Original article

Neoadjuvant pegylated liposomal doxorubicin in combination with cisplatin and infusional fluoruracil (CCF) with and without endocrine therapy in locally advanced primary or recurrent breast cancer

Rosalba Torrisi [a,d,*], Emilia Montagna [a,d], Eloise Scarano [a,d], Silvia Dellapasqua [a,d], Giuseppe Cancello [a,d], Monica Iorfida [a,d], Alberto Luini [b], Paolo Veronesi [b,e], Giuseppe Viale [c,e], Aron Goldhirsch [d], Marco Colleoni [a,d]

[a] Research Unit of Medical Senology, European Institute of Oncology, via Ripamonti 435 20141 Milano, Italy
[b] Division of Senology, European Institute of Oncology, via Ripamonti 435 20141 Milano, Italy
[c] Division of Pathology, European Institute of Oncology, via Ripamonti 435 20141 Milano, Italy
[d] Department of Medicine, European Institute of Oncology, via Ripamonti 435 20141 Milano, Italy
[e] University of Milan School of Medicine, via Festa del Perdono 7, 20135 Milano, Italy

ABSTRACT

Purpose: To explore the activity of pegylated liposomal doxorubicin (PLD) as neoadjuvant therapy of breast cancer.
Methods: The combination of PLD with cisplatin and infusional fluorouracil (CCF) for 8 courses was investigated in patients with primary or recurrent T2-T4a-d N0-3 M0 breast cancer. Patients with ER and/or PgR ≥10% tumors also received letrozole (±triptorelin).
Results: Forty patients entered the study. Four patients had recurrent tumors and 13 had cT4d tumors. Overall, clinical response rate was 77.5% whereas a pathological complete response (pCR) was obtained in 3 patients (7.7%), 4 when considering bilateral tumors. Noticeably 3 pCR were observed among the 10 patients with T4d ER positive tumors (33%). Eleven patients discontinued treatment before completion of the 8 planned courses.
Conclusions: Our results indicated that CCF yielded an appreciable rate of clinical responses in a series of very locally advanced tumors and an unusually high rate of pCR in T4d ER positive tumors, suggesting an enhanced cutaneous activity of PLD.

Introduction

Anthracyclines represent a key drug in the treatment of breast cancer at any stage. However, the use of these agents is burdened by several acute side effects as bone marrow and gastrointestinal toxicity, a very high rate of alopecia other than, most importantly, the risk of cardiac toxicity.[1] Since cardiac toxicity is dose dependent, it is recommended that the cumulative lifetime dose of conventional doxorubicin does not exceed 450 mg/sqm.[1,2] Recently, several liposomal anthracyclines formulations have been developed to increase the therapeutic index of conventional anthracyclines by maintaining antitumor efficacy.[3] Pegylated liposomal doxorubicin (PLD, Caelyx ®) is a formulation of doxorubicin in polyethylene glycol-coated liposomes with a prolonged circulation time and unique profile.[4] Pegylated liposomal doxorubicin has shown much lower toxicity compared with doxorubicin, in terms of cardiotoxicity, vesicant effects, nausea, vomiting and alopecia.[5] Pegylated liposomal doxorubicin's long circulation time seems to prevent the high peak concentration of anthracyclines that has been associated with the increased risk of cardiotoxicity.[6] A response rate up to 33% has been associated with PLD as single agent and ranged from 31 to 75% when PLD was administered in combination with other agents in patients with advanced breast cancer.[6] In a phase III study no significant difference either in terms of response rate and of disease free (DFS) and overall survival (OS) was observed between PLD and doxorubicin as first line therapy in patients with advanced breast cancer.[5] The activity and tolerability of PLD as primary therapy for locally advanced breast cancer have been investigated in small studies, showing good tolerability and a response rate up to 75%.[7–9]

* Corresponding author. Present address: Department of Oncology and Hematology, Istituto Clinico Humanitas, Viale A. Manzoni 56, 20089 Rozzano, Milano, Italy. Tel.: +39 02 82244502; fax: +39 02 82244590.
E-mail address: rosalba.torrisi@humanitas.it (R. Torrisi).

