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ORIGINAL ARTICLE

Liposomal pegylated doxorubicin plus vinorelbine combination as first-line chemotherapy for metastatic breast cancer in elderly women ≥65 years of age

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Abstract
Purpose No standard chemotherapy has been so far definitely settled for elderly patients with metastatic breast cancer (MBC). In order to identify a regimen with acceptable efficacy and low burden of non-overlapping toxic effects, a combination consisting of liposomal pegilated doxorubicin (PLD) with alternating oral and intravenous vinorelbine (NVB) has been investigated in a phase II study.
Methods Thirty-four consecutive patients (median age 71 years; range 65–82) with MBC have been enrolled. Based on 4-weekly cycles, PLD 40 mg/m^2 plus NVB 25 mg/m^2 i.v., have been administered intravenously on day 1 and oral NVB 60 mg/m^2 on day 15.
Results All patients were assessable for safety and efficacy. In all, 17 responses were documented with three complete responses (CR) and 14 partial responses, with an overall response rate of 50% (95% CI 36–66). Median overall survival time was 13 months and the median time to progression 8 months. Interestingly, all the patients with CR are still alive with a disease-free survival of more than 1 year. The main toxicity was neutropenia: grade 3 in 15% and grade 4 in 11% of patients, respectively. Febrile neutropenia was recorded in three patients not requiring dose reduction. Other frequently reported adverse events included: anemia, nausea, vomiting, stomatitis, all rarely severe. The evaluation of quality of life (QoL) did not show any significant change during the study.
Conclusions Our data suggest that this combination is active and well tolerated in elderly patients with MBC and could represent another efficacious chance for the management of this population.

Keywords Metastatic breast cancer · Vinorelbine · Liposomal pegylated doxorubicin · QoL · Elderly patients

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Introduction

Incidences of breast cancer are higher in elderly patients (≥65 years) as compared to younger ones and elderly associate to an improved risk of death up to a hazard ratio (HR) of 2.46 for ≥75 years [30]. Moreover, older patients may present with comorbid illnesses and frailty that limit therapeutic choice and patients aged 70 years and above are less likely to receive chemotherapy or radiotherapy [3, 5]. Part of this difference could be explained by their shorter survival time after the diagnosis of metastatic breast cancer (MBC) and their lower risk of developing brain and bone metastases [15, 19]. An important therapeutic option

of elderly MBC is hormonal therapy. When patients evolve toward hormone-refractory disease, they are often treated with monochemotherapy regimens including anthracyclines, taxanes, capecitabine, gemcitabine, trastuzumab, and bevacizumab and the new drugs in monotherapy [10]. Only few chemotherapy combinations have been designed for the specific needs of elderly patients. Some examples are docetaxel and capecitabine, Carboplatin/paclitaxel/trastuzumab, carboplatin and paclitaxel [10]. Consequently, the need to investigate better treatments for this age group seems to be even greater than for younger patients, especially considering that, for fear of excessive toxicity deriving from chemotherapy and the concern of the quality of life (QoL), elderly patients are often offered suboptimal treatments for advanced disease [3].

Anthracyclines such as doxorubicin are considered among the most active single agents in metastatic breast cancer. However, the use of anthracyclines is limited by the acute toxicities and by their potential to cause cardiac damage. This is characterized by myocardial injury whose initial clinical or instrumental signs can be sometimes detected even following the administration of the first dose [16]. Impaired cardiac function can eventually result in clinically overt congestive heart failure (CHF). In the retrospective series by Von Hoff et al. [28], a 7.5% incidence of clinical cardiomyopathy was recorded at cumulative doxorubicin doses of 550 mg/m^2. This incidence rises to 20% when careful prospective observations are made, including serial determinations of left ventricular ejection fractions (LVEF), and close clinical follow-up [15]. These observations have led to setting cumulative dose limitations, generally 450–500 mg/m^2, for treatments employing free doxorubicin given by bolus every 3 weeks.

An attempt to improve the therapeutic index of anthracyclines has been achieved by encapsulating the drug into liposomes [9]. Pegylated liposomal doxorubicin (PLD) (CAELYX, Schering Plough, Kenilworth, NJ, USA), a new formulation of doxorubicin, has demonstrated efficacy as single agent in patients with metastatic or recurrent breast cancer, reaching objective response rates ranging from 31 to 33% [18, 22]. Compared to conventional doxorubicin, PLD has a similar efficacy along with an improved safety profile, characterized by a significantly lower incidence of cardiac events as well as by a reduced incidence of myelosuppression, nausea, vomiting, and alopecia [4, 24]. In groups of patients with high risks for developing cardiotoxicity, the risk of developing a cardiac event was significantly lower for patients treated with PLD than for those treated with the conventional formulation. In fact, in a recent phase III trial the risk of developing cardiotoxicity was significantly higher for patients receiving doxorubicin than for those receiving PLD ($P < 0.001$, HR = 3.16 for comparison of cumulative anthracycline dose at the first, protocol-specified, cardiac event) [20].

