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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

Silvia Dellapasqua [a,b,*], Manuelita Mazza [a,b], Debora Rosa [a,b], Raffaella Ghisini [a,b], Eloise Scarano [a,b], Rosalba Torrisi [c], Patrick Maisonneuve [d], Giuseppe Viale [e,f], Enrico Cassano [g], Paolo Veronesi [h], Alberto Luini [h], Aron Goldhirsch [b,i], Marco Colleoni [a,b]

[a] Medical Senology Research Unit, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
[b] Department of Medicine, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
[c] Department of Oncology and Hematology, Istituto Clinico Humanitas, Via Manzoni 56, 20089 Rozzano, Milan, Italy
[d] Division of Epidemiology and Biostatistics, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
[e] Division of Pathology and Laboratory Medicine, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
[f] International Breast Cancer Study Group Central Pathology Office, University of Milan, Via Festa del Perdono 7, 20135 Milan, Italy
[g] Department of Radiology, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
[h] Division of Senology, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy
[i] Oncology Institute of Southern Switzerland, Via Tesserete 46, Lugano, Switzerland

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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

* Corresponding author. European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy. Tel.: +39 02 57489502; fax: +39 02 57489571.
E-mail address: silvia.dellapasqua@ieo.it (S. Dellapasqua).

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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.