In the present study we investigated the activity of PLD in combination with cisplatin and infusional fluorouracil (CCF) as neoadjuvant therapy in a population of patients with locally advanced (including inflammatory) primary and recurrent breast cancer. The combination of cisplatin, infusional fluoruracil and epirubicin (ECF) has been extensively investigated showing substantial activity in the treatment of locally advanced operable and inoperable and metastatic breast cancer.[10–13] In addition the combination of PLD and platinum derivates has been extensively investigated in ovarian cancer and has shown a benefit in terms of PFS as compared with platinum alone.[14]

Based on earlier studies that demonstrated similar activity for PLD as long as a dose intensity ≥10 mg/sqm/week was maintained as well as combination studies with gemcitabine, we chose a PLD dose of 25 mg/sqm every 3 weeks.[15]

The primary endpoint of the study was the rate of objective responses. Secondary endpoints were the rate of pathological complete responses (pCR) and the tolerability of the combination.

Patients and methods

Patients with histologically proven primary (T2-T3-T4a-d N0-N3c) or with locoregional recurrent (rT1-T4a-d, N0-3c, M0 or M1 for chest wall recurrence) HER2 negative, any ER and/or PgR breast cancer consecutively admitted at the Department of Medicine of the European Institute of Oncology from February 2007 to December 2007 were enrolled in the study.

A trucut biopsy was performed for diagnosis and for assessment of tumor biological characteristics. Investigations (chest X-ray, abdomen ultrasound, bone scan and/or FDG-PET) were performed to exclude distant metastasis and blood tests were performed to assess bone marrow, renal and hepatic function. Cardiac function was assessed at baseline by ECG and echocardiography. A left ventricular ejection fraction (LVEF) ≥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, age between 18 and 70 years, white blood cells ≥3000/mm3, platelets ≥100,000/mm3, aspartate aminotransferase, alanine aminotransferase, ≤2.5 × upper limit of normal and bilirubin ≤1.5 mg/100 ml.

Written informed consent was obtained from all patients and the protocol was approved by the Ethical Committee.

Treatment

Patients were treated with the CCF regimen containing PLD 25 mg/sqm intravenously (IV) on d 1 cisplatin 60 mg/sqm IV on day 1 and fluorouracil 200 mg/sqm as a continuous infusion from day 1 through day 21 for 8 courses. Cycles were repeated every 21 days. Pegylated liposomal doxorubicin (Caelyx®) was provided at no cost by Schering Plough. A central venous catheter (CVC) in the subclavian or in the jugular vein contralateral to the site of the tumor was implanted in all patients before starting chemotherapy.

Patients with ER and/or PgR ≥10% tumor received also endocrine therapy which consisted of letrozole 2.5 mg/day in combination with Triptorelin in premenopausal patients, according to our previous results showing the activity of this combination as preoperative therapy in premenopausal patients with ER positive tumors.[16] Letrozole started concomitantly with the first course of chemotherapy. In premenopausal patients GnRH analog (triptorelin 3.75 mg 1 fl intramuscular every 28 dd) started concomitantly with chemotherapy and letrozole was added when estradiol levels were in the postmenopausal range according to the EIO laboratory reference values.

Radiotherapy was indicated in patients undergoing breast conserving surgery and in patients with T4 tumors. Patients with recurrent tumors previously treated with radiotherapy were offered radiotherapy on supraclavicular nodes.

Response criteria

Tumor was evaluated at baseline by physical measurement with caliper of the two largest diameters and by means of mammography and ultrasound After 4 and 8 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 tumor and were graded according to standard RECIST criteria.[17]

Patients with stable disease, partial remission or complete remission after 4 courses were candidate to receive 4 more courses of therapy. Pathological complete remissions were evaluated according to Kuerer et al.[18] A pCR was defined as a total disappearance of invasive tumor either in the breast or in the axilla: the presence of intraductal carcinoma qualified for pCR.

Estrogen receptor and PgR status, assessment of the proliferative activity (% of Ki-67 stained cells) and overexpression of HER2 were determined on core biopsies obtained for diagnosis, as previously published.[19] The results were recorded as the percentage of immunoreactive cells over at least 2000 neoplastic cells. Steroid hormone receptors status was classified as negative, poor (ER 1–9% of the cells), or positive (ER and PgR >10% of the cells). The value of Ki-67 labelling index was used as a cut-off in distinguishing tumors with low (<20%) and high (≥20%) proliferative fraction. The value of 20% was selected based on previous data from our group indicating that this threshold significantly correlated with higher response rate to preoperative chemotherapy.[19] 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 hybridization (FISH) was performed to assess the amplification of the HER2 gene.

