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Clinical report

Prolonged infusion of gemcitabine in stage IV breast cancer: a phase I study

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Gemcitabine is an effective agent in the treatment of metastatic breast cancer. The phosphorylation of gemcitabine into the active gemcitabine triphosphate (dFdCTP) is catalyzed by deoxycytidine kinase. This enzyme is saturated at plasma concentrations achieved after an infusion over 30 min. Therefore accumulation of higher intracellular dFdCTP concentrations, which may result in an enhanced antineoplastic activity, cannot be achieved by higher dosage, but only by prolonged infusion time. The objectives of this phase I trial were to determine the dose-limiting toxicities (DLT) and the maximum tolerated dose (MTD) of gemcitabine given as a 6 h i.v. infusion. Patients with metastatic breast cancer were treated with gemcitabine as a 6 h infusion on days 1, 8 and 15 every 4 weeks. The starting dose was 200 mg/m^2 with an interindividual escalation in 50 mg/m^2 increments. Sixteen patients received 196 doses through three dose levels. All patients were assessable for toxicity, 13 assessable for response. The MTD was 250 mg/m^2. DLT was observed at 300 mg/m^2 consisting of a reversible elevation of transaminases WHO grade 3 in two patients and cutaneous toxicity grade 3 in one patient. Most common non-hematologic toxicities were mild to moderate and rapidly reversible elevation of liver enzymes in all patients, nausea and vomiting (four patients grade 2, five patients grade 3), and mild alopecia. Hematologic toxicity was mild with neutropenia WHO grade 3 and 4 in only one patient each, and no grade 3 thrombocytopenia. One patient achieved a complete remission and another patient a partial response, for an overall response rate of 15% (two of 13). In addition, seven patients (54%) had stable disease and four (31%) failed to respond to the treatment. We conclude gemcitabine 250 mg/m^2 days 1, 8 and 15 every 4 weeks can be safely administered as 6 h infusion. Toxicity, especially myelosuppression, is surprisingly mild. Based on this result a phase II study with 250 mg/m^2 administered over 6 h was initiated to determine the efficacy. []

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Introduction

Gemcitabine (2′,2′-difluorodeoxycytidine) is a new nucleoside analog that has shown a broad range of antitumor activity against both chemotherapy-naive and pretreated malignancies including breast cancer, with only low to moderate toxicity.[1–5] Gemcitabine is usually administered as a 30 min infusion of 1000 mg/m^2 on days 1, 8 and 15 every 4 weeks, as this schedule has been shown to have a favorable toxicity profile with consistent antineoplastic activity.[6]

Gemcitabine is a pro-drug that has to be phosphorylated by deoxycytidine kinase (dCK) to the active diphosphate (dFdCDP) and triphosphate (dFdCTP).[7–9] Gemcitabine triphosphate is incorporated on the end of the elongating DNA strand during S phase, resulting in chain termination, which in turn induces apoptotic cell death. Furthermore, dFdCTP inhibits DNA polymerases and therefore the capacity of DNA synthesis.

Pharmacological studies of gemcitabine have shown that the intracellular concentration of dFdCTP is the relevant parameter for the cytostatic activity of gemcitabine. The formation of the triphosphate involves several enzymatic reactions. Deoxycytidine kinase seems to be the rate-limiting step in the intracellular accumulation of gemcitabine triphosphate.[10–12] This enzyme is saturated at concentrations of 15–20 μM of gemcitabine, leading to a constant reaction rate at higher concentrations.[13] Therefore, a linear relationship between intracellular accumulation of dFdCTP and the AUC of gemcitabine can only be expected at plasma concentrations below this level, while at higher concentrations a non-linear dose-activity relationship with relatively small increases of [dFdCTP] results.