Several phase II studies in patients with MBC have also reported that PLD is effective in combination with other antineoplastic agents, achieving response rates ranging from 35 to 75% [12, 23, 26]. In this regard, vinorelbine seems one of the most appropriate drugs to be used in combination with PLD. Besides having been largely evaluated in the management of MBC with valuable results in terms of both efficacy and tolerability, the recently introduced oral form of this vinca alkaloid derivative has disclosed new and useful perspectives particularly for elderly patients. Comparative studies have shown that oral vinorelbine is characterized by a pharmacokinetic profile very similar to intravenous form [27]. The intra- and inter-patient variability of blood exposure of the two forms substantially do not differ and the observation that food intake does not have any influence on oral vinorelbine pharmacokinetic parameters [6], assure to achieve equal results in terms of both efficacy and safety [13]. The lack of ageing influence on the clearance of oral vinorelbine as compared to the injectable form [21] is also worth mentioning. Moreover, PLD (administered prior to vinorelbine) has shown to induce higher vinorelbine area under curve total (AUC_{tot}) and plasma levels during the elimination phase of vinorelbine. This effect was likely due to a P-gp membrane glycoprotein inhibition by PLD vescicles, which, in turn, may influence the plasma level of the associated VNR [8].

Based on these considerations, a phase II study to evaluate the safety and the efficacy of the combination of PLD plus alternating oral and intravenous vinorelbine as first-line chemotherapy for MBC in women ageing ≥65 years has been designed. Alternate intravenous and oral administration of vinorelbine was selected in order to avoid the hospitalization time related to the intravenous administration of vinorelbine at day 15.

Patients and methods

Patient selection

Women were eligible if they had a histologically proven MBC and were ≥65 years old. Previous adjuvant chemotherapy, also including anthracycline-containing regimens, was accepted provided the treatment had been withdrawn at least 12 months before the admission to the study. The patients enrolled in the study with positive or unknown status for estrogen receptor expression (21 patients) were all previously treated with one line of hormonal therapy (tamoxifen and/or aromatase inhibitor) and have experienced a PD. All the patients with negative status for

estrogen receptor expression were treated with PLD + vinorelbine combination as first line therapy. Hormonal therapy had to be discontinued at least 8 weeks prior entering the study. Radiation therapy was acceptable if it was completed >3 weeks before and did not include the only site of measurable disease. Patients were required to have at least one bidimensionally measurable target lesion (documented according to WHO criteria by CT scan or MRI), ECOG performance status 0–2; life expectancy ≥3 months; adequate bone marrow, hepatic and renal functions. Cardiac function had to be assessed by the evaluation of the LVEF using MUGA scan or bidimensional echocardiography and all the patients enrolled had a LVEF ≥ 50%.

Clinically detectable CNS involvement, a pre-existing heart disease determined by clinical signs of cardiac failure, left ventricular hypertrophy, ascites and severe pleural effusion were considered criteria for exclusion. The protocol was submitted to independent ethical committees and the approvals had to be obtained prior to the start of the study. Written informed consent was obtained from each participating patient at the entry into the study.

Treatment plan and evaluation

The combination regimen consisted of PLD 40 mg/m^2 plus NVB 25 mg/m^2 given by intravenous route on day 1, and NVB 60 mg/m^2 by oral route on day 15; cycles were repeated every 4 weeks. Each patient received the study drugs for a maximum of six cycles unless disease progression or unacceptable toxicity previously occurred.

Before entering the study, patients underwent a complete medical history and physical examination, including evaluation of performance status, body weight, and vital signs. Tumor assessment by imaging was performed to determine the extent of disease; photographs of all cutaneous lesions were also done. Laboratory data included complete blood cell count with differential, platelet count, blood chemistry and urine analysis.

During treatment, blood cell count and blood chemistry evaluation were repeated every 2 weeks. Cardiac monitoring included ECG before each cycle and the evaluation of LVEF every two cycles and at the end of therapy. Treatment was stopped if LVEF decreased to more than 15% of the initial pretreatment value and/or if the patients developed signs of cardiopathy. Imaging procedures for the assessment of response according to WHO criteria were repeated every three cycles and at the end of treatment. Patients' follow-up was carried out every 3 months and it included imaging. Target lesions, evaluated by computed tomography (CT) or gadolinium-enhanced magnetic resonance imaging (Gd-MRI), have been centrally reviewed by two blinded radiologists.

