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A randomised phase II study of two different schedules of pegylated liposomal doxorubicin in metastatic breast cancer (EORTC-10993)

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ABSTRACT

One hundred and sixteen women with measurable metastatic breast cancer participated in a randomised phase II study of single agent liposomal pegylated doxorubicin (Caelyx™) given either as a 60 mg/m^2 every 6 weeks (ARM A) or 50 mg/m^2 every 4 weeks (ARM B) schedule. Patients were over 65 years of age or, if younger, had refused or been unsuitable for standard anthracyclines. The aims of the study were to evaluate toxicity and dose delivery with the two schedules and obtain further information on the response rate of liposomal pegylated doxorubicin as a single agent in anthracycline naïve advanced breast cancer. Twenty-six patients had received prior adjuvant chemotherapy (including an anthracycline in 10). Sixteen had received non-anthracycline-based first-line chemotherapy for advanced disease. One hundred and eleven patients were evaluable for toxicity and 106 for response. The delivered dose intensity (DI) was 9.8 mg/m^2 (95% CI, 7.2–10.4) with 37 (69%) achieving a DI of >90% on ARM A and 11.9 mg/m^2 (95% CI, 7.5–12.8) with 37 (65%) achieving a DI of >90% on ARM B. The adverse event profiles of the two schedules were distinctly different. Mucositis was more common with the every 6 weeks regimen (35% CTC grade 3/4 in ARM A, 14% in ARM B) but palmar plantar erythrodysesthesia (PPE) was more frequent with the every 4 weeks regimen (2% CTC grade 3/4 in ARM A, 16% in ARM B). Confirmed objective partial responses by RECIST criteria were seen with both schedules; 15/51 (29%) on ARM A and 17/56 (31%) on ARM B. Liposomal pegylated doxorubicin showed significant activity in advanced breast cancer with a generally favourable side-effect profile. The high frequency of stomatitis seen with 6 weekly treatment makes this the less preferred of the two schedules tested.

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1. Introduction

Anthracyclines, particularly doxorubicin and epirubicin are the cornerstone of chemotherapy for breast cancer. However, the use of both agents is limited by dose related cardiotoxicity, myelosuppression and a range of toxicities such as alopecia and fatigue which, while not life-threatening, reduce the therapeutic index of conventional anthracyclines in the palliative setting, especially for older patients.

Polyethylene glycol liposomal doxorubicin, also known as pegylated doxorubicin, is registered as Caelyx™ in Europe (Schering-Plough, Brussels, Belgium) and as Doxil™ in the USA (Alza Pharmaceuticals, Mountain View, CA). The encapsulation of doxorubicin by pegylated liposomes impairs its uptake by the reticulo-endothelial system, resulting in significant prolongation of the serum half-life to around 50 h compared with 10 min for the free drug.[1] As a result, the tissue distribution of pegylated doxorubicin is favourably modified[2] and is associated with less myelotoxicity, alopecia and gastrointestinal toxicity than is typical with standard formulations of either doxorubicin or epirubicin. However, the altered pharmacology of pegylated doxorubicin leads to a number of side-effects that are more typical of prolonged infusion schedules of doxorubicin, namely plantar-palmar erythrodysesthesia (PPE) and mucositis.

The activity of pegylated doxorubicin has been demonstrated in a variety of solid tumours including breast cancer. Single agent treatments with doses of 45–50 mg/m^2 have shown response rates of 27–31%.[3,4] Using the latter dose and schedule, a randomised phase III study of 509 patients demonstrated similar activity and less toxicity, including reduced cardiotoxicity, than conventional doxorubicin at a dose of 60 mg/m^2 administered every three weeks.[4] Pegylated doxorubicin has also been given in combination with a variety of other cytotoxic agents including cyclophosphamide, docetaxel and gemcitabine.[5] To accommodate a 3 weekly regimen with these agents, the dose of pegylated doxorubicin has been reduced (24–30 mg/m^2), resulting in a dose intensity that may not be optimal.

Our group has previously explored the use of a 6 weekly schedule of pegylated doxorubicin.[6] In a phase I trial performed in 20 women with metastatic breast cancer, 60 mg/m^2 was defined as the maximum-tolerated dose with mucositis being the dose-limiting toxicity. Interestingly, grade III/IV PPE, the dose limiting toxicity with the 4 weekly schedule, was uncommon with the 6 weekly schedule. No other non-haematological grade III/IV toxicities were seen at the 60 mg/m^2 dose level. Following on from our phase I experience, and in light of a degree of uncertainty regarding the optimum dose and schedule of pegylated doxorubicin, we conducted a randomised phase II trial to evaluate more thoroughly the tolerability and activity of the 6 weekly schedule in parallel with patients treated on the more standard 4 weekly schedule.

