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Phase II trial of pegylated liposomal doxorubicin (Caelyx™) plus Gemcitabine in chemotherapeutically pretreated patients with advanced breast cancer

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Abstract

A phase II trial was performed to investigate the efficacy and tolerance of combined gemcitabine and liposomal doxorubicin ± recombinant human granulocyte colony-stimulating factor (G-CSF) in patients with chemotherapeutically pretreated metastatic breast cancer. Thirty-four patients were entered in this trial. Chemotherapy consisted of gemcitabine and liposomal doxorubicin ± G-CSF. Twenty seven patients received this regimen as 2nd line therapy, five patients as 3rd line and two patients as 4th line therapy after having failed taxane- and/or anthracycline-based chemotherapy or other drug combinations. After a median of six courses, an overall response rate of 26% (9 PR in 34 enrolled patients) was observed; 14 patients had disease stabilization (41%), and eight (24%) progressed. Three patients were not evaluable for response due to anaphylaxis after the first course and protracted thrombocytopenia. The median TTP was 7.5 months, and median overall survival was 15 months. Myelosuppression was the most frequently observed toxicity. Non-haematological side effects were generally mild to moderate. Our data suggest that gemcitabine and liposomal doxorubicin ± G-CSF is an effective and fairly well tolerated regimen for chemotherapeutically pretreated patients with advanced breast cancer.

Breast cancer represents a major health problem, being responsible for 20% of cancer deaths in the western world. Despite progress achieved in screening and management of early breast cancer including adjuvant treatment, 25–30% of patients with negative axillary lymph nodes, and more than two-thirds of those with axillary node involvement will have recurrent and/or metastatic disease within five years of their initial diagnosis [1–3]. Once recurrence or metastases are detected, the median survival is in the range of 18–24 months [4–8]. Conventional combination chemotherapeutic regimens result in objective responses in 50–80% of patients and most of these patients obtain partial or complete relief of cancer-associated symptoms. However, advanced breast cancer remains incurable and the great majority of patients present with disease progression after first-line chemotherapy [4,8]. There is a general consensus that the role of cytotoxic therapy in prolonging survival in advanced breast cancer patients is modest, and the efficacy of second and subsequent lines of palliative chemotherapy is poor with an objective response rate in the range of 20% and median survival times of less than 12 months [8]. Therefore, improvement or maintenance of quality of life is the main goal of salvage chemotherapy and palliation therefore needs to be balanced against survival and toxicity.

Pegylated liposomal doxorubicin (Caelyx™, Schering-Plough Corp) is a new formulation of doxorubicin [9]. Pegylation protects the liposomes from detection by the mononuclear phagocyte system and increases circulation time, allowing for more targeted delivery of doxorubicin to the tumour cells. Pegylated liposomal doxorubicin accumulates selectively in cancer tissue, resulting in ten-fold

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higher intracellular drug concentrations compared with adjacent normal tissue. Liposomal encapsulation of doxorubicin may reduce both the non-specific drug delivery to normal tissues as well as the high peak plasma levels of free drug responsible for its toxicity, particularly myelosuppression and cardiotoxicity [9]. The efficacy of pegylated liposomal doxorubicin as single agent in the treatment of metastatic breast cancer has been evaluated in several phase II trials with response rates in the range of 31 to 38% [9–11].

Gemcitabine (Gemzar, Eli Lilly, Indinapolis, USA) is a nucleoside analogue of deoxycytidine, which possesses a broad range of activity against various solid tumours, and is characterized by a favourable toxicity profile [12]. Used as single agent or in combination regimens gemcitabine showed an objective response rate of 25–46% in advanced breast cancer patients, depending whether this drug was used as first- or second-line treatment [13–18].

Encouraging therapeutic results have recently been reported when these two drugs were used in combination for the treatment of recurrent ovarian cancer [19] as well as in a phase I and phase II trial in patients with previously untreated advanced breast cancer (ABC): in addition to a notable objective response rate of 33% and 52%, a mild toxicity profile was described [20,21].

