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A pilot study to investigate the feasibility and cardiac effects of pegylated liposomal doxorubicin (PL-DOX) as adjuvant therapy in medically fit elderly breast cancer patients

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Contents

Abstract

In this pilot study, we examined the feasibility and toxicity in 16 elderly women age ≥65 receiving six cycles of pegylated liposomal doxorubicin (PL-DOX) cyclophosphamide as adjuvant chemotherapy for breast cancer. An extensive cardiologic assessment was also performed including echocardiographic Doppler-based strain rate imaging (SRI), a promising new sensitive technique to assess cardiac function. All but one patient finished the six planned cycles without major dose reductions or delay, and with limited serious toxicity showing the feasibility of this regimen. Significant decreases in radial strain and strain rate were found after six cycles of treatment while left ventricle ejection fraction

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remained unchanged. SRI may be a useful tool in the follow-up of elderly patients treated with anthracyclines, allowing early initiation of preventive measures in order to prevent further irreversible cardiac damage.

Keywords: Breast cancer; Pegylated liposomal doxorubicin; Cardiac effects; Doppler myocardial imaging; Elderly

1. Introduction

Doxorubicin and other anthracyclines are an important class of agents for the treatment of early and advanced stage breast cancer, but have substantial acute and chronic toxicities. Anthracycline-induced cardiotoxicity is an important potential side effect, not only because of early ventricular dysfunction, but also by inducing late-onset, often irreversible, cardiomyopathy years after treatment. Advancing age is an important risk factor for cardiotoxicity from anthracyclines [1]. A successful strategy for reducing the cardiac toxicity associated with conventional anthracycline is encapsulating them in liposomes; this alters the tissue distribution and pharmacokinetics of these agents with the objective of maintaining efficacy and improving their therapeutic index. Pegylated liposomal doxorubicin (PL-DOX; Caelyx® or Doxil®) at a dose of 50 mg/m^2 q4w has been shown to have comparable activity but less cardiac toxicity than conventional doxorubicin 60 mg/m^2 at equal cumulative doses [2].

PL-DOX is a promising drug for elderly patients. While similar in efficacy, it causes less cardiac toxicity and is better tolerated than classical anthracyclines, both subjectively and haematologically. Adjuvant anthracycline chemotherapy is often withheld from elderly breast cancer patients because of its toxicity profile. Replacing classical anthracyclines by PL-DOX could increase the feasibility of such a treatment. There has been reluctance to use adjuvant chemotherapy in elderly patients in the past, but treatment with adjuvant chemotherapy should not be an age-based decision but instead take into account individual patients' estimated absolute benefit, life expectancy, treatment tolerance, and preference. Older patients with node positive, hormone negative breast tumors potentially derive the largest benefit in survival gain [3]. Also at the 10th International Conference on Primary Therapy of Early Breast Cancer (St Gallen, Switzerland; 14–17 March 2007), it was decided to omit age by itself as a reason to omit adjuvant chemotherapy.

For adjuvant therapy, anthracyclines are generally combined with other cytotoxic drugs. AC × 4 (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 q3w) has been a standard regimen for many years, but probably six cycles of anthracyclines are superior to four cycles. Also PL-DOX has been safely combined with cyclophosphamide (PL-DOX 30–35 mg/m^2 + cyclophosphamide 600 mg/m^2 q3w). This regimen was relatively well tolerated and active as first line therapy for metastatic breast cancer [4] and in neoadjuvant therapy [5]. Also in combination with cyclophosphamide and vincristine, PL-DOX was well tolerated, with recommended doses of 750 mg/m^2, 1.2 mg/m^2, and 35 mg/m^2 q3w, respectively [6]. We decided for this phase II trial to use the dosage of PL-DOX 30 mg/m^2 and cyclophosphamide 500 mg/m^2 q3w in elderly breast cancer patients. The dose intensity of PL-DOX is 10 mg/m^2/w), which has similar efficacy compared to the registered dose of 50 mg/m^2 q4w, but less toxicity [7]. For cyclophosphamide 500 mg/m^2 rather than 600 mg/m^2 was chosen because there is some evidence of increased exposure in elderly [8], and because this is also the dose used in the commonly used $FE_{100}C$ regimen.