The plasma concentrations following a 30 min infusion of 1000 mg/m^2 gemcitabine most of the time exceed the concentration of saturation of dCK. Thus, to optimize the intracellular accumulation of the active metabolites of gemcitabine and to enhance the antineoplastic activity, it seems to be better to prolong the infusion time rather than to further increase the dosage. Pollera and collaborators showed that the maximum-tolerated infusion time at 300 mg/m^2 Gemcitabine was 6 h.[14] Based on these considerations and results, this phase I trial was conducted to determine the maximum tolerated dose (MTD) of gemcitabine administered as a 6 h infusion in a weekly schedule in patients with advanced breast cancer.

Patients and methods

Patient eligibility

Women with histologically confirmed locally advanced (stage III B) or metastatic breast cancer (stage IV) were eligible for this study. Other eligibility criteria included: age 18–75 years; Karnofsky performance status >60%; a life expectancy of at least 12 weeks; at least 6 months beyond adjuvant chemotherapy; adequate bone marrow function [white blood count (WBC) $\geq$ 3500 /μl, absolute granulocyte count (ANC) $\geq$ 1500/μl, platelets $\geq$ 100 000/μl, and hemoglobin $\geq$ 10 g/dl], renal function (creatinine $\leq$ 1.5 mg/dl) and hepatic function (bilirubin $\leq$ 1.5 mg/dl, ALAT/ASAT $\leq$ 3 times the upper limit of normal and prothrombin time within the normal range of the institution). Patients eligible for the response evaluation required bidimensionally measurable or assessable disease.

Patients were ineligible if they had received previous treatment with gemcitabine or extensive radiotherapy (more than 30% of bone marrow involved). Patients with previous radiotherapy were eligible if there was measurable disease outside the radiation area. Further exclusion criteria included brain metastases, a history of prior malignancy, severe concurrent medical conditions or acute infection. Written, informed consent was required.

Toxicity

Toxicities were assessed weekly and graded according to WHO toxicity criteria. DLT were defined as follows: grade 3 or 4 non-hematologic toxicity other than nausea, vomiting or alopecia; grade 4 neutropenia (ANC < 500/μl) or thrombocytopenia (platelet count < 25 000/μl); any grade 2 and more toxicity other than nausea, vomiting or alopecia, that persisted over day 28 of course 1.

Treatment schedule

Gemcitabine was administered on days 1, 8 and 15 every 4 weeks as a 6 h i.v. infusion with a Baxter Infusor (Intermate SV 50; 300 ml volume, 50 ml/h infusion rate) in the outpatient setting. Prophylactic antiemetics were used in most patients. Doses were assigned at registration. No dose escalation was permitted in individual patients.

The dose escalation followed the scheme shown in Table 1 with a starting dose of 200 mg/m^2 and increments of 50 mg/m^2. At least three patients assessable for toxicity were treated at each dose level. If none of the first three patients experienced DLT, the next dose level was entered. In case DLT occurred in one of the first three patients, two additional patients were treated at the same level. Dose escalation was continued if DLT was observed in a maximum of two patients of the expanded cohort. When a DLT occurred in three or more out of five patients, dose escalation was stopped and the next patients were treated at the previous level. This dose level was defined as the MTD, if DLT occurred in less than three of eight and four of 10 patients, respectively, treated at this dose level.

Within a course the weekly gemcitabine doses were reduced by 50%, if, on the day of treatment, ANC was 500–1499/μl and/or platelet count was 50 000–

Table 1. Dose escalation

Dose level	Dose (mg/m^2)	Dose rate (mg/m^2/min)	No. of patients	Assessable courses	DLT	Type	Response
1	200	0.56	3	14	0	–	1 CR; 2 NC
2	250	0.69	8	40	0	–	1 PR; 3 NC; 4 PD
3	300	0.83	5	9	3	2 × hepatotoxicity 1 × ulceration cutaneous	2 NC; 3 NE

99 000/μl. Gemcitabine was omitted for ANC <500/μl and a platelet count <50 000/μl. Hematopoetic growth factors were not supplied prophylactically. The dose for gemcitabine was permanently reduced by 50% for patients who experienced grade 3 non-hematologic toxicity (expect alopecia or nausea/vomiting). Patients with grade 4 non-hematologic toxicity (expect alopecia or nausea/vomiting) had to be withdrawn.

