REVIEW ARTICLE

Taylor&Francis healthsciences

Docetaxel in Advanced Gastric Cancer

Review of the Main Clinical Trials

Serena Di Cosimo, Gianluigi Ferretti, Nicola Fazio, Nicola Silvestris, Paolo Carlini, Andrea Alimonti, Alain Gelibter, Alessandra Felici, Paola Papaldo and Francesco Cognetti

From the Division of Medical Oncology 'A', Regina Elena Cancer Institute, Rome (S. Di Cosimo, G. Ferretti, P. Carlini, A. Alimonti, A. Gelibter, A. Felici, P. Papaldo, F. Cognetti), Division of Medical Oncology, European Institute of Oncology, Milan (N Fazio), and the Division of Medical Oncology, S. Maria Goretti Hospital, Latina (Nicola Silvestris) Italy

Correspondence to: Gianluigi Ferretti, Division of Medical Oncology 'A', Regina Elena Cancer Institute, Via Elio Chianesi 53, IT-00144 Rome, Italy. Tel: +39 06 5266 5354. Fax: +39 06 5266 5637. E-mail: gia.fer@flashnet.it

Acta Oncologica Vol. 42, No. 7, pp. 693–700, 2003

The aim was to investigate the activity of docetaxel in advanced gastric cancer either as single agent or in combination with other drugs. A systematic review was carried out using the databases of Medline, Embase and CancerLit. Results from ASCO and ESMO meetings during 2002 were also included. Eight phase II trials focused on docetaxel as a single agent. Considering collectively the 262 evaluable patients enrolled in these studies, the mean response rate (RR) was 19% (CI 95% 14–24%). Docetaxel was well tolerated with a dose-limiting myelosuppression (grade 3–4 neutropenia in 36–95% of cases). Adding fluorouracil, an RR ranging from 22% to 86% was registered, due to differences in populations studied (young vs. elderly) and modalities of drug administration (continuous vs. bolus infusion). RRs for docetaxel–cisplatin combination were 56%, 37% and 36% in three phase II trials and 35% in a phase III trial. The addition of both cisplatin and fluorouracil to docetaxel did not increase toxicity. Randomized trials comparing docetaxel–cisplatin–fluorouracil with ciplatin–fluorouoracil or epirubicin–cisplatin–fluorouracil, the most commonly used regimens, are ongoing. The future results of the above phase III studies could indicate docetaxel as a key drug to improve treatment of patients with advanced gastric cancer.

Received 11 December 2002
Accepted 29 April 2003

Gastric carcinoma was the leading cause of cancer death worldwide through most of the twentieth century. In the United States, it ranks 14th in incidence among the major types of cancer malignancies with an estimated 22 400 new cases expected in 2003 for both sexes combined (1, 2). The prognosis for this disease remains poor. The overall 5-year survival rate in most of the Western world ranges from 5% to 15%. The only proven potentially curative treatment is surgical resection of all gross and microscopic disease. Unfortunately, less than 50% of all patients present a resectable disease at diagnosis, and less than 50% of operated patients undergo radical surgery. Furthermore, even after a 'curative' gastrectomy, disease recurs in both regional and distant sites in more than 50% of patients (3). Efforts to improve these poor results have focused on developing effective pre- and postoperative systemic and regional adjuvant therapies. In patients with advanced disease new drugs, such as the taxanes, may potentially improve the disappointing results of chemotherapy.

The semisynthetic taxane docetaxel (Taxotere®; Aventis Pharma) is produced by the esterification of the side chain at C-13 of 10-deacetyl baccatin III, a non-cytotoxic precursor extracted from the needles of the European yew tree (Taxus baccata) (4). Docetaxel has been selected for clinical development because it is twice as potent as the natural taxane paclitaxel in promoting tubulin polymerization and in inhibiting microtubule depolymerization; docetaxel also showed equal or greater cytotoxicity than paclitaxel in relevant preclinical models (5, 6). Initial interest in studying docetaxel in gastric cancer patients grew out of laboratory investigations demonstrating antitumor activity and pro-apoptotic effects in human gastric cancer cell lines (7, 8). Docetaxel is able to activate transcription factor AP-1 in association with apoptotic cell death in gastric cancer cell lines. This paper details the current thinking regarding the treatment of gastric cancer with docetaxel. We report on data from the original studies documenting the clinical efficacy of docetaxel either as a single agent or in combination with widely used anticancer drugs both in chemotherapy-naïve and pre-treated patients.

