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Research paper

Phase II study of gemcitabine as first-line chemotherapy in patients with advanced or metastatic breast cancer

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In this phase II study, the efficacy and tolerability of gemcitabine were studied in 42 patients with locally advanced or metastatic breast cancer who had received up to one prior chemotherapy regimen in an adjuvant setting. Ten patients had received adjuvant chemotherapy. Twenty-eight patients (67%) had visceral disease spread at entry. Gemcitabine (1000 mg/m^2) was administered weekly on days 1, 8 and 15 of a 28-day cycle. The mean number of completed cycles was 3.9 and the mean dose delivered was 942.2 mg/m^2. Ninety-seven percent of injections were administered as assigned. No complete responses were observed, but there were six partial responses and 24 patients with stable disease lasting 2–9 months. The overall response rate was 14.3% (95% CI 5.4–28.5%). The median survival for all patients was 15.2 months. Maximum WHO grade 3 and 4 toxicities were observed in five patients for nausea and vomiting, one patient for diarrhea, one patient for pain, seven patients for alanine transaminase, and eight patients for segmented neutrophils. There were no grade 3 and 4 toxicities for alopecia. These data confirm modest single-agent gemcitabine activity in advanced or metastatic breast cancer. Gemcitabine's favorable toxicity profile makes it an ideal candidate for combination chemotherapy. [© 1999 Lippincott Williams & Wilkins.]

Key words: Advanced breast cancer, first-line therapy, gemcitabine.

Introduction

Advanced or metastatic breast cancer is usually not cured by current treatment modalities and most patients have a severely shortened life expectancy. In such advanced disease, the primary goal of treatment is a palliation of the symptoms. Any prolongation of survival is considered to be a significant additional benefit. Many cytotoxics like carboplatin, doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil (5-FU), mitomycin C and mitoxantrone have been used either as single agents, or more frequently in combination,[1] for the treatment of breast cancer. In recent years, two important new drugs have emerged for the treatment of breast cancer, i.e. paclitaxel[2] and epirubicin,[3] whilst another, docetaxel, is currently under clinical investigation. However, for all the above agents, the main concerns of the therapists remain their relatively high toxicity profiles in a palliative setting. In contrast, the new nucleoside analog gemcitabine (gemcitabine-HCl) has demonstrated significant antitumor activity across a wide range of tumors,[4–13] and combines therapeutic efficacy with low systemic toxicity and high patient tolerability.[14,15] Of particular significance for female breast cancer patients is the almost complete absence of alopecia associated with gemcitabine.

The present study was performed to determine the objective response rate [complete response (CR) and partial response (PR)] and toxicity profile of weekly single-agent gemcitabine at a dose of 1000 mg/m^2 in patients with advanced or metastatic disease. Patients were only included in this study if they had received no prior chemotherapy for metastatic disease. Patients could have received one previous chemotherapy regimen which had been administered in an adjuvant setting, but this must have been

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completed at least 12 months before enrollment in the study.

Patients and methods

Study design

This was an open-label, non-randomized, multi-center, phase II study conducted in centers in England, Wales, Germany and Sweden. The study was conducted according to the guidelines for Good Clinical Practice and approved by each of the local ethical committees. A total of 42 patients from six centers were enrolled into the study. Patients were enrolled into the study in a two-stage sequence, to allow for early discontinuation of the study, if no evidence of activity was seen in the first cohort of 20 patients.

Patients with histologically or cytologically diagnosed advanced or metastatic breast cancer were enrolled into the study according to the following inclusion and exclusion criteria. Patients were included if they had documented evidence of progressive disease; had received up to one previous chemotherapy regimen administered in an adjuvant setting which must have been completed at least 12 months before enrollment; had bidimensionally measurable disease; had a life expectancy of at least 3 months; a Karnofsky performance status of greater than 60 and adequate bone marrow reserves. Patients were excluded if they had received tamoxifen or other endocrine therapy in the last 4 weeks; had received extensive radiotherapy in the last 4 weeks or had received radiotherapy in which the field included the only measurable disease; had hypercalcemia; bony lesions as the only evidence of disease or CNS involvement; had inadequate liver or renal function or an active infection, a second malignancy or other serious concomitant medical disorder.

