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ORIGINAL ARTICLE

Phase II study of paclitaxel combined with capecitabine as second-line treatment for advanced gastric carcinoma after failure of cisplatin-based regimens

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Abstract
Purpose To determine the safety and the efficacy of paclitaxel and capecitabine as second-line combination chemotherapy after failure of platinum regimens in advanced gastric cancer.
Methods Patients with histologically proven gastric cancer and measurable metastatic disease received capecitabine 825 mg/m^2 twice daily (1,650 mg/m^2 per day) on days 1–14 and paclitaxel 175 mg/m^2 by intravenous infusion on day 1 every 3 weeks until disease progression or unacceptable toxicities.
Results Between June 2003 and October 2005, 26 patients, of median age 59 years (range 41–84 years) were included in the study and were treated by paclitaxel/capecitabine combination. Overall response rate was 34.6% (95%CI = 17.2–55.7%) with one complete response and 42.3% (95%CI = 17.2–55.7%) of patients achieved a stable disease. Median progression-free survival was 4.5 months (95%CI = 4–4.5 months). Median overall survival was 7.5 months (95%CI = 6–10 months). Cumulated overall survival including cisplatin regimens was 15.5 months (95%CI = 11–18 months). Grade 3/4 adverse events included alopecia (30.8%), neutropenia (11.5%), hand foot skin reaction (11.5%), neuropathy (11.5%), arthralgias (7.5%), and anemia (3.8%).
Conclusions Paclitaxel and capecitabine combination was safe and effective in advanced gastric cancer after failure of cisplatin regimens. The cumulated overall survival of 15.5 months suggests a particular interest of taxanes in second-line treatment after failure of platinum salts.

Keywords Advanced gastric cancer · Capecitabine · Paclitaxel · Second-line chemotherapy

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Introduction

Gastric cancer remains a significant problem in global health terms despite a falling incidence in western countries [1, 2]. The majority of patients with gastric cancer present with advanced inoperable tumors [3]. The aim of therapy in this situation is usually palliation. Several trials have been performed comparing best supportive care with best supportive care plus chemotherapy [4–7]. All have shown statistically significant improvements in median survival and one also showed that delayed treatment following symptomatic deterioration lead to the loss of this benefit [5]. Recently, a meta-analysis of randomized controlled trials in patients with advanced cancers confirmed these data and in addition demonstrated that combination chemotherapy is associated with a survival benefit comparing single-agent chemotherapy [8]. In this meta-analysis, it was also demonstrated that three-drug combination (epirubicin/cisplatin/5FU) is superior to doublets (cisplatin/5FU or anthracycline/5FU) but with a mean average survival gain between 1 and 2 months [8]. In 2006, the V-325 study demonstrated that adding docetaxel to cisplatin/5FU provided benefits with regard to overall survival and health-related quality of life [9]. Although the DCF regimen provides these advantages, great increase in grade 3/4 toxicities has been reported

and so proper patient selection and monitoring is recommended. If triplets had demonstrated their superiority to doublets, the median overall survival did not exceed 10 months, even if 18% 2-year survival rate has been observed in the V-325 study.

Paclitaxel (Taxol, Bristol-Meyers Squibb Company) is an antimicrotubule agent that enhances polymerization of tubulin into stable microtubules and inhibits microtubule depolymerization. Paclitaxel induces apoptosis in human gastric carcinoma cell-lines [10] and appears to be useful for clinical application against gastric cancer due to its different antitumor spectrum as compared to conventional agents [11].

Capecitabine (Xeloda, Roche Laboratories Inc Company) is an orally administered fluoropyrimidine carbamate that is absorbed as an intact molecule by the gastrointestinal tract and converted in a three-step enzymatic process to 5FU. The final rate-limiting step producing the active drug is catalyzed by thymidine phosphorylase (dThdPase). This enzyme is present in multiple normal tissues but is found at higher levels in tumors, resulting in preferential intratumor generation of the cytotoxic drug [12].

Capecitabine is effective in gastric cancer [13]. Clinical trials of capecitabine in combination with paclitaxel, have been based on the observed up-regulation of dThdPase in model of athymic mice bearing capacitabine-resistant human colon cancer xenografts [14]. Taxanes plus 5FU, in the same models showed only an addictive effect [14]. The rationale of a 3-weekly schedule is based on breast cancer studies. Doses recommended are paclitaxel 175 mg/m^2 by intravenous infusion every 3 weeks and capecitabine 1,650 mg/m^2 per day orally for 14 days [15].