Traditionally, the detection of anthracycline-induced cardiotoxicity has been based on the echocardiographic measurement of resting left ventricular (LV) ejection fraction (EF) or fractional shortening. These parameters are, however, insensitive in detecting subtle changes in myocardial function in early cardiotoxicity. Possibly, a certain critical amount of irreversible damage is necessary to cause appreciable changes in global systolic function or volumes. Then, functional deterioration progresses rapidly and is mostly irreversible [9]. Echocardiographic Doppler-based strain rate imaging (SRI) is a promising new, sensitive technique to assess cardiac function [10–12]. It allows to measure strain (myocardial deformation) and strain rate (rate of deformation), and has been proven clinically useful in other settings [10,13]. In oncology, it may be used to detect early subtle myocardial function changes such as in anthracycline-induced cardiac dysfunction [14–16].

B-type natriuretic peptide (BNP) [17,18] reflecting cardiac haemodynamic stress, and troponins [19,20] reflecting myocyte injury, are biochemical markers that also have been proposed as early and sensitive indicators of anthracycline-induced cardiotoxicity. Troponin I was found to be useful in the cardiac risk stratification of patients receiving classical anthracyclines and high-dose chemotherapy [20].

The aim of this study was to investigate the feasibility and toxicity of a regimen of PL-DOX and cyclophosphamide in the elderly population in adjuvant setting. A second goal was to study the cardiac effects of this therapy, and to investigate whether biomarkers like Troponin I and BNP and new, sensitive tools for assessing myocardial function can be used to detect cardiac toxicity at an early phase. A detailed report on the cardiac effects is discussed elsewhere, but a brief summary relevant for oncologists is shown here.

2. Methods

2.1. Patients

Eligible patients had histologically proven early breast cancer requiring adjuvant chemotherapy according to the

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judgment of the treating physician (lymph node positive or other features of high risk according to St Gallen criteria). The patients had to be aged ≥65 years at the time of inclusion. Other inclusion criteria were normal cardiac function (LVEF by scintigraphy or echocardiography within the normal range applicable in the local lab), performance status 0–2 (WHO scale), and adequate organ function. The main exclusion criteria were metastatic disease (M1), prior systemic anticancer therapy or radiotherapy for breast cancer, congestive heart failure or unstable angina pectoris, previous history of myocardial infarction within 1 year from study entry, uncontrolled hypertension or uncontrolled arrhythmias. The institutional review board of the two participating institutions approved the study protocol. All patients gave written informed consent.

2.2. Study design

This was a prospective open-label exploratory study of PL-DOX and cyclophosphamide in elderly breast cancer patients in adjuvant setting, performed in two Belgian centres, Leuven and Gent. The chemotherapy was initiated within 8 weeks after surgery. The regimen consisted of six cycles of PL-DOX 30 mg/m^2 over 1 h followed by cyclophosphamide 500 mg/m^2 over 30 min administered intravenously every 3 weeks. G-CSF is only allowed in secondary prophylaxis, i.e. in case of febrile neutropenia or prolonged grade 4 neutropenia. Each cycle could be started after 3 weeks if the neutrophil count was $\geq 1.0 \times 10^9\,L^{-1}$ and the platelet count $\geq 100 \times 10^9\,L^{-1}$, if stomatitis and plantar erythrodysesthesia had recovered to ≤grade 1, and if other toxicities had recovered to ≤grade 2. A patient was discontinued from the study if the start of a given cycle has to be postponed due to toxicity for more than 2 weeks. Dose re-escalation was not allowed. In case of neutropenia (absolute neutrophil count (ANC) $<0.5 \times 10^9\,L^{-1}$ for >5 days) or febrile neutropenia (temperature ≥38.5 °C, ANC $<1.0 \times 10^9\,L^{-1}$), the next cycle was given at 100%, but with prophylactic G-CSF. In case of a second episode of prolonged neutropenia or febrile neutropenia under prophylactic G-CSF, or in case of grade 4 thrombocytopenia, the dose of both drugs had to be decreased by 25%.