We used computerized bibliographic databases (MEDLINE, EMBASE, CANCERLIT) without language restric-

 ISSN 0284-186X
DOI: 10.1080/02841860310011014

tions from January 1966 to February 2003 with the aim of identifying all randomized and prospective trials. This was combined with the medical subject heading 'gastric cancer and docetaxel' and other keywords pertaining to upper gastrointestinal malignancy and their treatment. We also hand searched relevant conference proceedings and reviewed textbooks and reference lists of all retrieved articles. Abstracts and letters were included if they contained enough methodological information and results. We excluded case reports and studies with no clinical outcome measures. Finally, we collected the novelties from the 38th American Society of Clinical Oncology (ASCO) and 28th European Society for Medical Oncology (ESMO) meetings during 2002, regarding docetaxel and gastric cancer.

DOCETAXEL AS A SINGLE AGENT IN CHEMOTHERAPY-NAÏVE AND PREVIOUSLY TREATED GASTRIC CANCER PATIENTS

Table 1 summarizes the results of phase II studies of docetaxel administered as a single agent either in chemotherapy-naïve or in pretreated patients with advanced gastric cancer (9–16). Collectively, 262 patients were evaluable for response. Response rate (RR) varied from 17% to 24%, with a mean of 19.1% (CI 95% 14.3–23.8%). In 5 of the trials docetaxel was administered at 100 mg/m^2 (in one trial plus G-CSF), in two of the trials at 75 mg/m^2 and 60 mg/m^2, every 3 weeks (q 3 w). Graziano et al. used docetaxel at 35 mg/m^2 every week, 6 out of 8 weeks. In all studies docetaxel was given intravenously over 1 hour. The most common toxicity was non-cumulative neutropenia (36–95%) with leucopenic fever (5–46%) and grade 1–3 hypersensitivity reactions (24%) (Table 2). Alopecia and fluid retention were seen in the majority of patients. There were no treatment-related deaths. It is noteworthy that 4 phase II studies used docetaxel in pre-treated patients.

SEQUENTIAL SCHEME

A particular use of single agent docetaxel in gastric cancer patients is that proposed by Cascinu et al. in a phase II study of sequential chemotherapy (17). Forty chemotherapy-naïve patients were treated with weekly PELF (cisplatin 40 mg/m^2, fluorouracil 500 mg/m^2, epirubicin 35 mg/m^2, 6S-stereoisomer of leucovorin 250 mg/m^2 and glutathione 1.5 g/m^2, plus filgrastim 5 microg/kg on the other days) over 8 consecutive weeks. Then, patients with partial response or stable disease received three courses of docetaxel 100 mg/m^2, q 3 w. After the PELF regimen, 3 patients achieved complete response (CR), 13 patients partial response (PR) (overall RR 40%; 95% CI: 25% to 55%), 21 patients stable disease (SD), and three patients progressive disease (PD). After docetaxel, 9 of the 34 patients showed an improved outcome (27%); 7 patients with SD achieved PR and 2 patients with PR achieved CR. The overall response rate in the 40 patients was 58% (95% CI: 42.5–72.5%). Adverse events that occurred during the 102 cycles of docetaxel therapy included grade 3–4 neutropenia (10%) and thrombocytopenia (19%), and grade 3 nausea and vomiting (15%). The authors conclude that the PELF/docetaxel sequential combination represents an interesting evolution of the PELF regimen with respect to the major objective responses and the manageable toxicities achieved. Their sequential use demonstrates a favorable toxicity-to-efficacy ratio and prompts further investigation in the palliative or neoadjuvant setting.

COMBINATION REGIMENS

Two-drug regimens

The encouraging results as a single agent, the lack of cross-resistance with other drugs, and the favorable toxicity profile inspired a series of clinical investigations on docetaxel in combination with other traditional chemotherapeutic agents in gastric cancer treatment (18–20). Based on a demonstrated synergism between the two compounds (21), docetaxel was added to 5-FU, either at high or at low doses. Table 3 summarizes the results of docetaxel in two-drug combination therapy. Two phase II trials were presented at the 35th and 37th American Society of Clinical Oncology annual meeting in recent years (22, 23). They

Table 1

Activity of docetaxel as a single agent

	Evaluable/ eligible patients	Previous chemotherapy	Docetaxel dose (mg/m^2)	Schedule	Overall response rate	Stable disease	Median response duration	Median time to progression
Sulkes (9)	33/37	N	100	q 3 w	24% (95% CI: 9–39%)	11/33	7.5 months	–
Einzig (10)	36/41	N	100	q 3 w	17% (95% CI: 8–30%)	–	–	–
Mavroudis (11)	30/30	N	100+G-CSF	q 3 w	20% (95% CI: 6–34%)	7/30	4.5 months	6 months
Giuliani (12)	18/24	Y	100	q 3 w	3/18	6/18	–	–
Vanohefer (13)	25/27	Y	100	q 3 w	20% (95% CI: 7–41%)	–	–	–
Bang (14)	40/75	N	75	q 3 w	18% (95% CI: 7–33%)	–	–	–
Taguchi (15)	59/66	Y	60	q 3 w	23.7% (95% CI: 13.6–36.6%)	19/59	–	–
Graziano (16)	21/21	Y	36	Weekly	1/21	8/21	–	–

