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An EORTC-IDBBC phase I study of gemcitabine and continuous infusion 5-fluorouracil in patients with metastatic breast cancer resistant to anthracyclines or pre-treated with both anthracyclines and taxanes

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Abstract

The aim of this study was to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), and potential activity of combined gemcitabine and continuous infusion 5-fluorouracil (5-FU) in metastatic breast cancer (MBC) patients that are resistant to anthracyclines or have been pretreated with both anthracyclines and taxanes. 15 patients with MBC were studied at three European Organization for Research and Treatment of Cancer centres. 13 patients had received both anthracylines and taxanes. Gemcitabine was given intravenously (i.v.) on days 1 and 8, and 5-FU as a continuous i.v. infusion on days 1 through to 14, both drugs given in a 21-day schedule at four different dose levels. Both were given at doses commonly used for the single agents for the last dose level (dose level 4). One of 6 patients at level 4 (gemcitabine 1200 mg/m^2 and 5-FU 250 mg/m^2/day) had a DLT, a grade 3 stomatitis and skin toxicity. One DLT, a grade 3 transaminase rise and thrombosis, occurred in a patient at level 2 (gemcitabine 1000 mg/m^2 and 5-FU 200 mg/m^2/day). Thus, the MTD was not reached. One partial response and four disease stabilisations were observed. Only 1 patient withdrew from the treatment due to toxicity. The MTD was not reached in the phase I study. The combination of gemcitabine and 5-FU is well tolerated at doses up to 1200 mg/m^2 given on days 1 and 8 and 250 mg/m^2/day given on days 1 through to 14, respectively, every 21 days. The clinical benefit rate (responses plus no change of at least 6 months) was 33% with one partial response, suggesting that MBC patients with prior anthracycline and taxane therapy may derive significant benefit from this combination with minimal toxicity.

Keywords: Anthracycline and taxane pre-treated; Combination chemotherapy; Metastatic breast cancer

1. Introduction

There are few chemotherapy options available to patients with metastatic breast cancer (MBC) who have already received anthracyclines and taxanes. There are no published phase III trials in this population and phase II trials have reported response rates of 20 and 24% for capecitabine (2510 mg/m^2/day) in two trials of 162 and 75 patients, respectively [1,2], 18% with docetaxel (after paclitaxel; $n=44$) [3], 0% for vinorelbine ($n=14$) [4], 25% for high-dose vinorelbine (30–35 mg/m^2/week) with growth colony stimulating factor (G-CSF) ($n=40$) [5], and 12% for continuous infusion 5-fluorouracil (5-FU) ($n=35$; retrospective study) [6]. Gemcitabine is a nucleoside analogue that causes premature DNA chain termination. The single agent activity of gemcitabine reported in phase II MBC trials is 15–45%, depending on the prior therapy received [7–10].

Patients become less able to tolerate chemotherapy-associated toxicity, particularly haematological, with

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progressively greater lines of prior chemotherapy and greater disease burden, often making combination chemotherapy difficult to give. Although it has not been shown to improve overall survival compared with sequential monotherapy in MBC [11], combination chemotherapy is recommended in women with visceral or debilitating disease, in order to achieve a more rapid response.

Both 5-FU and gemcitabine are relatively well tolerated when given as monotherapy, and they have different toxicity profiles and mechanisms of action. The major toxicities observed with continuous infusion 5-FU are diarrhoea and, particularly with protracted use, hand–foot syndrome. Gemcitabine given as a single agent has a relatively modest haematological toxicity (leucopenia and thrombocytopenia) and low non-haematological toxicity (chiefly fatigue). Synergistic antitumour activity has been observed *in vitro* when colon cancer cells were treated with the combination of gemcitabine and 5-FU [12]. These features make exploration of the two drugs in combination a reasonable strategy to try to improve their individual efficacies. Based on this rationale, a phase I trial was designed and carried out between December 1998 and July 1999 at three European Organization for Research and Treatment of Cancer (EORTC) Investigational Drug Branch for Breast Cancer (IDBBC) centres in order to explore the optimal dose and schedule of combined gemcitabine and 5-FU in pretreated MBC patients.