The aim of the present study was to evaluate the antitumour activity and tolerance of pegylated liposomal doxorubicin and gemcitabine in patients with advanced breast cancer who had failed one or more prior palliative chemotherapy regimens. To counteract myelosuppression that was likely to constitute the dose-limiting toxicity of this combination [20] the haematopoietic growth factor G-CSF was given depending on absolute neutrophil counts on the day of scheduled chemotherapeutic drug administration.

Patients and methods

Patients selection

Patients eligible for this study had histologically confirmed metastatic breast cancer with documented progressive, bidimensionally measurable disease. All patients were required to be aged 80 years or younger, to have a World Health Organization (WHO) performance status of less than 3, an expected survival time of more than 12 weeks, and to have adequate bone marrow (absolute neutrophil count [ANC] $\geq 2\,000/\mu l$, and platelet count $\geq 100\,000/\mu l$), adequate renal (serum creatinine concentration < 132 μmol), and adequate hepatic function (serum bilirubin level and serum transaminase level $<$ two times the upper limit of normal). Prior radiation therapy (with at least one target lesion outside the radiation port), prior hormonal therapy for advanced disease, and $\geq$ one prior regimen of palliative chemotherapy were allowed. Prior therapy must have been completed at least 4 weeks before study entry with full resolution of toxicities. All patients gave informed consent according to institutional regulations. Patients with osteoblastic bone lesions as the only site of disease, patients with CNS metastases and those with a prior or second coexisting invasive malignancy were excluded.

Treatment protocol

Chemotherapy consisted of pegylated liposomal doxorubicin 24 mg/m^2 on day 1 (2-hour infusion) and gemcitabine 800 mg/m^2 on days 1+8 (30-minutes infusion). When the ANC was 1 000 to 2 000 on the day of planned chemotherapeutic drug administration, in order to maintain dose-intensity, a 5-day course of the haematopoietic growth factor G-CSF (5 μg/kg/day given subcutaneously) was to be started on the subsequent day. In patients experiencing neutropenia, G-CSF support was not continued routinely during subsequent courses, the decision was always dependent an actual ANCs. Treatment courses were repeated every 3 weeks, and were to be continued in patients achieving complete response (CR), partial response (PR), or stabilization of disease (SD) for a total of six courses. As antiemetic prophylaxis, granisetrone 3 mg and dexamethasone 4 mg were routinely administered before cytotoxic drug administration.

Toxicity and dosage modification guidelines

Adverse reactions were evaluated according to WHO standard criteria [22].

Pretreatment and follow-up evaluation

Pretreatment evaluation included a complete medical history, and physical examination with measurement of all tumour associated lesions. Laboratory evaluation consisted of a complete blood count with platelet count and leukocyte differential count, and an 18-function biochemical profile. Imaging procedures included chest x-ray, bone scan, skeletal bone survey, and computed tomographic (CT) scan of the abdomen. Complete blood cell counts and differential counts were performed weekly, and biochemical profiles were assessed before each treatment cycle. Tumour size was measured every 8 weeks by CT-scan, x-ray, or any other technique that allows retrospective and independent reassessment.

Assessment of response

The primary efficacy end point was response rate. A complete response (CR) required the complete disappearance of all objective evidence of disease on two separate measurements at least 4 weeks apart. A partial remission (PR) was defined as a more than 50% reduction in the sum of the products of the perpendicular diameters of measurable bidimensional lesions without CR, no progression of any lesion by more than 25% or the appearance of any new lesion, confirmed on two separate measurements that were 4 weeks apart. In case of bone metastases, CR was attributed only when there was complete disappearance of all lesions on x-ray, and PR was attributed when decrease in size and/or recalcification of lytic lesions occurred. Decreased densities of blastic lesions or improvement in bone scan positive, x-ray negative disease were not taken into account. Progressive disease (PD) was defined as the enlargement of any existing measurable lesion by more than 25% or the development of new metastatic lesions. Stable disease (SD) was any measurement that did not fulfil the criteria for PR or PD. All tumour measurements in patients who responded were reviewed and confirmed by an independent review committee (IRC) of radiologists and oncologists. Secondary efficacy end points included the duration of response (measured from the onset of the best response to the date of disease progression), time to treatment failure (calculated from the start of treatment to the time of progression or relapse), and overall survival.

