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Original article

Pegylated liposomal doxorubicin in combination with low-dose metronomic cyclophosphamide as preoperative treatment for patients with locally advanced breast cancer

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ABSTRACT

Aim: To evaluate the role of pegylated liposomal doxorubicin with low-dose metronomic cyclophosphamide as primary systemic treatment in locally advanced breast cancer.
Patients and Methods: The activity and safety of intravenous pegylated liposomal doxorubicin 20 mg sqm^{-1} biweekly for eight courses in combination with metronomic cyclophosphamide 50 mg day^{-1} orally were evaluated in 29 patients with locally advanced breast cancer who were not suitable to receive a standard chemotherapy due to age or co-morbidities or who asked for a regimen with low incidence of toxic effects irrespective of age.
Results: The rate of breast-conserving surgery was 44.8%. Eighteen patients (62.1%) achieved a partial response (including one pathological complete response), 10 (34.5%) a stable disease and one patient experienced a progressive disease. Treatment was well tolerated, with no grade 4 toxicities, and with grade 3 skin toxicity in three patients and hand–foot syndrome in four patients.
Conclusion: The regimen was well tolerated but with limited activity in the preoperative setting. Other options (e.g., endocrine therapy in estrogen receptor -positive disease) should be considered in locally advanced breast cancer patients who are not suitable to receive a standard chemotherapy.

Introduction

Anthracyclines are among the most widely used agents in the treatment of early and advanced breast cancer. Doxorubicin-based regimens have demonstrated benefits in terms of response rate, time to disease progression and overall survival. Despite its excellent antitumour activity, conventional doxorubicin has a relatively low therapeutic index, and its use is limited by the development of myelosuppression, alopecia, nausea and vomiting, stomatitis and cumulative cardiotoxicity.[1,2] The use of conventional doxorubicin is also not generally recommended in patients with greater risks of developing cardiac toxicity, such as those with pre-existing cardiac disease, history of mediastinal irradiation and the elderly.[3,4]

Pegylated liposomal doxorubicin (PLD) is a formulation of doxorubicin in polyethylene glycol-coated liposomes with a prolonged circulation time and specific accumulation in tumour tissues, accounting for the much lower toxicity shown by PLD in comparison to free doxorubicin in terms of cardiotoxicity, vesicant effects, nausea, vomiting, alopecia and myelotoxicity.[2,5–7] Typical forms of toxicity associated to PLD are acute infusion reaction, mucositis and palmar-plantar erythrodysesthesia, which occur especially at high doses or short dosing intervals.[8] Although the single maximum tolerated dose (MTD) of PLD is actually lower than

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that of conventional doxorubicin, the cumulative MTD dose of PLD may be substantially greater than that of free doxorubicin.[9]

Metronomic chemotherapy refers to the chronic administration of low doses of cytotoxic drugs at close, regular intervals, with an effect on tumour cells and particularly on endothelial cells.[10] Several common anticancer agents have been shown to have anti-angiogenic activity. Chronically administered low-dose cyclophosphamide produces apoptosis of endothelial cells in the tumour microvasculature with a compromised repairing process, therefore inducing a prolonged anti-angiogenic effect.[11] We previously demonstrated the antitumour activity of oral low-dose cyclophosphamide and methotrexate delivered as metronomic chemotherapy in metastatic breast cancer.[12]

Preliminary results of a randomised phase III study (SWOG 0012) comparing standard intravenous (i.v.) doxorubicin + cyclophosphamide with weekly doxorubicin and daily oral low-dose cyclophosphamide, both followed by weekly paclitaxel for primary therapy of locally advanced and inflammatory breast cancer, indicated a significantly higher activity in terms of clinical partial responses (PRs) for the continuous therapy.[13]

We conducted a phase II trial to evaluate the safety and activity of the association of PLD and metronomic cyclophosphamide in patients with locally advanced breast cancer who were not suitable to receive a standard chemotherapeutic treatment due to age or co-morbidities or who asked for a regimen with low incidence of toxic effects, irrespective of age.

