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Clinical study

Phase II trial of gemcitabine as prolonged infusion in metastatic breast cancer

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Gemcitabine is an active 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. In a previous phase I trial the maximum tolerated dose of gemcitabine given as a 6 h i.v. infusion was 250 mg/m^2. The objective of this phase II trial was to determine the efficacy and safety of gemcitabine as prolonged infusion in patients with metastatic breast cancer. Twenty patients [median age 50.4 years, range 35–63 years; performance status EORTC 0 (17 patients), 1 (two patients), 2 (one patient)] with metastatic breast cancer were treated with 250 mg/m^2 gemcitabine as infusion over 6 h on days 1, 8 and 15 q3 weeks for up to six courses (median 3.9 courses). Treatment was first line for four patients, second line for five patients and third line or higher for 11 patients. Metastatic sites were liver in 14 patients, bone in 12 patients, lung in eight patients and lymph nodes in nine patients. Nine patients presented two metastatic sites, three patients three and five patients four. All patients were evaluable for response and toxicity. One patient (5%) achieved a complete remission (CR) and four patients (20%) a partial remission (PR) (one patient with CR of visceral metastases but stable bone metastases), for an overall response rate of 25% (five of 20). In addition, six patients (30%) had stable disease and nine (45%) failed to respond to the treatment. Time to progression ranged from 2 to 23 months with a median of 6.3 months. Hematologic toxicity was mild with leukopenia grade 3 in only three patients (15%) and no grade 3 thrombocytopenia. Moderate elevations of liver enzymes (three patients grade 3), nausea and vomiting (two patients grade 2), and mild alopecia were observed, but only one patient had to be withdrawn due to toxicity. In conclusion gemcitabine as prolonged infusion is an effective treatment in metastatic breast cancer. Toxicity, especially myelosuppression, is surprisingly mild. Therefore, gemcitabine seems to be ideal for combination therapies. [© 1999 Lippincott Williams & Wilkins.]

Key words: Breast cancer, gemcitabine, infusion, phase II, prolonged infusion.

Introduction

Gemcitabine (2′,2′-difluorodeoxycytidine) is a novel pyrimidine antimetabolite with considerable activity and a favorable toxicity profile in both chemotherapy-naive and pretreated malignancies including breast cancer.[1–5] Gemcitabine is a pro-drug that has to be phosphorylated by deoxycytidine kinase (dCK) to the active diphosphate (dFdCDP) and triphosphate (dFdCTP).[6–8] Both dFdCDP and dFdCTP inhibit processes required for DNA synthesis. Gemcitabine triphosphate is incorporated into the DNA and terminates DNA strand elongation. Thus, the relevant parameter for the cytostatic activity of gemcitabine is the intracellular concentration of dFdCTP.

The formation of dFdCTP involves several enzymatic reactions with dCK being the rate-limiting step.[9–11] This enzyme is saturated at concentrations of 15–20 μM of gemcitabine, leading to a constant reaction rate at higher concentrations.[12] 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.

Gemcitabine is usually administered as a 30 min infusion of 1000–1200 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.[13] The plasma concentrations following a 30 min infusion of 1000 mg/m^2 gemcitabine exceed the concentration of saturation of dCK

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most of the time. Thus, higher intracellular concentrations of the active metabolites with a potentially increased efficacy may result after a prolonged administration as indicated in pharmacological studies.[9,14]

In a first clinical trial Pollera and collaborators investigated the effect of a prolonged administration of gemcitabine by step-wise escalating the duration of the infusion.[15] 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 the 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 and collaborators determined the maximum-tolerated dose (MTD) of gemcitabine administered as a fixed rate infusion (10 mg/m^2/min) on a weekly schedule.[16] 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.

In a phase I study we determined the MTD of gemcitabine given as a 6 h i.v. infusion.[17] Sixteen patients with metastatic breast cancer were treated with gemcitabine as 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. The MTD was 250 mg/m^2. Dose-limiting toxicity 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 and 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.

Based on these results this phase II study was initiated to determine the efficacy of 250 mg/m^2 gemcitabine administered over 6 h.

Patients and methods

Patient eligibility

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

Patients were ineligible if they had received previous treatment with gemcitabine or extensive radiotherapy ($>30\%$ 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, bone metastases as the only metastatic site, a history of prior malignancy, severe concurrent medical conditions or acute infection. Written, informed consent was required.

