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Clinical report

Phase II study of weekly paclitaxel plus 24-h continuous infusion 5-fluorouracil, folinic acid and 3-weekly cisplatin for the treatment of patients with advanced gastric cancer

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The aim of this study was to evaluate the toxicity and efficacy of combination chemotherapy with weekly 24-h continuous infusion of 5-fluorouracil (5-FU)/folinic acid, weekly paclitaxel and 3-weekly cisplatin in patients with unresectable, locally advanced or metastatic gastric adenocarcinoma. Between November 1999 and November 2001, 29 chemotherapy-naive patients (13 male and 16 female) with a median age of 56 years (range 22–72) were consecutively enrolled at three centers. 5-FU 2 g/m^2 was given weekly over 24 h i.v. preceded by folinic acid 500 mg/m^2 as a 2-h infusion. Paclitaxel 80 mg/m^2 was administered as a 1-h infusion weekly and cisplatin 50 mg/m^2 as 1-h infusion on days 8 and 29. Six weeks of therapy (days 1, 8, 15, 22, 29 and 36) followed by 1 week of rest was considered one cycle. A median of 3 cycles (range 1–5) was administered to 29 patients with a total of 73 cycles applied. All patients were assessable for toxicity and survival, 28 patients were assessable for response (one patient received less than one complete cycle and could not be evaluated for response). Four patients (14%) obtained a complete response and 10 patients (34%) a partial response (overall response rate 48%, 95% CI 29–68%). Seven patients (24%) had stable disease. Seven patients (24%) had progressive disease during or within 4 weeks after treatment. The median progression-free and overall survival times were 8 months (range 1–23) and 11 months (range 1–23), respectively. Overall toxicity was acceptable. Hematological toxicity was favorable with only one patient (3%) experiencing WHO grade 3/4 leukocytopenia and one patient (3%) WHO grade 3/4 anemia. Non-hematologic WHO grade 3/4 toxicities included alopecia in 19 (66%), nausea/vomiting in six (21%), diarrhea in six (21%), neurotoxicity grade 3 in three (10%) and infection in three (10%) patients. A total of 42 applications (10%) (range 0–5) had to be postponed and dose reductions of at least one drug was necessary in 37% of applications. In three patients (10%) treatment was stopped because of toxicity. All patients were treated on an outpatient basis. Thus, the combination of weekly paclitaxel, cisplatin and continuously infused 5-FU/folinic acid appears to be a highly active regimen for the treatment of patients with advanced gastric cancer. Compared with our previous experience with the same combination of drugs but using paclitaxel at 175 mg/m^2 given every 3 weeks, the protocol with weekly application of paclitaxel 80 mg/m^2 shows a reduced incidence of hematologic toxicity, particularly leukopenia. Other organ toxicities apart from a slightly higher incidence of peripheral neuropathy were comparable between the two treatment protocols. Efficacy with a response rate of 50% was well preserved by this weekly regimen. [© 2002 Lippincott Williams & Wilkins.]

Key words: 5-Fluorouracil, cisplatin, folinic acid, gastric cancer, paclitaxel, phase II.

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Introduction

Metastatic gastric cancer remains an incurable disease with a median survival time of only 4–8 months. Both a survival benefit and a positive impact on quality of life for patients with unresectable or metastatic gastric cancer receiving systemic chemotherapy plus supportive care as compared to best supportive care alone have been demonstrated in randomized studies.[1–4] Although there is no generally accepted standard regimen, palliative chemotherapy for advanced gastric cancer is now widely used in Europe and the US. A number of drugs have demonstrated activity, including 5-fluorouracil (5-FU), etoposide, doxorubicin, methotrexate and cisplatin. Combination regimens, usually based on 5-FU, have achieved response rates between 20 and 40%.[5,6] Several studies have shown that the combination of 5-FU and cisplatin is active and well tolerated in patients with gastric cancer.[7–10]

