. Aapro,[3] O. Pagani,[4] R. Morant,[5] M. M. Borner,[6] R. Herrmann,[7] H. Honegger,[8] F. Cavalli,[4] P. Alberto,[9] M. Castiglione[2,6] & A. Goldhirsch[3,10] on behalf of the Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland and the European Institute of Oncology (EIO), Milan, Italy

[1]*Oncosurgery, Department of Surgery, Hôpital Cantonal Universitaire, Geneva;* [2]*SIAK coordinating center, Bern, Switzerland;* [3]*European Institute of Oncology, Milan, Italy;* [4]*Division of Oncology, Ospedale San Giovanni, Bellinzona;* [5]*Division of Oncology, Department of Medicine C, Kantonspital, St. Gallen;* [6]*Institute of Medical Oncology, Inselspital, Bern;* [7]*Division of Oncology, Department of Medicine, Kantonspital, Basel;* [8]*Institute of Oncology and Haematology, Stadtspital Triemli, Zürich;* [9]*Division of Oncology, Department of Medicine, Hôpital Cantonal Universitaire, Geneva;* [10]*Division of Oncology, Ospedale Civico, Lugano, Switzerland*

Summary

Purpose: A multi-centric trial was performed to explore the clinical activity, in terms of response and toxicity (primary objectives), duration of response and survival (secondary objectives), of docetaxel with cisplatin in advanced gastric cancer (AGC).

Patients and methods: Patients with measurable unresectable and/or metastatic gastric carcinoma, performance status ≤ 1, normal hematological, hepatic and renal functions and not pretreated for advanced disease by chemotherapy received up to eight cycles of TC (docetaxel 85 mg/m^2 d1, cisplatin 75 mg/m^2 d1) q3w. Dose escalation to 100 mg/m^2 was performed in five patients and was discontinued for excessive toxicity.

Results: Forty-eight patients were accrued. A median of 5 cycles/patient was given. We observed 2 complete and 25 partial responses for an overall intent to treat response rate of 56% (95% CI: 41%–71%). Twelve patients had stable disease for ≥ 9 weeks (3 cycles). The median time to progression and overall survival were 6.6 and 9 months, respectively. Grade ≥ 3 toxicities were neutropenia 81%, anemia 32%, thrombocytopenia 4%, alopecia 36%, fatigue 9%, mucositis 9%, diarrhea 6%, nausea/vomiting 4%, neurologic 2%, and one anaphylaxis precluding treatment administration. We recorded nine episodes of non-fatal febrile neutropenia in eight patients, two of them with docetaxel at 100 mg/m^2. There were no direct treatment-related deaths.

Conclusions: TC is active in AGC with a high response rate in a multicentric trial. Despite its hematotoxicity, this regimen is well tolerated and can be recycled as originally planned in 78% of the cases. These results may serve as basis for further developments of docetaxel containing regimens in this disease.

Key words: chemotherapy, docetaxel, gastric cancer

Introduction

Despite a decline in its incidence, gastric carcinoma remains one of the 10 leading causes of death by neoplasia in the Western countries [1]. For a long period of time gastric carcinoma was considered to be poorly chemoresponsive. For instance, a combination of mitomycin C, adriamycin and 5-fluorouracil (5-FU) (FAM) was used with shortlived responses in 20%–40% of patients [2].

'Second generation' cytotoxic regimens such as 5-FU–cisplatin (FUP), 5-FU–adriamycin–methotrexate (FAMTX), etoposide–adriamycin–cisplatin (EAP) or etoposide–5-FU–leucovorin (ELF) were developed in the late eighties and early nineties and were originally shown to yield high response rates (RR) [3–6]. However, results observed in subsequent randomized trials were less convincing with response rates staying in the 20%–25% range with a median time to progression not exceeding five months [7, 8].