In Europe, the most commonly used chemotherapy regimens include cisplatin with continuously infused 5FU (FP) and FP plus epirubicin (ECF) [16, 17]. A major unresolved issue is the impact of a second-line chemotherapy on overall survival. The clinical evaluation of paclitaxel in combination with capecitabine is based on a sound molecular rationale synergy documented in preclinical models. A possible approach to optimize quality of life and overall survival is to study the efficacy of this two-drug combination in second-line chemotherapy after failure of cisplatin regimens. We, therefore, performed a phase II study to evaluate the safety and the efficacy of the combination of paclitaxel and capecitabine as second-line therapy in patients with advanced gastric cancer.

Patients and methods

Patients

Eligible patients were 18–75 years old and had histologically proven adenocarcinoma of the stomach with metastatic or recurrent disease. All patients were treated with first-line therapy by platinum regimens, either 5FU plus cisplatin (FP) or the combination of epirubicin, cisplatin and infusional 5FU (ECF). In addition, patients were required to have an Eastern Cooperative Oncology Group performance status $\leq$2 and a life expectancy of at least 3 months. Toxicity was evaluated before each treatment cycle according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0. To begin the next treatment cycle, each patient was required to have no clinical grade 3 or greater toxicity and to have a white blood cell count $>4.0 \times 10^9$/l, an absolute neutrophile count $>1.5 \times 10^9$/l, a platelet count $>100 \times 10^9$/l, a serum creatinine $<1.25 \times$ the upper limit of normal (ULN), and a total serum bilirubin $<1.25 \times$ ULN. Patients with gastric linitis, mucinous carcinoma or uncontrolled medical illnesses were excluded. This study was performed according Helsinki criteria and a written informed consent was obtained from each patient.

Treatment schedule

All the patients received paclitaxel 175 mg/m² as a 3-h intravenous infusion on day 1 followed by oral capecitabine 825 mg/m^2 twice daily from the evening of day 1 to the morning of day 15. To avoid hypersensitivity reactions, patients were treated with dexamethasone 20 mg orally 12 and 6 h before infusion of paclitaxel, ranitidine 50 mg and diphenhydramine 50 mg by intravenous infusion 30 min before administration of paclitaxel. Cycles were repeated every 21 days in the absence of unacceptable toxicity or until disease progression.

To begin the next treatment cycle, each patient was required to have no hematological toxicity and resolution or improvement of clinical adverse events, except to alopecia, to grade 1 or 0. Treatment was delayed and the dose of both agents was reduced by 25% in patients who experienced a second occurrence of any grade 2 toxicity or at the first occurrence of grade 3 toxicity. If neutropenia required dose delays or was associated with fever, granulocyte colony-stimulating dose factor was administered in subsequent treatment cycles. Termination of treatment occurred after the third appearance of grade 3 toxicity or after the fourth appearance of grade 2 toxicity. Patients experiencing grade 4 toxicities discontinued study participation. Compliance to capecitabine treatment was controlled by specific questioning subjects at each treatment in day's hospital.

Outcome evaluation

Responses were classified according to World Health Organization (WHO) criteria. All the patients had at least one measurable lesion and underwent computed tomography (CT) scans prior to chemotherapy initiation. Tumor evaluation

was assessed every 9 weeks. A complete response (CR) was defined as the total disappearance of all measurable lesions over at least 4 weeks, while a partial response (PR) was defined as a decrease, of at least 50%, in the measurable tumor mass. Stable disease (SD) was defined as a decrease of less than 50% in tumor mass or a progression of less than 25%. Progressive disease (PD) was defined as an increase in tumor mass greater than 25%. Patients were considered assessable for response if they had early disease progression or had received at least 2 cycles of treatment with at least one tumor assessment.

Statistical methods

Sample size was calculated according to a single-stage phase II Fleming design [18]. Paclitaxel plus capecitabine would be considered unsuccessful if objective response rate was 10% or less, and it would be considered active enough to pursue further if objective response rate was 30% or greater. With 25 subjects, power would be 80% to detect a 30% objective response rate with a 3% alpha error.

The primary end point of this study was to estimate the time to progression, secondary end points were overall survival and safety. The time to progression was defined as the duration from the date of starting treatment to the date of confirmed disease progression or of death by any cause. Overall survival was defined as the duration from the date of starting treatment to the date of death. Time to event distribution was estimated according to the Kaplan–Meier method.