Paclitaxel has shown *in vitro* antitumor activity against various tumor cell lines including gastric cancer.[11,12] In clinical studies Ajani *et al.* reported a 17% response rate for single-agent paclitaxel in patients with gastric cancer.[13] A 22% response rate was observed in pretreated patients with gastric cancer by Cascinu *et al.*, with single-agent paclitaxel administered over 3 h.[14] With the combination of 5-FU given as a weekly 24-h continuous infusion plus folinic acid over 6 consecutive weeks in combination with paclitaxel at 3-weekly intervals we have reported a response rate of 32% in 22 previously untreated patients with metastatic gastric cancer.[15] Progression-free survival (PFS) and overall survival (OS) times were 8 and 11 months, respectively. Toxicity was mild with neutropenia (14%), alopecia (45%), and nausea and vomiting (5%) being the most frequent WHO grade 3–4 toxicities. Similar results for the combination of 5-FU/folinic acid and paclitaxel have been reported by other investigators.[16]

In order to further investigate the efficacy of infusional 5-FU/folinic acid plus paclitaxel we have previously added cisplatin as another active compound in gastric cancer. This triple drug combination of paclitaxel, cisplatin and 5-FU/folinic acid in advanced gastric cancer has demonstrated favorable results and acceptable toxicity in a phase II study.[17] One of the main side effects in this study using the application of paclitaxel 175 mg/m^2 (3 h) every 3 weeks was neutropenia. Since weekly applications of paclitaxel 80 mg/m^2 as an 1-h infusion instead of 175 mg/m^2 every 21 days have been suggested to be associated with lower hematologic toxicity while achieving an even higher dose intensity of the drug, we have examined the feasibility and efficacy of a combination regimen with weekly applications of paclitaxel 80 mg/m^2, cisplatin and weekly 24-h continuous infusion 5-FU/folinic acid in patients with metastatic or locally unresectable gastric cancer in a subsequent phase II study.[18]

Patients and methods

Patients

Inclusion criteria were as follows: histologically proven unresectable locally-advanced or metastatic gastric cancer; ECOG performance status 0–2; presence of measurable disease; age between 18 and 75 years; life expectancy >3 months; no prior chemotherapy; adequate hematological, renal and hepatic function as defined by a granulocyte count $\geqslant 1.5 \times 10^9$/l, thrombocytes $\geqslant 100 \times 10^9$/l, serum creatinine $\leqslant 1.5$ mg/dl, creatinine clearance $\geqslant 60$ ml/min, bilirubin level <2-fold and liver enzymes <3-fold the upper normal limits; and written informed consent. All patients had to be available for follow-up.

Patients were excluded from the study in case of one of the following: active bleeding, diffuse, non-measurable liver metastases; history of a secondary malignancy except for non-melanomatous skin cancer or carcinoma *in situ* of the cervix; concurrent insufficiently treated disease such as heart, renal or hepatic failure or uncontrolled infection; prior chemotherapy; presence of a concurrent psychiatric disorder; pregnancy.

Prior to therapy, clinical history and physical examination, complete blood count and serum chemistry including liver and kidney function tests, creatinine clearance as well as an audiogram were obtained. All measurable tumor lesions were radiologically assessed either by computed tomography scan, chest X-ray or abdominal ultrasound.

The study was approved by the Ethics Committee of the University of Tübingen.

Treatment plan

Treatment was given once weekly for a total of 6 weeks followed by 1 week of rest. This period was defined as one treatment cycle. 5-FU was administered weekly at a dose of 2000 mg/m^2 as 24-h continuous infusion preceded by 500 mg/m^2 folic acid as a 2-h infusion. Pyridoxine 100–300 mg p.o. daily was given for the prophylaxis of hand–foot syndrome. Paclitaxel was administered weekly at a dose of 80 mg/m^2 as a 1-h infusion. All patients received dexamethasone 20 mg at 1 h and ranitidine 300 mg as well as diphenhydramine 50 mg at 30 min prior to paclitaxel in order to avoid hypersensitivity reactions. Cisplatin 50 mg/m^2 was added on days 8 and 29. All patients received adequate antiemetic pre-medication prior to chemotherapy. A permanent venous access (Port-A-Cath; Baxter, Munich, Germany) was implanted in all patients in order to facilitate the continuous 5-FU application with portable single-use 24-h infusion pumps in the ambulatory setting. All patients were treated on an outpatient basis.