Table 2

Major toxicity of phase II trials with docetaxel as single agent therapy in advanced gastric cancer patients

	Evaluable patients	Grade 3–4 neutropenia	Febrile neutropenia	Other common toxicities
Sulkes (9)	33	95%	5%	Hypersensitivity reactions (24%) fluid retention (24%)
Einzig (10)	41	88%	46%	Hypersensitivity reactions (10/41)
Mavroudis (12)	30	36%	10%	Vomiting (6.6%) diarrhea (3%) fatigue (3%)
Taguchi (15)	45	53%	–	Vomiting (15%) anorexia (17%) diarrhea (6%) fatigue (11%)

enrolled a total of 41 patients. Twenty-six patients received docetaxel 100 mg/m^2 over 1 hour with 5-FU 1,800 mg/m^2 plus leucovorin, 500 mg/m^2 over 24 hours on days 1, 8 and 15, q 4 w. Fifteen elderly patients received weekly docetaxel 25 mg/m^2 and continuous infusion of 5-FU, 150 mg/m^2, for 14 days q 3 w. High-dose 5-FU combination produced an overall response and clinical benefit, defined as rates of 22% and 80%, respectively, despite quite relevant bone marrow toxicity, with grade 4 neutropenia occurring in 52% of treated patients. Low-dose 5-FU was associated with an RR of 86% in the 14 elderly patients, with a mild and reversible toxicity. Considering the little accrual, the short-term follow up and the differences in the populations studied, a joint analysis of the two trials appears to be useless and the superiority of 5-FU infusion over the traditional schedule of bolus administration can be neither stated nor excluded. Dose intensity and infusion duration have a complex interaction that may contribute meaningfully to the therapeutic index, but this issue can only be resolved by randomized clinical studies.

Enrech et al. conducted a phase II study (24) with docetaxel/irinotecan combination in patients with locally advanced or metastatic gastric cancer. At the time of this report, 14 patients have been enrolled and treated with docetaxel, 60 mg/m^2, and irinotecan, 250 mg/m^2, both administered on day 1, q 3 w. During the 52 administered cycles, grade 3–4 toxicities included neutropenia (12%), leucopenia (8%), asthenia (6%), anemia (2%), nausea/vomiting (2%), and diarrhea (2%). Of four evaluable patients, two achieved SD. The authors' preliminary analysis indicates that the q 3 w administration of docetaxel and irinotecan appears to be feasible, and the study is ongoing. A phase II study presented by Andre et al. at the 35th American Society of Clinical Oncology in 1999 (25), reported a 21% of RR with docetaxel 75 mg/m^2 plus epirubicin 75 mg/m^2, q 3 w in advanced gastric cancer

Table 3

Docetaxel in two-drug combination therapy

	Docetaxel dose (mg/m^2)	In combination with	Schedule	Patients	Overall response rate	Clinical benefit	Grade 3–4 toxicity
Constenla (22)	100	5-FU 1800 mg/m^2+Leucovorin 500 mg/m^2 (d 1, 8, 15)	q 4 w	26	22%	80%	Neutropenia (52%)
Chun (23)	25 (weekly)	5-FU 150 mg/m^2 continuous infusion	q 3 w	14 (elderly)	86%	–	Neutropenia and mucositis (14%)
Enrech (24)	60	Irinotecan, 250 mg/m^2	q 3 w	14	–	2 stable disease/4 evaluable patients	Neutropenia (12%)
Andre (25)	75	Epirubicin, 75 mg/m^2	q 3 w	25 (2 line)	21%	56%	Neutropenia (28%)
SAKK and EIO (26)	85	Cisplatin 75 mg/m^2	q 3 w	48	56%	–	Neutropenia (81%)
Ridwelski (27)	75	Cisplatin 75 mg/m^2, d1	q 3 w	39	37%	–	
Kettner (28)	75	Cisplatin 75 mg/m^2, d1	q 3 w	85	36%		
Ajani, (30) (TC)	85	Cisplatin 75 mg/m^2, d1	q 3 w	35	45%, over 29 evaluable patients	–	Neutropenia (72%)

patients previously treated with 5-FU and cisplatin-based chemotherapy regimens.