The manufacturer's recommendations for dose reduction in case of hand-foot syndrome, stomatitis, and other non-haematological toxicity were followed.

In patients with hormone sensitive disease, hormonal therapy was recommended but left at the discretion of the investigator. Hormone therapy was then started at least 3 weeks after the last chemotherapy administration. Loco-regional radiotherapy, if indicated along the institution's guidelines, was allowed and was preferably delivered within 30 days after the last chemotherapy cycle according to standard procedures. There was no radiotherapy session during the period of administration of PL-DOX cycles. Adjuvant trastuzumab was allowed after the end of chemotherapy and radiotherapy in Her-2 positive patients.

2.3. Cardiac evaluation

Blood samples for Troponin I and BNP, electrocardiograms and conventional echocardiograms with LVEF measurement as well as echocardiographic Doppler-based strain (S) and strain rate (SR) imaging were obtained within 4 weeks before beginning of chemotherapy, before the fourth cycle and within 7–14 days after the sixth cycle as well as prior to starting radiotherapy. Echocardiographies with S and SR data were acquired by two cardiologists in Leuven and one in Gent, who were all trained before the start of the study to use the same procedure. All echocardiographic studies were performed on a regular high-end scanner (Vivid 7, GE Vingmed, Horten, Norway). Troponin I was taken 4 h after the start of PL-DOX administration. At 1 and 3 years, tests are planned to be repeated. Data were routinely post-processed off-line using commercially available (EchoPac, GE Vingmed, Horton, Norway) and dedicated research software (SPEQLE, Lab on Cardiac Imaging and Haemodynamics, Cath. University Leuven, Belgium) [16] and evaluated by one reader.

2.4. Statistical analysis

This pilot trial was designed as an exploratory trial. The aim was to obtain data on toxicity and feasibility of this regimen, and on the magnitude and consistency of changes that occur in the measurements of Doppler myocardial echocardiography. The primary hypothesis was that no significant drop in strain rate would occur in patients treated with PL-DOX since in previous studies [2], only a very small part (3.9%) had a significant decline in LVEF measured by classical echocardiography, and no patients had clinical heart failure. A "significant drop" in strain rate was defined as a drop by more than two standard deviations from baseline in strain rate. With "events" thus defined, if 16 patients are treated with PL-DOX and no event is observed, there is 80% confidence that the true rate of events is less than 10% (0–10%). If one event is observed, the true rate is 0–27% with 95% confidence.

Continuous variables are reported as means ± standard deviations. The echocardiographic parameters for LV function were compared between the three follow-up visits (baseline, after three cycles and after six cycles) with repeated measures ANOVA (analysis of variance) followed by post hoc comparisons using *t*-test. We report on the differences versus baseline of the echocardiographic parameters. A *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Patients and treatment characteristics

Enrollment began in February 2006 and was completed in September 2006. Patients details are shown in Table 1.

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Table 1
Baseline characteristics of the 16 patients included in the study

Characteristic	
Age (year)	
Median	69
Range	65–74
ECOG performance status—no. (%)	
0	12 (75%)
1	1 (6%)
Unknown	3 (19%)
Tumor stage—no. (%)	
Stage I	2 (12%)
Stage II	3 (19%)
Stage III	11 (69%)
Histology	
Invasive ductal carcinoma	13 (81%)
Invasive lobular carcinoma	3 (19%)
Hormone receptor status—no. (%)	
ER and/or PR positive	10 (63%)
ER and PR negative	6 (37%)
Her2 positive—no. (%)	
IHC 3+ or FISH positive	8 (50%)
IHC 0-1 or 2+ and FISH negative	8 (50%)

ER: estrogen receptor; PR: progesterone receptor; IHC: immunohistochemistry; FISH: fluorescence in situ hybridization.