Response and toxicity evaluation

Complete blood count, renal and liver function tests, history, and physical examination were recorded weekly. Prior to each cycle, creatinine clearance was rechecked. Toxicity was recorded every week based

on WHO criteria. Dose modifications and treatment delays were performed as necessary according to the extent of the hematological and organ toxicity. Planned dose modifications included the following: 20% dose reduction of paclitaxel and cisplatin in case of WHO grade 2 peripheral neurotoxicity; stopping paclitaxel and cisplatin in case of WHO grade 3/4 peripheral neurotoxicity; a 20% dose reduction of paclitaxel and cisplatin in case of WHO grade 3 granulocytopenia or grade 2 thrombocytopenia and 40% dose reduction of paclitaxel and cisplatin in case of WHO grade 4 granulocytopenia or grade 3 thrombocytopenia; 20% dose reduction of all three drugs in case of mucositis WHO grade $\geqslant 2$. A 1-week treatment delay was planned in case of any WHO grade 3–4 toxicity that had not resolved until the next week of treatment. Hematopoietic growth factors were not routinely used in the present study.

Assessment of measurable disease was performed after each cycle according to WHO criteria.[19] Complete remission (CR) was defined as the complete disappearance of all clinical, radiological and biochemical evidence of the disease, and partial response (PR) was defined as a greater than 50% reduction of all measurable tumor lesions lasting for at least 4 weeks. Stable disease (SD) was classified for all patients who achieved less than a PR but no evidence of progressive disease (new lesions or increase in any area of measurable disease $>25\%$). Treatment was continued if the patient showed a remission or stable disease. A maximum of three treatment cycles was planned per patient; however, further continuation was left to the treating physician's discretion.

Study endpoints

Objectives of the present study were the determination of the overall (CR and PR) response rate (ORR), the median PFS, the OS and the toxicity of the treatment regimen. PFS, follow-up duration and OS were calculated from the start of treatment to the date of disease progression or the date of the last evaluation or death, respectively. Survival was assessed on an 'intention to treat' basis. Survival curves were estimated by the Kaplan–Meier method.[20] All statistical analysis was performed using SPSS software (SPSS Inc, Chicago, IL, version 10.0.7).

Results

Between November 1999 and November 2001 29 patients with a median age of 56 years (22–72 years) were enrolled in the study. Patient characteristics are given in Table 1. Presence of primary tumor, lymph node and liver metastases as well as peritoneal metastases were the most common tumor sites, and all patients had measurable tumor lesions. Twelve patients (41%) had undergone gastrectomy prior to chemotherapy. Overall, 73 complete treatment cycles were administered to the 29 patients (median 3 cycles per patient; range 0–5).

Table 1. Baseline characteristics ($n=29$)

Characteristic	No. of patients (%) (median range)
Median age	56 years (22–72)
Male/female	13 (45%)/16 (55%)
ECOG performance status (median)	1 (0–2)
Gastrectomy	12 (41%)
Metastatic sites	
tumor at the primary site	19 (66%)
lymph nodes	14 (48%)
liver	12 (41%)
peritoneum	10 (35%)
lungs	7 (24%)
bone	2 (8%)
other	8 (28%)
Median follow-up	10 months (1–23+)

Response and survival

All patients were assessable for toxicity and survival, and all but one were assessable for response. Two patients stopped treatment during the first cycle, one due to toxicity and one because of a deteriorating performance status. This latter patient was considered as having progressive disease. Overall, in three patients (10%) treatment was stopped due to toxicity: one patient had grade 3 diarrhea and infection in cycle 1, one had grade 3 neurotoxicity in cycle 3 and one had a reversible acute renal failure in cycle 3.