2. Patients and methods

Between April 2000 and July 2002, 116 women with histologically confirmed, measurable metastatic breast cancer were entered into a randomised phase II clinical trial of pegylated liposomal doxorubicin (Caelyx™) performed at seventeen European Organisation for Research and Treatment of Cancer (EORTC) sites (eight Investigational Drug Branch for Breast Cancer (IDBBC) and nine Early Clinical Studies Group (ECSG) centres). The study was conducted in concordance with the Declaration of Helsinki and EU Guidelines on Good Clinical Practice. The protocol was reviewed and approved by the Protocol Review Committee of the EORTC and by the institutional review board (ethical committee) of each participating centre. The study was financially supported by Schering Plough who also provided the study drug.

Eligibility required written informed consent, progressive or recurrent metastatic disease, at least one target lesion measurable in two dimensions, ECOG performance status $\leqslant 2$ and adequate organ function. The latter was defined as neutrophils $\geqslant 1.5 \times 10^9$/l, platelets $\geqslant 100 \times 10^9$/l, bilirubin and serum creatinine within normal limits, transaminases <2× upper limit of normal, and left ventricular function (LVEF) within normal limits by echocardiography (ECHO) or multigated (MUGA) cardiac imaging. Eligibility also required an age of >65 unless there was a medical contraindication to a standard anthracycline-containing regimen at a younger age or the patient had refused standard anthracycline-containing chemotherapy due to reasons such as the high probability of alopecia.

Exclusion criteria included more than one line of chemotherapy for metastatic disease, pregnancy or lactation, concurrent malignancy other than contralateral breast cancer, adequately treated basal cell carcinoma of the skin or in situ carcinoma of the cervix, treatment with any anthracycline-based chemotherapy for metastatic disease, significant cardiac history including congestive heart failure, even if medically controlled, and clinical or electrocardiagraphically documented myocardial infarction diagnosed during the preceding year, or significant angina. Prior adjuvant anthracycline-based chemotherapy was allowed if the total cumulative doses received were $\leqslant$300 mg/m^2 for doxorubicin, $\leqslant$450 mg/m^2 for epirubicin and $\leqslant$75 mg/m^2 for mitoxantrone.

Patients were randomised to receive Caelyx as a single agent by intravenous infusion at either a dose of 60 mg/m^2 every six weeks (ARM A) or the usual dose of 50 mg/m^2 every four weeks (ARM B). Treatment was to be continued for a minimum of 36 weeks unless progressive disease, unacceptable toxicity or patient refusal to continue. Originally, the infusions were planned to be administered over 60 min but this was increased to 90 min by a protocol amendment following three allergic reactions in the first six patients treated. Five percent of the total dose was administered over 15 min. If tolerated, without reactions, the infusion rate was doubled for the next 15 min, and if tolerated the infusion was completed over the next 60 min to give a total infusion time of 90 min.

Concomitant anti-emetics were left to the discretion of the treating physician. No prophylactic antibiotics or bone marrow growth factors were recommended. Again a protocol amendment was required after the first 28 patients had been enrolled to the 60 mg/m^2 every 6 weeks arm due to a high (43%) incidence of grade III/IV mucositis/oesophagitis. This amendment instructed a specific mouth-care protocol using a mouth rinse of sodium bicarbonate 0.167 M with xylocaine 2% and nystatin 4.8 million international units (IU). This mouthwash or a similar preparation consistent with local

institutional practice was to be used three to six times a day beginning on day 1 and continued for at least three weeks following each administration of Caelyx, irrespective of the schedule allocated.

Response was assessed every 12 weeks (after every two cycles on ARM A and after every third cycle on ARM B). Objective response was determined using standard RECIST criteria. Patients were defined as responders if they had a complete response (CR) or partial response (PR) that included a confirmation of this at least 4 weeks afterward. Patients were classified as achieving stable disease (SD) if there was neither disease progression nor a response to Caelyx treatment. Duration of response was defined as the interval between the initiation of treatment and the first observation of progressive disease (PD) in patients who achieved a confirmed response to therapy. Time to disease progression (TTP) was defined as the time from treatment to either the first recording of disease progression or the date of death in patients with no evidence of disease progression. Time to first response was defined as the period between the initiation of treatment and the first record of CR or PR. Survival was calculated from the date of randomisation to the date of death or censored at the date of last follow-up.