Two recently proposed regimens seem more promising in gastric cancer. Epirubicin–cisplatin–5-FU in continuous infusion (ECF) was developed in the UK and is based on a new administration modality of 5-FU. An impressive response rate of 71% with 12% CR was obtained in a phase II setting [9–11]. Compared with FAMTX in a phase III randomized study, ECF yielded a superior response rate (45% vs. 21%) and a superior median time to progression (7.4 months *versus* 3.4 months). These data led the investigators to propose ECF as standard practice [12]. An intensive weekly chemotherapy called PELF (cisplatin, epirubicin, 5-FU and leucovorin) was studied in Italy and reported to yield a 62% response rate in a large phase II trial enrolling 105 patients [13]. However, toxicity was substantial requiring regular use of colony stimulating factors. Although both regimens gave very encouraging results and might deserve further development, they did not incorporate new promising agents in this disease [14].

Docetaxel, a semisynthetic taxoid developed in the eighties, is derived from the needles of the European yew tree, *Taxus baccata* [15]. Phase II studies showed that docetaxel was active against a broad spectrum of human solid tumors, among them ovarian, breast, gastric, head and neck, and lung cancers [16–19]. Three phase II trials in the United States, Europe and Japan, testing docetaxel (60–100 mg/m^2) as a single agent in advanced gastric cancer, totaling 113 evaluable patients with measurable disease yielded a response rate of 17%–24% [20–22]. These results prompted us to investigate docetaxel in combination with other active agents in gastric carcinoma. Cisplatin is widely used in gastric carcinoma in combinations like ECF, FUP or PELF as discussed above. *In vitro* studies with docetaxel have shown a lack of cross resistance to cisplatin, etoposide and 5-FU [23].

Since the toxicity profiles of cisplatin and docetaxel have little significant overlap, a combination of these agents seemed to constitute a logical step of investigation. A phase I study testing the association of cisplatin and docetaxel was conducted by the Rotterdam Cancer Institute and showed that a dose of 85–100 mg/m^2 of docetaxel combined with 75 mg/m^2 of cisplatin was manageable and could be given for multiple courses [24]. Of note, among the 52 patients treated, 3 had gastric cancer and 2 responded.

We report the results of a phase I–II trial investigating the efficacy and the tolerability of the association of docetaxel and cisplatin (TC) in metastatic gastric cancer (SAKK 42/95) initiated in January 1996.

Patients and methods

Patients and treatment

Patients with metastatic or locally advanced adenocarcinoma of the stomach not previously treated palliatively by systemic therapy and not amenable to curative resection were enrolled in this study. The patients were required to have a performance status ≤ 1, normal blood counts, creatinine clearance ≥ 60 ml/min, normal liver function tests, no history of anaphylaxis and no peripheral neuropathy of any origin greater than grade 1.

The treatment consisted in docetaxel 85 mg/m^2 d1 in a one hour i.v infusion followed by cisplatin 75 mg/m^2 d1 in a one hour i.v. infusion given every three weeks for up to eight cycles. If this dose was well tolerated in the first cycle of the first six patients (no dose limiting toxicity [DLT] defined as grade 4 hematological toxicity with infection and/or grade 3 non-hematological toxicity except for alopecia and nausea/vomiting), the dose of docetaxel was to be increased to 100 mg/m^2 for subsequent patients in a phase I fashion. All patients received a standard supportive regimen consisting of hyperhydration (3 liters of normal saline or 5% dextrose/24 hours) during each course of treatment and Fortecortine* (dexamethasone) 8 mg p.o. administered 12 and 6 hours before docetaxel infusion and 8 mg twice daily for an additional 4 days. 5-HT$_3$ inhibitors were used for emesis prophylaxis.

The next cycle of treatment could be postponed for no more than two weeks to allow the resolution of toxicities. Patients were to be removed from the study for any treatment delay longer than two weeks. A 20% dose reduction of docetaxel was mandatory in case of prolonged grade 4 neutropenia (> 7 days), grade 4 thrombocytopenia, grade ≥ 2 liver toxicity, grade ≥ 3 diarrhea and grade 3 cutaneous toxicity. A further 25% dose reduction was foreseen in the event that

the same type/grade toxicity was observed in subsequent cycles. If grade 2 neurotoxicity was recorded the dose of docetaxel was to be reduced by 20% along with a 25% reduction in cisplatin dose. The study therapy was discontinued in the event of transitory grade > 2 renal toxicity or definitive decrease in renal function (creatinine clearance < 60 ml/min), grade 3 liver toxicity, grade ≥ 3 neuropathy, grade 4 cutaneous toxicity, grade 3 anaphylactoid reaction and if a toxicity recurred despite dose reductions.