The clinical activity of docetaxel was also investigated in combination with cisplatin in patients with untreated metastatic gastric cancer. The Swiss Group for Cancer Research (SAKK) and EIO (European Institute of Oncology, Milan) treated 48 patients with docetaxel 85 mg/m^2 and cisplatin 75 mg/m^2, q 3 w (26). Up to eight courses were administered to the responding patients. Docetaxel dose-escalation to 100 mg/m^2 was performed in five cases, but was discontinued because of high toxicity (two episodes of febrile neutropenia and one grade 3 mucositis). A median of five cycles per patient was administered. The overall RR among the 48 evaluable patients using intent-to-treat analysis was 56% (95% CI: 41–71%). The median time to progression (TTP) and overall survival (OS) rate were 6.6 and 9 months, respectively. Grade 3–4 neutropenia occurred in 81% of the patients and in 56% of the courses; however, only nine episodes of neutropenic fever were recorded, including those occurring in patients receiving docetaxel at the dose of 100 mg/m^2. All grade 3–4 non-hematologic toxicities were below 3%. These results were partially confirmed by Ridwelski et al., who treated 39 previously untreated patients with advanced gastric cancer with docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2, q 3 w (27). The lower dose of docetaxel was associated with mild toxicities, but the overall RR was only 37% (95% CI: 23–54%). Median TTP was 6.1 months and median OS was 10.4 months. The same dosage and schedule were used by Kettner et al., who reported an RR of 33% and 41% in a single center and in a multi-institutional phase II trial, respectively. Combining the results from both studies, a total of 85 patients were evaluable with an overall RR of 36% (28). The promising results of docetaxel in two-drug combination therapy served as a basis for the development of three-drug docetaxel combinations.

Three-drug regimens

Table 4 summarizes the major outcomes of docetaxel three-drugs regimens. The SAKK and EIO group performed a phase I/II trial in which peripheral venous infusion (PVI) of 5-FU over 14 days every 21 was added to docetaxel and cisplatin, administered q 3 w (29). This combination resulted in less toxicity than expected, so that dose escalation of 5-FU was continued for three further levels (from 250 mg/m^2/d to 350 mg/m^2/d) before reaching the dose limiting toxicity. The definitive maximal tolerated dose in 52 untreated patients was docetaxel 85 mg/m^2, cisplatin 75 mg/m^2, and PVI-FU 300 mg/m^2/day. The RR was similar to the TC phase II trial, with a comparable tolerability. Therefore, in order to avoid bias deriving from different population samples, the authors decided to compare TC versus TCF versus ECF in a multicenter three-armed phase II randomized trial. The planned accrual is 111 patients. So far, 83 patients have been enrolled and an interim analysis is ongoing (personal communication).

Another ongoing randomized phase II trial compares TC with or without 5-FU (30). In arm A (TC) docetaxel (85 mg/m^2) and cisplatin (75 mg/m^2) were administered on day 1, q 3 w. In arm B (TCF) docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 were administered on day 1, q 3 w and 5-FU 750 mg/m^2/day, d1 to d5, q 3 w. Presently, 158 patients had been randomized. On May 2002 data of 124 patients were available with an RR of 32%/54% ArmA/ArmB. ArmA/ArmB NCIC grade 3–4 adverse events per course were: neutropenia 59%/49%; febrile neutropenia/infection 3.5%/4.4%; stomatitis 0%/9%; nausea 3%/5%; vomiting 2%/4%; diarrhea 1%/4%. There were no toxic deaths.

The addition of irinotecan to the docetaxel/cisplatin combination has been reported by Fuchs et al. (31). A phase I study enrolled 15 patients to receive docetaxel at 25 or 30 mg/m^2, cisplatin 22 or 30 mg/m^2 and irinotecan at 25 to 55 mg/m^2, all administered on a weekly basis for 2 consecutive weeks of a three-week cycle. At the time of this report the study is ongoing, but preliminary results suggest activity and synergy among the three drugs. Finally, at the 28th European Society for Medical Oncology meeting in 2002, Di Lauro et al. (32) presented their own experience with the combination of docetaxel (60 mg/m^2), epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2), q 3 w. Preliminary data of this phase II study show an overall RR of 55% (2 CR and 9 PR, over the 21 evaluable patients), with an acceptable toxicity profile. The trial is ongoing.