Toxicity was assessed according to the NCIC common toxicity criteria at the end of each cycle. Left ventricular function was assessed before treatment and at regular intervals on study by either isotopic or echocardiographic methods. A significant decline in LVEF was defined as either a reduction of $\geqslant$10% from baseline and below normal lower limit (Definition 1); or a decline of 5% below normal lower limit (Definition 2).

Descriptive data are presented. No statistical comparisons are made between the two treatment arms as the study was not powered to show differences with any reliability.

3. Results

Of 116 patients accrued into the study, 10 were deemed to be ineligible, six in ARM A and four in ARM B. This was due to concomitant endocrine treatment (five patients), non-measurable disease according to the protocol definitions (two patients), prior epirubicin dose of >450 mg/m^2 (one patient who had received 588 mg/m^2), baseline neutrophils below protocol limits (one patient) and a concurrent second cancer (one patient).

The patient characteristics are shown in Table 1. The median age was 69 (range 37–87). Thirty-four patients with an age of <65 were included. This was due to refusal of anthracycline-based therapy in 32 and ineligibility for anthracycline-based therapy in the other two patients. 38 patients had received prior chemotherapy. This was in the (neo)adjuvant setting in 22 and included anthracyclines in 10, in the first-line metastatic setting in 12 and for both adjuvant and advanced disease treatment in four patients.

Forty-three patients (12 in ARM A and 31 in ARM B) experienced a delay of at least one cycle (Table 2). The median number of cycles delayed by $\geqslant$4 days was one in each arm with a range of 1–7 in ARM A and 1–9 in ARM B. The median duration of delay was 7 days in each arm with a range of 4–24 days in ARM A and 4–15 days in ARM B. No specific reason for dose delays in ARM A could be identified with administrative reasons stated in three patients and mucositis in two. In ARM B, with more delays, the reasons for delay were much clearer and due to bone marrow suppression, PPE and mucositis in 12, 8 and 4 patients, respectively.

Table 1 – Patient characteristics

	ARM A (60 q 6) (N = 57)	ARM B (50 q 4) (N = 59)
Median age (range)	69 (37–87)	69 (43–85)
Age <65	17	17
Performance status		
0	13	11
1	37	39
2	7	9
Median disease free interval (range)	3.3 (0–18.0)	3.5 (0–22.8)
Oestrogen receptor status		
Positive	37	31
Negative	20	20
Unknown	19	27
Prior endocrine therapy		
Adjuvant	4	11
Metastatic	18	20
Both	20	18
Prior chemotherapy	19	19
Adjuvant/neoadjuvant	11	11
Metastatic	7	5
Both	1	3
Adjuvant anthracyclines	3	7
Prior radiotherapy	44	47
Dominant site of disease		
Soft tissue	8	8
Bone	5	4
Visceral	21	20
Multiple visceral	23	27
Number of sites involved		
1	11	5
2	16	17
3 or more	30	37

Thirty-six patients (18 in ARM A and 18 in ARM B) required at least one dose reduction. The median number of cycles reduced per patient was three with a range of 1–8 in both arms of the study. The median dose reduction in each arm was similar at 25% with a range of 10–50% in ARM A and 16–30% in ARM B. The reasons for dose reductions were most frequently mucositis in ARM A (13 patients) and PPE, mucositis and bone marrow suppression in ARM B (eight, five and four patients, respectively).

Table 3 shows the response data. Of the 106 eligible patients, 11 were not evaluable for response. A confirmed partial response was achieved in 15 patients on ARM A (29%) and 17 patients on ARM B (31%). The median duration of response was 8.7 months (95% CI 8.0–12.9 months) in ARM A and 9.3 months in ARM B (95% CI 6.9–14.0 months). Responses were seen at all sites of disease. The numbers of patients who had previously received chemotherapy for metastatic disease was small but the results suggest a lower response frequency in previously treated patients (1/14). The median TTP was 5.8

Table 2 – Drug administration for patients who received at least one course[a]

	ARM A (60 q 6) (N = 54)	ARM B (50 q 4) (N = 57)
No of cycles	249	295
Median (range)	4 (1–9)	4 (1–15)
Median treatment duration in months (range)	5.5 (1.4–14.1)	4.4 (0.9 – 13.8)
Cumulative dose delivered mg/m^2 (range)	241 (60–544)	204 (49–713)
Median delivered dose intensity (DI) mg/m^2/week (range)[b]	9.8 (7.2–10.4)	11.9 (7.5–12.8)
Median relative DI % (range)	98.3 (72.4–103.7)	95.1 (59.7–102.2)
Number of patients (%) with DI >90%	37 (68.5)	37 (64.9)

a Two patients never started treatment, two patients stopped infusion within minutes due to allergic reaction and withdrew from study and one patient died 3 weeks after first infusion.
b Planned DI in mg/m^2/week was 10 for ARM A and 12.5 for ARM B.