Responses were assessed according to WHO criteria at the end of every other cycle of treatment. The statistical analysis of the response rate was by intention to treat. Patients not evaluable for response were therefore kept in the denominator of the response rate. Complete or partial responses had to be confirmed by a second evaluation performed four or more weeks after the initial one. After completion of eight cycles of treatment or discontinuation of chemotherapy, disease status was reevaluated every three months. Toxicity was assessed according to WHO grading for each cycle.

An 'optimal two-stage' design was chosen for this phase II trial [25]. Such a design serves to build into the trial a safety measure leading to early stopping in case the response rate is lower than expected. Thirteen consecutive pts were enrolled in the first stage and we recorded a sufficient number of responses to safely exclude that the response rate was as low as 20%. This allowed us to proceed to the second stage, in which an additional 35 cases were recruited up to a total of 48

The trial was accepted by the ethical review boards of all participating institutions. Every patient gave his or her written informed consent.

Results

Forty-eight patients were enrolled in the study. Patient characteristics are summarized in Table 1. There were 36 males and 12 females, whose performance status was 0 (48%) and 1 (52%). Forty-eight percent of the patients had previously undergone a surgical resection of their primary tumor (total or subtotal gastrectomy), and two had received neoadjuvant or adjuvant chemotherapy. At the time of study inclusion there was a median 4.5 kg weight loss over the last three months. Of the 48 patients enrolled 45 were fully evaluable for response. Two patients died early before the first response assessment (one suicide and one pulmonary embolism) and one patient had unmeasurable disease (protocol violation). These three patients were kept in the final intent-to-treat analysis of response.

The first six patients were given docetaxel 85 mg/m^2 d1 in one hour infusion followed by cisplatin 75 mg/m^2 d1. Because of a good tolerance of TC at this dose level, the docetaxel dose was then increased to 100 mg/m^2. However, we observed two febrile neutropenias and one episode of grade 3 mucositis in the five patients enrolled at this dose level. The trial was therefore carried on with docetaxel at 85 mg/m^2 thereafter. The five patients treated with docetaxel at 100 mg/m^2 were kept in the final analysis.

Two complete (CR) and 25 partial responses (PR) were recorded, giving a response rate (RR) of 56% (27 of 48 patients) (95% CI: 41%–71%) (Table 2). Twelve patients had stable disease during at least three cycles of treatment, four patients progressed immediately during therapy and two went off treatment due to excessive

Table 1. Patient characteristics.

Number of patients	48
Age (years)	
Median	55
Range	27–75
Sex, n (%)	
Male	36 (75)
Female	12 (25)
Performance status, n (%)	
0	23 (48)
1	25 (52)
Appetite, n (%)	
Good	13 (27)
Fair	28 (58)
None	7 (15)
Weight change in last three months (kg)	
Median	−4.5
Range	−16−+5
Previous surgery	23 (48)
Curative	14
Palliative	9
Previous adjuvant chemotherapy	2 (4)
Number of affected disease sites per patient	
Median	3
Range	1–5
Patients with locally advanced disease only	7
Number of disease sites per patient (number of patients)	
1	6
2	14
3	17
≥ 4	11
Disease sites (measurable and not measurable)	
Lymph nodes	36
Stomach	33
Liver	16
Peritoneum	15
Lung	9
Bone	9
Ovary	3
Others	12

Table 2. Tumor response.