Patients and methods

Patients

Patients with stage II–III (T2-4a-d, N0-3 M0) breast cancer, aged 66 years or older, or not candidates to more intensive chemotherapy regimens due to co-morbidities or patients who asked for a regimen with a low incidence of toxicity irrespective of age, consecutively admitted at the Department of Medicine of the European Institute of Oncology from May 2007 to December 2009 were enrolled in this phase II study.

A tru-cut biopsy was performed for diagnosis and for assessment of biological characteristics of the tumour. Investigations (chest X-ray, abdomen ultrasound, bone scan and/or fludeoxyglucose (^{18}F)-positron emission tomography (FDG-PET)) were performed to exclude distant metastases and blood tests were performed to assess bone marrow, renal and hepatic function. Cardiac function was assessed at baseline by electrocardiogram and echocardiography. A left ventricular ejection fraction $\geq$55% and no impairment of ventricular kinesis were required for study enrolment. Eligibility criteria also included Eastern Cooperative Oncology Group (ECOG) performance status 0–2, measurable lesions, white blood cells $\geq$3000 mm^{-3}, platelets $\geq$100 000 mm^{-3}, aspartate aminotransferase and alanine aminotransferase $\leq$2.5 $\times$ upper limit of normal and bilirubin $\leq$1.5 mg dl^{-1}. Written informed consent was obtained from all patients and the protocol was approved by the Ethical Committee of the European Institute of Oncology.

Treatment

PLD (Caelyx®) was administered intravenously at the dose of 20 mg m^{-2} once every 2 weeks for eight courses. Caelyx® was provided at no cost by Schering Plough. Cyclophosphamide (Endoxan®) was administered at the dose of 50 mg day^{-1} orally for 16 weeks in a metronomic schedule. Cyclophosphamide was commercially available at no cost for patients.

A central venous catheter (CVC) in the subclavian or in the jugular vein contralateral to the site of the tumour was implanted in all patients before starting chemotherapy.

Definitive surgery (breast-conserving surgery or mastectomy, with either sentinel lymph node biopsy or complete axillary lymph node dissection) was performed 4 weeks after the eight courses of Caelyx®. Radiotherapy was indicated in patients undergoing breast-conserving surgery and in patients with T4 tumours.

Response criteria

Tumour was evaluated at baseline by physical measurement with calliper of the two largest diameters and by means of mammography and ultrasound. Patients underwent a physical examination (including measurement of the tumour's two largest diameters with a calliper) every 2 weeks, before each chemotherapy administration. After four and eight cycles, patients also had mammography and ultrasound breast examination to assess response. Clinical responses were evaluated according to both radiological (breast ultrasound or mammography) and clinical evaluation, by measuring the largest diameters of the tumour and were graded according to standard Response Evaluation Criteria In Solid Tumors (RECIST) criteria.[14] In inflammatory breast cancer, clinical response was defined as the disappearance of erythema, oedema and decreased swelling of the breast at physical examination.

Patients with stable disease (SD), partial response or complete response after four courses qualified as candidates to receive four more courses of therapy. Pathological complete responses (pCRs) were evaluated according to Kuerer et al.[15] A pCR was defined as a total disappearance of invasive tumour either in the breast or in the axilla; the presence of intraductal carcinoma qualified for pCR.

Estrogen receptor (ER) and progesterone receptor (PgR) status, assessment of the proliferative activity (percentage of Ki-67-stained cells) and overexpression of HER2 were determined on core biopsies obtained for diagnosis, as previously published.[16] The results were recorded as the percentage of immunoreactive cells over at least 2000 neoplastic cells. Steroid hormone receptor status was classified as negative, poor (ER 1–9% of the cells) or positive (ER and PgR >10% of the cells). As for Ki-67 labelling index, we considered the value of 20% as a cut-off in distinguishing tumours with low (<20%) and high ($\geq$20%) proliferative fraction. The value of 20% was selected based on previous data from our group indicating that a value of Ki-67 $\geq$ 20% significantly correlated with higher response rate to preoperative chemotherapy.16 HER2 status was defined at immunohistochemistry (IHC) as negative (absent or faint and partial staining in >10% of cells = 1+) and equivocal (faint and complete staining in >10% of cells = 2+). In the latter cases, fluorescence *in situ* hybridisation (FISH) was performed to assess the amplification of the HER2 gene.