Statistical considerations

The main objective of the study was to evaluate the rate of clinical response (partial and complete remission) after primary therapy with CCF. Secondary objectives were the rate of pCR and the safety of the combination.

Previous studies with infusional chemotherapy and anthracyclines have shown an overall response rate ranging from 75 to 98%.[20] Due to the comparable activity of PLD and doxorubicin, we expected similar clinical activity in our series.

Considering a Simon's two-stage optimal design with a significance level of $\alpha = 0.10$ and power of $(1 - \beta) = 0.90$, a total sample size of 38 patients was required in order to test the hypothesis of a maximum response rate of 60% for a poor treatment versus a minimum response rate of 80% for a good treatment.[21]

Results

From February 2007 to December 2007, 40 patients were enrolled in the study and all are evaluable for both clinical response and toxicity. Thirty-six women had primary breast cancer and 4 had recurrent breast cancer, 2 received both local and systemic treatment and 2 received only local treatment for the previous cancer.

Patient and baseline tumor characteristics are reported in Table 1. Only 12 patients had large T2 tumors, one patient had T4b tumor whereas 13 patients had inflammatory (T4d) tumors. Two

Table 1
Patient and tumor characteristics at baseline.

Characteristic	No. of patients	%
Total enrolled/evaluable	40/39	−
Age, years		
Median	46	−
Range	30−67	−
Menopausal status		
Premenopausal	24	60
Postmenopausal	16	40
Type of tumor		
Primary	36	90
Recurrent	4	10
Clinical Tumor size		
T2	17	42.5
T3	9	22.5
T4b	1	2.5
T4d	13	32.5
Clinical nodal status		
Nx	2	5
N0	13	32.5
N1	15	37.5
N2	5	12.5
N3	5	12.5
ER status		
ER absent	9	22.5
ER 1−9%	1	2.5
ER ≥10%	30	75
PgR status		
PgR absent	14	35
PgR 1−9%	2	5
PgR ≥10%	24	60
Ki-67		
<20%	9	22.5
≥20%	31	77.5
Grading		
1	0	−
2	16	40
3	14	35
NA	10	25

NA: not avaiable.

Table 2
Response after treatment.

	No	%
Evaluable patients	39	
Pathological complete response	3*	7.7
Clinical response	40	
Complete	2	5
Partial	29	72.5
Stable disease	7	17.5
Progression	2	5
Pathological tumor size	39	
Tx	3	7.8
Tis	1	2.6
T0	5	12.8
T1	12	30.7
T2	12	30.7
T3	5	12.8
T4b	1	2.6
T4d	0	−
Nodal status at surgery	39	
Nx	3	7.8
N0	14	35.8
N1	11	28.1
N2	3	7.8
N3	8	20.5
Type of surgery		
Breast conserving surgery	16	41
Mastectomy	23	59

•pCR were 4 when considering separately bilateral tumors.

patients had bilateral tumors. Two-third of patients had clinical (at ultrasound and/or at FDG-PET) positive nodes and in five patients sub and/or infraclavicular nodes were shown (cN3b).

Thirty patients had ER ≥10% tumors, 9 patients had ER and PgR absent tumors and 1 patient had ER <10% tumor. HER2 was overexpressed ($n = 1$) or equivocal ($n = 2$) by IHC in 3 patients but no gene amplification was shown by FISH and these patients were considered to have HER2 negative disease. The majority of patients (78%) had high proliferating (Ki-67 ≥20%) tumors. Surgery was performed in 39 patients, 1 patient refused to continue treatment after 4 cycles and subsequent surgery and was not evaluated for pCR.

Breast conserving surgery was feasible in 16 patients (41%) but this rate raised up to 62% when excluding patients with T4 tumors who were candidates to mastectomy irrespective of clinical response. Thirteen out of 36 patients underwent sentinel node biopsy only with no need for further axillary clearance.