2. Patients and methods

2.1. Eligibility

Patients with histologically-confirmed adencarcinoma of the breast and evidence of metastatic disease were eligible for this phase I study, provided that they were anthracycline-resistant or pretreated with both anthracyclines and taxanes in either the adjuvant or metastatic settings (or both). Anthracycline resistance was defined as either a disease-free interval from the end of adjuvant anthracyclines of <12 months, or a disease stabilisation of <6 months or disease progression as the best response to anthracycline treatment for metastatic disease. Other eligibility criteria included a Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, age >18 years, a maximum of two prior lines of chemotherapy for metastatic disease, adequate haematological function (granulocyte count $>2\times10^9$ cells/l, and platelet count $>100\times10^9$ cells/l), adequate renal function (serum creatinine $\leqslant1.5\times$ the upper limit of normal (ULN)), adequate hepatic function (bilirubin $\leqslant2\times$ the ULN and transaminases $\leqslant2\times$ the ULN). Patients who were pregnant or breast feeding, had had a myocardial infarction or angina pectoris within the previous 6 months, or who had prior therapy with continuous infusion 5-FU or gemcitabine were not eligible. The study protocol was approved by local ethics committees, and all study procedures were in accordance with the Helsinki declaration of the World Medical Association. All patients provided written informed consent to participate in the study.

Complete history and physical examination were performed in all patients prior to treatment start. Height, weight and performance status were recorded. The extent of disease, including measurements for target lesions in patients with measurable disease, was evaluated by physical examination, chest imaging (radiographs plus or minus computerised axial tomography (CAT) scans), abdominal imaging (ultrasound plus or minus CAT scan), and bone imaging studies (bone scan and complimentary radiographs of areas that were suspicious for metastases on bone scan). Other tests were not mandatory, but performed according to clinical suspicion. Patients were recruited at three centres, in Brussels (Belgium), Ljubljana (Slovenia) and Nijmegen (The Netherlands). The data was collected on standard case report forms and analysed at the EORTC-IDBBC Data Center.

2.2. Drug dosage

Gemcitabine and 5-FU were given in combination at four dose levels as summarised in Table 1. Gemcitabine was diluted to a volume of 500 ml of physiological fluid and administered as a 30-min infusion on days 1 and 8 every 21 days with antiemetics such as intravenous (i.v.) metoclopramide. 5-FU was given as a continuous infusion over 14 days beginning with day 1 of the gemcitabine infusion and was to be continued during the day 8 gemcitabine administration, unless there was significant toxicity. Both drugs were given on a 21-day cycle, with no maximum number of cycles being forseen. Daily prophylactic anti-fungal mouth rinse was instituted from day 1 of cycle 1. Prophylactic G-CSFs and antibiotics were not allowed, even after an episode of grade 4 neutropenia or febrile neutropenia.

A minimum of 3 patients were treated at each level: if no dose-limiting toxicity (DLT) was observed in the first cycle of therapy, patients could then be treated at the

Table 1
Dose levels for gemcitabine and 5-fluorouracil given in combination

Dose level	Gemcitabine dose (mg/m^2 days 1 and 8 every 21 days)	5-fluorouracil dose (mg/m^2/day, days 1–14 every 21 days)	Patients treated (n)
1	800	200	3
2	1000	200	3
3	1000	250	3
4	1200	250	6

next level. A DLT was defined as any grade 4 neutropenia lasting 7 days or longer, grade 4 thrombocytopenia, complicated grade 3 or 4 haematological toxicity (such as bleeding or febrile neutropenia, defined as a temperature of $\geqslant 38.5$ °C and absolute neutrophil count $< 1.0 \times 10^9$/l), or grade 3 or 4 non-haematological toxicity, excluding vomiting and alopecia, using the Common Toxicity Criteria (CTC) version 2.0 to grade the toxicities. If a DLT was observed at any level during the first cycle of therapy, the number of patients treated at that level was expanded to 6. Two or more DLTs occurring among 6 patients in the first cycle within a dose level was considered evidence of excessive toxicity. The study was to be terminated at this point and the dose level immediately below that was to be declared the maximum tolerated dose (MTD) and the recommended dose for phase II and further studies.