Overall best response	Number of patients (total = 48 (%))
CR	2 (4)
PR	25 (52)
SD (for ≥ 3 cycles)	12 (25)
PD[a]	6 (12)
Early deaths	2 (4)
Non-measurable disease	1 (2)

[a] Including two patients who went off treatment due to toxicity.

Figure 1. Overall survival for all patients.

Figure 2. Time to progression for all patients.

toxicity. One patient had his primary resected after six cycles of treatment. There is no significant difference in response according to disease site. The RR in patients with locoregional disease (stomach and regional lymph nodes ± adjacent pancreas) was 44% (4 of 9), whereas for patients with distant metastatic disease ± locoregional disease with no more than three disease sites or more than three disease sites the RR were 59% (16 of 27) and 58% (7 of 12), respectively. The median progression free survival defined as the interval from start of the treatment to disease progression or death in all patients
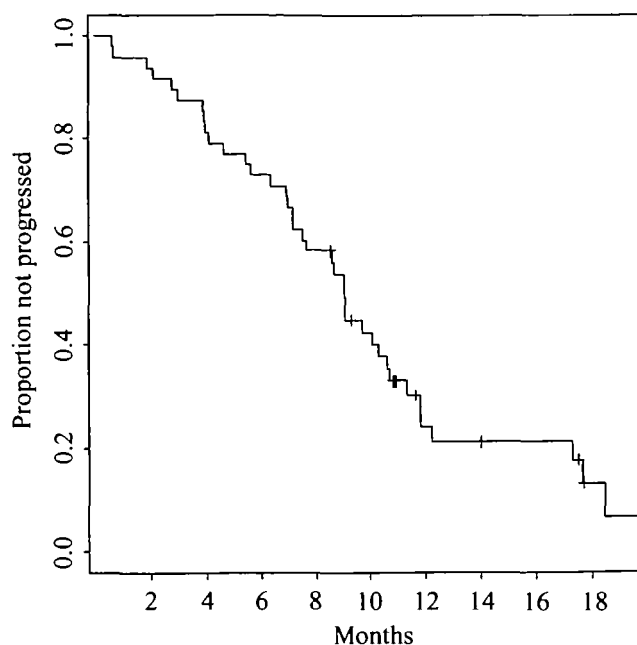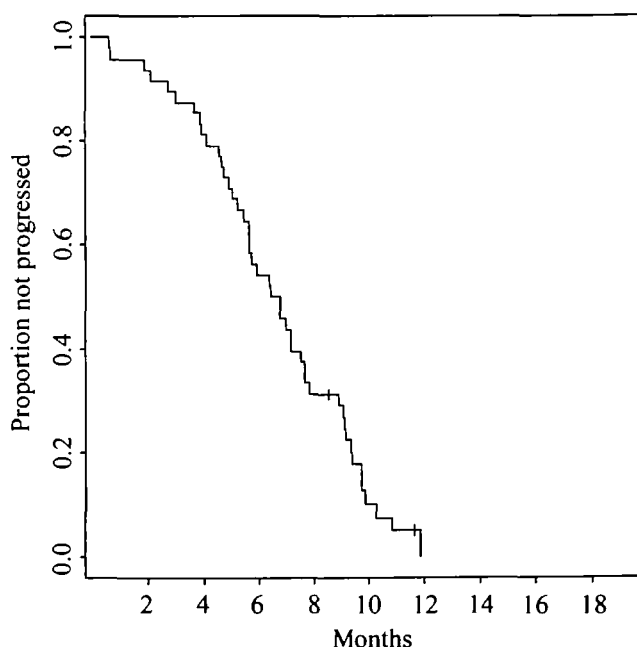
was 6.6 months (Figure 1). The median progression-free survival in responders was 7.1 months. The median overall survival was 9 months (Figure 2). Thirty-nine patients had died at the time of the present evaluation.

Twenty-three patients received a second-line therapy after disease progression or after failing TC. The regimens the most frequently used were etoposide–leucovorin–5-FU (ELF), 5-FU–adriamycine, 5-FU ± leucovorine, epirubicin–mitomycin C–5-FU (EMF) or CPT11–5-FU. Twelve patients received ≥ 4 cycles and seven of them ≥ 6 cycles. Although this trial was not designed to

Table 3 Hematoxicity.