All patients were evaluable for clinical response (Table 2). Two (5%) and 29 (72.5%) patients achieved a complete and partial response respectively with a cumulative clinical response rate of 77.5% [95% CI: 61.5−89.2]. Seven patients had stable disease and 2 patients (5%) progressed, one after 3 cycles and the latter at the 7th cycle after achieving a partial response. A pCR was obtained in 3 patients (7.7% 95%CI: 1.6−20.9) (4 when considering bilateral tumors because 1 patient with bilateral tumor obtained a pCR only in the inflammatory tumor). Tumor microfoci or isolated tumor cells were found in the breast in 2 additional patients.

Thirteen patients had inflammatory breast cancer (10 ER positive and 3 ER negative). Among patients with T4d tumors clinical

response rate also was high 77% [46−95] and comparable to that observed in non inflammatory tumors. Interestingly, 3 pCR were observed among the 10 patients with the T4d ER positive tumors (33%).

Twenty-nine patients completed 8 cycles of treatment whereas treatment was discontinued early in 11 patients. Reasons for discontinuation included patient refusal (1), port-a-cath related complications (1 deep venous thrombosis and 1 oedema), chemotherapy related toxicity (5), poor patient compliance (1), disease progression (2) and stability (1). Dose reduction of one of more drug was required in a relevant proportion of patients, albeit in most cases it was performed out of the protocol predetermined criteria of toxicity. The requirement for a 25% dose reduction was similar for each of the 3 drugs and was reasoned mainly by cutaneous and gastrointestinal toxicity other than prolonged leukopenia and neutropenia, although grade 3 events were unfrequent except of neutropenia.

The main grade ≥2 toxicities are summarized in Table 3.

Discussion

Anthracyclines represent the mainstay preoperative treatment for locally advanced and operable breast cancer.[22] However, cumulative limiting doses for either doxorubicin and epirubicin typically prevent the feasibility of retreating with anthracyclines. Given the widespread use of anthracyclines in the adjuvant treatment of early stage breast cancer, alternative agents should be exploited in case of locoregional recurrent inoperable breast cancer.

The availability of PLD, characterized by a low cardiotoxicity profile may allow extended use of anthracyclines in pretreated patients and/or to frail patients who are not suitable for receiving standard anthracyclines and/or to patients who refuse to receive hair-loss inducing treatments.

The present study demonstrated substantial activity of PLD in the neoadjuvant treatment of patients with locally advanced

Table 3
Main toxicities grade ≥2.

	Grade 2		Grade 3		Grade 4	
	N	%	N	%	N	%
Anaemia	7	17.5	0	–	0	–
Leukopenia	13	32.5	1	2.5	0	–
Neutropenia	8	20	18	45	2	5
Nausea	27	67.5	1	2.5	0	–
Vomiting	12	30	1	2.5	0	–
Diarrhea	2	5	0	–	0	–
Stipsis	9	22.5	1	2.5	0	–
Mucositis	12	30	1	2.5	0	–
PPE	21	52.5	2	5	0	–
Folliculitis	5	12.5	0	–	0	–
Asthenia	7	17.5	0	–	0	–
Epigastralgya	6	15	0	–	0	–
Biochemical*	1	2.5	1	2.5	0	–
Headache	3	7.5	0	–	0	–
Hypertension	1	2.5	1	2.5	0	–
DVT	0	–	2	5	0	–
Hypertrigliceridemia	0	–	0	–	1	2.5
Neurological	3	7.5	0	–	0	–
Alopecia	0		0			

*Included alteration of liver function (AST, ALT, bilirubin).
PPE: palmar-plantar erythrodysesthesia.
DVT: deep venous thrombosis.

primary and recurrent breast cancer. The overall clinical response rate was 78% although our study population included a large proportion of locally far advanced tumors as a 35% of patients presenting with T4 tumors, of which 3 were recurrent inflammatory tumors and 5 had sub or infraclavicular (N3b) node involvement. Interestingly, we obtained an impressive number of clinical responses (77%) and of pCR (23%) in patients with T4d tumors, a population with a particularly hominous prognosis.[23] These figures favorably compare with results obtained with standard anthracyclines in this tumor subset.[24] Clinical response and pCR have been shown to be surrogate markers of outcome also for inflammatory breast cancer,[24,25] and an increased pCR rate may represent an encouraging step forward to improve long term prognosis for this tumor subset.[24] Pegylated liposomes, due to their small size (ca. 100 nm) and long half-life, are able to penetrate the altered tumor vasculature, resulting in an enhanced delivery in the tumor site, as shown by the 10–15 fold higher selective accumulation of PLD in the Kaposi sarcoma skin lesions.[4,26] The increased angiogenesis, which has been clearly documented in inflammatory breast cancer[27] together with a damage of the vasculature due to the dermal lymphatic involvement may lead to an enhanced extravasation of liposomes and their selective accumulation in the skin.

