Cancer Chemother Pharmacol (2005) 55: 466–470
DOI 10.1007/s00280-004-0912-0

ORIGINAL ARTICLE

**Aristides Polyzos · Konstantinos Syrigos
John Stergiou · Christos Panopoulos · Anna Potamianou
Lambros Vamvakas · Vassilios Georgoulias**

Phase I trial of weekly docetaxel with a 4-weekly cisplatin administration in patients with advanced gastric carcinoma

Received: 27 May 2004 / Accepted: 20 August 2004 / Published online: 20 January 2005

Abstract The docetaxel-cisplatin combination is active against several tumors including gastric cancer but it is followed by severe myelosuppression. Recent experience with weekly taxanes has demonstrated a mild myelotoxicity with high dose intensity. We investigated in a phase I study a weekly schedule of docetaxel on days 1, 8 and 15 and cisplatin on day 1 every 4 weeks in 19 patients with advanced gastric cancer with no prior chemotherapy. Cohorts of patients were treated with escalating doses of docetaxel (starting dose 30 mg/m^2 per week and increments of 10 mg/m^2 per week) and cisplatin (starting dose 70 mg/m^2 and increments of 5 mg/m^2). Febrile neutropenia was the only dose-limiting event occurring in four (20%) patients; the dose-limiting toxicity was reached at dose level three (docetaxel 40 mg/m^2 per week and cisplatin 75 mg/m^2). The maximum-tolerated dose was 40 mg/m^2 per week for docetaxel and 70 mg/m^2 every 4 weeks for cisplatin. Grade 3/4 neutropenia occurred in six patients (30%); early death occurred in one patient with septic shock because of neutropenia and another with acute coronary ischemia. Two (11%) complete and two (11%) partial responses were documented (ORR 22%; 95% CI 3–39%), with a median response duration of 5 months and median time to progression of 7 months. In conclusion, the combination of weekly docetaxel plus cisplatin is feasible with moderate toxicity and merits further investigation in phase II studies in advanced gastric cancer.

Keywords Weekly docetaxel · Gastric carcinoma · Cisplatin

Presented as an abstract at the 15th International Congress on Anti-Cancer Treatment, Paris, 9–12 February 2004.

A. Polyzos (✉)
Medical Oncology Unit, Laikon General Hospital,
Athens University School of Medicine, Athens, Greece
E-mail: r-e-poly@hol.gr
Tel.: +30-210-7706606
Fax: +30-210-7791839

K. Syrigos
Medical Oncology Unit of Third Department of Medicine,
Sotiria General Hospital,
Athens University School of Medicine,
Athens, Greece

J. Stergiou
First Department of Medical Oncology,
Theagenion Anticancer Hospital,
Thessaloniki, Greece

C. Panopoulos
Second Department of Medical Oncology,
Agios Savas Cancer Hospital, Athens, Greece

A. Potamianou
First Department of Medical Oncology,
Metaxa's Anticancer Hospital, Pireas, Greece

L. Vamvakas · V. Georgoulias
Department of Medical Oncology,
University General Hospital of Heraklion, Crete, Greece

Introduction

Advanced gastric carcinoma is to be regarded as an incurable disease with a median survival of 6–9 months [1]. Although systemic chemotherapy as compared to best supportive treatment can improve survival and quality of life, only a small number of chemotherapeutic agents provide active palliation. Single-agent trials with anthracyclines, fluoropyrimidines, mitomycin C, etoposide or platinum compounds, that are considered the most active agents in gastric cancer, have yielded response rates of 20–30% [2]. Regimens combining two or three agents often achieve higher response rates (between 30% and 50%), but without significant improvement in median survival [2]. The objective results achievable with several combinations are almost similar in terms of response rate and survival, although the ECF combination has shown superior survival compared to the FAMtx combination [3]. Therefore, there is an unmet need for the identification of new active agents.