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.

Toxicities were assessed weekly and graded according to WHO toxicity criteria. 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 50 000–99 000/μl. Gemcitabine was omitted for an ANC less than 500/μl and a platelet count less than 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 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 continued for up to six courses 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.

Table 1. Patient characteristics

	No. of patients	(%)
Registered and treated	20	
Age (years)		
median	50.4	
range	35–63	
WHO/ECOG performance status		
0	17	(85)
1	2	(10)
2	1	(5)
Prior adjuvant treatement		
chemotherapy	10	(50)
hormone therapy	4	(20)
none	9	(45)
No. of prior palliative hormone therapy agents		
0	4	(20)
1	10	(50)
2	6	(30)
No. of prior palliative chemotherapy regimens		
0	4	(20)
1	5	(25)
2	2	(10)
3	3	(15)
4	6	(30)
Metastatic sites		
liver	14	(70)
lung	8	(40)
lymph nodes	9	(45)
bone	12	(60)
skin	1	(5)
soft tissue	3	(15)
No. of metastatic sites per patient		
1	3	(15)
2	9	(45)
3	3	(15)
4	5	(25)
Disease-free interval (months)		
median	20.6	
range1	0–72	

Results

Patient characteristics

A total of 20 patients with advanced breast cancer (stage IV) were treated within this study. All patients were assessable for response and toxicity. Patient characteristics at the time of study registration are listed in Table 1. The median age was 50.4 years (range 35–63) and the median performance status 0 (range 0–2). Most patients had visceral-dominant disease. Most common sites of metastatic disease were liver (70%), bone (60%), lymph nodes (45%) and lung (40%). Eighty-five percent had two or more involved sites at study entry. All patients had bidimensionally measurable disease.

Ten patients had received prior adjuvant chemotherapy. Six patients had been treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), and the remaining four patients had received an anthracycline-based chemotherapy. Gemcitabine was the first palliative chemotherapy for four and second-line treatment for five patients. Eleven patients had received two or more prior chemotherapies for metastatic disease. Prior chemotherapy exposure included anthracyclines in 15 (two patients adjuvant only, 13 patients for metastatic disease; doxorubicin in five, epirubicin in 12 and mitoxantrone in three patients), paclitaxel in 12, alkylating agents in 17 and vinca alkaloids in eight patients. Ten patients had failed one and six patients two hormonal therapies, respectively, for metastatic disease before participation in this trial.

Dose administration

A total of 236 doses in 78 courses were administered during this study. The mean number of completed courses was 3.9 with a range of 1-6. Twenty-five doses (10.5%) were reduced and five courses (2.1%) had to be delayed.

Efficacy

Of 20 assessable patients, one (5%) achieved a CR and four (20%) a PR, for an overall response rate of 25% (five of 20) (Table 2). In addition, six patients (30%) had stable disease and nine (45%) failed to respond to the treatment. Responses were seen in three patients with liver metastases, in two patients with pulmonary metastases and in two patients with lymphadenopathy. One previously untreated patient with lymph node metastases achieved a CR after five courses, which has been lasting for 15 months. In another chemonaive patient, a CR of liver metastases was observed after six courses, while bone metastases stayed stable. The remission has been lasting for 23 months to present. Treatment was first line in three responders, while two patients had received three prior palliative chemotherapies. Four responders had failed prior hormonal therapy.

The median time to progression was 6.3 months overall (range 2-23+) and 11.2 months for patients responding to treatment. Two of the four partial responders remain alive. The median survival duration for all 20 patients at the time of data analysis was 51.9 months (range 11-152+).