Toxicity

Patients were assessed for toxicity every 2 weeks, before each chemotherapy administration. Toxicity was recorded and classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.[17]

Treatment was postponed by 1 week if the blood count on day 15 showed a neutrophil count <1000 mm^{-3} and/or platelet count was <100 000 mm^{-3}. In case of febrile neutropenia, or anaemia, mucositis, hand and foot syndrome, gastrointestinal and biochemical toxicity grade 2, a dose reduction by 25% of the related drug was performed.

Statistical considerations

The principal end points of the study were (a) clinical response rate (complete and partial) according to RECIST criteria and (b) pCR. A secondary end point was the assessment of the tolerability of PLD in a homogeneous population of naive elderly patients.

In a previous study of primary therapy in endocrine-responsive postmenopausal patients, we observed 50% clinical responses (partial + complete) and 6% pCRs. If we consider 15% pathological complete response (pCR) rate to induction chemotherapy as acceptable and 3% as unacceptable, in a two-stage minimax design with 10% significance level and 80% power, we needed to enrol 18 patients in the first stage; if none achieved a pCR, the study was to be closed for lack of activity. If one or more patients achieved a pCR, the study proceeded with the enrolment of the other 10 patients (for a total of 28). If overall three or more patients yielded a pCR, it could be assumed that a success rate of 15% was possible. Considering a drop-out of 10%, we planned to recruit 30 patients within 2 years.

Results

From May 2007 to December 2009, 29 patients were enrolled in this phase II trial. All patients were evaluable for clinical response, pathological response and toxicity.

Table 1
Patients and tumor characteristics at baseline.

Characteristic	N	%
Enrolled	29	
Evaluable for clinical response	29	100.0
Evaluable for pathological response	29	100.0
Evaluable for toxicity	29	100.0
Age, years		
Median	54	
Range	33–76	
Menopausal status		
Premenopausal	13	44.8
Postmenopausal	16	55.2
Clinical Tumor Size		
2	17	58.6
3	8	27.6
4b	2	6.9
4d	2	6.9
Clinical Nodal Status		
0	9	31.0
1	19	65.5
2	0	–
3	1	3.4
ER status		
Negative	3	10.3
1–9%	0	–
≥ 10%	26	89.7
PgR status		
Negative	8	27.6
1–9%	5	17.2
≥ 10%	16	55.2
Ki-67		
< 20%	9	31.0
≥ 20%	20	69.0
HER2		
Absent	22	75.9
1+	6	20.7
2+	0	–
3+	1	3.4
Grading		
1	0	–
2	13	44.8
3	11	37.9
NA	5	17.2

NA: Not available.

Patients and tumour characteristics at baseline and at final surgery are summarised in Table 1. Median age was 54 years (range: 33–76 years). Thirteen patients were premenopausal, 16 patients were postmenopausal, with six patients 66 years or older at the time of study entry (so-called 'elderly patients').

Most patients were diagnosed with a clinical T2 ($n = 17$, 58.6%) or T3 ($n = 8$, 27.6%) disease, two patients had a T4b tumour and two patients had an inflammatory disease (T4d). Nearly one-third of the patients ($n = 9$, 31.0%) did not have clinically involved lymph nodes at baseline, while two-thirds ($n = 19$, 65.5%) had clinical N1 stage, with one patient with cN3 stage.

Most patients had an endocrine-responsive tumour at baseline (ER positive, $n = 26$, 89.7%; PgR positive, $n = 16$, 55.2%). HER2 status was negative in 28 (96.6%) patients. Most tumours ($n = 20$, 69.0%) were classified as highly proliferating (Ki-67 $\geq$ 20%) at baseline.

Surgery was performed in all patients. Thirteen patients underwent a breast-conserving procedure after preoperative treatment, 13 had a mastectomy, three patients underwent surgery for bilateral disease, with bilateral mastectomy in one case. Six patients underwent sentinel node biopsy only, with the majority of patients undergoing an axillary clearance.