Patient evaluation and follow-up

On study entry, patients had a complete history and physical examination, performance status (PS) evaluation, complete blood cell counts with differentials, and routine laboratory studies were performed. Routine laboratory tests included serum electrolytes, blood urea nitrogen, creatinine, total protein, albumin, glucose, uric acid, alkaline phosphatase, total bilirubin, AST, ALT, prothrombin time, thrombin time and urinalysis. Imaging studies (chest X-ray, abdominal ultrasound, computerized tomographic or radionuclide scans of the chest, abdomen, bone and brain, as necessary to document the extent of disease) used for tumor measurements were obtained within 4 weeks from the study. All patients had an ECG before entry on the study.

Toxicity and quality of life were evaluated weekly during therapy. Assessment of tumor response was performed after every two courses of therapy, and treatment was continued as long as there was no evidence of disease progression and disease permitted. If response was documented, imaging scans were performed 4 weeks later to confirm the response. A complete response (CR) was defined as the disappearance of all clinical and radiographic evidence of cancer on two measurements separated by at least 4 weeks. A partial response (PR) required a greater than 50% decrease in the sum of the product of the bidimensional parameters of all measurable disease documented by two measurements separated by at least 4 weeks.

Results

Patient characteristics

A total of 16 patients with advanced breast cancer (stage IV) were entered onto this study at three dose levels. All patients were assessable for toxicity, 13 for response. Patient characteristics at the time of study registration are listed in Table 2. The median age was 56.6 years (range 42–70) and the median performance status was 0. Most patient had visceral-dominant disease (12 of 16). The median number of involved sites at study entry was 2 (range 1–4). All patients but one had not received prior palliative chemotherapy. Three patients had failed one and five patients had failed two hormonal therapies for metastatic disease before participation in this trial.

Table 2. Patient characteristics

Dose level	1	2	3	Total
Gemcitabine (mg/m^2/week × 3)	200	250	300	
Patients entered	3	8	5	16
Age				
median	54.6	58.0	55.8	56.6
range	53–56	44–70	42–63	42–70
Performance				
0	3	7	5	15
1	0	1	0	1
2	0	0	0	0
Adjuvant chemotherapy	2	5	4	11
Adjuvant hormone therapy	0	4	3	7
Prior hormone therapy				
0	1	4	3	8
1	0	2	1	3
2	2	2	1	5
Prior palliative				
0	3	8	4	15
1	0	0	1	1
Dominant metastatic site				
visceral	2	7	3	12
bone	1	0	2	3
soft tissue	0	1	0	1
No. of involved sites				
1		2	3	5
2	2	3	2	7
3	1	2		3
4		1		4
Rezidiv-free interval				
median	44.3	40.0	37.8	40.1
range	36–48	20–61	0–108	0–108

Drug delivery

One-hundred and ninety-six doses of gemcitabine with 65 completed courses were given during this study. A median of 3.9 courses per patient was administered with a range of 1–8. Two patients on dose level 2 completed eight courses of therapy without any severe adverse events (one patient with PR, one NC). Three patients received only one course of therapy due to DLT. Fifteen doses had to be delayed for 1 week or longer, three of them on the first, six on the second

and third dose level, respectively. The reasons for the delays included patient requests (seven patients), delayed recovery from myelosuppression (two patients), hepatotoxicity (one patient), cutaneous toxicity (one patient) and dyspnoea (one patient).

DLT

The DLT of gemcitabine were hepatotoxicity and cutaneous toxicity. Three and eight patients received a total of 54 courses at dose levels 1 and 2, respectively, with no dose-limiting events. Three of five patients treated with 300 mg/m^2 gemcitabine developed DLT during the first course. Two patients experienced a grade 3 transaminase level elevation in association with hyperbilirubinemia grade 2 and grade 2 elevation of the alkaline phosphatase after two applications of gemcitabine. Treatment was discontinued and the values returned to the normal range within 4 weeks in a patient with liver metastases and 2 weeks in the other patient without hepatic disease. One patient developed grade 3 cutaneous toxicity (edema and ulcerations at both ankles) that resolved after 3 weeks. Thus, the MTD of gemcitabine administered as a 6 h infusion is 250 mg/m^2.