Therapy schedule

Gemcitabine was administered on an outpatient basis as a 30 min i.v. infusion on days 1, 8 and 15 of a 28-day cycle, at a dose of 1000 mg/m^2. This 4 week cycle defined one course of chemotherapy. At least two therapy cycles were to be given unless this was clearly not in the patient's best interests. Dose modifications were made based on blood counts before infusion. The dosing schedule remained fixed and any doses that could not be given on time were not administered. Patients who had completed one cycle of therapy at 1000 mg/m^2 could have their dose in subsequent cycles increased to 1250 mg/m^2, provided that no significant hematologic and non-hematologic toxicity was observed.

Patient monitoring

Patients were assessed no more than 1 week before entering the study for their complete blood count (CBC) including differential and platelet counts, their blood chemistries (creatinine, blood urea nitrogen, bilirubin, alkaline phosphatase, alanine transaminase, aspartate transaminase, glucose, electrolytes, calcium, total protein and uric acid), and their vital signs (blood pressure and pulse rate) including weight measurements. Urine analyses and electrocardiograms were also performed, and an echocardiograph was performed if the patient had a history of cardiac failure or hypertension. Performance status was assessed for all patients.

During therapy, patients were assessed for the number of units required for transfusions during each cycle, and before each dose of gemcitabine for their CBC and blood chemistries. Dose modifications were based on blood counts taken before infusion. White blood cell (WBC) >2000 and platelets $>100\,000$ =100% of dose, WBC >1000–1900 and platelets 50 000–99 000=75% of dose and WBC <1000 and platelets $<50\,000$=no dose. Urine analyses and coagulation studies were also performed before each cycle. Toxicities were assessed using the WHO rating scale, and blood pressures and pulse rates were assessed weekly except during the rest week. Patients were questioned at follow-up visits about the occurrence and nature of any adverse events. Quality of life was assessed in this study with the EORTC QLQ-C30 (version 1.0), which measures functional scales (i.e. physical, role, cognitive, emotional, social and global) and symptom scales (e.g. fatigue, nausea/vomiting, pain and dyspnea).[16] The QLQ-C30 was self-administered at baseline and at the end of each cycle.

Efficacy measures were performed by radiologic imaging tests every other therapy cycle using the baseline method throughout the study. Standard WHO definitions were used. There was no review of the responders by independent experts.

Statistics

Confidence intervals were computed for the response rate using the exact binomial method at the 0.05 level. Medians and other quartiles were computed using the Kaplan–Meier method. Efron's bootstrap method[17]

was used for determining confidence intervals for the median at the 0.05 level.

Results

Of the 42 patients enrolled in the study, all fulfilled the primary efficacy qualification criteria. The characteristics for all 42 patients (Table 1) were typical of patients with advanced breast disease. The most common sites of metastatic disease were liver (36% of assessable patients), lung (36% of assessable patients) and lymph nodes of the supraclavicular fossa (17% of assessable patients). In total, 67% of patients presented with visceral disease. All patients had bidimensionally measurable disease. The median time from initial diagnosis to treatment was 48.2 months (range 8.1-231.3 months). In keeping with the conventional treatment of breast cancer, the majority of patients had received prior surgery, radiotherapy and hormonal therapy (Table 2). Ten out of the 42 patients had received prior chemotherapy in the adjuvant setting.

Table 1. Patient characteristics

Characteristics	No.	%
No. patients enrolled	42	
Age (years)		
median	58	
range	28–75	
Performance status		
70	5	11.9
80	9	21.4
90	8	19.0
100	20	47.5
Menopausal status		
pre-menopausal	2	4.8
menopausal	1	2.4
post-menopausal	39	92.9
Histology		
breast cancer (not specify)	4	9.5
ductal breast cancer	31	73.8
lobular breast cancer	7	16.7
Differentiation		
well	3	7.1
moderately	15	35.7
poorly	10	23.8
undifferentiated	2	4.8
unknown	12	28.6
Spread		
recurrent	2	4.8
metastatic	40	95.2
No. sites of disease		
1	16	38.1
2	18	42.9
3	5	11.9
4	2	4.8
5	1	2.4
Estrogen receptor status		
positive	9	21.4
negative	11	26.2
unknown	22	52.4

Table 2. Prior therapy

Therapy type	No.	%
Prior surgery	41	97.6
Prior radiotherapy	27	64.3
Prior chemotherapy	10	24.0
Prior hormonal therapy		
1 therapy	18	43.0
2 therapies	9	21.4
3 therapies	4	9.5
4 therapies	1	2.4
Total	32	76.0