Results

Patient characteristics

Patient characteristics are summarized in Table 1. All patients were assessable for safety and response. Between June 2003 and October 2005, 26 patients, of median age 59 years (range 41–84 years) were included in the study. Five patients had prior gastrectomy without adjuvant treatment. For these patients, the interval between surgery and chemotherapy ranged from 6 to 26 months (median 8 months) and their survival in our study was comparable with patients without gastrectomy. All patients received cisplatin regimens in first-line treatment, FP in 16 cases and ECF in 10 cases. The performance status was ≤ 1 for the majority of patients (69.3%). Localization of primary tumor was antrum in 14 cases and cardia in 12 cases. Histologic type was found well differentiated in 7 cases, moderately differentiated in 12 cases and poorly differentiated in 7 cases. The most common sites of metastases were liver (19 cases) and lymph nodes (6 cases). Peritoneum metastases were associated with liver metastases in 2 cases and with lymph nodes involvement in 2 cases. Bone metastases were associated with liver metastases in 1 case. One patient presented lung metastases.

Table 1 Patients' characteristics

Characteristics	Number of patients
Gender (male/female)	17/9
Median age (years) (range)	59 (41–84)
Disease at presentation	
Gastric proximal tumors	12 (46%)
Gastric distal tumors	14 (54%)
Site of metastases	
Liver	19 (73%)
Lymph nodes	6 (23%)
Lung	1 (4%)
Peritoneum	4 (15.4%)
Bone	1 (4%)
ECOG performance status	
0	7 (27%)
1	11 (42.3%)
2	8 (30.7%)

Drug delivery

A total of 176 cycles were given every 3 weeks, with a median of 6.8 (range 3–22). Five patients during 5 cycles needed one additional week to normalize biological grade 2 events according to our treatment schedule without dose modifications. Ten patients required dose reductions (34.6%). Three patients have had more than one grade 3 toxicity in the same cycle. Dose reductions concerned both agents for six patients. Dose reduction concerned only capecitabine for four patients because the observed side effect was hand foot syndrome which was not attributable to paclitaxel. Dose reductions were not achieved in two patients with arthralgia or neuropathy because grade 3 toxicity occurred at time to progression. Grade 3 toxicities underwent at least after 4 cycles of treatment for all patients. Treatment was delayed more than 1 week in 6 patients with grade 3 toxicities (23%) during 6 cycles (3.4%), due to neutropenia (3 cycles) and hand foot syndrome (3 cycles). Delivered dose intensity, defined as actual dose/planned dose was 93.7% for capecitabine and 95.4% for paclitaxel.

Safety

All patients showed normal leukocyte, neutrophil, red cell and platelets count at the start of paclitaxel/capecitabine administration as required by the protocol of this study. Table 2 shows the toxicity occurring during treatment. The toxicity observed was grade 1/2 in majority of cases. The

Table 2 Hematological and non-hematological toxicity, % of patients

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	8 (30.8)	5 (19.2)	3 (11.5)	0
Anemia	9 (34.6)	5 (19.2)	1 (3.8)	0
Thrombocytopenia	3 (11.5)	2 (7.6)	1 (3.8)	0
Alopecia	0	18 (69.3)	8 (30.8)	0
Asthenia	11 (42.3)	4 (15.3)	0	0
Hand foot skin reaction	12 (46)	5 (19.2)	3 (11.5)	0
Neuropathy	4 (15.3)	12 (46)	3 (11.5)	0
Arthralgia	10 (38.4)	5 (19.2)	2 (7.5)	0
Nausea	4 (15.3)	5 (19;2)	0	0
Vomiting	3 (11.5)	4 (15.3)	1 (3.8)	0
Diarrhea	2 (7.6)	1 (3.8)	0	0

most common hematological adverse event was neutropenia, which occurred at grade 3 intensity in 3 patients (11.5%). There was no febrile neutropenia in this study. Anemia and thrombocytopenia were rare. Only one patient developed grade 3 anemia after 19 cycles of treatment. Non-hematological toxicity was frequent but rarely severe except for alopecia. Grade 3 toxicity consisted in alopecia (30.8%), neuropathy (11.5%), hand foot syndrome (11.5%) and arthralgia (7.5%). There were no treatment-related deaths.