Statistical methods

Using standard statistical methods, a two-stage design was employed in the protocol [23]. If no CR or PR was noted in the first 14 patients, a response rate of $\geq$20% could be excluded with 95% confidence and accrual would stop. If at least one CR or PR was observed $>$30 patients were to be entered in the study to determine the response rate more accurately. For response rates, 95% confidence intervals were calculated as previously described [24]. The distribution of time to death from the date of study entry was estimated using the Kaplan-Meier product-limit method [25]. All patients who were enrolled onto the study were included in the intent-to-treat analysis.

Results

Patient characteristics

Between October 2001 and November 2002, a total of 34 patients were enrolled in this trial, all of whom were evaluable for toxicity assessment and 31 patients for response evaluation; two patients were discontinued early due to a severe anaphylactic reaction to pegylated liposomal doxorubicin during the 1st treatment course, and one patient suffered from protracted thrombocytopenia after the 2nd course. The demographic data, sites of metastatic tumour, and prior therapies are listed in Table I. Except for eight patients, all had multiple metastases involving two or more organ systems with predominant visceral disease sites. All patients had at least one prior cytotoxic chemotherapy for metastatic

Table I. Patient characteristics.

	Number of patients
Entered	34
Age in years	
Median	64
Range	37–80
WHO Performance status*	
0	8
1	20
2	6
Disease-free interval (months)	
Median	26
Range	0–108
Menopausal status	
Premenopausal	7
Postmenopausal	27
Estrogen receptor status	
Positive	17
Negative	17
Dominant disease site	
Visceral	26
Bone	6
Soft-tissue	2
Number of organ systems involved	
1	8
2	17
3	9
Prior therapy	
Adjuvant	
Hormones	4
Chemotherapy	8
Hormones and chemotherapy	13
Radiation therapy	22
Palliative	
Hormones	17
Radiation therapy	10
Chemotherapy	34
Taxane-based	15
Anthracycline-containing	5
Docetaxel+epirubicin	8
Vinorelbine+capecitabine	11
CMF or other regimens	4
Number of palliative chemotherapy regimens	
1	27
2	5
3	2

*World Health Organization.

disease, 17 had palliative hormonal therapy, and ten patients had undergone palliative radiation therapy for skeletal or soft-tissue lesions. Previous palliative chemotherapy consisted of taxane- and/or anthracycline-based regimens in the large majority of patients. The median chemotherapy-free interval before study entry was 4 months (range 0–7 months).

A total of 153 courses of study treatment were administered to the 34 patients. The median number of treatment courses was 6 (range 1–6), and the median duration of follow-up at the time of this analysis was 25 months (range 17–32).

Response to treatment

After a median treatment duration of 3 months (range 2.5–4.0) we observed an overall response rate of 26% (9/34) (95% confidence interval, 13.5–44.6%); these partial remissions occurred in 7/27 (26%) patients with one previous palliative chemotherapeutic treatment line, and in 2/5 and 0/2 with two and three previous treatment lines, respectively. Fourteen patients (41%) had disease stabilization, and eight (24%) progressed. The median duration of response was 5.5 months (range 4.5–8.0) and disease was stabilized for a median of 7 months (range 5–20); median time to progression was 7.5 months (range 1.0–20). All patients who experienced objective response had visceral tumour manifestations involving 1 (n = 2), 2 (n = 5) or 3 (n = 2) organ systems.

Toxicity

All 34 patients were assessable for toxicity. Side effects associated with treatment are listed in Table II. Myelosuppression was the most common adverse reaction, though according to the ANC-adapted use of a haematopoietic growth factor, the time to WBC/ANC recovery was generally short: in 96% episodes of leukocytopenia/neutropenia resolved within 7 days.