Among the new agents, paclitaxel in combination with fluorouracil or platinum compounds has shown considerable antitumor activity both as first-line chemotherapy and in pretreated patients [4–8] with locally advanced and metastatic gastric cancer. Docetaxel, another tubulin-inhibiting agent, has yielded response rates similar to those reported with paclitaxel in patients with advanced gastric cancer [9–11]. Docetaxel has also been combined with cisplatin or epirubicin or fluorouracil or in a three drug combination, with an interesting response rate, both in chemotherapy-naive and in pretreated patients [12–17].

An interesting regimen in terms of objective antitumor activity is the combination of docetaxel and cisplatin. In two recently reported studies, the combination has achieved high response rates, ranging from 40% to 53% [13, 14]. Although the dose of docetaxel was reduced to 75–85 mg/m^2, severe myelosuppression was the common feature of these studies [13, 14]. However, several studies have demonstrated that the weekly administration of taxanes is associated with a marked reduction in myelosuppression relative to the drug dose intensity [18, 19]. Based on these observations, we decided to conduct a phase I study in previously untreated patients with advanced gastric cancer administering cisplatin every 4 weeks and docetaxel on a weekly schedule. The purpose of the study was to further intensify the docetaxel-cisplatin regimen without causing a relative increase in its myelotoxicity.

Patients and methods

Patient population Patients (aged ≥18 years) with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 and histologically confirmed locally advanced or metastatic previously untreated gastric adenocarcinoma were enrolled in the study. Additional inclusion criteria were: hematologic parameters and blood chemistry indicating normal organ function (absolute neutrophil count ≥1.5×10^9/l; platelet count ≥100×10^9/l; hemoglobin ≥10 g/dl); normal total serum bilirubin, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (2.5 times the upper limit of normal value (ULN); alkaline phosphatase not more than six times ULN; and normal renal function tests (serum creatinine < 1.5 mg/dl). Patients were excluded if they had prior chemotherapy for metastatic disease. Adjuvant treatment was permitted provided that chemotherapy had ended at least 6 months before study entry. Other exclusion criteria included: prior treatment with taxanes; history of bone irradiation encompassing > 25% of bone marrow; history of prior malignancies, excluding excised carcinoma in situ of the cervix and nonmelanoma skin cancer; known central nervous system metastases; pregnancy; active infection or congestive heart failure or uncontrollable myocardial ischemia. The ethics and scientific committees of all participating centers approved the study and written informed consent was obtained from all patients.

Treatment Plan Treatment was given on an outpatient basis and comprised the administration of escalating doses of docetaxel (Taxotere; Aventis Pharma Collegeville, Pa.) given as a 1-h i.v. infusion on days 1, 8 and 15 (starting dose 30 mg/m^2 with increments of 10 mg/m^2). Cisplatin was also administered at escalating doses (starting dose 70 mg/m^2 with increments of 5 mg/m^2) in normal saline with appropriate hydration and forced diuresis on day 1. Antiemetic treatment was given before chemotherapy and consisted of dexamethasone (8 mg) plus ondansetron (24 mg) given as an i.v. bolus. To avoid hypersensitivity reactions and to prevent docetaxel-induced skin toxicity and fluid retention, dexamethasone (8 mg) was administered orally 12, 8 and 1 h before docetaxel and 24, 36, and 42 h after infusion. Docetaxel and cisplatin were given every 4 weeks for a maximum of six cycles, unless there was evidence of disease progression, unacceptable toxicity or patient refusal.

Dose escalation schedule, DLTs, and dose modifications Dose-limiting toxicities (DLTs) were assessed during the first chemotherapy cycle and were considered to have been reached when one of the following was met: (1) grade 4 neutropenia of 2 days or longer duration, (2) any episode of febrile neutropenia, (3) any episode of grade 4 thrombocytopenia, (4) any grade 3 of 4 nonhematologic toxicity excluding nausea/vomiting, musculoskeletal/arthritic pain, and alopecia. Cohorts of six, six and seven patients were entered at three dose levels (DLs), respectively, as shown in Table 1. If DLT was encountered in three out of six patients at a certain DL, no further accrual to the next higher DL was undertaken and the level immediately before the DLT level was considered as the maximum tolerated dose (MTD). If three out of the first six patients at a certain level experienced the same DLT, no more patients were accrued at that level and further dose escalation was stopped. The MTD was recommended for further phase II testing.