One potentially eligible patient was not included in the study because of poor echocardiographic images. In one patient, treatment was prematurely stopped after four cycles because of neutropenia and intolerance. Six patients (37.5%) had a dose reduction due to toxicity, while eight patients (50%) had a dose delay of 1–5 weeks, mainly because of neutropenia (four) and/or hand-foot syndrome (two). Mean and median dose intensity for the 15 patients who completed the six cycles were 27.5 and 27.7 mg/m^2 per 3 weeks, respectively for PL-DOX, and 462.5 and 459.9 mg/m^2 per 3 weeks, respectively for cyclophosphamide. All Her-2 positive patients ($n = 8$) received adjuvant trastuzumab for 1 year after the end of radiotherapy and chemotherapy, but this did not interfere with the results which were obtained prior to radiotherapy and trastuzumab administration.

3.2. General toxicity

Treatment was relatively well tolerated, although grade 3 side effects occurred (see Table 2). Observed toxicities are consistent with previously reported studies on PL-DOX.

Table 2
Toxicities[a]

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	9 (56%)	1 (6%)	0	0
Neutropenia	8 (50%)	4 (25%)	3 (19%)	0
Anorexia	6 (38%)	1 (6%)	0	0
Nausea	7 (44%)	4 (25%)	1 (6%)	0
Vomiting	4 (25%)	2 (13%)	0	0
Constipation	7 (44%)	2 (13%)	0	0
Diarrhea	2 (13%)	2 (13%)	0	0
Fatigue	6 (38%)	7 (4%)	1 (6%)	0
Hand-foot syndrome	3 (19%)	6 (38%)	2 (13%)	0
Rash	2 (13%)	4 (25%)	0	0
Stomatitis	6 (38%)	1 (6%)	0	0
Alopecia	7 (44%)	0	0	0

[a] Expressed as the highest grade per patient; according to CTC-NCI rating scale (Version 3.0): http://ctep.info.nih.gov/reporting/ctc.html.

3.3. Cardiac effects of pegylated liposomal doxorubicin and cyclophosphamide

Cardiac data on all 16 patients are summarized in Table 3. No patients developed clinical signs of heart failure. Neither significant rhythm disturbances, or conduction abnormalities, nor signs of myocardial injury were seen on electrocardiograms.

Conventional echocardiography showed there was no change in average EF between baseline and after six cycles. In contrast, a significant reduction in radial peak systolic S and SR were noted after six cycles of PL-DOX (Table 3). Three patients had significant drops (more than two standard deviations from baseline) in longitudinal deformation, and three patients had significant drops in radial deformation (two patients had significant drop in both longitudinal and radial deformation while one patient had a drop only in radial and longitudinal directions, respectively).

4. Discussion

This pilot study shows that a combination of PL-DOX and cyclophosphamide is feasible in an elderly breast cancer population. Although a significant proportion of patients needed some delay or dose reduction, the large majority of patients were able to finish the planned six cycles. The median PL-DOX dose intensity of 9.2 mg/m^2 per week was close to 10 mg/m^2 per week which is considered as an optimal dose intensity. Although the study was not intended to directly

Table 3
Cardiac evaluation of PL-DOX and cyclophosphamide ($n = 16$)

	Baseline (±S.D.)	After three cycles (±S.D.)	After six cycles (±S.D.)	p (six cycles vs. baseline)
LVEF (%)	69 ± 7	70 ± 6	68 ± 5	$p = 0.46$
LV radial systolic SR (s^{-1})	4.6 ± 1.2	3.6 ± 1.5	3.3 ± 1.0	$p < 0.01$
Radial sys S (%)	50 ± 12	38 ± 10	33 ± 8	$p < 0.01$
BNP (ng/l)	202 ± 107	188 ± 170	159 ± 105	$p = 0.39$
Troponin I (ng/ml)	0.014 ± 0.01	0.018 ± 0.01	0.012 ± 0.004	$p = 0.51$

LVEF: left ventricle ejection fraction; LV: left ventricle; SR: strain rate; S: strain; BNP: brain natriuretic peptide; S.D.: standard deviation.

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compare side effects between PL-DOX and classical anthracycline therapy, the present and other studies suggest that toxicity is less pronounced in the PL-DOX regimens. This regimen needs further evaluation in elderly patients.