Hematologic toxicity

Myelosuppression was generally mild at all dose levels. Hematologic toxicities are listed in Table 3 using the worst toxicity on study for individual patients. The cumulative toxicities are shown on Table 4. The principal hematologic toxicity was neutropenia. During the first dose, only one grade 3 and no grade 4 neutropenia was observed. In a total of 196 doses, four episodes of grade 3 neutropenia occurred. One patient developed grade 4 neutropenia at day 8 of the second course that lasted for 5 days. An episode of febrile neutropenia was not observed and no patient had to be admitted to the hospital.

Table 3. Maximum individual toxicity

	Dose level																			
	I (*n*=3)					II (*n*=8)					III (*n*=5)					Total (*n*=16)				
WHO grade	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Hematologic toxicity																				
leukopenia	0	1	2	0	0	2	0	4	1	1	3	1	1	0	0	5	2	7	1	1
thrombocytopenia	1	2	0	0	0	5	1	2	0	0	3	2	0	0	0	9	5	2	0	0
anemia	1	1	1	0	0	5	3	0	0	0	2	2	1	0	0	8	6	2	0	0
Non-hematologic toxicity																				
hepatic																				
ALT	0	1	1	1	0	1	1	6	0	0	0	2	2	1	0	1	4	9	2	0
AST	2	0	1	0	0	3	4	1	0	0	2	1	1	1	0	7	5	3	1	0
GGT	0	1	2	0	0	5	1	1	1	0	0	3	1	1	0	5	5	4	2	0
AP	2	1	0	0	0	6	2	0	0	0	3	1	1	0	0	11	4	1	0	0
renal																				
creatinine	3	0	0	0	0	8	0	0	0	0	4	0	1	0	0	15	0	1	0	0
hematuria	3	0	0	0	0	8	0	0	0	0	4	0	1	0	0	15	0	1	0	0
proteinuria	3	0	0	0	0	8	0	0	0	0	4	0	1	0	0	15	0	1	0	0
skin rash	3	0	0	0	0	8	0	0	0	0	5	0	0	0	0	16	0	0	0	0
fever/flu like	1	0	2	0	0	5	2	1	0	0	1	2	2	0	0	7	4	5	0	0
asthenia/fatigue	2	1	0	0	0	4	3	1	0	0	3	1	1	0	0	9	5	2	0	0
edema	3	0	0	0	0	8	0	0	0	0	3	0	2	0	0	14	0	2	0	0
pulmonary	3	0	0	0	0	5	2	1	0	0	3	2	0	0	0	11	4	1	0	0
nausea/vomiting	0	0	1	2	0	0	5	3	0	0	0	2	0	3	0	0	7	4	5	0
peripheral	3	0	0	0	0	7	0	1	0	0	5	0	0	0	0	15	0	1	0	0
constipation	1	1	1	0	0	6	2	0	0	0	4	1	0	0	0	11	4	1	0	0
alopecia	0	0	2	1	0	2	3	2	1	0	3	1	1	0	0	5	4	5	2	0
cutaneous	1	2	0	0	0	7	1	0	0	0	4	0	0	1	0	12	3	0	1	0
infection	3	0	0	0	0	7	0	1	0	0	4	0	1	0	0	14	0	2	0	0