The following guidelines were applied with respect to dose reductions for toxicity: (1) for neutropenia and thrombocytopenia, meeting the aforementioned criteria, docetaxel and cisplatin doses were reduced by 20% in subsequent cycles and if toxicity reappeared after a total

Table 1 Weekly docetaxel and cisplatin dose-escalation scheme

Dose level	No. of patients	Drug doses (mg/m^2)			
		Cisplatin	Docetaxel		
		Day 1	Day 1	Day 8	Day 15
1	6	70	30	30	30
2	6	70	40	40	40
3	7	75	40	40	40

of 40% reduction from the starting dose in consecutive cycles, treatment was stopped; however, the patient was evaluable for toxicity and response; (2) for grade 3 or worse mucositis, the doses of docetaxel and cisplatin were reduced by 20% in subsequent cycles; (3) for neuropathy of grade 3 or worse, treatment was interrupted; and (4) for renal toxicity of grade 3 or worse toxicity (serum creatinine elevations more than three times normal) treatment was withheld until recovery (serum creatinine < 1.5 mg/dl).

Patient evaluation Baseline evaluations included patient history, physical examination, chest radiographs, complete blood cell count with differential and platelet count, complete blood chemistry and ECG. Computed tomography (CT) scans of the chest, abdomen, pelvis, and whole body bone scans were performed at study entry. Additional imaging studies were performed whenever clinically indicated. Complete blood cell counts with differential and platelet counts were performed twice weekly or daily in case of grade 3/4 neutropenia, thrombocytopenia or febrile neutropenia until hematologic recovery; blood chemistry and physical examination were performed weekly. Toxicities were evaluated according to the NCI common toxicity criteria (NCI-CTC) [20].

Tumor evaluation and criteria for response Tumor response was assessed after every two cycles (classified using WHO response criteria) [20]. An independent radiologist reviewed all tumor responses. Response duration was calculated from the day the patient was first documented to have at least a 50% reduction in tumor volume until first documentation of progressive disease, with the exception of CR, which was measured from the day on which no evidence of disease was first documented until first documentation of progressive disease. Time to progression (TTP) was assessed from the day of registration until the date of disease progression. Overall survival was measured from the date of enrollment to the study until the date of death. Patients without progression who died while on study were considered treatment failures.

Results

Patient characteristics From July 1999 to October 2002, eight patients with locally advanced and 11 with metastatic gastric cancer were enrolled in the present dose-escalation study. Patient characteristics are presented in Table 2; 15 patients (79%) were male and 90% had a PS of 0–1. Five patients (26%) had received adjuvant chemotherapy and three (16%) adjuvant radiotherapy. All patients were evaluable for toxicity and 14 for response.

Dose escalation, dose-limiting events The main dose-limiting event observed during the study was febrile neutropenia observed in one out of six patients enrolled in DL1 and three out of seven patients enrolled in DL3. The dose-limiting toxicity was, therefore, reached at the DL3. Patients developing febrile neutropenia required hospitalization. The patient who developed grade 2 neutropenia was predicted to show a fall in neutrophil count below 500 cells/mm^3 because of early toxicity, and this patient died because of sepsis despite the use of broad-spectrum antibiotics. All the other patients recovered uneventfully. Another patient suffered an unexpected myocardial infarct and expired. There were no other grade 3 or 4 hematologic or nonhematologic dose-limiting events, except for a grade 3 neutropenia in DL2. Table 3 summarizes the hematologic toxicity in all patients and all cycles. Grade 3/4 neutropenia, associated or not with fever, was the most frequent toxicity. Moreover, the nonhematologic toxicity was mainly of grade 1/2, occurring in 15–20% of the patients (Table 4).