In the present study, conventional parameters of systolic or diastolic function did not show any significant changes throughout treatment follow-up. No patient showed decrease in LVEF of ≥20% from baseline to a final value of ≥50%, or a decrease of ≥10% from baseline to a final value of less than 50%, nor did they show any clinical evidence of CHF. This is in concordance with previous studies that showed that liposomal anthracyclines had reduced cardiotoxicity as defined by these parameters, as compared to classical anthracyclines. O'Brien et al. conducted a prospective phase III trial comparing pegylated liposomal doxorubicin 50 mg/m^2 (every 4 weeks) or conventional doxorubicin 60 mg/m^2 (every 3 weeks) in 509 patients with metastatic breast carcinoma and no prior evidence of cardiac disease [2]. Overall risk of cardiotoxicity was significantly higher with doxorubicin than PL-DOX (during study follow-up, 10 patients in PL-DOX group and 48 patients in doxorubicin group developed cardiotoxicity by the defined criteria). In our study group, the cumulative dose of PL-DOX was 180 mg/m^2, which is lower than in previous studies assessing cardiotoxicity, also explaining the fact that no patient presented a significant decrease in LVEF or clinical signs of heart failure.

In contrast to conventional echocardiography, however, myocardial deformation parameters obtained by Doppler echocardiography allowed the detection of subtle but significant changes in radial LV function after six cycles of PL-DOX. Although the numbers were small, 3 out of 16 patients (19%) had a significant drop in SRI, and for the whole group the decline was significant. Conventional echocardiography does not show significant LVEF changes unless a critical amount of irreversible myocardial damage has taken place and thus might alert too late for anthracycline-associated cardiotoxicity. Our study shows abnormalities in regional myocardial function that might appear before any noticeable change in global systolic function as assessed by LVEF. Our data support the notion the SRI is a more sensitive method to detect early anthracycline-associated cardiotoxicity [15,16]. The prognostic value of the early detected changes might be evaluated during the long-term follow-up of the patients until 3 years after inclusion.

The biomarkers BNP and Troponin I were also studied. BNP is a cardiac hormone [17] whose plasma level begins to increase in response to increased cardiac wall stress in patients with asymptomatic heart failure and increases markedly according to the severity of heart failure. BNP values are useful for the evaluation, management, and prognosis of patients with heart failure, and have been proven as a useful tool in the screening of patients at high-risk for LV dysfunction, including those treated with an anthracycline-containing regimen [18]. Troponin T and Troponin I have emerged as specific and sensitive biomarkers for myocardial damage. Elevations of serum levels of Troponin T after anthracycline chemotherapy have been reported to indicate early myocardial damage and were found to predict subsequent subclinical and clinical cardiac morbidity and mortality [19]. In our study, there were no significant or relevant changes in BNP or Troponin I levels at the different time points versus baseline. This might be due to the fact that cardiac function changes were too small to induce a release of these biomarkers. This may also be related to the lower cumulative chemotherapy doses used in the present population as compared to previous studies.

A limitation of this study is the small sample size; it is clear that the effects of anthracyclines (classical and liposomal) on deformation parameters need to be explored further in larger groups. A second limitation is the lack of geriatric assessment. However, this study was directed to a 'healthy' elderly population that benefits most from adjuvant chemotherapy, as shown by the ECOG PS (knowing that this only partially reflects the general status), and also by the inclusion criteria for this study that did not allow frail patients. Moreover, the population was not very old (65–74 years).

In conclusion, PL-DOX and cyclophosphamide is a feasible regimen in elderly patients with early breast cancer although dose modifications are required in several patients. Further studies evaluating differences between classical anthracyclines and PL-DOX are ongoing. Echocardiographic Doppler-based regional myocardial functional assessment is feasible and sensitive and documents subtle changes before conventionally used indices like LVEF and long before obvious clinical problems arise. SRI might be a useful tool to allow early initiation of preventive measures in order to prevent further irreversible cardiac damage.

Conflict of interest

There is no conflict of interest for any of the authors. This study was supported by an unrestricted grant from Schering Plough, Belgium, but was conducted independently.

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Biography

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