38TH AMERICAN SOCIETY OF CLINICAL ONCOLOGY MEETING, 2002

In a phase II trial, Murad et al. (33) treated 37 locally advanced unresectable or metastatic gastric cancer cases with docetaxel 75 mg/m^2 plus 5-FU 500 mg/m^2 IV bolus plus epirubicin 50 mg/m^2, once q 3 w (Table 4). The RR was 35% (95% CI 14–44%), but two toxic deaths occurred. Moiseyenko et al. (34) reported the results of a phase III randomized trial comparing docetaxel-cisplatin-5-FU (DCF) versus cisplatin-5-FU (CF). This study was based on their previous results of a phase II trial, in which DCF combination produced a RR of 54% (95% CI: 40.8–66.9%), with TTP and OS of 5.9 and 9.6 months, respectively. Patients with locally advanced unresectable or metastatic gastric cancer were randomized to DCF (docetaxel 75 mg/m^2 d1, cisplatin 75 mg/m^2 d1 and 5-FU 750 mg/m^2/d d1–5) q 3 w or CF (cisplatin 100 mg/m^2 d1 and 5-FU 1000 mg/m^2/d d1-5) q 4 w. Two-hundred eighty-four patients of the planned 460 have been accrued. Interim analysis demonstrated acceptable hematological toxicity, with gastrointestinal toxicity being the most frequently observed adverse event in both arms.

Recently, the Italian experience (35) with 5-FU (7 days' protracted venous infusion, 200 mg/m^2/day) combined with

Table 4

Three-drug docetaxel combinations in advanced gastric cancer: major results

	Docetaxel dose (mg/m^2)	In combination with	Schedule	Patients	Overall response rate	Clinical benefit	Grade 3–4 toxicity
SAKK and EIO, (TC+5-FU)	85	Cisplatin 75 mg/mq, d1 5-FU 300 mg/mq, over 14 days	q 3 w	83	56%, over 52 evaluable patients	–	Neutropenia (81%)
Ajani, (30) (TC+5-FU)	75	Cisplatin 75 mg/mq, d1 5-FU 750 mg, d1→5	q 3 w	35	54%, over 31 evaluable patients	–	Neutropenia (50%)
Fuchs (31)	25-30 w	Cisplatin 22-30 mg/mq,w Irinotecan 25–55 mg/mq, w	w	15	–	–	–
Murad (33)	75	Epirubicin 50 mg/mq, d1 5-FU 500 mg/mq, bolus, d1	q 3 w	37	35%	30%	2 toxic deaths Neutropenia (68%)
Ostellino (35)	17.5–30 w	5-FU, 7 days protracted venous infusion Cisplatin 20 mg/mq	w	21	6/14 evaluable patients	–	None
Di Lauro (32)	60	Epirubicin 50 mg/mq, d1 Cisplatin 60 mg/mq, d2	q 3 w	20	55%	–	Neutropenia (50%)

weekly docetaxel (at escalating doses 17.5 to 30 mg/m^2/week) and cisplatin has been presented. The dose-finding step was stopped at the docetaxel dose of 30 mg/mq/week as the dose density reached was close to that planned for docetaxel administered alone every 3 weeks and because of the promising overall RR (6 PR, 3 SD, 5 PD over the 14 evaluable patients). Among the 21 patients enrolled in this phase I–II study no reduction due to toxicity was required.

COMPARISON BETWEEN DOCETAXEL COMBINATIONS AND REGIMENS CONTAINING 5-FU/CISPLATIN

Patience et al. (36) reported the preliminary results of a randomized phase II study comparing DF (docetaxel, 75 mg/m^2 on day 1 and 5-FU 200 mg/m^2 days 1–21, q 21 days) versus ECF (epirubicin, 50 mg/m^2 day 1, cisplatin, 60 mg/m^2, day 1 and 5-FU 200 mg/m^2 days 1–21). Fifty patients were evaluable for response, 25 for each arm. ECF produced 1 CR, 10 PR and 7 SD; DF produced 2 CR, 9 PR and 5 SD. The authors concluded that DF appeared to be at least as tolerable as ECF (grade 3–4 leuco/neutropenia 45% and 54% in DF and ECF, respectively) and showed promising efficacy. The study is ongoing.

DISCUSSION

One of the most commonly used regimens for advanced gastric cancer is represented by ECF (epirubicin, cisplatin, fluorouracil) (37). In the first phase II trial, ECF produced a RR of 71% in 128 evaluable untreated patients with advanced gastric or esophageal cancer (38). The median OS was 8.2 months with 1- and 2-year survivals of 30% and 10%, respectively. Grade 3–4 emesis occurred in 13%, stomatitis in 7%, diarrhea in 4%, infection in 6%, leucopoenia in 21% and thrombocytopenia in 8% of patients. A more extensive description of all randomized trials has been provided by Janunger et al. (39). Table 5 summarizes the outcomes of the major randomized studies for advanced gastric cancer. In a phase III trial, ECF has been demonstrated to be superior to FAMTX (fluorouracil, adriamycin, methotrexate, teucovorin) in terms of RR (45% vs. 21%),