Compliance with treatment Of a total of 53 cycles administered with a median of 2 cycles per patient (range 1–6), 16 (30%) were delayed for 3–14 days (median 8 days). However, only 4 cycles were delayed because of hematologic toxicity; the other 12 cycles were delayed due to patients own choice or late admission because of evaluation procedure. Five (9%) cycles required dose reduction because of hematologic toxicity.

Table 2 Patient characteristics

		No.	%
Patients enrolled		19	
Age (years)			
Median	64		
Range	34–77		
Sex			
Male/female		15/4	79/21
Performance status (ECOG)			
0		10	53
1		7	37
2		2	10
Histology: adenocarcinoma			
Enteric type		11	58
Diffuse type		6	32
Other		2	10
Degree of differentiation			
Well differentiated		3	15
Moderately differentiated		10	53
Poorly differentiated		6	32
Disease extent			
Locally advanced		8	42
Metastatic disease		11	58
Tumor location			
Stomach		7	37
Lymph nodes		8	42
Peritoneal implants		4	21
Liver		7	37
Bone		2	10
Lung		3	16
Prior treatment			
Radical resection		8	42
Partial resection		6	32
Jejunostomy		1	5
Adjuvant chemotherapy		5	26
Adjuvant radiotherapy		3	16
None		5	26

Table 3 Hematologic toxicity of weekly docetaxel/cisplatin dose escalation in phase I

Dose level	Number of cycles	Hematologic toxicity (all cycles/all patients)								
		Neutropenia grade			Anemia grade			Thrombocytopenia grade		
		2	3	4	2	3	4	2	3	4
1	18	2	0	1 (1 febrile)	1	0	0	0	0	0
2	18	5	1	0	2	0	0	0	0	0
3	17	2 (1 febrile)	2	2 (2 febrile)	5	1	0	0	0	0

Table 4 Nonhematologic toxicities (NCI-CTC grade)

Toxicity	Grade (% of patients all cycles)	
	1/2	3/4
Nausea and vomiting	15	0
Diarrhea	10	0
Fluid retention	20	0
Asthenia/fatigue	20	0
Alopecia	100	0

Response to treatment and survival Among 14 patients with measurable disease there were two complete responses (CR) and two partial responses (PR) for an overall response rate (CR + PR) of 29% (95% CI 3–39%). Moreover, two patients (14%) had stable disease and eight (57%) progressive disease. The median duration of response was 5 months (range 3–30 months) and the median time to progression 7 months (range 4–30 months). The median overall survival for the entire group was 5 months (range 1–30 months) and the 1-year survival 32%.

Discussion

The results of the present phase I study demonstrate that the toxicity profile of docetaxel-cisplatin combination can be markedly modified when docetaxel is administered on a weekly schedule. The maximum tolerated weekly dose of docetaxel is 40 mg/m^2 when combined with a "standard" dose of 75 mg/m^2 of cisplatin. This weekly dose, for docetaxel as a single agent, is equivalent in dose intensity to 120 mg/m^2 every 3 weeks. Such a high dose is usually followed by severe myelosuppression in the majority of patients [9–11]. In a prior phase I study, where docetaxel as a single agent was administered by weekly infusion, even higher doses, as high as 52 mg/m^2 per week, were not followed by severe myelosuppression. In that study, the MTD was 43 mg/m^2 per week, but with fatigue and asthenia as DLTs [19]. The toxicity profile of weekly docetaxel parallels in some way the toxicity with weekly paclitaxel. With both agents myelotoxicity is mild compared to that observed with an equivalent dose intensity of 300 mg/m^2 for paclitaxel and 120 mg/m^2 for docetaxel when the two drugs are given on a 3-week schedule [21]. In the present study, myelotoxicity was, as expected, the main toxicity with one death due to sepsis. Grade 1 or 2 fatigue and asthenia were the only nonhematologic toxicities. Neuropathy or arthralgias, two of the bothersome toxicities encountered with weekly paclitaxel administration, were not observed with weekly docetaxel. In addition, although nine patients in the present study received more than three courses, the incidences of some of the cumulative side effects of docetaxel administration, such as edema, neuropathy and severe fatigue, usually observed with the 3-week schedule, were low.