Tumor response

The objective response rate was 34.6% (95%CI = 17.2–55.7%) with complete response in one case. This patient had an antral tumor with metastatic hilar lymph nodes. After initial stabilization, he developed a biliary compression due to lymph nodes progression with apparition of jaundice and a biliary stent was put in palliative intent. After 6 cycles of paclitaxel/capecitabine combination, CT scan showed a complete response. Surgery consisted in subtotal gastrectomy with extended lymphadenectomy and histological examination confirmed a complete necrosis of the different lesions. Stabilization of disease occurred in 42.3% (95%CI = 17.2–55.7%). Median progression-free survival was 4.75 months with cisplatin regimens in first-line treatment (Fig. 1) and 4.5 months with paclitaxel/capecitabine combination in second-line treatment (Fig. 2). Median overall survival after starting pacitaxel/capecitabine combination was 7.5 months (95%CI = 6–10 months). Cumulated overall survival combining the two lines of treatment was 15.5 months (95%CI = 11–18 months) (Fig. 3) with a 18 months survival rate of 23%.

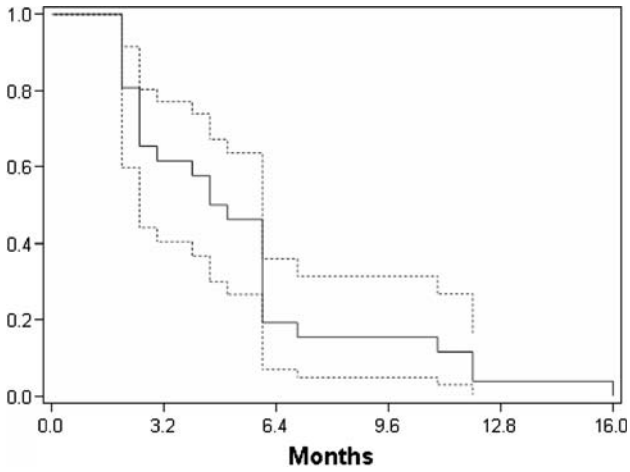

Fig. 1 Progression-free survival (PFS, by Kaplan–Meier method) in patients treated by platinium regimens

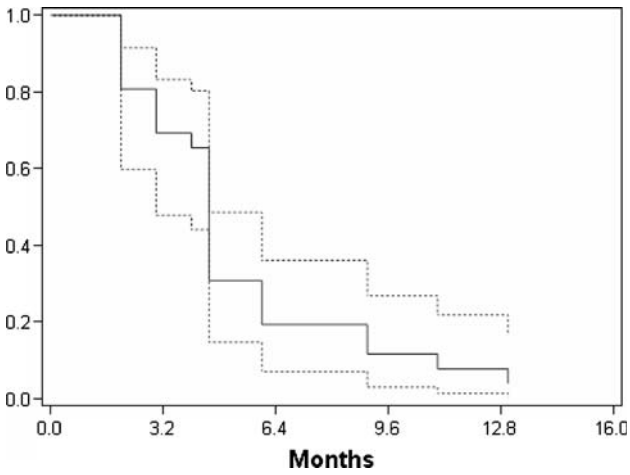

Fig. 2 Progression-free survival (PFS, by Kaplan–Meier method) in patients treated by paclitaxel/capecitabine combination

Discussion

Advanced gastric cancer remains a challenge for oncologists. In this situation, histologic types in patients with stage IV disease do not seem to be associated with survival except for signet ring cell carcinoma which was an exclusion criteria in our study [19]. In Europe, platinum-based regimens are usually employed in first-line treatment. Previous clinical

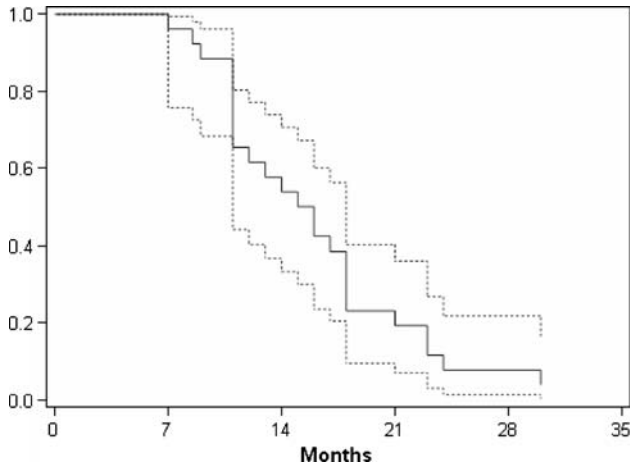

Fig. 3 Overall survival (by Kaplan–Meier method) after cisplatin regimen plus paclitaxel/capecitabine combination

trials using paclitaxel or capecitabine as a single agent have demonstrated their potential interest in palliative situation. Paclitaxel as a single agent has been given in pretreated advanced gastric cancer at doses between 210 and 225 mg/m^2 with response rates ranging from 22 to 28% but with a significant myelosuppression due to the dose intensity of paclitaxel [20–22]. Capecitabine as a single agent has been studied mainly in first-line treatment using lower-doses (828–1250 mg/m^2) with a good safety profile and with response rates ranging from 29 to 32% [23, 24]. Only one study has evaluated capecitabine in patients who have received prior chemotherapy. In this study, response rate was low (6%) with a median survival of 8.1 months [25].