Table 5

Prospective randomized trials of combination chemotherapy in advanced gastric cancer

Drugs	Evaluable patients	Response rate (%)	Median survival (months)
ECF vs.	126	45	8.7 ($p = 0.0005$)
FAMTX (40)	30	21	6.1
FAMTX[1] vs.	45	12	6.7 (n.s.)
ELF vs.	42	9	7.2
Cisplatin–FU (41)	44	20	7.2
FAMTX vs.	30	33	7 (n.s.)
EAP (42)	30	20	6
FAMTX vs.	97	21	6.9 (n.s.)
PELF (43)	98	38	7.7

[1]Analysis of patients with measurable disease.

survival (9 vs. 6 months) and quality of life (40). Similarly, FAMTX was not superior to ELF (etoposide, leucovorin, fluorouracil) and FUP (fluorouracil, cisplatin) in a randomized phase III trial, with RR of 12% vs. 9% vs. 20%, respectively (41). The conclusion of the authors was that none of the regimens should be regarded as standard treatment for advanced gastric cancer. FAMTX has also been compared with EAP (etoposide, adriamycin, cisplatin) in a randomized trial, with RRs of 33% and 20%, and OSs of 7 and 6 months, respectively (42). Finally, three-weekly PELF (platin, epidoxorubicin, fluorouracil, leucovorin) appeared to be more active than FAMTX with response rates of 38% and 21% in 195 randomized patients, but without significant improvement of survival (43).

Docetaxel is a promising chemotherapeutic agent in advanced gastric cancer. As a single agent it produced an interesting RR both in pretreated (17%) and previously untreated (24%) patients with locally advanced or metastatic disease (see Table 1). While previous regimens have failed to improve survival over single-agent therapy, the aim of combining docetaxel with other active agents is to improve palliation and possibly survival of patients with gastric cancer. Apparently, good results have been obtained with combination regimens. The docetaxel–cisplatin regimen produced RRs of 56%, 37% and 36% in three phase II trials and 35% in one arm of a phase III trial. The main toxicities were manageable neutropenia and diarrhea. The addition of 5-FU as an intravenous continuous infusion did not increase the toxicity of docetaxel and cisplatin, as demonstrated in the SAKK/EIO and MD Anderson trials. However, available data suggest that about 20% to 30% of patients treated with these regimens did not receive the treatment according to schedule because of dose reductions or delays, and up to 20% of patients discontinued the therapy as a result of toxicity. Perhaps the addition of G-CSF would have been useful. The combination of docetaxel with cisplatin and 5-FU continuous infusion appears similar to ECF in terms of response rate and toxicity. Several phase III trials are now ongoing, including a large European phase III randomized trial comparing TCF with ECF and an American large-scale trial of docetaxel–cisplatin–5-FU versus cisplatin–5-FU in patients with advanced disease. We are awaiting the final results in order to confirm docetaxel advantage in terms of response, as suggested by preliminary trials, and survival rates.

Combining old anti-cancer regimens with new compounds is a formidable challenge and requires several attempts for optimization of the efficacy/toxicity ratio. Sequential chemotherapy (44) and dose-dense schedules (45) may offer this opportunity. Enhanced tumor shrinkage was gained in patients treated with sequential docetaxel following weekly PELF induction therapy and suggested that the PELF/docetaxel sequential combination would represent an interesting evolution of the PELF regimen. Their sequential use demonstrated a favorable toxicity-to-efficacy ratio and deserves further investigation in the palliative or neoadjuvant setting. Finally, the good activity of TCF in advanced disease has inspired SAKK and EIO to begin a phase III multicenter randomized trial to compare TCF in the adjuvant and neo-adjuvant setting in patients with operable gastric cancer.

CONCLUSION

Researchers keep looking for new and better ways to use chemotherapy to treat gastric cancer. In some patients, chemotherapy may provide substantial palliation and occasional durable remission, although it does not prolong life or provide cure. Because survival is poor with all available single and multimodal approaches to treatment, no single strategy can be considered state of the art and all newly diagnosed gastric cancer patients with hematogenous or peritoneal metastases should be considered candidates for clinical trials, if possible.

Docetaxel is currently used as single agent for second-line therapy of metastatic gastric cancer. Clinical trials are also in progress to test its effectiveness, alone or in combination with other anticancer drugs, as front-line chemotherapy for several types of cancer, including cancers of the upper gastrointestinal tract. In addition, researchers are studying some ways to overcome the cancer's resistance to taxanes. Literature review shows that docetaxel has a good activity and a low toxicity profile. Side effects appear to be manageable with appropriate monitoring and intervention, and reversible with dose modification or discontinuation. However, it is in the authors' opinion that phase III studies are necessary to draw any firm conclusion about its extensive use in clinical practice.