Administration of G-CSF because of ANCs of 1 000–2 000/μL on the day of scheduled chemotherapeutic drug administration, as indicated in the protocol, was effected in 22 patients (65%), most commonly on day 8 of the cycle. A total of 72 five-day courses of G-CSF were delivered, with most of the patients (64%) receiving fewer than four courses. Leukopenia occurred in 30 patients (88%), and was grade 3 in nine cases (26%). Thrombocytopenia was seen in 15 patients (44%) and was grade 3 and 4 in 2 and 1 patients, respectively. Only one patient developed severe anaemia requiring packed RBC transfusion, and four additional patients received rHu-erythropoietin at a dose of 10 000 IU s.c. × 3/week; mild, asymptomatic anaemia was recorded in 19 patients (59%). Two patients (6%) developed documented infection; none of them required hospitalization for intravenous antibiotics.

Among non-haematological side effects, gastrointestinal symptoms were the most frequently encountered toxicities. Except for one patient, nausea and vomiting was in general mild or moderate, confined to the day of drug administration, and responsive to standard antiemetic therapy. Stomatitis was noted in 17 patients (50%) including only one case (3%) with WHO grade three symptoms. Mild to moderate diarrhoea was seen in three patients (9%). Hand-foot-syndrome, including one severe reaction, was noted in 15 patients (44%), and allergic reactions were observed in three (9%). Alopecia occurred in 12 patients (35%), but complete hair loss was seen in only five (15%). Other symptomatic toxicities were infrequent and clinically insignificant.

Treatment was discontinued prematurely in three cases because of anaphylactic reactions (n = 2), and protracted thrombocytopenia after the 2nd course (n = 1), respectively. Ten patients (19%) had at least one treatment delay of one week at some time during therapy, and the total number of delayed courses was 18 (12%). The reasons for delayed courses were neutropenia in six, non-haematological side-effects in two, both in one case, and personal reasons in one. Only three patients required a 25% dose reduction of cytotoxic drugs during treatment according to the study protocol because of grade 3 stomatitis, nausea/vomiting, and hand-foot syndrome, respectively.

Dose-intensity was calculated for each patient and for each drug. The mean given dose-intensity of the combination was 95% of the projected dose with no difference between patients with one or more previous treatment lines. The mean dose of gemcitabine was 710 mg/m2/ week (range 510–950 mg/m2/week), and the mean dose of liposomal doxorubicin was 23.6 mg/m2/week (range 17–25 mg/m2/week).

Survival

After a median follow-up duration of 25 months (range 17–32), 24 of all 34 patients had died because of PD. Ten patients (29%) are still alive with metastatic disease, all of whom had received other oncological therapy (chemotherapy ± hormonal therapy) after subsequent PD. The median survival duration was 15 months (range 1.5 to 28+). The one-year and two-year survival rate was 76% and 24%, respectively.

Table II. Highest grade of haematological and non-haematological toxicities experienced (n = 34).

	Number of patients (%) with toxic effects of WHO			
	Grade 1	Grade 2	Grade 3	Grade 4
Leukocytopenia	6 (18%)	15 (44%)	9 (26%)	–
Neutropenia	4 (12%)	10 (29%)	14 (41%)	1 (3%)
Thrombocytopenia	6 (18%)	6 (18%)	2 (6%)	1 (3%)
Anaemia	19 (56%)	4 (12%)	1 (3%)	–
Nausea	9 (26%)	7 (21%)	1 (3%)	–
Vomiting	–	5 (15%)	1 (3%)	–
Stomatitis	9 (26%)	7 (21%)	1 (3%)	–
Diarrhoea	3 (9%)	–	–	–
Hand-foot-syndrome	8 (24%)	6 (18%)	1 (3%)	–
Infection	1 (3%)	1 (3%)	–	–
Alopecia	4 (12%)	3 (9%)	5 (15%)	–
Peripheral neurotoxicity	4 (9%)	2 (6%)	–	–
Constipation	2 (6%)	2 (6%)	–	–
Fatigue	6 (18%)	9 (26%)	–	–
Anaphylactic reactions	–	1 (3%)	2 (6%)	–
Liver enzymes	6 (18%)	1 (3%)	1 (3%)	–
Fever (drug related)	–	1 (3%)	–	–