Table 3 – Response data

	ARM A (60 q 6) (N = 51)	ARM B (50 q 4) (N = 55)
CR	–	–
PR	15 (29%)	17 (31%)
Soft tissue (n = 7; n = 8)	3 (42%)	9 (38%)
Bone (n = 4; n = 3)	3 (75%)	1 (33%)
Single visceral (n = 20; n = 17)	5 (25%)	3 (18%)
Multiple visceral (n = 20; n = 27)	4 (20%)	10 (37%)
Prior first line chemo (n = 6; n = 8)	–	1 (13%)
No prior chemo (n = 45; n = 47)	15 (29%)	16 (34%)
NC	22 (43%)	18 (33%)
PD	8 (16%)	13 (24%)
Early death	–	2 (4%)
Not evaluable	6 (12%)	5 (9%)

months (95% CI 5.3–8.3 months) and 5.4 months (95% CI 4.4–6.9 months) months in arm A and B, respectively. Progression-free survival probabilities at 1 year were 10.9 (95% CI 1.1–20.7%) in ARM A and 9.0 (95% CI 0.7–17.3%) in ARM B.

One hundred and eleven patients were evaluable for toxicity and the adverse events reported in more than 10% of patients on either arm are shown in Table 4. Thirty-seven and thirty-eight patients in ARM A and ARM B, respectively, experienced at least one grade III toxicity. Grade IV toxicity occurred somewhat more frequently on ARM A affecting 15 patients compared with five on ARM B. Haematological toxicity was generally mild and broadly similar irrespective of schedule. Febrile neutropaenia occurred in five patients (9%) on ARM A only with no episodes of febrile neutropaenia on ARM B.

In ARM A, mucositis was the most significant toxicity with 19 (35%) experiencing grade III/IV mucositis at some time during treatment. By comparison only eight (14%) of patients on ARM B developed grade III/IV mucositis. The introduction of the amendment to administer regular mouth-care was not formally assessed but appeared to ameliorate the duration and severity of the mucositis with the 6 weekly schedule, in that the incidence of grade III/IV mucositis was 43% in the first 28 patients enrolled, but only 27% in the subsequent 26 patients recruited to the same schedule. In ARM B, PPE was more frequent with nine patients (16%) reporting grade III/IV PPE, whereas this occurred in only two patients (4%) on ARM A.

Not all patients were evaluable for changes in left ventricular ejection fraction (LVEF) measurements (43 in ARM A and 30 in ARM B). Of these, 12 and 11 patients in ARM A and B, respectively, showed a decline in LVEF. These were mild and asymptomatic except for one patient on ARM B who experienced a grade III change and developed congestive heart failure. Using the protocol specified definitions for significant declines in LVEF, one patient on ARM B met the criteria for Definition 1 and 3 patients in both ARM A and ARM B met the criteria for Definition 1 and 2 with a decline of $\geqslant$10% from baseline to a level of >5% below normal lower limit.

Significant allergic reactions occurred in three of the first six patients treated (two serious adverse events). The early amendment to prolong the infusion time to 90 min by starting the administration of Caelyx very slowly and only increasing the rate if tolerated was largely successful in preventing subsequent allergic reactions. Following the amendment, only one further serious allergic reaction occurred and the overall frequency of infusion reactions thereafter of any grade was <10%.

4. Discussion

Pegylated liposomal doxorubicin (Caelyx) offers an alternative to conventional doxorubicin (or epirubicin) for advanced breast cancer. The maximum tolerated dose is 60 mg/m^2 on either a 4 weekly[7] or a 6 weekly schedule.[6] In first-line treatment, Caelyx and doxorubicin have similar activity but the toxicity profiles are different with less cardiotoxicity, nausea and vomiting, myelosuppression and alopecia with Caelyx but at the expense of increased incidence of PPE and mucositis. In a recent randomised phase III trial, the incidence of grade III or IV PPE was 17% with Caelyx compared with 2% on doxorubicin while mucositis and stomatitis were reported in 23% and 22%, respectively, with Caelyx compared with 13% and 15% following doxorubicin. However, grade III leucopaenia (9% vs. 1%), neutropaenia (7% vs. 2%), alopecia (66% vs. 20%), nausea (5% vs. 3%), vomiting (4% vs. <1%), 5 HT3 use (54% vs. 46%) and protocol defined falls in LVEF (19% vs. 8%) were all more frequent with conventional doxorubicin.