Toxicity	Percentage of cycles (n = 229)		Percentage of cycles (n = 47)	
	Grade 3	Grade 4	Grade 3	Grade 4
Leucocytes	21	4	40	11
Granulocytes	25	31	24	57
Thrombocytes	0	1	0	4
Anemia	–	–	21	11

Table 4. Non-hematologic toxicity in percentage of 47 patients.

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Nausea/vomiting	38	30	4	0
Diarrhea	9	19	6	0
Mucositis	26	13	9	0
Fatigue	26	49	9	0
Alopecia	6	51	36	–
Neurological	21	23	2	0
Fluid retention[a]	19	13	0	–
Hypersensitivity reaction[a]	6	0	2	–

[a] Grades: 1 = mild, 2 = moderate, 3 = severe.

Table 5. Non-hematologic toxicity in percentage of 229 cycles of treatment.

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Nausea/vomiting	29	12	1	0
Diarrhea	5	5	2	0
Mucositis	13	4	2	0
Fatigue	40	21	2	0
Neurological	14	8	0.4	0
Fluid retention[a]	9	4	0	–
Hypersensitivity reaction[a]	2	0.4	0.4	–

[a] Grades. 1 = mild, 2 = moderate, 3 = severe.

record responses to second line regimens, it can be deduced from the number of cycles administred that a good half of the patients treated in second line enjoyed at least a stabilisation of their disease for several months.

Treatment with TC was well tolerated. Two hundred thirty cycles of treatment were administred with a median of 5 cycles per patient. Seventy-nine percent of the cycles were administered on schedule. The performance status improved in 20%, 15%, 8% and 6% of the patients during cycles 1, 2, 3 and 4, respectively, while it remained stable in more than half of the patients. During the same period the appetite stayed stable in about half of the patients while it improved in 10% of them. Seven patients died while on treatment. Four patients died of progressive disease, two of pulmonary embolism, and one committed suicide. The latter patient suffered from Alzheimer's disease and developed grade 4 neurological disturbances consisting in disorientation and depression during the first cycle of treatment. This state of confusion was attributed by the treating physicians to the concomitant medication with morphine and dexamethasone, and not to the chemotherapy agents.

The toxicity analysis is based on 47 patients and 229 cycles of treatment. Cycle 1 of one patient was not available due to early death on day 20 from pulmonary embolism. Table 3 summarizes grade 3–4 hematological toxicities per patient and per cycle. Despite the relatively frequent occurrence of profound granulocytopenia, only nine episodes of non fatal febrile neutropenia were seen in eight patients (19% of the patients, 4% of the treatment cycles). Two of the episodes of febrile neutropenia occurred during the first cycle of treatment in the five patients treated with docetaxel at 100 mg/m². Other main toxicities are reported per patient in Table 4 and per cycle in Table 5. Grade 3–4 events were infrequent. One patient presented with esophageal perforation of unclear origin, another had one episode of upper GI tract hemorrhage. Neither of these events appeared to be related to the study chemotherapy. Two patients experienced cutaneous reactions which could be attributed to docetaxel. The first one had grade 1 erythema with pruritus during the second cycle of treatment which resolved spontaneously with moisturizing cream application and never reoccurred. The second patient had grade 3 diffuse xeroderma with erythrodermia and pruritus of the sun exposed skin treated with topical

steroids. This occurred during his fifth, and last cycle of treatment.

Eight patients discontinued therapy due to toxicity. One patient refused to continue the treatment because of severe (grade 3) asthenia. One patient could not be treated because of severe hypersensitivity reaction developed on two occasions despite adequate premedication. One patient had prolonged thrombopenia precluding further therapy. Because of very strict recommendations for stopping therapy in case of grade 1 sustained renal toxicity, five additional patients had their treatment stopped after a median of 5 cycles. The protocol was amended after the inclusion of the 30th patient. It was recommended to give the cisplatin in a four-hour infusion instead of one hour and a dose reduction scheme of cisplatin in case of mild renal toxicity was proposed in order to allow responding patients to receive further treatment. Thereafter none of the 18 remaining patients went off treatment due to renal toxicity.