Table 3. Summary of dose administration

Summary of administered injections	
no. injections given	478
no. potential injections	492
% injections given	97.2
Dose omissions	
thrombocytopenia	7
leucopenia	1
pain	1
abnormal vision	1
patient decision	1
social	3
total	14 (2.8%)
Dose delays	
flu syndrome	1
coagulation disorder	1
leucopenia	1
social	6
other	1
total	10 (2.0%)
Dose reductions	
thrombocytopenia	17
leucopenia	1
asthenia	2
anemia	1
anaphylaxis	1
other	15
rash	6
total	43 (8.7%)
Dose escalations	9 (1.8%)

Dose administrations

A total of 97% (478 of 492) infusions were administered as assigned. Fourteen doses (3%) were omitted principally due to thrombocytopenia (Table 3). There were 43 (9%) dose reductions which were also frequently due to thrombocytopenia (17 incidences) and, in one patient, there were six dose reductions due to a cutaneous rash. One patient received escalated doses (nine infusions) at 1250 mg/m^2. The mean number of completed cycles was 3.9 (median 4.0, range 0-8.0). The mean dose delivered was 942.2 mg/m^2, range 70-1319 mg/m^2 (median 994.0 mg/m^2).

Efficacy

Of the 42 assessable patients, no patient achieved a complete response, but six achieved a partial response to give an overall response rate of 14.3% (95% CI 5.4-28.5%). Twenty-four patients demonstrated stable disease lasting 2-9 months and 10 had progressive disease (Table 4). For two patients there were no follow-up scans because they discontinued due to toxicity.

Table 4. Summary of tumor response data for gemcitabine (n=42)

Type of response	No.	%
Complete response	0	0
Partial response	6	14.3
Stable disease	24	57.1
Progressive disease	10	23.8
Not assessed	2	4.8
Total no. of responders	6	14.3

Details of responders

There was no correlation between site of secondary disease and partial response (Table 5). Similarly, no correlation could be made between prior adjuvant chemotherapy and partial response. Two of the six patients (Table 5) had received prior adjuvant chemotherapy and four had not. All but two of the six patients had received and failed prior hormonal therapy, and three had received prior radiotherapy. There was no correlation between partial response and tumor histology or Karnofsky performance status (data not shown).

Median duration of response

The median time to partial response was 1.9 months for the six responders (range 1.9-2.8 months). The median time to progressive disease for all patients (n=42) was 3.8 months (range 0.9-13.6 months). The median time to progressive disease for responders was 5.6 months (range 4.3-13.6 months). The median survival for all patients was 15.2 months (range 1.6-$\geqslant$30.8 months). Of the responding patients all six were alive at $\geqslant$12 months and one patient was alive at $\geqslant$30 months (see Table 5). The median survival for the 24 patients with stable disease was 13.6 months (range 2.9-25.5 months).

Toxicity profile

Treatment was generally well tolerated with only two patients not re-evaluated due to early discontinuation. Maximum WHO symptomatic toxicity grades 3 or 4 were only seen in six patients for nausea and

Table 5. Summary of characteristics of responders

Patient	Prior adjuvant chemotherapy	No. of cycles	Prior hormonal therapy	Prior radiotherapy	Sites of secondary disease	Duration of response (months)	Survival (months)
						3.9	
32	N	5	Y	Y	chest/node	5.6	$\geqslant$30.8
36	CMF	6	N	N	node/spleen lung/liver	6.3	$\geqslant$23.5
39	N	7	Y	N	soft tissue/node	5.6	$\geqslant$26.1
5	N	4	Y	Y	chest/axilla	6.4	$\geqslant$23.6
64	CMF	6	Y	N	node/skin	13.6	$\geqslant$23.1
2	N	4	N	Y	breast	5.943	13.8

Median duration of response (range)=5.6 (4.3-13.6) months.
CMF=Cyclophosphamide/methotrexate/5-fluorouracil.

vomiting, one patient for diarrhea, and one patient for pain (Table 6). Maximum WHO grade 3 or 4 laboratory toxicities were seen in eight patients for alanine transaminase, eight patients for segmented neutrophils, five patients for WBC and two patients for platelets (Table 7). Only two patients needed one or more transfusions. As stated previously, there were 43 dose reductions and 14 dose omissions out of 492 doses. Only six patients were hospitalized during the study due to adverse events such as anemia (two patients), dyspnea (one patient), liver toxicity (one patient), thrombocytopenia (one patient) and collapse (one patient). There were 10 dose delays (Table 3).

Quality of life

Thirty-nine of the 42 patients completed at least one questionnaire (median 4, range 1-8). Patients were included in the analysis if they completed a baseline and at least one post-baseline questionnaire; 34 patients met this criteria. The analysis was performed by comparing the mean score of the last observation (end-point) to baseline using a non-parametric paired *t*-test. Mean scores of functional scales and select symptom scales are reported in Table 8.