Table 2. Overall response

	CR	PR	NC	PD
No. of patients (n=20)	1	4	6	9
%	5	20	30	45

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

Table 3. Maximum individual toxicity (20 patients)

	WHO grade				
	0	1	2	3	4
Hematologic toxicity					
leukopenia	4 (20)	7 (35)	6 (30)	3 (15)	0 (0)
thrombocytopenia	14 (70)	3 (15)	3 (15)	0 (0)	0 (0)
anemia	15 (75)	4 (20)	1 (5)	0 (0)	0 (0)
Non-hematologic toxicity					
hepatic					
ALT	13 (65)	2 (10)	2 (10)	3 (15)	0 (0)
AST	12 (60)	3 (15)	2 (10)	3 (15)	0 (0)
GGT	15 (75)	2 (10)	1 (5)	2 (10)	0 (0)
AP	17 (85)	2 (10)	1 (5)	0 (0)	0 (0)
renal					
creatinine	20 (100)	0 (0)	0 (0)	0 (0)	0 (0)
hematuria	20 (100)	0 (0)	0 (0)	0 (0)	0 (0)
proteinuria	19 (95)	1 (5)	0 (0)	0 (0)	0 (0)
skin rash	17 (85)	2 (15)	0 (0)	0 (0)	0 (0)
fever/flu-like symptoms	18 (90)	1 (5)	1 (5)	0 (0)	0 (0)
asthenia/fatigue	13 (65)	5 (25)	2 (10)	0 (0)	0 (0)
edema	17 (85)	2 (10)	1 (5)	0 (0)	0 (0)
pulmonary	20 (100)	0 (0)	0 (0)	0 (0)	0 (0)
nausea/vomiting	11 (55)	6 (30)	1 (5)	2 (10)	0 (0)
peripheral neuropathia	20 (100)	0 (0)	0 (0)	0 (0)	0 (0)
constipation	18 (90)	2 (10)	0 (0)	0 (0)	0 (0)
alopecia	10 (50)	6 (30)	3 (15)	1 (5)	0 (0)
cutaneous	17 (85)	2 (10)	1 (5)	0 (0)	0 (0)
infection	18 (90)	2 (10)	0 (0)	0 (0)	0 (0)

Percentages in parentheses.

Toxicity profile

The treatment was generally well tolerated. Toxicities are listed in Table 3 using the worst toxicity on study for individual patients. The cumulative toxicities are shown in Table 4.

Myelosuppression was mild with neutropenia being the principal hematologic toxicity. In a total of 78 courses, only three episodes of grade 3 and no grade 4 neutropenia occurred. Granulocytopenia resolved rapidly. An episode of febrile neutropenia was not observed. Thrombocytopenia was mild with no grade 3 or 4 episode at all dose levels. Dose reductions due to delayed hematological recovery were required in 25 episodes (10.5%).

The most common non-hematologic toxicity were nausea, vomiting and elevation of the hepatic enzymes. The majority were of mild to moderate intensity. Grade 4 toxicities were not recorded. Elevation of transaminases was the predominant non-hematologic toxicity, observed in eight patients and graded as severe in three patients. This side effect tended to occur earlier and with an increased intensity after higher cumulative doses. Hepatotoxicity resolved rapidly in all patients after discontinuation of the treatment and was clinically not significant.

Mild to moderate nausea and vomiting (grade 1 and 2) were reported in seven patients. Two patients developed grade 3 nausea and vomiting despite prophylactic administration of parenteral antiemetics. However, nausea and vomiting remained under control with a combination of 5-HT_3 antiemetics and corticosteroids. Mild constipation (grade 1) was observed in two patients, but might be related to the prophylactic administration of 5-HT_3 antiemetics. Other non-hematologic toxicities were uncommon. Alopecia of mild to moderate degree was observed in half of the patients and mild to moderate asthenia occurred in seven patients. Transient flu-like symptoms, which included fevers, myalgias, arthralgias, headaches or fatigue, affected two patients. Hypersensitivity reactions were not observed.

Discussion

Gemcitabine is an interesting agent for the treatment of metastatic breast cancer. Studies with gemcitabine

Table 4. Cumulative toxicity (78 courses)

