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Short report

A phase II trial of paclitaxel and weekly 24 h infusion of 5-fluorouracil/folinic acid in patients with advanced gastric cancer

Carsten Bokemeyer, Christine S Lampe, Michael R Clemens,[1] Jörg T Hartmann, Detlev Quietzsch,[2] Lutz Forkmann,[2] Christian Kollmannsberger and Lothar Kanz

Department of Hematology/Oncology/Immunology, Eberhard-Karls-University Medical Center II, Otfried-Müller-Strasse 10, 72076 Tübingen, Germany. Tel: (+49) 7071-29-87121; Fax: (+49) 7071-29-3675. [1]Department of Internal Medicine, Krankenanstalt Mutterhaus, Trier, Germany. [2]Department of Internal Medicine, Städtische Kliniken, Chemnitz, Germany.

A phase II trial was performed to evaluate the efficacy and toxicity of the combination of paclitaxel and 5-fluorouracil (5-FU)/folinic acid in patients with advanced gastric carcinoma. Twenty-two patients (six female and 16 male) with advanced or metastatic disease were enrolled. None of them had received prior chemotherapy. Paclitaxel was administrated as a 3 h infusion of 175 mg/m² at days 1 and 22, 5-FU 2000 mg/m² i.v. over 24 h and folinic acid 500 mg/m² i.v. 2 h prior to 5-FU weekly from days 1 to 36. Seven patients (32%) had partial remissions including the lungs, skin, lymph nodes and locally advanced primary tumor. The median overall survival was 11 months (range 1 17+) and the median progression-free interval was 8 months (range 1 13+). Neutropenia (WHO grade III/IV) occurred in 14% of patients. Other main toxicities were alopecia in 45%, fever/infection in 9%, and nausea/vomiting and diarrhea in 5%. In conclusion, the combination of paclitaxel and continuously infused 5-FU/folinic acid appears to be an active regimen for advanced gastric carcinoma with a remission rate comparable to ELF or FAMtx. The moderate toxicity allows treatment on an outpatient basis.

Key words: Advanced gastric cancer, 5-fluorouracil, folinic acid, paclitaxel, phase II trial.

Introduction

Despite a declining incidence over the past 40 years, gastric carcinoma is the seventh most common cause of cancer death in the USA. Advanced gastric carcinoma is an incurable disease and patients will be treated with palliative chemotherapy. A number of drugs such as 5-fluorouracil (5-FU), etoposide, adriamycin, methotrexate or cisplatin have demonstrated activity in gastric cancer and schedules like ELF (etoposide, folinic acid and 5-FU) or FAMtx (5-FU, adriamycin and methotrexate) yield remission rates between 20 and 40%.[1]

Paclitaxel is a novel cytotoxic agent with the unique cytotoxic mechanism of tubulin stabilization and polymerization. Antitumor activity of paclitaxel was shown in gastric carcinoma cell lines with an additive cytotoxic effect when combined with 5-FU.[2–4] An ongoing study has reported eight of 13 patients with gastric cancer responding to 5-FU plus paclitaxel with a PR/CR rate of 38%.[4] In patients with breast cancer the combination of paclitaxel and prolonged infusion of 5-FU/folinic acid revealed no severe toxicity,[5] and this combination may therefore be suitable as palliative treatment for patients with advanced gastric carcinoma.

The objectives of the current study were (i) to evaluate the activity of three-weekly paclitaxel in combination with weekly 24 h continuous infusion of 5-FU and folinic acid, (ii) to evaluate the toxicity and safety of this schedule, and (iii) to determine the feasability of paclitaxel/5-FU/folinic acid treatment on an outpatient basis.

Materials and methods

Patient selection

Twenty-two patients with histologically proven advanced or metastatic gastric carcinoma were enrolled in this multicenter phase II trial. Inclusion criteria for patients were non-pregnant, non-lactating female or male patients; age between 18 and 75 years; ECOG performance status of 0–2; life expec-

Correspondence to C Bokemeyer

tancy of at least 12 weeks; written informed consent. Adequate hematological, renal and hepatic functions were required, defined as a granulocyte count of more than 1.5×10^9/l, platelets of more than 100×10^9/l, bilirubin levels < 1.5-fold and liver enzymes < 3-fold upper normal values. None of the patients was previously treated with chemotherapy. All patients had to be available for the management of complications and for follow-up. At least 20 consecutive patients were planned to be enrolled for the evaluation of toxicity and response.