REFERENCES

1. Jemal A, Murray T, Samuels A, et al. Cancer statistics, 2003. CA Cancer J Clin 2003; 53: 5–26.
2. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin 1999; 49: 8.
3. Karpeh MS, Kelsen DP, Tepper JE. Cancer of the stomach. In: De Vita VT, Hellman S, Rosenberg SA. 'Cancer. Priciples and practice of oncology, 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 1092.
4. Pazdur R, Kudelka AP, Kavanagh JJ, et al. The taxoids: paclitaxel and docetaxel. Cancer Treat Rev 1993; 19: 351–86.
5. Diaz JF, Andreu JM. Assembly of purified GDP-tubulin into microtubules induced by taxol and taxotere. Reversibility, ligand stoichiometry, and competition. Biochemistry 1993; 32: 2747–55.
6. Schiff PB, Horwitz SB. Taxol stabilized microtubules in mouse fibroblast cells. Proc Natl Acad Sci USA 1980; 77: 1561–5.
7. Tanaka M, Obata T, Sasaki T, et al. Evaluation of antitumor effects of docetaxel (Taxotere) on human gastric cancer in vitro and in vivo. Eur J Cancer 1996; 32A: 226–30.

8. Kim R, Ohi Y, Inoue H, Toge T. Taxotere activates transcription factor AP-1 in association with apoptotic cell death in gastric cancer cell lines. Anticancer Res 1999; 19: 5399–405.
9. Sulkes A, Smythe J, Sessa C, et al. Docetaxel (Taxotere) in advanced gastric cancer. Results of a phase II clinical trial. Br J Cancer 1994; 70: 183–4.
10. Einzig AI, Neuberg D, Remick SC, et al. Phase II trial of docetaxel 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.
11. Giuliani F, Gebbia V, De Vita F, et al. Docetaxel (Taxotere) as a salvage chemotherapy in patients with advanced gastric cancer. A phase II study of the Southern Italian Oncology Group (GOIM). Proc Eur Soc Med Oncol 2000; 25th meeting: 296 abstract.
12. Mavroudis D, Kourousis C, Androulakis N, et al. Frontline treatment of advanced gastric cancer with docetaxel and granulocyte colony-stimulating factor: a phase II trial. Am J Clin Oncol 2000; 23: 341–4.
13. Vanhoefer U, Wilke H, Harstrick A, et al. Phase II study of docetaxel as second-line chemotherapy in metastatic gastric cancer. Proc Am Soc Clin Oncol 1999; 35th annual meeting: 1163 abstract.
14. Bang YJ, Kang WK, Kang YK, et al. Docetaxel 75 mg/m(2) is active and well tolerated in patients with metastatic or recurrent gastric cancer: a phase II trial. Jpn J Clin Oncol 2002; 32: 248–54.
15. Taguchi T, Sakata Y, Kanamaru R, et al. Late phase II clinical study of RP56976 (docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese Cooperative Study Group trial (group A). Gan To Kagaku Ryoho 1998; 25: 1915–24.
16. Graziano F, Catalino V, Baldelli AM, et al. A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer. Ann Oncol 2000; 11: 1263–6.
17. Cascinu S, Graziano F, Barni S, et al. A phase II study of sequential chemotherapy with docetaxel after the weekly PELF regimen in advanced gastric cancer. A report from the Italian group for the study of digestive tract cancer. Br J Cancer 2001; 84: 470–4.
18. 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 New Drugs 1994; 12: 169–82.
19. Roth AD. Chemotherapy in gastric cancer: a never ending saga. Ann Oncol 2003; 14: 175–7.
20. Mavroudis D, Kourousis C, Androulakis N, et al. Frontline treatment of advanced gastric cancer with docetaxel and granulocyte colony-stimulating factor: a phase II trial. Am J Clin Oncol 2000; 23: 341–4.
21. Burris HA 3rd. Docetaxel in combination with fluorouracil for advanced solid tumors. Oncology (Huntingt) 1997; 11: 50–2.
22. Constenla M, Lorenzo I, Carrete N, et al. Docetaxel with weekly high-dose 5-FU and lecovorin: a new combination in advanced gastric cancer. Proc Am Soc Clin Oncol 1999; 35th annual meeting: 1079 abstract.
23. Chun HG, Puccio CA, Mittelman A. Weekly docetaxel and continuous infusion 5-FU in elderly patients with cancer of the stomach and lower esophagus. Proc Am Soc Clin Oncol 2001; 37th annual meeting: 645 abstract.