This phase II comparison of a 4 and 6 weekly schedule of Caelyx was specifically established for the palliative treat-

Table 4 – Adverse events reported in >10% of patients in either ARM and classified according to CTC version 2.0 (worst grade per patient)

Type	ARM A (60 q 6)						ARM B (50 q 4)					
	G0	G1	G2	G3	G4	% G3/4	G0	G1	G2	G3	G4	% G3/4
Haematological												
Anaemia	18	23	11	1	–	2	20	19	18	–	–	–
Leucopaenia	13	8	19	6	7	25	21	10	19	6	1	12
Neutropaenia	14	6	17	9	7	30	22	10	10	12	3	26
Thrombocytopaenia	38	14	–	1	–	2	44	13	–	–	–	–
Non-haematological												
Abdominal pain	48	2	4	–	–	–	53	3	1	–	–	–
Allergy	51	–	2	1	–	2	47	2	5	2	1	5
Alopecia	23	19	12	–	–	–	25	15	7	–	–	–
Anorexia	37	7	5	4	1	9	45	5	6	1	–	2
Bone pain	48	2	2	2	–	4	46	4	6	1	–	2
Cardiac LVEF	42	6	6	–	–	–	46	6	4	1	–	2
Constipation	40	10	3	–	–	–	41	11	4	1	–	2
Cough	47	6	1	–	–	–	53	1	2	1	–	2
Diarrhoea	45	3	5	1		2	47	8	2	–	–	–
Dizzyness	48	4	1	1	–	2	55	2	–	–	–	–
Dyspnoea	45	4	2	3	–	6	50	1	2	1	–	2
Fatigue/asthenia	26	13	10	4	1	9	30	12	11	4	–	7
Infection	42	3	4	4	1	9	36	10	5	6	–	11
Nausea	23	19	12	–	–	–	28	18	9	2	–	4
Neurosensory	49	5	–	–	–	–	46	7	3	1	–	2
Pain	42	7	5	–	–	–	35	11	9	2	–	4
Stomatitis	11	5	19	18	1	35	22	13	14	8	–	14
Skin: PPE	35	14	3	1	–	2	24	10	14	8	1	16
Skin: other	36	14	3	1	–	2	30	11	12	4	–	7
Vomiting	35	10	8	1	–	2	37	12	7	1	–	2
Weight loss	32	17	4	1	–	2	38	10	8	1	–	2

ment of elderly patients (>65 years) with metastatic disease as either first-line treatment or as second-line treatment following a non-anthracycline containing regimen. Both treatment priorities and the acceptable and safe balance between efficacy and toxicity may be different in an older population, and there is a clinical need for a broader range of more gentle palliative treatments in this age group. However, approximately one third of the patients recruited were aged less than 65 but had specifically refused conventional chemotherapy and requested a treatment with less subjective toxicity associated with a high probability of avoiding significant hair loss.

It was possible to administer the vast majority of courses on time and at full dose on both schedules with two thirds receiving a dose intensity of $\geqslant$90% of the planned dose. Slowing the infusion time down reduced the frequency of allergic reactions. The efficacies of the two schedules tested were qualitatively similar (no formal statistical comparisons were made) and in line with the 33% objective response reported for Caelyx in the phase III registration study comparing Caelyx and doxorubicin.[4] Caelyx was generally well tolerated in this study with only 20% discontinuing treatment due to toxicity. The toxicity profiles of the two schedules were somewhat different with more frequent severe stomatitis with the 6 weekly schedule but more troublesome PPE with the 4 weekly standard dose and schedule. Cardiotoxicity was mild, uncommon and asymptomatic in all but one patient. Other larger studies have defined the reduced cardiotoxicity of Caelyx more precisely.[4,8,9] Although the incidence of grade III/IV mucositis was at first sight very high in the 6 weekly schedule, it was often of only a few days duration out of a 6 week cycle, partially ameliorated by prophylactic mouth-care, and overall only four patients discontinued therapy because of this particular adverse event. By comparison, seven patients on the 4 weekly treatment discontinued therapy because of either PPE or skin toxicity.

In summary, our study supports previous reports that indicate that Caelyx is an active, well-tolerated alternative to conventional anthracyclines that may be particularly appropriate for older patients or in those refusing or unsuitable for standard treatments. The preferred schedule is 50 mg/m^2 every 4 weeks but for patients for whom travel to hospital to receive chemotherapy is particularly difficult or for those experiencing troublesome skin or PPE toxicities, the 60 mg/m^2 every 6 weeks is a reasonable alternative.

Conflict of interest statement

None declared.

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