Table 4. Cumulative toxicity

	Dose level																			
	I (14 courses)					II (40 courses)					III (11 courses)					Total (65 courses)				
WHO grade	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Hematologic toxicity																				
leukopenia	5	4	5	0	0	18	11	10	1	1	8	2	1	0	0	31	17	16	1	1
thrombocytopenia	12	2	0	0	0	36	1	3	0	0	10	1	0	0	0	58	4	3	0	0
anemia	9	1	4	0	0	26	14	0	0	0	4	3	4	0	0	39	18	8	0	0
Non-hematologic toxicity																				
hepatic																				
ALT	5	5	3	1	0	20	9	11	0	0	1	5	4	1	0	26	19	18	2	0
AST	9	4	1	0	0	27	12	1	0	0	7	2	1	1	0	43	18	3	1	0
GGT	8	4	2	0	0	24	11	4	1	0	1	7	2	1	0	33	22	8	2	0
AP	12	2	0	0	0	32	9	0	0	0	8	1	2	0	0	52	11	2	0	0
renal																				
creatinine	14	0	0	0	0	40	0	0	0	0	10	0	1	0	0	64	0	1	0	0
hematurina	14	0	0	0	0	40	0	0	0	0	10	0	1	0	0	64	0	1	0	0
proteinuria	14	0	0	0	0	40	0	0	0	0	10	0	1	0	0	64	0	1	0	0
skin rash	14	0	0	0	0	40	0	0	0	0	10	1	0	0	0	64	1	0	0	0
fever/flu like	9	3	2	0	0	34	4	2	0	0	6	3	2	0	0	49	10	6	0	0
asthenia/fatigue	9	5	0	0	0	28	9	3	0	0	5	4	2	0	0	42	18	5	0	0
edema	14	0	0	0	0	40	0	0	0	0	9	0	2	0	0	63	0	2	0	0
pulmonary	14	0	0	5	0	35	4	1	0	0	9	2	0	0	0	58	6	1	0	0
nausea/vomiting	2	1	6	5	0	12	18	10	0	0	2	3	3	3	0	16	22	19	8	0
peripheral	14	0	0	0	0	39	0	1	0	0	11	0	0	0	0	64	0	1	0	0
constipation	7	5	2	0	0	35	5	0	0	0	10	1	0	0	0	52	11	2	0	0
alopecia	2	4	7	1	0	10	15	13	2	0	8	2	1	0	0	20	21	21	3	0
cutaneous	11	3	0	0	0	39	1	0	0	0	10	0	0	1	0	50	4	0	1	0
infection	14	0	0	0	0	39	0	1	0	0	10	0	0	1	0	63	0	2	0	0

Thrombocytopenia was mild with no grade 3 or 4 episode at all dose levels. Dose reductions due to delayed hematological recovery were required in 19 episodes (9.7%).

Non-hematologic toxicity

Non-hematologic toxicity data are listed in Tables 3 and 4. There was limited grade 3 and no grade 4 non-hematologic toxicity. The major non-hematologic toxicities were nausea, vomiting and elevation of the hepatic enzymes. Moderate (grade 2 and 3) nausea and vomiting were reported in nine patients through all dose levels despite prophylactic administration of parenteral antiemetics. They remained under control with a combination of 5-HT_3 antiemetics and corticosteroids. Mild to moderate constipation (grade 1 and 2) was observed in five patients, but might be related to the prophylactic administration of 5-HT_3 antiemetics.

Elevation of transaminases was the predominant, dose-related non-hematologic toxicity observed in all patients and graded as severe in four patients. This side effect tended to occur earlier and with an increased intensity at higher dose levels and after higher cumulative doses. Hepatotoxicity resolved in all patients after discontinuation of the treatment.

Other non-hematologic toxicities were uncommon. One patient developed reversible grade 2 proteinuria, hematuria and elevation of serum creatinine. Alopecia of mild to moderate degree was observed in 11 patients and mild asthenia occurred in seven patients. One patient developed grade 2 dyspnea during therapy although her lung metastases remained stable. Transient flu-like symptoms, which included fevers, myalgias, arthralgias, headaches or fatigue, affected nine patients. Four patients developed mild to moderate infections (herpes simplex labialis, cystitis and infection of the upper respiratory tract). Hypersensitivity reactions were not observed.

Response

Thirteen patients were assessable for response. One patient with lung metastases and pulmonary carcinomatous lymphangiosis, treated at dose level 1, achieved a CR that lasted 8 months. A PR which remained for 10 months was observed in a patient with nodal metastases treated at dose level 2. Seven patients had stable disease for 5–9 months and four patients failed to respond to the treatment.