In a phase I study from Japan in patients with lung cancer, the same agents and a similar schedule as used in our study were evaluated. Following administration of smaller dose levels of docetaxel (from 15 to 30 mg/m^2) and cisplatin every 4 weeks, the authors were able to recommend dose levels of cisplatin of 80 mg/m^2 day 1 and of docetaxel of 25 mg/m^2 days 1, 8 and 15 for a phase II study [22]. The schedule of weekly infusion of docetaxel has also been evaluated in several recent studies. In a randomized phase II study from Germany, weekly versus 3-weekly docetaxel were compared, with neutropenia 4.5% and infection 9% as the main toxicities of the 3-week schedule and with no other toxicity on the weekly schedule, except for 9% grade 3/4 myalgia [23]. In a study from Spain in lung cancer patients, weekly versus 3-weekly docetaxel administration were also compared, with no differences in response rate or in median survival, but weekly docetaxel proved to be less myelotoxic [24]. Additionally, in an Italian trial where quality of life was the main objective of the study, weekly docetaxel was associated with improved cognitive function, pain, cough, hair loss and myelotoxicity as compared to 3-weekly administration [25]. Finally, in a most recent study in Japan, docetaxel (20 mg/m^2) and cisplatin (25 mg/m^2) were given on days 1, 8 and 15 every 4 weeks to elderly lung cancer patients and yielded a 52% response rate with only 12% grade 3 neutropenia [26].

Although efficacy was not the objective of the present study, 14 patients treated in all three levels were evaluable for response and survival. The response rate (two CRs and two PRs) was 22%, while 11% of the patients had stable disease. The median survival of the group was 5 months, while 32.5% achieved a survival of 1 year. There are probably two reasons for this relatively low

survival: toxicity of the regimen and patient refusal to receive second-line treatment.

In conclusion, weekly docetaxel administration plus cisplatin every 4 weeks, provides interesting new possibilities for these agents for the treatment of advanced gastric cancer or other tumors. The increased dose intensity achieved with weekly docetaxel and its moderate myelotoxicity in combination with cisplatin makes the regimen attractive for testing in a phase II study, either as induction treatment in locally advanced disease or in the palliative setting.