The present trial shows the efficacy of the combination of paclitaxel and capecitabine as second-line chemotherapy after failure of platinum-based regimens in patients with metastatic gastric cancer. This combination demonstrated a significant anti-tumor activity based on an overall objective response rate of 34.6 with 42.3% of stabilization. Most importantly, median survival was 7.5 months and progression-free survival was 4.5 months. This progression-free survival was comparable with our first-line treatment based on cisplatin regimens (4.75 months). Paclitaxel/capecitabine combination was well tolerated over multiple cycles of therapy, although doses modifications were necessary, particularly with longer duration of chemotherapy. In our study, grade 3/4 hematological toxicity was low with 11.5% of neutropenia and comparable to previous studies in gastric cancer [26]. No severe treatment-related morbidity such as febrile neutropenia was observed. Grade 3 neuropathy occurred in 11.5% probably because our patients were pretreated by cisplatin. It is known that patients treated by paclitaxel in second-line treatment and who have received previous treatment with neurotoxic drugs appear in particular to be predisposed to this reaction [27].

In second-line treatment, combination of paclitaxel and capecitabine had not been reported in previous studies and would be taken in consideration comparing to combination of docetaxel and capecitabine. Rosati et al. [28] have reported the results of combination regimen with docetaxel (60 mg/m^2 on day 1) and capecitabine 1,000 mg/m^2 twice daily on days 1–14) in patients having a confirmed progressive disease during a previous cisplatin-based chemotherapy treatment. Clearly, this combination seems less effective than paclitaxel/capecitabine schedule (overall response rate of 29% with 36% of stable disease and median time to progression of 4 months) and more toxic with 36% of grade 3/4 neutropenia, 7% of neutropenic fever and 11% of diarrhea [28]. Then, a reduced dose intensity of docetaxel and capecitabine seems to limit the effectiveness of the treatment in second-line chemotherapy comparing to paclitaxel/capecitabine combination.

Recently, using the same combination of paclitaxel and capecitabine, Kang et al. [26] have reported a higher response rate in first-line chemotherapy (48.9%), a median time to progression of 5.6 months and a median overall survival of 11.3 months. Interestingly, a triplet combining paclitaxel/cisplatin/5FU in first-line treatment had shown an overall response rate of 48% and an overall survival times of 11 months [29] comparable to the study reported by Kang et al. [26]. The substitution of capecitabine by infusional 5FU is an alternative regimen. The combination of paclitaxel, infusional 5-fluorouracil and leucovorin has been evaluated in first-line treatment in a phase II study and seems to be less effective and more myelotoxic [30, 31] than a similar combination of paclitaxel/capecitabine in first-line chemotherapy as reported by Kang et al. [26].

Docetaxel is a potential alternative to paclitaxel. In chemonaive patients, combination docetaxel/cisplatin/5FU (DCF) is considered as one of the reference regimens but its toxicity profile is acceptable only with appropriately selected patients [32]. A study has compared paclitaxel (175 mg/m^2 on days 1) plus 5FU (500 mg/m^2 on days 1–5) or docetaxel 75 mg/m^2 on day 1 plus 5FU (500 mg/m^2 on days 1–5) and showed the same therapeutic efficacy against gastric cancer in first-line treatment, but dose reduction was required more frequently in the docetaxel/5FU group [33].

In conclusion, our study showed the efficacy and the safety profile of paclitaxel/capecitabine combination in second-line treatment of advanced gastric cancer. The choice of taxane may be determined by the safety profile which appears in favor of paclitaxel. An area of controversy that relates to the treatment of metastatic gastric cancer is whether patients are better served by receiving three-drug combination chemotherapy or sequential two-drug combination based on safety profile. The choice of sequential or combination therapy may be an option for future phase III clinical trials to resolve the issue concerning

the impact of second-line chemotherapy on overall survival.

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