Patients were excluded if they had cerebral metastases; secondary malignancies, except for non-melanomatous skin cancer or curatively treated cervical carcinoma *in situ*; psychiatric disorders; active bleeding of the stomach cancer; actual febrile infection or non-measurable disease. All patients underwent a pretreatment evaluation consisting of a history and complete physical examination, hematological testing and serum chemistry, and ECG and radiological evaluation of all measurable tumor lesions.

Ethical approval was given by Tübingen University ethical commitee.

Treatment plan

Chemotherapy was given once weekly and a total of 6 weeks were considered as one treatment cycle. Each cycle was followed by a 2 week break. Paclitaxel was given at a dosage of 175 mg/m^2 i.v. as 3 h infusion on days 1 and 22, 5-FU weekly at a dosage of 2000 mg/m^2 i.v. as 24 h continuous infusion and 500 mg/m^2 of folinic acid i.v. over 2 h prior to 5-FU. To avoid hypersensitivity reactions patients were treated with dexamethasone 20 mg orally 12 and 6 h before the application of paclitaxel and with ranitidine 300 mg and diphenhydramine 50 mg i.v. 30 min prior to paclitaxel. Most patients were implanted a s.c. intravenous port chamber which was used for 5-FU administration in the outpatient setting (Baxter, Intermate-System LV2, Unterschleißheim, Germany). In one of the participating study centers port chambers systems were not available for the first patients, but were used during the later course of the study.

Response and toxicity evaluation

Patients were assessed weekly for toxicity by physical examination and laboratory testing. Assessment of measurable disease was performed after each cycle. In case of progressive disease patients were removed from the study. Patients with stable disease or remission received a maximum of four treatment cycles.

Complete response was defined as the complete disappearance of all measurable disease for a duration of at least 4 weeks and partial response as a greater than 50% reduction of all measurable tumor sites. Stable disease was considered for all patients who had less than a partial response but no evidence of disease progression according the standard WHO criteria.

Results

Twenty-two patients with a median age of 58 years (range 35–71) were enrolled in the trial. All patients were evaluable for response and toxicity. The patient's characteristics are listed in Table 1. Fourteen patients had been previously operated with complete removal of the primary stomach tumor in six cases. A total of 58 chemotherapy cycles was administered with a mean of 2.6 cycles per patient (range, 1–4).

Response

No complete remission was observed but seven patients achieved a partial response lasting for 13+, 11, 10+, 10, 8+, 8 and 7 months (PR = 32%; $CI_{95\%}$: 12–52%). Sites of PRs included the lungs, skin, locally advanced primary tumors and the perigastric lymph nodes. Twelve patients (55%) had

Table 1. Patient characteristics

Characteristic	No. of patients (%)
Median age (years)	58 (35–71)
Sex (M/F)	16/6
Gastric adenocarcinoma	22 (100%)
Prior gastrectomy	6 (27%)
Metastatic sites[a]	
gastric lymph nodes	14 (64%)
liver	8 (36%)
bone	2 (9%)
peritoneal involvement	4 (18%)
skin	1 (5%)
lungs	4 (18%)
locally advanced disease	2 (9%)

[a]Evaluable by radiological methods.

a stable disease and three (14%) disease progression (PD). Three patients with PRs had a previous gastrectomy.

The median follow-up for all patients was 12 months ranging from 1 to 17. Currently, 10 patients are alive, two patients with progressive disease. Eleven patients have died from their tumor and one patient was lost to follow-up. The median overall survival for all patients was 11 months (range 1–17+). The median progression-free interval was 8 months (range 1–13+).

Toxicity

Toxicity according to WHO criteria is listed in Table 2 counting the worst toxicity per patient during the whole study period. The major non-hematological toxicities (WHO grade III/IV) were alopecia (45%), fever/infection, nausea/vomiting and diarrhea in 5% of the patients. One patient had pneumonia (WHO grade II), one patient had temperatures above 40°C (WHO grade III) which responded to antibiotics, though no focus could be detected. A third patient developed meningitis during a non-neutropenic period at the beginning of the second cycle, probably due to aspergillosis, and died subsequently. In all patients fever was not associated with neutropenia.