2.3. Safety

Toxicity was assessed for each patient prior to each cycle of therapy and prior to the day 8 gemcitabine delivery. In addition, a physical examination and blood sampling for complete blood count, coagulation parameters and biochemistry were performed at the beginning of each cycle. A complete blood count was repeated at days 8, 15 and 21, and biochemistry at day 15 of each cycle. Patients who experienced a DLT could continue on therapy provided that the doses of both drugs were reduced to the doses in the previous level (to 75% of the starting dose if a DLT occurred at level 1). Patients had to discontinue therapy if they experienced disease progression, two episodes of febrile neutropenia, angina pectoris, myocardial infarction, or any other unacceptably severe toxicity, as judged by the treating physician and patient.

2.4. Criteria for response

Re-evaluation of disease was performed every two cycles of therapy using the same imaging and physical examination techniques that were used at baseline. Measurable disease was not required for eligibility. Patients with measurable disease ($n = 11$) were assessed using standard World Health Organization (WHO) criteria to determine response [13]. Patients without measurable lesions were assessed for complete response and progression using the same definitions.

3. Results

3.1. Patient characteristics

15 patients were treated in the study: 3 each at dose levels 1–3, and 6 at dose level 4. Patient characteristics are shown in Table 2. One patient was ineligible because she was neither anthracycline-resistant nor taxane pretreated; however, she did receive the study medications and was included in the analyses of toxicity and activity. The dominant disease site was visceral in 14 patients, and 13 patients had at least two disease sites.

3.2. Drug delivery

Details of the median number of cycles per patient, per cent of planned drug delivered, and number of

Table 2
Patient characteristics

Characteristic	Patients
Median age, years (range)	48 (35–74)
Performance status (*n*)	
0	5
1	8
2	2
Prior local therapy (*n*)	
Surgery	14
Radiotherapy	12
Median disease-free interval,[a] months (range)	29 (0–111)
Prior anthracyclines (*n*)	
Neoadjuvant	1
Adjuvant	4
Metastatic	9
All three	1
Efficacy of anthracyclines (*n*)	
Adjuvant:	
>12 months from end	4
$\leqslant 12$ months from end	1
Metastatic:	
PR as the best response	6
NC $\geqslant 6$ months as the best response	0
NC < 6 months as the best response	3
PD as the best response	1
Neoadjuvant:	
Unknown response	2
Prior taxanes (*n*)	
Adjuvant	1
Metastatic	12
Prior hormone therapy (*n*)	
Adjuvant only	4
Metastatic only	3
Adjuvant and metastatic	2
Dominant disease site (*n*)	
Soft tissue	0
Bone	1
Visceral	11
Multiple visceral	3
Number of disease sites (*n*)	
1	2
2	8
3 or more	5

NC, no change; PD, progressive disease; PR, partial response.
[a] From the end of adjuvant therapy.

Table 3
Drug delivery

Item	Level 1	Level 2	Level 3	Level 4	Total
Patients treated (*n*)	3	3	3	6	15
Number of cycles given	53	15	12	25	105
Median cycles/patient	16	3	2	4	6
Median relative dose intensity (%)					
Gemcitabine	93	84	100	100	–
5-FU	99	99	100	100	–

5-FU, 5-fluorouracil.

patients with dose reductions can be found in Table 3. One patient each in levels 1 and 2 did not receive the day 8 dose of gemcitabine in several cycles due to neutropenia of grades 3 and 4. One patient each in levels 3 and 4 had inadvertent reduction in the 5-FU delivery in one cycle due to pump and central line failures. One patient in level 2 discontinued treatment in mid-cycle 3 due to a decline in general condition. Planned cycle delivery was only delayed in 1 patient, for personal convenience.

3.3. Toxicity

Toxicity was evaluable in all 15 patients. The most frequently reported adverse events are presented in Table 4. Only one patient, who was treated at level 4, discontinued therapy due to toxicity (grade 3 stomatitis and skin toxicity). Grade 3–4 neutropenia occurred in 40% of patients. There were no episodes of febrile neutropenia, and no other grade 3 or 4 haematological toxicities.

Very few grade 3 or 4 non-haematological toxicities occurred. At level 1, there was none. At levels 2–4, there were no grade 4 non-haematological toxicities. Grade 3 toxicities at level 2 (all cycles) were one each of asthenia, thrombosis, increased transaminases and two grade 3 pain. At level three, there was one each of grade 3 asthenia, pain, a rise in transaminases and in gamma glutaryl transferase (GGT), and at level 4, there was one case each of grade 3 stomatitis and skin toxicity (DLT), and a rise in GGT. Only asthenia, pain and a rise in liver enzymes occurred at grade $\geqslant 3$ in more than 10% of the patients. The proportion of patients treated with >5 cycles of chemotherapy ($n=8$) who developed grade 2 and 3 toxicities was not greater than the proportion treated with less than five cycles, suggesting that there was little cumulative toxicity.