Discussion

This trial shows that the association of cisplatin and docetaxel (TC) is active in gastric carcinoma. It confirms the results of earlier phase I studies regarding the feasibility of the regimen and its good tolerability.

With an intent to treat response rate of 56%, a median time to progression of 6.6 months and a median overall survival of 9 months observed in an international multiinstitutional trial with 10 participating centers, TC

can be considered as an active two drug combination in gastric carcinoma with at least an additive effect between both drugs. This result could have been influenced in part by recrutment selection since only patients with a performance status ≤1 were enrolled in the study. However, it is common that patients enrolled in gastric cancer trials have predominantly a good performance status since otherwise their survival is poor [5, 8, 12, 26–28]. The nonrandomized phase II design of this trial does not allow any definitive conclusions nor any direct comparison with other regimens. However, if we consider data from other phase II or III trials, this two drug regimen seems to be at least as good as second generation regimens in gastric cancer like EAP, FAMTX, FUP or ELF [7, 8]. Our results are also very similar to what can be expected from a more recent regimens like ECF [12], or the more intensive and more toxic PELF [13]. It is of interest to note that 37% of the responders had met the partial response criteria after already two cycles of treatment only (six weeks). The high response rate as well as the rapidity of response observed make TC a regimen highly suitable for neoadjuvant treatment, where high efficacy over a short time period is expected.

Despite the reported hematological toxicity, TC was well tolerated with a median of 5 cycles of treatment given per patient and only nine episodes of non fatal febrile neutropenia. The three fatalities recorded during the treatment period (one suicide and two pulmonary embolisms) do not seem to be directly and specifically related to the treatment. This compares very favourably with other regimens like EAP where fatalities were reported or FAMTX where poor tolerance led to frequent omission of d15 methotrexate administration and to reconsider the dosage of the original regimen [29–32]. TC is also certainly easier to prescribe and better tolerated than PELF, which is considered to be an intensive regimen requiring growth factor support [13, 28]. Apart from its hematotoxicity rate, which does not seem to translate into an inacceptable number of febrile neutropenic episodes, TC is probably as well tolerated as ECF and seems to give very similar results without the need of an indwelling catheter and an external pump with its risks and costs [33–35]. The renal problems observed in five patients at the beginning of the trial did not reappear after the change in cisplatin administration time. In our experience the only adverse effect which could preclude TC administration is anaphylaxis to the docetaxel formula, an event observed in one patient enrolled in this study.

Because the phase I study conducted by the Rotterdam Cancer Institute recommended a dose of 85–100 mg/m² of docetaxel combined with 75 mg/m² of cisplatin, we designed our trial with a dose escalation of docetaxel from 85–100 mg/m² and observed that docetaxel at the latter dose in combination with cisplatin at 75 mg/m² was too toxic according to our DLT criteria [24]. Other more recent phase I reports confirm that this drug combination is relatively toxic at this dose level. An Australian group recommended to use it at 75/75 mg/m²

in lung cancer patients [36]. Others reported that this combination at 100/75 mg/m² was 'manageable' inspite of 87% of short-lasting grade 3–4 leukopenia and granulopenia leading to infections and neutropenic fever in 10% and 4.5% of the courses, respectively [37]. In our study where hematotoxicity was the DLT, dose escalation of docetaxel with colony-stimulating factors support might seem to be the next logical step. However, the peripheral neuropathy generated by this drug association at a relatively low cumulative dose of both drugs might impair its feasibility [38].