Response and survival rates are given in Table 2. Fourteen patients (48%; 95% CI 29–68%) achieved an objective response including four CRs (14%). Seven patients (24%) had SD as the best response to therapy and the remaining seven patients (24%) developed progressive disease during treatment. Taking only the 27 patients into account, who received at least one complete cycle of therapy, the ORR was 52% (95% CI 32–71%). Overall tumor control rate (CR, PR and SD) was 72% (95%

Table 2. Response ($n=28$) and survival ($n=29$)

Response	No. of patients (%)
CR	4 (14%)
PR	10 (34%)
No change	7 (24%)
Progressive disease	7 (24%)
Termination of treatment because of toxicity	3 (10%)
Survival	
median OS	11 months (95% CI 7.4–14.6) (range 1–23)
median PFS	8 months (95% CI 5.5–9.8) (range 1–23)

CI 53–87%). Responses occurred mainly at the primary tumor site, and at liver, lymph node and lung metastases. So far, two patients with a CR as best response have relapsed. The durations of CRs are currently 7.8, 11.4, 10.1+ and 22.3+ months.

After a median follow-up of 10 months (range 1–23), 17 patients had died of their disease, one patient died of another cause and 11 patients are alive with six of them having progressive disease. Twelve (41%) patients received second-line chemotherapy. The median PFS and OS intervals are 8 months (range 1–23; 95% CI 5.5–9.8) and 11 months (range 1–23; 95% CI 7.4–14.6), respectively.

Toxicity

Toxicity according to WHO criteria was assessable in all 29 patients and is listed in Table 3 as the worst toxicity per patient during the total study period.

Hematologic toxicity: 15 patients (52%) experienced a grade 1–2 leukocytopenia and one patient had grade 3–4 leukocytopenia (3%). No thrombocytopenia was observed. Anemia grade 1–2 was observed in 21 patients (72%) and grade 3 anemia in one patient (3%).

Six patients (21%) had a hypersensitivity reaction to paclitaxel which led to discontinuation of this drug in three patients (10%). One patient had grade 3 fungal esophagitis which responded well to antifungal treatment. Two patients had to be hospitalized. One patient had acute renal failure, most likely due to diarrhea and dehydration. The patient recovered completely. The other patient had non-neutropenic fever, infection and diarrhea. In two patients treatment was stopped within the first cycle of therapy as stated above. In accordance with the protocol, in 37% of all applications the dose of at least one of the drugs had to be reduced and 42 of 412 applications (10%) had to be postponed either because of toxicity ($n=34$) that had not completely resolved before the next application or because of the patient's wishes ($n=8$).

Table 3. Toxicity: worst toxicity per patient during study ($n=29$)

Toxicity	No. of patients (%)	
	WHO grade 1–2	WHO grade 3–4
Leukocytopenia	15 (52%)	1 (3%)
Thrombocytopenia	0	0
Infection	15 (52%)	3 (10%)
Fever	6 (21%)	1 (3%)
Alopecia	2 (7%)	19 (66%)
Nausea/vomiting	17 (59%)	6 (21%)
Mucositis	6 (21%)	0
Hypersensitivity reaction[a]	6 (21%)	0
Neurotoxicity	7 (24%)	3 (10%)
Diarrhea	13 (45%)	6 (21%)
Hand–food syndrome	1 (3%)	0
Constipation	3 (10%)	0
Myalgia	1 (3%)	0
Esophagitis	0	1 (3%)
Pre-renal acute renal failure (reversible)	0	1 (3%)
Other (all grade 1–2): one each (3%): fatigue, taste disturbance, edema, orthostatic dysregulation, muscle weakness, epistaxis, vertigo, dimness of vision		

[a]Flush and exanthema.

Discussion

Second-generation protocols for the treatment of advanced gastric cancer are mainly based on 5-FU, methotrexate, cisplatin and anthracyclines. In phase II trials, response rates of 40–60% have been reported for regimens such as FAMTX, ELF, EAP, cisplatin/5-FU or ECF.[5,21–24] However, in randomized phase III trials, a comparable level of activity has only been confirmed for the ECF regimen, whereas for the FAMTX, ELF or cisplatin/5-FU regimens response rates of 10–25% have been reported.[25–28] In addition, the FAMTX and EAP regimens were particularly associated with severe toxicity. Thus, no definitive standard regimen for the palliative treatment of metastatic gastric cancer has yet been defined.