Our results are hardly comparable with earlier results obtained with ECF in a series of 34 patients with inflammatory breast cancer reporting 79% of clinical responses. However, in this series, cisplatin was replaced by carboplatin and cyclophosphamide in almost 2/3 of patients and pCR rate was not reported.[13]

On the other hand, the data of the present study compare favorably with results from a retrospective series of 38 patients with ER and/or PgR ≥10% inflammatory breast cancer treated with ECF plus endocrine therapy.[28] While a similar rate of clinical responses was observed, there was a substantially lower proportion of pCR (7.8 vs 23%) with ECF vs CCF. A longer duration of both chemotherapy (6 vs 8 courses) and endocrine therapy may account for this difference.

Another interesting finding is that pCR were obtained in 3 patients with ER positive/PgR negative tumors and 1 patient with highly ER positive/PgR positive tumor. The absence of hormone receptors is generally recognized as the most powerful predictor of pCR after primary chemotherapy.[19] In a recent retrospective analysis of >500 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 tumors, respectively.[29] In the present series, either clinical or pathological response rates were lower in ER- and PgR- negative tumors. The small sample size and in particular the negligible number of patients with ER negative tumors, does not allow to draw conclusions on the activity of the treatment in different tumor subsets, but endocrine therapy may have contributed to the improved results obtained in hormone receptor positive tumors in the present series. The concomitant administration of preoperative chemotherapy and endocrine therapy is not commonly pursued, mainly due to the concern raised by the INT-0100 study which showed an advantage in the sequential rather than the concomitant administration of adjuvant CAF and tamoxifen.[30] In the preoperative setting inconclusive rather than detrimental data are available. The combination failed to show an improvement of pCR rate in populations unselected for hormone receptor status, but on the other hand, suggestions of an increased effect in proliferative rate decrease in patients with ER positive tumors have emerged.[31–33] We have also previously observed an increased clinical and pathological response rate by the addition of GnRH analog to chemotherapy in premenopausal women with ER and/or PgR ≥10% locally advanced tumors as compared to a historical control group treated with chemotherapy alone.[34]

Limited data are available with PLD in the preoperative setting. Preliminary data with the combination of PLD and cyclophosphamide has yielded a 73% clinical response rate.[7] The combination of PLD and weekly paclitaxel has yielded a clinical response rate of 74% and a pCR rate of 8–9%, although a lower proportion of patients with inflammatory tumors were included in both studies as compared with our series.[8,9]

The CCF regimen was quite well tolerated. Five patients discontinued treatment due to chemotherapy related events whereas the majority of patients completed treatment as planned, although dose reduction was applied in most cases. We observed a high rate of cutaneous toxicity (up to 65%) particularly palmar-plantar erythrodysesthesia (PPE), although only 5% of these events were grade 3, which is less than that reported in other studies, and all were reversible after treatment discontinuation.[6] The combination with infusional fluorouracil may explain the high incidence of G1-G2 cutaneous toxicity as well as the longer duration of PLD administration (8 cycles) as compared with other preoperative studies may account for the higher rate of grade 3 neutropenia (45%).[9] The availability of capecitabine could provide an attractive option to continuous infusional treatment. The combination with PLD has been investigated in a phase I study showing some activity in several solid tumors, but PPE remains the main toxicity with a 27% of grade 3 events.[35] Only 1 patient experienced a grade 4 non hematologic toxicity (hypertriglyceridemia). No grade 2 alopecia was observed.

In conclusion, the results of our study support the activity of PLD as preoperative treatment of locally advanced primary or recurrent breast cancer. Our results show that PLD may safely be proposed in this setting, as well as in patients with very locally advanced breast cancer.

The high activity in terms of clinical and pathological response rate observed with CCF in T4d endocrine responsive tumors, warrants further confirmation in a larger study.

Acknowledgments

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