	WHO grade				
	0	1	2	3	4
Hematologic toxicity					
leukopenia	26 (33)	29 (37)	20 (26)	3 (4)	0 (0)
thrombocytopenia	66 (84)	9 (12)	3 (4)	0 (0)	0 (0)
anemia	65 (83)	10 (13)	3 (4)	0 (0)	0 (0)
Non-hematologic toxicity					
hepatic					
ALT	41 (53)	15 (19)	14 (18)	8 (10)	0 (0)
AST	43 (55)	14 (18)	13 (17)	8 (10)	0 (0)
GGT	37 (47)	21 (27)	14 (18)	6 (8)	0 (0)
AP	71 (91)	5 (6)	2 (3)	0 (0)	0 (0)
renal					
creatinine	78 (100)	0 (0)	0 (0)	0 (0)	0 (0)
hematuria	78 (100)	0 (0)	0 (0)	0 (0)	0 (0)
proteinuria	75 (96)	3 (4)	0 (0)	0 (0)	0 (0)
skin rash	70 (90)	8 (10)	0 (0)	0 (0)	0 (0)
fever/flu-like symptoms	73 (93)	2 (3)	3 (4)	0 (0)	0 (0)
asthenia/fatigue	59 (76)	12 (15)	7 (9)	0 (0)	0 (0)
edema	72 (92)	4 (5)	2 (3)	0 (0)	0 (0)
pulmonary	78 (100)	0 (0)	0 (0)	0 (0)	0 (0)
nausea/vomiting	47 (60)	22 (28)	6 (8)	3 (4)	0 (0)
peripheral neuropathia	78 (100)	0 (0)	0 (0)	0 (0)	0 (0)
constipation	71 (91)	7 (9)	0 (0)	0 (0)	0 (0)
alopecia	42 (54)	26 (33)	8 (10)	2 (3)	0 (0)
cutaneous	73 (93)	3 (4)	2 (3)	0 (0)	0 (0)
infection	74 (95)	4 (5)	0 (0)	0 (0)	0 (0)

Percentages in parentheses.

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%.[18] At this schedule, gemcitabine is extremely well tolerated, even in heavily pretreated patients, and can easily be administered on an outpatient basis. The adverse events typically experienced with cytotoxic agents, i.e. myelosuppression, nausea and vomiting, and alopecia, are not seen to such a degree with gemcitabine, and this non-overlapping toxicity profile suggests that gemcitabine is a promising agent for combination chemotherapy regimens.

When administered as short-time infusion, the most common toxicity of gemcitabine is mild and short-lived myelosuppression.[19] Dose-dependant elevations of transaminases are frequently observed, but they are usually mild and rarely dose limiting. Mild proteinuria and haematuria 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 displays 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 dependant on the schedule. In phase I studies with more frequent administration, non-hematologic toxicity was more apparent.[20,21]

The presented trial confirms the data of our previous phase I study, showing that 250 mg/m^2 gemcitabine can be safely administered as a 6 h infusion with surprisingly mild myelosuppression and non-hematologic toxicity. Both the short-time and the prolonged infusion have a very similar and favorable toxicity profile. The predominant non-hematologic toxicity after the 6 h infusion was a rapidly reversible, mild to moderate elevation of the liver transaminases recorded in 40% of the patients. In comparison, Tonato *et al.* reported transaminase elevations in 65% of patients after short-time infusions of gemcitabine with approximately 10% being grade 3 or 4. Thus, hepatoxicity appears not to be increased after prolonged application of gemcitabine. Myelosuppression and especially thrombocytopenia was mild, and seems to be even lower then previously reported for short-time infusions. In conclusion, toxicity of the 6 h infusion was extremely low and comparable to that reported for short-time infusions.

With an overall response rate of 25%, this regimen showed, at doses far below the dosage commonly used, equivalent activity even in heavily pretreated patients, compared with other studies using short-time infusions of gemcitabine. This means that the required amount of gemcitabine and hence the costs of the treatment can be markedly reduced by simply prolonging the infusion time.

Due to its resonable single-agent activity, its novel mode of action and its modest toxicity profile, gemcitabine is an ideal candidate for combination with other cytotoxic drugs. Previous combination chemotherapies including docetaxel,[22,23] paclitaxel,[24] epirubicin,[25,26] doxorubicin[27] or cisplatin[28] showed sustained antitumor activity. However, since gemcitabine appears to cause a lower degree of thrombocytopenia when given over 6 h, it might be more favorable for combination chemotherapies compared with short-time infusions. Thus, the prolonged application could offer the chance of increasing the dosages with a potential higher efficacy. Furthermore new combinations and new indications might be developed.

Conclusion

In conclusion, gemcitabine administered as 6 h infusion on days 1, 8 and 15 every 4 weeks is an effective treatment in metastatic breast cancer. In view of the substantial antineoplastic activity even in heavily pretreated patients and the low toxicity, this regimen warrants further investigation. The favorable toxicity profile and the novel mode of action suggest the combination with other cytotoxic drugs.

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