References

1. Ajani JA (1998) Current status of therapy for advanced gastric cancer. Oncology 12 [Suppl 6]:99–102
2. Preusser P, Achterrath W, Wilke H, et al (1988) Chemotherapy of gastric cancer. Cancer Treat Rev 15:257–277
3. Webb A, Cunningham D, Scarffe JH, et al (1997) Randomized trial comparing epirubicin cisplatin and fluorouracil versus fluorouracil, doxorubicin and methotrexate in advanced esophagogastric cancer. J Clin Oncol 15(1):261–267
4. Cascinu S, Ficarelli R, Safi MAA, et al (1997) A phase I study of paclitaxel and 5-fluorouracil in advanced gastric cancer. Eur J Cancer 33:1699–1702
5. Murad AM, Petroianu A, Guimaraes RC, et al (1999) Phase II trial of the combination of paclitaxel and 5-fluorouracil in the treatment of advanced gastric cancer: a novel, safe, and effective regimen. Am J Clin Oncol 22:580–586
6. Kim YH, Shin SW, Kim BS, et al (1999) Paclitaxel, 5-fluorouracil, and cisplatin combination chemotherapy in the treatment of advanced gastric carcinoma. Cancer 85:295–301
7. Kollmannsberger C, Quietzsch D, Haang C, et al (2000) A phase II study of paclitaxel, weekly, 24-hour continuous infusion 5-fluorouracil, FA and cisplatin in patients with advanced gastric cancer. Br J Cancer 83:458–462
8. Stathopoulos GR, Rigatos SK, Fountzilas G, et al (2002) Paclitaxel and carboplatin in pretreated advanced gastric cancer: a phase II study. Oncol Rep 9:89–92
9. Mavroudis D, Kakolyris S, Kouroussis, et al (1999) First line treatment of advanced gastric cancer with docetaxel monotherapy and granulocyte colony-stimulating factor (G-CSF) (abstract 977). Proc Am Soc Clin Oncol 18:254a
10. Vanhoefer U, Wilke H, Harstrick A, et al (1999) Phase II study of docetaxel as second line chemotherapy (CT) in metastatic gastric cancer (abstract 1163). Proc Am Soc Clin Oncol 18:303a
11. Graziano F, Catalano V, Baldelli AM, et al (2000) A phase II study of weekly docetaxel as salvage chemotherapy for advanced gastric cancer. Ann Oncol 11:1263–1266
12. Ajani JA, Fodor M, van Cutsem E, et al (2000) Multinational randomized phase II trial of docetaxel (T) and cisplatin (C) with or without 5-fluorouracil (FU) in patients (pts) with advanced gastric or GE junction adenocarcinoma (AGC-AGEJC) (abstract 957). Proc Am Soc Clin Oncol 19:247a
13. Roth AD, Maibach R, Martinelli G, et al (2000) 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 11:301–306
14. Ridwelski K, Gebauer T, Fahlke J, et al (2001) Combination chemotherapy with docetaxel and cisplatin for locally advanced and metastatic gastric cancer. Ann Oncol 12:47–51
15. Constenla M, Lorenzo I, Carrete N, et al (1999) Docetaxel with weekly high-dose-5-FU and leucovorin: a new combination in advanced gastric cancer (abstract 1079). Proc Am Soc Clin Oncol 18:281a
16. André T, Louvet C, Ychou M, et al (1999) Docetaxel-epirubicin as second-line treatment for patients with advanced gastric cancer (abstract 1062). Proc Am Soc Clin Oncol 18:277a
17. Murad AM, Vinholes J, Skare N, et al (2002) 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 (abstract 650). Proc Am Soc Clin Oncol 21:163a
18. Fennely D, Aghajanian C, Shapiro F, et al (1997) Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 15:187–192
19. Hainswoth JD, Burris HA III, Erland JB, et al (1998) Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol 16(6):2164–2168
20. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207–214
21. Seidman AD, Murphy B, Hudis C, et al (1997) Activity of Taxol by weekly 1-hour infusion in patients with metastatic breast cancer: a phase II and pharmacologic study (abstract). Proc Am Soc Clin Oncol 16:148A
22. Koizumi T, Tsunoda T, Fujimoto K, et al (2001) Phase I trial of weekly docetaxel combined with cisplatin in patients with non-small cell lung cancer. Lung Cancer 34(1):125–131
23. Schütte W, Nagel S, Lantenschläger C, et al (2002) Randomized phase II study of weekly versus three-weekly docetaxel as second line chemotherapy for advanced non-small cell lung cancer (abstract 1228). Proc Am Soc Clin Oncol 21:308a
24. Camps C, Massuti B, Jinenez AM, et al (2003) Second-line docetaxel administrated every 3 weeks versus weekly in advanced non-small cell lung cancer: a Spanish Lung Cancer Group (SLCG) phase III trial (abstract 2514). Proc Am Soc Clin Oncol 22:625
25. Gridelli C, Illiano A, Salvagui S, et al (2003) Effect on quality-of-life of weekly vs 3-weekly docetaxel in second-line treatment of advanced non-small-cell-lung cancer. The DISTAL randomized phase 3 study (abstract 2515). Am Soc Clin Oncol 22:625a
26. Ohe Y, Niho S, Kakinuma R, et al (2004) A phase II study of cisplatin and docetaxel administered as three consecutive weekly infusions for advanced non-small-cell lung cancer in elderly patients. Ann Oncol 15:45–50