Overall, patients noted worsening of physical, role and social functioning, but the changes were only statistically significant for physical and role function-

Table 6. Maximum WHO toxicity grades for symptomatic toxicity

Toxicity parameter	Maximum WHO grade (% of patients) (*n*=41)				
	0	1	2	3	4
Allergic	92.7	2.4	4.9	0.0	0.0
Constipation	75.6	17.1	7.3	0.0	0.0
Cutaneous	68.3	22.0	9.8	0.0	0.0
Diarrhea	87.8	9.8	0.0	2.4	0.0
Fever	85.4	2.4	12.2	0.0	0.0
Cardiac function	100.0	0.0	0.0	0.0	0.0
Hair	73.2	22.0	4.9	0.0	0.0
Hemorrhage	95.1	0.0	4.9	0.0	0.0
Infection	85.4	12.2	2.4	0.0	0.0
Nausea/vomiting	14.6	41.5	29.3	12.2	2.4
Oral	82.9	17.1	0.0	0.0	0.0
Pain	82.9	9.8	4.9	2.4	0.0
Pericarditis	100.0	0.0	0.0	0.0	0.0
Peripheral neurotoxicity	92.7	7.3	0.0	0.0	0.0
Pulmonary	85.4	9.8	4.9	0.0	0.0
Cardiac rhythm	97.6	2.4	0.0	0.0	0.0
State of consciousness	82.9	14.6	2.4	0.0	0.0

Table 7. Maximum WHO toxicity for laboratory data

Toxicity parameter	No. of patients with data	Maximum WHO grade (% of patients) (*n*=41)				
		0	1	2	3	4
Alkaline phosphatase	42	57.1	33.3	7.1	2.4	0.0
Alanine transaminase	42	23.8	31.0	26.2	16.7	2.4
Aspartate transaminase	42	21.4	47.6	26.2	4.8	0.0
Bilirubin	41	100.0	0.0	0.0	0.0	0.0
Blood urea nitrogen	42	97.6	2.4	0.0	0.0	0.0
Creatinine	42	100.0	0.0	0.0	0.0	0.0
Hemoglobin	42	38.1	47.6	14.3	0.0	0.0
White blood cells	42	28.6	28.6	31.0	11.9	0.0
Segmented neutrophils	41	39.0	14.6	26.8	14.6	4.9
Platelets	42	78.6	14.3	2.4	4.8	0.0

Table 8. Mean EORTC QLC-C30 scores (SD)

	All patients		Responders	
	Baseline	End-point	Baseline	All patients
Functional scales (0–100; 100=perfect functioning)				
physical	77.5 (22.0)	63.0 (25.9)[a]	70.0 (30.3)	76.7 (15.1)
role	75.0 (31.1)	56.3 (33.0)[a]	66.7 (40.8)	50.0 (31.6)
cognitive	88.5 (16.6)	88.5 (17.7)	83.3 (21.1)	88.9 (20.2)
emotional	63.0 (22.2)	66.9 (24.1)	47.2 (18.8)	62.5 (18.8)
social	78.6 (28.2)	70.3 (29.2)	61.1 (44.3)	63.9 (40.0)
global QoL	54.7 (19.6)	54.4 (20.3)	48.6 (11.1)	61.1 (13.6)
Symptom scales (0–100; 0=no symptoms)				
fatigue	36.2 (22.4)	46.6 (22.1)[a]	40.7 (15.2)	42.6 (27.6)
nausea/vomiting	9.7 (15.4)	26.3 (29.1)[a]	0.0 (0.0)	11.1 (17.2)
pain	31.7 (29.0)	29.6 (31.5)	33.3 (35.0)	27.8 (27.2)
dyspnea	28.0 (28.7)	37.6 (34.1)	16.7 (27.9)	16.7 (27.9)
insomnia	40.9 (29.5)	32.3 (31.6)	33.3 (29.8)	33.3 (36.5)
appetite loss	17.2 (32.1)	24.7 (35.5)	16.7 (27.9)	11.1 (27.2)

[a] $p < 0.05$.

ing. Emotional functioning was slightly improved, while cognitive and global quality of life were unchanged. Responders noted improvement in most domains of functioning, especially emotional functioning and global quality of life, but these changes were not statistically significant due to the small number of patients.