Discussion

Despite high objective response rates achieved with some anticancer drug combinations, metastatic breast cancer remains an incurable disease with very few patients being progression-free beyond 5 years [4–7]. When first-line chemotherapy fails in these patients, subsequent treatment lines generally result in unsatisfactory duration of response and overall survival. Therefore symptom palliation and quality-of-life, which should not be adversely affected by cytotoxic chemotherapy, are important aims of second-line therapy [8].

The rationale for combining gemcitabine and pegylated liposomal doxorubicin in the present study included (1) their distinct mechanism of action with different intracellular targets, (2) high levels of single activity of both drugs in ABC [9–15], (3) encouraging results of a recently conducted phase I and II trial of this particular combination in ABC [20,21], and (4) the much lower cardiotoxic potential of liposomal doxorubicin compared to its conventional formulation, which makes this combination suitable even in case of prior anthracycline exposure.

With an overall intent-to treat, IRC-confirmed response rate of 26% and disease control (PR+SD) in 68%, our results suggest that gemcitabine plus pegylated liposomal doxorubicin is active in chemotherapeutically pretreated patients with metastatic breast cancer. Responses occurred invariable of the constitution of first-line therapy, and even in patients who had received more than one regimen. Similarly, the therapeutic effectiveness was not influenced by adverse prognostic factors such as negative estrogen-receptor status (50% of patients), predominant visceral disease (76%), liver involvement (53%), and presence of multiple metastatic sites (76%). An observed median survival time of 15 months, and a 1-year and 2-year-survival rate of 76% and 26% further substantiate the therapeutic potential of this combination.

As it concerns the tolerance of the treatment, myelosuppression was the most frequently encountered toxicity associated with this regimen. Grade 3 or 4 neutropenia occurred in 41% and 3%, compared to 36% and 38% observed by Rivera et al. in their phase II study using the same combination regimen as first-line therapy [21]. Most likely, this difference can be explained by the ANC-adapted use of G-CSF in our study population. Treatment delays for haematological reasons were also required in only seven patients in the present series, and there was a remarkable low incidence of febrile episodes associated only with mild neutropenia. Thrombocytopenia was frequently seen (44%) but was grade 3 in only two and grade 4 in one patient, respectively; Rivera et al. [21] reported severe thrombocytopenia in 28%, a difference that probably corresponds with the cumulative chemotherapeutic drug doses administered, i.e., their "treatment until progression" versus our "limited treatment duration" strategy. Non-haematological toxicity was generally mild and fully reversible in all our patients. In agreement with the above mentioned first-line study of pegylated liposomal doxorubicin plus gemcitabine, the most frequent side-effects included nausea, fatigue, stomatitis, and hand-foot syndrome (HFS). All reactions were grade 1 or 2, except one patient each experiencing grade 3 nausea, stomatitis and HFS. The relative low incidence of HFS is likely to be related to the lower dose of pegylated liposomal

doxorubicin as used in our combination regimen. Significant hair loss, which is an important factor in female patients, was observed in only 15% of the patients.

In conclusion, the results of this trial indicate that gemcitabine and pegylated liposomal doxorubicin is an active and fairly well tolerated second-line/salvage therapy for advanced breast cancer patients. Its advantage over other commonly used and more intensive, equally effective regimens such as taxane-based or platinum-containing combinations seems to be its superior tolerance, particularly as it concerns the incidence and severity of gastrointestinal toxicity, alopecia, neurological symptoms and/or haematological complications. These side effects of therapy are of significant subjective burden, and represent important issues when discussing treatment options with patients. Results from this study suggest that the combination of gemcitabine and pegylated liposomal doxorubicin warrants further investigation in larger, randomized trials, including formal measurements of quality of life.

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