Table 2. Worst toxicity per patient experienced during the total treatment period with paclitaxel and 5-FU/folinic acid for advanced gastric cancer ($N = 22$)

Toxicity	WHO grade I/II (*N*)	WHO grade III/IV (*N*)	No. of patients with WHO grade III/IV (%)
Leukopenia	13	3	14
Anemia	6	0	0
Thrombopenia	2	0	0
Infection/fever	6	2	9
Neurotoxicity	13	0	0
Nausea/vomiting	11	1	5
Pain	8	0	0
Allergy	0	0	0
Mucositis	12	0	0
Alopecia	9	10	45
Hand foot syndrome	10	0	0
Diarrhea	12	1	5
Constipation	3	0	0
Myalgia	10	0	0

Twelve patients were completely treated on an outpatient basis, 10 were treated as inpatients for 1 day each week depending on the participating center. During the course of the study, only the three patients with infections mentioned above had to be hospitalized for toxic complications and start of the next treatment cycle had to be delayed for another 2 weeks. No dose reductions for toxicity had to be performed and no hypersensitivity reaction due to paclitaxel occurred. Skin toxicity, as mild thrombophlebitis-like changes with erythema or hyperpigmentation, related to 5-FU administration over a periphal drip was seen in 35%. Additionally hand–foot syndrome and mucositis occurred in 45 and 55% of patients (WHO grade I/II). Hematological toxicity was moderate and mainly consisted of non-cumulative neutropenia (14%) but was not associated with septic episodes or fever in these patients.

Discussion

We achieved a response rate of 32% in chemotherapy-naive patients with advanced gastric cancer which is comparable to the activity of regimens such as ELF or FAMtx.[1,6] However, the current study was not designed to demonstrate the activity of paclitaxel independently from 5-FU/folinic acid. However, *in vitro* and *in vivo* data seem to support the activity of paclitaxel in gastric adenocarcinoma.[2–4] In four human carcinoma cell lines the application of paclitaxel prior to 5-FU produced enhanced cytotoxicity *in vitro*, while the use of paclitaxel after 5-FU displayed a less than additive cytotoxicity efficiency of both drugs.[7] In a phase I study of weekly paclitaxel and concurrent radiation in patients with advanced gastric carcinoma, 27% PR and 83% SD were achieved.[8] In a study by Ajani including patients with adenocarcinoma of the esophagus and the GI junction, paclitaxel alone given at a dosage of 250/m^2 over 24 h showed a PR rate of 36% with one patient achieving a CR.[9,10] Thus, paclitaxel may be of value in the therapy of patients with gastric cancer. The addition of paclitaxel to weekly 5-FU bolus therapy has resulted in a PR/CR rate of 38% in 13 patients treated for gastric cancer.[4] For the combination of paclitaxel with 5-FU we have used protracted weekly 5-FU infusions over 24 h, since this mode of application is associated with less hematotoxicity compared to bolus 5-FU. Protracted infusion of 5-FU has shown a remission rate of 18% in previously treated patients with gastric cancer.[11]

The dose intensity of paclitaxel with a three-weekly application of 175 mg/m^2 followed by two weeks rest after every two injections may be considered rather low in our treatment schedule. However, comparative doses of paclitaxel have been used in the studies by Ajani and Murad.[4,10]

The major non-hematological toxicities (WHO grade III/IV) mainly related to 5-FU/folinic acid were nausea/vomiting (5%) and diarrhea (5%). Fever/infection occured in 9% of patients. Neutropenia grade III/IV was seen in three patients (14%). Three other patients had to be hospitalized because of fever/infection. One patient died of infectious complications possibly related to treatment. No severe paclitaxel-related side effects such as allergy, arrythmia, myalgia or neuropathy were observed. Mild or moderate neuropathy, mainly appearing as neurosensory toxicity, occurred in 13 of 22 patients. The extent of side-effects was in accordance with previous investigations using the combination of paclitaxel and 24 h continuous 5-FU/folinic acid.[5]

The addition of cisplatin may further improve the response rates of 5-FU therapy. Cisplatin can be combined with 5-FU due to its different spectrum of toxicity. A recent study in patients with advanced gastric cancer achieved a response rate up to 43%[12] in combination with 24 h continuous infusion of 5-FU. Due to the moderate toxicity of the 5-FU/paclitaxel treatment and with *in vitro* studies showing a synergistic effect of cisplatin with paclitaxel,[13] it is currently planned to study the toxicity and activity of paclitaxel when given in combination with weekly 5-FU/folinic acid 24 h infusions plus cisplatin at three-weekly intervals.

Conclusion

We conclude that the combination of paclitaxel plus 5-FU/folinic acid is associated with a promising response rate and with a moderate toxicity profile. It can be performed on an outpatient basis. The addition of cisplatin due to its different spectrum of toxicity and its synergism with paclitaxel seems to offer the chance to further enhance the activity of chemotherapy in advanced gastric cancer.

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