Overall, patients noted worsening of most symptoms assessed by the QLQ-C30, but the changes were statistically significant only for fatigue and nausea/vomiting. No statistically significant differences were noted for responders in any of the symptom scales. Breast cancer-specific symptoms could not be assessed with the QLQ-C30; the QLQ-BR23, the EORTC's breast cancer module, was not available at the time this study was initiated.

Discussion

To date, the efficacy data for single-agent gemcitabine in the treatment of advanced or metastatic breast cancer range from no objective response in the first phase II study which took place in the US[11,18] to response rates up to 25–37.1%.[10,19,20] A number of possible reasons for the differences in efficacy reported in the two completed studies have been put forward. These include differences in dose, previous treatment and patient selection. With regard to patient selection, some important variables might include interval from previous chemotherapy, the number of prior chemotherapy regimens and their dose intensity, and the number of sites of metastatic disease. In the US study,[11,12] gemcitabine was given as the second- or third-line treatment for advanced breast cancer with 90% of patients having received prior chemotherapy for metastatic disease and only one patient (5%) having received adjuvant chemotherapy. In the European study,[10] 68% of the patients had received prior chemotherapy for metastatic disease and again only three patients had received adjuvant therapy.

Although the efficacy data from the present study are less impressive, with an overall response rate of only 14%, they confirm that gemcitabine does have single-agent activity in advanced breast cancer and this was associated with a median survival of 15.2 months for all patients and a median survival time of 23.5 months (range 13.8–$\geqslant$30.8 months) for responders. These survival data compare favorably with those from other regimens[21] and may be a consequence of the large number of patients in this study (57%) with stable disease (Table 4). The median time to relapse for patients with stable disease was 3.8 months (range 2.3–9.4 months) with 18 patients surviving more than 6 months and a median survival time of 13.6 months. The resulted efficacy may be a consequence of the fact that 76% of patients in the present study had received prior hormonal therapy with 33% of the total patient population having received more than one type of hormonal therapy (Table 2) and thus had disease that had progressed during therapy. There were no sites of metastasis or prior treatment strategies that were predictive of response. Another explanation for the activity might be the gemcitabine dosage chosen for this study. Gemcitabine was administered as a weekly

30 min infusion at a dose of 1000 mg/m^2. Only one patient receivd 1250 mg/m^2. The results of ongoing studies using higher dosages of gemcitabine will indicate whether a dose escalation might increase the efficacy of gemcitabine monotherapy in this category of patients.

In contrast to the studies with other agents like paclitaxel,[2,22] the toxicity profile was favorable (Tables 6 and 7) and quality of life was not affected by gemcitabine (Table 8). The mean dose achieved in the present study was 942 mg/m^2 from a starting dose of 1000 mg/m^2, with only 43 (9%) dose reductions and only 14 (3%) dose omissions principally due to thrombocytopenia. Only six (14.3%) patients experienced WHO grades 3 and 4 for nausea and vomiting. No patient experienced grade 3 or 4 alopecia. Although the gemcitabine dose in the previous European study[9] had been only 738 mg/m^2, gemcitabine had been the second- or third-line treatment for some patients. Moreover, only 50% of patients had visceral (lung and liver) disease. In contrast, the present patient group was more homogeneous. None of the patients in the present study had received any form of prior chemotherapy for metastatic disease, only 21% had received adjuvant chemotherapy and patient prognosis was already poor at enrollment with 67% of patients having visceral (lung and liver) disease. Two other studies nearing completion[19,20] have confirmed the initial efficacy of single-agent gemcitabine in the treatment of advanced breast cancer, with preliminary response rates of 27% (all anthracycline pretreated) and 36% (no prior treatment for metastatic disease). The higher of these two response rates was achieved in the study in which a higher proportion of the patients had received adjuvant chemotherapy than in any other study, including the present one.[19]

Consistent with these observations of single-agent activity in advanced breast cancer are some of the high response rates reported as preliminary observations from phase II studies of gemcitabine given in combination with doxorubicin[23] and taxol[24] of 68.4 and 41%, respectively, for the treatment of advanced and metastatic breast cancer.

In conclusion, the results from the present study confirm that gemcitabine is active in first-line treatment for metastatic breast cancer, including those patients with poor prognostic factors. The discrepancy between a modest response rate and the enhanced survival, a trend that has been observed in other gemcitabine studies, may indicate a different mode of action. The combination of an active drug with a very favorable toxicity profile and a novel mechanism of action makes it a particularly attractive candidate for use in combination with other agents for the treatment of breast cancer. Thus, gemcitabine warrants further exploration in the treatment of breast cancer.

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