Discussion

Gemcitabine is an interesting agent for the treatment of metastatic breast cancer. Studies with gemcitabine given as a 30 min i.v. infusion on days 1, 8, and 15 of a 28 day cycle have shown single-agent activity with response rates of 25–46%.[15] At this schedule, gemcitabine is extremely well tolerated, even in heavily pretreated patients and can easily be administered on an outpatient basis.

The concept of gemcitabine as prolonged infusion is based on pharmacological studies, indicating a higher efficacy of continuous-infusion schedules compared to short-term administration. Grunewald *et al.* showed that the AUC for accumulation of dFdCTP in mononuclear cells is higher at lower dose rates of gemcitabine.[10] Veerman *et al.* observed considerably better antitumor activity of gemcitabine in two of three murine colon carcinoma lines using prolonged administration as compared with a standard bolus protocol.[16]

In a first clinical trial Pollera *et al.* investigated the effect of a prolonged administration of gemcitabine by step-wise escalating the duration of the infusion.[14] Forty-seven patients with advanced solid tumors were treated at two different doses of gemcitabine (300 and 875 mg/m^2). The maximum-tolerated infusion time was 6 h at 300 mg/m^2. At 875 mg/m^2, no escalation was attempted following the 1 h infusion, due to the limiting rate (58% of 12 patients) of toxic delay requiring shorter infusions. Toxicity was mild with a similar profile to that following short-time infusions. However, a trend towards increased non-hematologic toxicity, especially abnormalities of liver function, was observed. This study not only defined the toxic profiles and the maximum-tolerated infusion time of the selected dose levels, but demonstrated that gemcitabine shows a remarkable antitumor activity at doses as small as 300 mg/m^2, when given as a prolonged infusion.

In a different setting Brand *et al.* determined the MTD of gemcitabine administered as a fixed rate infusion (10 mg/m^2/min) on a weekly schedule.[17] Twenty-seven patients with untreated non-hematologic malignancies were enrolled at three different dose levels (1200, 1500 and 1800 mg/m^2). The MTD was defined as 1500 mg/m^2 with myelosuppression being dose-limiting. Non-hematologic toxicities included nausea, vomiting and fever and were generally mild.

When administered as short-time infusion, the most common toxicity of gemcitabine is mild and short-lived myelosuppression.[18] Dose-dependant elevations of transaminases are frequently observed, but they are usually mild and rarely dose limiting. Mild proteinuria and hematuria may occur but are rarely clinically significant. There is no evidence of cumulative hepatic or renal toxicity. Flu-like symptoms are reported in a small proportion of patients but are of short duration. Gemcitabine causes minimal nausea and vomiting, and significant hair loss is extremely uncommon. Furthermore, gemcitabine displayed minimal toxicity in elderly patients and the side-effect profile does not seem to be affected by patient age. However, phase I studies have shown that the toxicity of gemcitabine is remarkably dependent on the schedule. In phase I studies with more frequent administration, non-hematologic toxicity was more apparent.[19,20]

This study demonstrated that gemcitabine can be safely administered as a 6 h infusion. On the basis of the trial by Pollera *et al.*, the infusion time was fixed at 6 h, with a starting dose of 200 mg/m^2 gemcitabine. The MTD was 250 mg/m^2 with hepatotoxicity and cutaneous toxicity being dose limiting. As in the study published by Pollera, elevation of transaminases was the predominant non-hematologic toxicity. However, since hepatotoxicity appeared to be dose related and resolved after discontinuation of the treatment, it seems to be of minor clinical relevance at the MTD. Other non-hematologic toxicities and especially myelosuppression were surprisingly mild, transient and easily manageable in most patients. Although efficacy was not a primary outcome measure, objective responses were noted in two patients.

Conclusion

In conclusion, gemcitabine can be safely administered as a 6 h infusion. This regimen is well tolerated and seems to have substantial antineoplastic activity that has to be further investigated in a subsequent phase II study. The recommended dose and schedule for the phase II study is 250 mg/m^2 gemcitabine given over 6 h on days 1, 8 and 15 every 4 weeks.

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