Table 4
Most frequently reported adverse events[a]

Dose level	1 ($n=3$)			2 ($n=3$)			3 ($n=3$)			4 ($n=6$)		
Grade	2	3	4	2	3	4	2	3	4	2	3	4
Alopecia	0	0	0	0	0	0	0	0	0	0	0	0
Anorexia	0	0	0	0	0	0	2	0	0	0	0	0
Nausea	2	0	0	0	0	0	1	0	0	4	0	0
Vomiting	1	0	0	0	0	0	1	0	0	2	0	0
Diarrhoea	0	0	0	0	0	0	0	0	0	0	0	0
Constipation	0	0	0	0	0	0	0	0	0	1	0	0
Fever	0	0	0	1	0	0	2	0	0	0	0	0
Stomatitis	0	0	0	0	0	0	0	0	0	1	1	0
PPE	0	0	0	0	0	0	0	0	0	0	0	0
Skin toxicity (non-PPE)	0	0	0	1	0	0	1	0	0	0	1	0
Asthenia	1	0	0	0	1	0	2	1	0	1	0	0
Pain	0	0	0	0	2	0	2	1	0	1	0	0
Thrombosis/central line occlusion	0	0	0	0	1	0	1	0	0	1	0	0
Dyspnoea	0	0	0	2	0	0	2	0	0	1	0	0
Rise in GGT	0	0	0	1	0	0	0	1	0	1	1	0
Rise in transaminases	1	0	0	2	1	0	0	1	0	2	0	0
Neutrophils	1	1	1	0	2	0	1	1	0	2	1	0

PPE, palmer plantar erythrodysesthesia; GGT gamma glutaryl transferase.

[a] Toxicities are expressed as the number of patients experiencing each grade.

3.4. Activity

Among the 15 treated patients, 1 had a confirmed partial response after six cycles and progression after eight cycles at dose level 4. 4 patients had stabilisation of their disease lasting at least 6 months and 3 had less than 6 months of stabilisation. The median duration of stabilisation was 6.74 months (range 1.4–14.9 months). 6 patients had disease progression as the best response to therapy and 1 patient could not be evaluated for response due to discontinuation of treatment after the first cycle (excessive toxicity). Considering responders and the patients with stable disease for at least 6 months, the clinical benefit rate was 33%. The reason for eventual therapy discontinuation was disease progression in 10 patients, suspected progression (increased tumour marker) in 1, excessive toxicity in 1, and other reasons for the other 3 patients (1 due to a general decline in status without obvious progression, and two, after 10 and eight cycles, because it was judged that there was no anticipated benefit in continuing treatment).

4. Discussion

This phase I study found that MBC patients with a disease-free interval of $\leqslant$12 months from adjuvant anthracycline therapy or less than 6 months of disease stabilisation or progression as the best response from metastatic anthracycline therapy, or who were pretreated with both anthracyclines (any response and progression-free interval) and taxanes, were able to tolerate the combination of gemcitabine and 5-FU at doses up to and including commonly used single agent doses. No MTD was reached, however because the single agent doses were reached, further dose escalation was not attempted. One DLT was observed at level 4 among 6 treated patients and one retrospectively at level 2 among 3 patients (a grade 3 transaminase rise and thrombosis). The frequency of grade 3–4 non-haematological toxicities was low and non-cumulative with successive cycles. The incidence of grade 3 and 4 neutropenia was not excessive, considering that all had received prior anthracyclines and most also had received taxanes (13 of 15). Although there was only one response (7%), the clinical benefit rate was reasonably high (33%) given that in this patient population, in addition to receiving prior anthracyclines, almost all had received prior taxanes, had visceral disease and at least two metastatic sites.