All patients were evaluable for clinical response (Table 2). Overall, 18 patients (62.1%; 95% confidence interval (CI), 42.4–78.7%) had a PR, of whom one patient achieved a pCR (3.4%; 95%CI, 0.09–17.8%), 10 patients (34.5%) had an SD and one patient (3.4%) had a progression of disease (PD). No conclusion could be drawn on the activity of the treatment in different tumour subsets, since ER-negative patients constituted only about 10% of the total number of patients.

Among patients with an inflammatory tumour ($n = 2$), one patient had a PR and one patient had an SD. Both T4d tumours were endocrine-responsive, as was the tumour which progressed.

Median number of treatment cycles was eight (range: 3–8). Twenty-two patients (75.9%) completed the number of planned cycles, while seven patients discontinued chemotherapy earlier than planned: four patients due to skin toxicity/hand–foot syndrome (of these, one patient discontinued treatment after the third, one patient after the fourth, one patient after the sixth and one patient after the seventh cycle), two patients due to medical decision (they both had an SD after four and six cycles, respectively, and were proposed to anticipate surgical intervention) and one

Table 2
Response after treatment.

	N	%
Clinical Response		
Complete response	0	–
Partial response	18	62.1
Stable disease	10	34.5
Progression	1	3.4
Pathological Tumor Size		
x	1	3.4
is	0	–
0	1	3.4
1	6	20.7
2	13	44.8
3	8	27.6
4b	0	–
4d	0	–
Nodal Status at Surgery		
0	8	27.6
1	6	20.7
2	6	20.7
3	9	31.0
Type of Surgery		
Breast conserving surgery	13	44.8
Mastectomy	13	44.8
Bilateral surgery	3	10.4

Table 3
Toxicity.

	Grade 1		Grade 2		Grade 3	
	N	%	N	%	N	%
Anemia	1	3.4	0	–	0	–
Leukopenia	0	–	3	10.3	0	–
Neutropenia	0	–	1	3.4	0	–
Nausea	7	24.1	0	–	0	–
Vomiting	1	3.4	0	–	0	–
Diarrhea	1	3.4	0	–	0	–
Stipsis	5	17.2	1	3.4	1	3.4
Mucositis	5	17.2	2	6.9	0	–
Hand-foot syndrome	8	27.6	6	20.7	4	13.8
Folliculitis	1	3.4	0	–	0	–
Asthenia	5	17.2	0	–	0	–
Gastric Pain	2	6.9	1	3.4	0	–
Hepatic	2	6.9	3	10.3	0	–
Skin	11	37.9	3	10.3	3	10.3
Neurological	1	3.4	0	–	0	–
Conjunctivitis	1	3.4	0	–	0	–
Fever	1	3.4	0	–	0	–
Hitching	1	3.4	0	–	0	–
Pharyngitis	1	3.4	0	–	0	–
Otitis	1	3.4	0	–	0	–
Rhinitis	1	3.4	0	–	0	–
Alopecia	0	–	0	–	0	–

patient due to progressive disease. Overall, treatment was well tolerated, with no grade 4 and grade 3 toxicities mainly related to hand–foot syndrome (four patients, 14%) and skin toxicity (three patients, 10%). Main toxicities are summarised in Table 3. Treatment with Caelyx® was delayed in eight and doses modified in 13 patients, while treatment with cyclophosphamide was delayed in only four patients. Alopecia was not observed during treatment.

Discussion

Anthracyclines are usually prescribed in the preoperative treatment for locally advanced and operable breast cancer,[18] but their limit resides in their low therapeutic index, especially for cumulative cardiotoxicity. For this reason, current standard chemotherapy regimens might not be adequate for patients in whom the issue of safety is particularly relevant, such as elderly patients or patients with co-morbidities. PLD has a favourable safety profile and comparable clinical activity as compared with conventional doxorubicin; therefore, this drug may be suitable for the treatment of elderly and/or frail patients and of patients who refuse a standard anthracycline regimen because of possible alopecia. The activity of PLD (50 mg sqm^{-1}) in combination with full-dose oral cyclophosphamide (100 mg sqm^{-1} days 1–14) every 28 days was shown to be active in advanced breast cancer, although the toxicity profile compared unfavourably with the i.v. administration of cyclophosphamide. The results of the SWOG trial provided the rationale for investigating intermittent i.v. bolus administration of an anthracycline in combination with metronomic oral cyclophosphamide. Studies on PLD in different tumours, although insufficient to define an ideal dose schedule, indicate that lower doses (35 mg sqm^{-1}) are as effective as higher doses as long as dose intensity is maintained at $\geq$10 mg sqm^{-1} per week.[19] We have previously investigated the activity of this low-dose frequent schedule, which mimics a metronomic administration with the aim of increasing activity and lowering toxicity, in heavily pretreated advanced breast cancer patients. We obtained a clinical benefit (defined as objective responses + SD lasting $\geq$24 weeks) in 33% of patients, with a favourable toxicity profile.