24. Enrech S, Belon J, Mendez M, et al. A phase II study of docetaxel in combination with irinotecan (CPT-11) in locally advanced or metastatic gastric cancer. GOTI study group. Proc Am Soc Clin Oncol 2001; 37th annual meeting: 2325 abstract.
25. Andre T, Louvet C, Ychou M, et al. Docetaxel–epirubicin as second-line treatment for patients with advanced gastric cancer. Proc Am Soc Clin Oncol 1999; 35th annual meeting: 1062 abstract.
26. Roth AD, Maibach R, Martinelli G, et al. Docetaxel (Taxotere)–cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology (EIO). Ann Oncol 2000 Mar; 11(3): 301–6.
27. Ridwelski K, Gebauer T, Fahlke J, et al. Combination chemotherapy with docetaxel and cisplatin for locally advanced and metastatic gastric cancer. Ann Oncol 2001; 12: 47–51.
28. Kettner E, Ridwelski K, Keiholz U, et al. Docetaxel and cisplatin combination chemotherapy for advanced gastric cancer. Results of two phase II studies. Proc Am Soc Clin Oncol 2001; 37th annual meeting: 657 abstract.
29. Roth AD, Maibach R, Fazio N, et al. 5FU as protracted continuous iv infusion can be added to full dose taxotere–cisplatin in advanced gastric carcinoma. Eur J Cancer 1999; 35(Suppl 4): 139.
30. Ajani JA, Fodor M, Van Cutsem E, et al. Multinational randomized trial of docetaxel, cisplatin with or without 5-fluorouracil in patients with advanced gastric or GE junction adenocarcinoma. Proc Am Soc Clin Oncol 2000; 36th annual meeting: 957 abstract.
31. Fuchs CS, Lynch TJ, Earle CC, et al. Phase I trial of Taxotere, cisplatin, and CPT-11 in advanced solid tumor malignancies. ProcAm Soc Clin Oncol 2001; 37th annual meeting: 2087 abstract.
32. Di Lauro L, Belli F, Del Monte G, Carpano S. Epirubicin, cisplatin, and docetaxel (ECD) for measurable advanced gastric carcinoma. Preliminary data. Proc Eur Soc Med Oncol 2002; 27th meeting: 739 abstract.
33. Murad AM, Garcia RF, Vinholes J, et al. A phase II multicentric trial of docetaxel (Taxotere), 5-fluorouracil (5-FU) and epirubicin (EPI) in previously untreated advanced gastric cancer: a novel and effective regimen. Proc Eur Soc Med Oncol 2002; 27th meeting: 710 abstract.
34. Moiseyenko M, Van Cutsem E, Tjulandin S, et al. Docetaxel–cisplatin–5-FU (DCF) versus cisplatin-5-FU (CF) as first line therapy for gastric cancer: interim analysis results on efficacy and safety in a multicenter randomized phase III study. Proc Am Soc Clin Oncol 2002; 38th annual meeting: 587 abstract.
35. Ostellino O, Porcile G, Alabiso O, et al. TCFW: 5 FU pvi in combination with weekly docetaxel and CDDP in advanced gastric cancer, a phase I–II study: the dose finding step. 'Rete Oncologica Piemontese'. Proc Am Soc Clin Oncol 2002; 38th annual meeting: 2234 abstract.
36. Patience PC, Kretzschmar A, Vielhaber A, et al. Docetaxel and 5-FU continuous infusion (DF) versus epirubicin, cisplatin and 5-FU (ECF) for advanced gastric adenocarcinoma: a randomized phase II study. Proc Am Soc Clin Oncol 2002; 38th annual meeting: 647 abstract.
37. 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: 269–72.
38. 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.
39. Janunger KG, Hafstrom L, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in gastric cancer. Acta Oncol 2001; 40: 309–26.

40. 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.
41. Vanhoefer U, Rougier P, Wilke H, et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 2000; 18: 2648–57.
42. 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.
43. Cocconi G, Carlini P, Gamboni A, et al. PELF is more active than FAMTX in Metastatic Gastric Carcinoma (MGC). Proc Am Soc Clin Oncol 2001; 37th annual meeting: 501 abstract.
44. Day RS. Treatment sequencing, asymmetry, and uncertainty: protocol strategies for combination chemotherapy. Cancer Res 1986; 46: 3876–85.
45. Fizazi K, Zelek L. Is one cycle every three or four weeks' obsolete? A critical review of dose-dense chemotherapy in solid neoplasms. Ann Oncol 2000; 11(2): 133–49.