Combination chemotherapy is recommended for the treatment of visceral or debilitating disease, in order to achieve a more rapid response. At least one study, in first-line therapy, demonstrated an improved survival with the use of combination chemotherapy, using docetaxel plus capecitabine over docetaxel alone [14]. One hypothesis for this finding is the chronic exposure to cytotoxic drug with this schedule, namely capecitabine; however, this remains to be proven. A survival advantage following combination chemotherapy is most likely to occur in first-line therapy, when the disease burden is lowest and patients tend to have a good performance status and bone marrow reserve. Nevertheless, combinations of non-cross resistant cytotoxic drugs may be of value after first-line chemotherapy, if they are well tolerated and produce durable disease stabilisation, or improve the patient's quality of life.

Studies combining gemcitabine with 5-FU, cisplatin (CDDP), paclitaxel, doxorubicin, vinorelbine and docetaxel in MBC have been reported [15–23]. For patients with no prior chemotherapy for metastatic disease, response rates of 68% were reported for gemcitabine plus paclitaxel [15], 56% for gemcitabine plus vinorelbine [16], and 55% for gemcitabine plus doxorubicin [17]. Phase I–II trials in patients who had received at least one line of chemotherapy for metastatic disease reported response rates of 50% for gemcitabine plus CDDP [18], 22, 40 and 48% for gemcitabine plus vinorelbine [16,19,20], and 36% for gemcitabine plus docetaxel [21]. Haematological toxicity was high when gemcitabine was combined with docetaxel: seven febrile neutropenias; 90% requiring G-CSF in anthracycline-resistant patients. The studies that combined gemcitabine with vinorelbine had relatively low haematological toxicity when the dose intensity was low (48% grade 3 neutropenia using a vinorelbine schedule of 25 mg/m^2 days 1 and 8 every 3 weeks) and when G-CSF was used prophylactically [16,20]. One phase II trial combining gemcitabine and 5-FU has been reported in abstract form [23]. 15 patients who had progressed after both anthracycline and taxane treatment were treated with gemcitabine 2000 mg/m^2 day 1 every 21 days and 5-FU 350 mg/m^2/day by continuous infusion until progression or excess toxicity. The incidence of grade 3–4 palmar plantar erythrodysesthesia (PPE) and stomatitis was greater than in the current study (4 and 5 patients, respectively), presumably due to the higher dose of 5-FU. Haematological toxicity occurred in only one patient at the grade 3–4 level. 7 of the 13 evaluable patients had a complete (1) or partial (6) response (54%; 47% of the entire study population) and 2 patients had stable disease.

Among the reported trials in which gemcitabine was combined with one other cytotoxic drug in pretreated MBC patients, the combination with 5-FU appears to be the one with the lowest incidence of haematological toxicity. Comparisons of activity in this and other combination trials are difficult to make because other combinations were studied in the phase II setting, with all patients receiving the same doses of drugs, while in this study only 6 of 15 patients received the level 4 doses (with gemcitabine doses comparable to other published phase II combination trials). The results of the phase II study of gemcitabine and 5-FU is available only in abstract form, thus it is impossible to compare the treated patients in this and our study. Differences in the doses of both drugs and in patient characteristics, particularly disease burden and performance status, may explain the difference in the observed response rates in the two studies.

It should be noted that the combination of gemcitabine and 5-FU may not be better than continuous infusion 5-FU or capecitabine alone, although there have been no comparative studies. In phase II trials, capecitabine produced response rates of 20–24% in MBC patients pretreated with anthracyclines and taxanes, however toxicity, particularly diarrhoea and PPE, required a dose reduction in a significant proportion of patients [1,2]. It is difficult to determine the activity of 5-FU in this patient population from the literature. One retrospective study reported a response rate of 12% and good toxicity profile among 35 patients with prior anthracycline and taxane treatment [6]. Another retrospective study reported a response rate of 16% among 24 heavily pretreated patients (79% had prior 5-FU and 33% had prior high-dose chemotherapy with autologous stem cell support) [24]. Given the relatively good

toxicity profile coupled with a 33% clinical benefit rate, the association of gemcitabine 1200 mg/m^2 days 1 and 8, and 5-FU 250 mg/m^2/day, days 1–14, every 21 days in a phase II trial may be worth exploring as an additional chemotherapeutic option in women who have already received anthracyclines and taxanes, the most active drug classes against breast cancer. Alternate schedules, such as the one explored by Andres and colleagues, may improve efficacy [23].

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