Another interesting aspect of TC is that it is a two drug regimen which could be used as basis for the development of potentially more potent docetaxel based combinations incorporating three or more active drugs in gastric cancer. Because of the observed toxicity, we felt that a non hematotoxic drug would be most suitable to be added to TC. The SAKK and EIO are presently conducting a dose finding trial in advanced gastric cancer adding 5-FU given in protracted continuous infusion (p.c.i.) to the TC combination. Preliminary data show that p.c.i. 5-FU can be added to TC without decreasing the dose of docetaxel and cisplatin [39]. This is one example of the several new generation regimens incorporating docetaxel which may be developed on the basis of our experience with TC in this tumor.

In conclusion, we show here that docetaxel in combination with cisplatin is a very potent regimen in gastric cancer and is well tolerated.

Acknowledgements

References

1. Hisamishi S. Screening for gastric cancer. World J Surg 1989; 13: 31–7.
2. The Gastrointestinal Tumor Study Group. Randomized study of combination chemotherapy in unresectable gastric cancer. Cancer 1984; 53: 13–7.
3. 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.
4. Preusser P, Wilke H, Achterrath W. Phase II study with the combination etoposide, doxorubicin and ciplatin in advanced measurable gastric carcinoma. J Clin Oncol 1989; 7: 1310–7.
5. Wils JA, Klein HO, Wagener DJT 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 Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. J Clin Oncol 1991; 9: 827–31.

6. Leichman L, Berry BT. Cisplatin therapy for adenocarcinoma of the stomach. Semin Oncol 1991; 18 (Suppl 3): 25–33

7. Rougier P, Wils J, Wilke H et al. Advanced gastric cancer: Comparison of FAMTX (5-FU, adriamycine, methotrexate) versus ELF (etoposide, 5-FU, leucovorin) versus FUP (infusional 5-FU + cisplatin). Results from an EORTC trial of the GITCCG and the Arbeitsgemeinschaft für innere Onkologie (AIO). Eur J Cancer [A] 1995; 31A: S116 (Abstr).

8. 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. North Central Cancer Treatment Group. J Clin Oncol 1994; 12: 412–6.

9. 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.

10. Bamias A, Hill ME, Cunningham D et al. Epirubicin, cisplatin, and protracted venous infusion of 5-fluorouracil for esophagogastric adenocarcinoma: Response, toxicity, quality of life, and survival. Cancer 1996; 77: 1978–85.

11. Zaniboni A, Barni S, Labianca R et al. Epirubicin, cisplatin, and continuous infusion 5-fluorouracil is an active and safe regimen for patients with advanced gastric cancer. An Italian Group for the Study of Digestive Tract Cancer (GISCAD) report. Cancer 1995, 76: 1694–9.

12. Webb A, Cunningham D, Scarffe JH et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997; 15: 261–7.

13. Cascinu S, Labianca R, Alessandroni P et al. Intensive weekly chemotherapy for advanced gastric cancer using fluorouracil, cisplatin, epi-doxorubicin, 6S-leucovorin, glutathione, and filgrastim: A report from the Italian Group for the Study of Digestive Tract Cancer. J Clin Oncol 1997; 15. 3313–9.

14. Fuchs CS. Chemotherapy for advanced gastric cancer: Where do we stand? J Clin Oncol 1997; 15: 3299–300.

15. Pazdur R, Kudelka AP, Kavanagh JJ et al. The taxoids: paclitaxel (Taxol) and docetaxel (Taxotere). Cancer Treat Rev 1993; 19: 351–86.

16. Verweij J, Clavel M, Chevalier B. Paclitaxel (Taxol) and docetaxel (Taxotere): Not simply two of a kind. Ann Oncol 1994; 5: 495–505.

17. Catimel G, Verweij J, Mattijssen V et al. Docetaxel (Taxotere): An active drug for the treatment of patients with advanced squamous cell carcinoma of the head and neck. EORTC Early Clinical Trials Group. Ann Oncol 1994; 5: 533–7.

18. Francis PA, Rigas JR, Kris MG et al. Phase II trial of docetaxel in patients with stage III and IV non-small-cell lung cancer. J Clin Oncol 1994; 12: 1232–7.