Several new agents have now been included into third-generation regimens in gastric cancer including topoisomerase I inhibitors such as CPT–11 or taxanes such as docetaxel and paclitaxel. An additive cytotoxic effect has been reported *in vitro*

for the sequence of paclitaxel followed by 5-FU, whereas the exposure to 5-FU followed by paclitaxel showed subadditive effects.[8,29,30] Furthermore, a synergistic effect has been described not only for the combination of 5-FU and cisplatin, but also for the combination of paclitaxel and cisplatin in human gastric cancer cell lines.[31–33] Based on this rationale, we have previously performed a phase II trial with the combination of cisplatin, paclitaxel and 5-FU/folinic acid, demonstrating a high activity with a response rate of 51% and a median OS of 14 months.[17] Non-hematologic toxicity was acceptable; however, leukocytopenia WHO grade 3–4 occurred in 27% of patients. For the application of 5-FU, a protracted, weekly 24-h infusion combined with folinic acid was chosen, since this mode of application appears to be less toxic and potentially more active compared with the bolus administration. This schedule of 5-FU/folinic acid has been investigated in gastric cancer patients by Vanhöfer *et al.*, showing a remission rate of 24% and a stable disease rate of 59% in patients previously treated with bolus 5-FU therapy.[34]

The present study has extended our previous experience of the combination of 5-FU/folinic acid, paclitaxel and cisplatin in gastric cancer. Instead of using paclitaxel at a dose of 175 mg/m^2 every 3 weeks, this new study has employed paclitaxel at a weekly dose of 80 mg/m^2. This modification was introduced in order to increase the dose intensity but at the same time reduce hematologic toxicity.

With this regimen an ORR of 48% (52% if only those patients receiving at least one complete cycle of therapy are taken into account) including 14% (15%) CRs was achieved in previously untreated patients with gastric cancer. This is comparable to the response rate observed in our previous study and confirms the high activity of this regimen. Favorable response rates with regimens combining 5-FU, folinic acid, cisplatin and paclitaxel were also reported by Kim *et al.* and Chun *et al.*, but their regimens did not use high-dose 5-FU as continuous infusion nor weekly paclitaxel. In both studies the survival time was shorter than in our trial.[35,36]

The PFS interval of 8 months and median OS time of 11 months are as encouraging as in our previous study.[17] The overall toxicity of the present combination of paclitaxel, 24-h continuous infusion of high-dose 5-FU/folinic acid and cisplatin was acceptable. The weekly schedule of paclitaxel appears to be associated with even lower hematologic toxicity compared with the previous study. The incidence of mucositis, nausea and vomiting appeared comparable with our previous results. A slightly higher incidence of neurotoxicity was seen with three of 29 (10%) showing grade 3 neurotoxicity at the end of treatment. Yet, the neurotoxicity observed was not typical for cisplatin- or paclitaxel-induced polyneuropathy in two of three cases. One of the patients with longstanding diabetes and grade 1 sensory polyneuropathy at the onset of the study developed grade 3 polyneuropathy weeks after treatment had been discontinued for other reasons in cycle 2. Another patient exhibited a one-sided peroneal pressure paralysis in week 1 of cycle 2. This was considered not to be related to treatment and 3 cycles could be completed without worsening of symptoms. Peripheral polyneuropathy had also been described at higher cumulative doses of paclitaxel in a regimen using 175 mg/m^2 paclitaxel every 3 weeks, combined with infusional 5-FU, folinic acid and cisplatin in patients with advanced breast cancer.[37] It is still controversial whether weekly paclitaxel with shorter infusion times (1-h infusion) leads to a higher incidence of peripheral polyneuropathy, compared with 3-h regimens.[38] However, careful assessment of neurologic function and early dose reduction clearly is important when using this combination of cytotoxic agents.

Based on the high response rate combined with a tolerable toxicity profile, we are currently investigating the combination of high-dose 5-FU/folinic acid, cisplatin plus paclitaxel and radiotherapy in the adjuvant setting in patients with completely resected high-risk gastric cancer.

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