In the present study, the overall clinical response rate was 62.1% (95%CI, 42.4–78.7%), with a pCR rate of 3.4% (95%CI, 0.09–17.8%). The small sample size, and in particular the small number of patients with ER-negative tumours, did not allow to draw conclusions on the activity of the treatment in different tumour subsets.

Limited data are available with PLD in the preoperative setting. Preliminary data with the association of PLD and cyclophosphamide have yielded a 73% clinical response rate.[20] The combination of PLD and weekly paclitaxel has yielded a clinical response rate of 74% and a pCR rate of 8–9%.[21,22] In a previous trial conducted in our Institution, the combination of PLD with cisplatin and continuous infusion fluorouracil (CCF) for eight courses provided a clinical response rate of 77.5%, whereas a pCR was obtained in three patients (7.7%).[23]

In our trial, 14% of the patients had locally far advanced tumours (T4b and T4d) which may partly account for the different outcomes seen in this as compared to previous series. Most importantly, the great majority (90%) of the patients included in this trial had an endocrine-responsive tumour at baseline. The absence of hormone receptors is generally recognised as the most powerful predictor of pCR after primary chemotherapy16. In a recent retrospective analysis of patients treated with preoperative chemotherapy at our Institution, we obtained a 3.3% and 0% pCR rates in patients with incomplete and highly endocrine-responsive tumours, respectively.[24] In the preoperative setting, inconclusive data are available on the association of endocrine therapy with chemotherapy: the combination did not show an improvement of pCR rate in populations unselected for hormone receptor status; however, an effect in proliferative rate decrease in patients with ER-positive tumours has been shown.[25–27] In a trial conducted in our Institution in premenopausal women with endocrine-responsive locally advanced tumours, we observed an increased clinical and pathological response rate by the addition of Gonadotropin Releasing Hormone (GnRH) analogue to chemotherapy as compared to a historical control group treated with chemotherapy alone.[28]

Moreover, the presence of a specific histotype might be correlated with the probability of response and with the outcome of patients. Response to primary chemotherapy is lower in terms of pCR (0–3%) in locally advanced invasive lobular carcinoma (ILC) compared with invasive ductal carcinoma (IDC).[29–31] In our series, 21 patients had a ductal infiltrating carcinoma, six a lobular infiltrating carcinoma and one a mucinous infiltrating carcinoma. Infiltrating lobular and mucinous carcinomas are characterised by significantly higher expression of steroid hormone receptors when compared with IDC, and this might have contributed to the lower response to preoperative chemotherapy.

Treatment was well tolerated. No grade 4 toxicities were observed. Treatment-related grade 3 toxicities were mostly associated to cutaneous toxicity, in particular hand–foot syndrome (n = 4, 13.8%) and skin toxicity (n = 3, 10.3%). Cutaneous toxicity was reversible after treatment discontinuation. There were no severe or prolonged neutropenia or leucopoenia, and alopecia was not observed in any of the patients treated in the trial.

In conclusion, the results from this phase II trial of preoperative PLD in association with metronomic cyclophosphamide demonstrate that this regimen was well tolerated, although with a limited activity in the preoperative setting. Other options, including endocrine therapy, should be considered in ER-positive locally advanced breast cancer in patients who are not suitable to receive a standard preoperative chemotherapy. Due to its favourable toxicity profile, this regimen may be further studied in the metastatic setting, especially in elderly patients or in patients who are not suitable to receive a standard chemotherapy.

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