19. Verweij J, Catimel G, Sulkes A et al. Phase II studies of docetaxel in the treatment of various solid tumours. EORTC Early Clinical Trials Group and the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 1995; 31A (Suppl 4): S21–4.

20. Einzig AI, Neuberg D, Remick SC et al. Phase II trial of docetaxel (Taxotere) in patients with adenocarcinoma of the upper gastrointestinal tract previously untreated with cytotoxic chemotherapy: the Eastern Cooperative Oncology Group (ECOG) results of protocol E1293. Med Oncol 1996; 13: 87–93.

21. Sulkes A, Smyth J, Sessa C et al. Docetaxel (Taxotere) in advanced gastric cancer: Results of a phase II clinical trial. EORTC Early Clinical Trials Group. Br J Cancer 1994; 70: 380–3.

22. Taguchi T. An early phase II clinical study of RP56976 (docetaxel) in patients with cancer of the gastrointestinal tract. Gan To Kagaku Ryoho 1994; 21: 2431–7.

23. Hill BT, Whelan RD, Shellard SA et al. Differential cytotoxic effects of docetaxel in a range of mammalian tumor cell lines and certain drug resistant sublines in vitro. Invest N Drugs 1994; 12: 169–82.

24. Verweij J, Planting AST, van der Burg MEL et al. A phase I study of docetaxel and cisplatin in patients with solid tumors. Ann Oncol 1994; 5 (Suppl 5): 504 (Abstr).

25. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clin Trials 1989; 10: 1–10.

26. Roth AD, Herrmann R, Morant R et al. Cisplatin, doxorubicin and etoposide (PAV) in advanced gastric carcinoma: The SAKK experience. Eur J Cancer 1998; 34: 2126–8.

27. Kim NK, Park YS, Heo DS et al. A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. Cancer 1993; 71: 3813–8.

28. 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.

29. Katz A, Gansl RC, Simon SD et al. Phase II trial of etoposide (V), adriamycin (A), and cisplatinum (P) in patients with metastatic gastric cancer. Am J Clin Oncol 1991; 14: 357–8.

30. Lerner A, Gonin R, Steele GD Jr, Mayer RJ. Etoposide, doxorubicin, and cisplatin chemotherapy for advanced gastric adenocarcinoma: Results of a phase II trial. J Clin Oncol 1992; 10: 536–40.

31. 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.

32. 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.

33. Kock HJ, Pietsch M, Krause U et al. Implantable vascular access systems: Experience in 1500 patients with totally implanted central venous port systems. World J Surg 1998; 22: 12–6.

34. Young C, Gould JR. The timing and sequence of multiple device-related complications in patients with indwelling subcutaneous ports. Am J Surg 1997; 174: 417–21.

35. Lemmers NW, Gels ME, Sleijfer DT et al. Complications of venous access ports in 132 patients with disseminated testicular cancer treated with polychemotherapy. J Clin Oncol 1996; 14: 2916–22.

36. Millward MJ, Zalcberg J, Bishop JF et al. Phase I trial of docetaxel and cisplatin in previously untreated patients with advanced non-small-cell lung cancer. J Clin Oncol 1997; 15: 750–8.

37. Pronk LC, Schellens JH, Planting AS et al. Phase I and pharmacologic study of docetaxel and cisplatin in patients with advanced solid tumors. J Clin Oncol 1997; 15: 1071–9.

38. Hilkens PH, Pronk LC, Verweij J et al. Peripheral neuropathy induced by combination chemotherapy of docetaxel and cisplatin. Br J Cancer 1997; 75: 417–22.

39. Roth AD, Maibach R, Fazio N et al. 5-FU as protracted continuous i.v. infusion (5-FUpiv) can be added to full dose Taxotere-cisplatin (TC) in advanced gastric carcinoma (AGC). Eur J Cancer [A] 1999; 35 (Suppl 4): S139.

Correspondence to:
A. D. Roth, MD
Oncosurgery
Geneva University Hospital
24 Micheli-Du-Crest
CH-1211 Geneva 14
Switzerland
E-mail: arnaud.roth@dim.hcuge.ch