The clinical response on target lesions was evaluated according to the following criteria derived from World Health Organization (WHO): a complete response (CR) was defined as the disappearance of all clinical, radiological and laboratory evidences of disease lasting at least 4 weeks; partial response (PR) was defined as a reduction in the sum of the product of the largest perpendicular diameters of target lesions of at least 50% lasting 4 weeks or more; stable disease (SD) was defined as a <50% decrease or <25% increase in the size of tumor lesions; progressive disease (PD) was defined as an increase of the size of target lesions >25% or the appearance of any new lesion [29]. All the patients who experienced an objective response had continued to be treated with the same schedule until progression and up to 12 total cycles. All the patients with SD continued the same schedule of therapy for maximum six cycles and then they underwent to follow-up until a PD was recorded. In details, all the 26 patients with a disease control (CR ± PR ± SD) received more than 6 cycles of chemotherapy and 15 patients continued to respond up to 12 cycles. At that time the patients were subjected to a second-line therapy.

Toxicity was evaluated using the National Cancer Institute criteria (version 2.0).

Dose-adjustment criteria were mainly based on hematologic toxicity. Treatment was delayed if the absolute neutrophil count in the day of treatment was less than 1,500 dl^{-1} and platelets less than 100,000 dl^{-1}. In case of grade 3 or 4 neutropenia, the same doses of the drugs were given with prophylactic administration of recombinant human granulocyte colony stimulating factor (rhG-CSF; Granocyte, Aventis Pharma, Bridgewater USA) at the dose of 150 μg/m^2 subcutaneously from day 2 to day 8 or/and from day 15 to day 21 according to the nadir of neutrophils. If grade 3 or 4 neutropenia reappeared, the doses of both drugs were reduced by 25%. In case of grade 3 thrombocytopenia or grade 2–4 hand-foot syndrome the dose of PLD was reduced by 25%. In case of decrease of LVEF > 15%, the PLD dose was reduced by 20%, whereas a decrease of LVEF > 40% obliged the discontinuation of PLD, irrespective of the presence or absence of clinical signs of heart failure.

Quality of life was evaluated using the EORTC QLQ-C30 (appropriately validated for Italian population) questionnaire at study entry, every 8 weeks during the treatment, and 8 weeks after the end [1].

For the assessment of patient's self-maintenance, each individual was evaluated before chemotherapy and after six cycles using a geriatric multidimensional evaluation

method, including Activity of Daily Living (ADL) [3, 14] and instrumental activity of daily living (IADL) [31].

Statistical analysis

All registered patients were included in the efficacy analysis (intent-to-treat analysis). The phase II study was prospectively projected according to the Simon's two-stage optimal design to test the hypothesis that the combination PLD-vinorelbine was an active treatment. The objective response rate (CR + PR) was the primary end-point. Secondary objectives included safety evaluation, estimate of time to progression (TTP), survival, and the effect of treatment on QoL. According to the selected design, a number (n1) of patients enter the first stage of the trial. The accrual continues to a total of n2 patients only if a specified r1 response rate is achieved in the first series. We have selected as target activity at 30–50% response rate, with a 0.05 alpha error and a 0.20 beta error. In this case the treatment under investigation should be considered non-active if it produced less than seven responses out of 22 consecutive patients in the first series and less than 17/46 pts in the overall series. As tumor responses occurred in seventeen patients of 34 women enrolled, no additional patients were recruited.

Survival plots were constructed by the Kaplan Meyer method and survival data were analyzed by the GraphPad Instat 3.2 statistic software. Median follow-up was 13 months.

Results

Patient characteristics

Between October 2003 and December 2004, 34 women have been enrolled in the trial. Main patient and tumor characteristics are summarized in Table 1. The median age was 71 years (range 65–82) and the median performance status was 1. Thirteen patients (38%) had received prior adjuvant chemotherapy (of whom, 9 with anthracycline-containing regimens), 17 patients (50%) had received prior adjuvant hormone therapy with tamoxifen, and 13 (38%) had undergone prior adjuvant radiation therapy. Interestingly, seven patients experienced recurrence during the adjuvant hormonal therapy with tamoxifen and, for the patients who received adjuvant chemotherapy, the mean time from the last course of chemotherapy prior to inclusion in the study was 12.2 ± 7.4 months. Twenty-one patients were subjected to a first-line hormonal therapy with aromatase inhibitors for their metastatic disease prior to their enrolment in the study. All the patients who were subjected to first-line hormonal therapy developed a PD and subsequently were included in the study.

Table 1 Patient characteristics

	Number (%)
Enrolled patients	34 (100)
Age (years)	
Median	71
Range	65–82
PS ECOG	
0	16 (47)
1	15 (44)
2	6 (9)
Estrogen receptors status	
Positive	13 (38)
Negative	13 (38)
Unknown	8 (38)
Prior therapy	
Surgery	30 (88)
Radiotherapy	13 (38)
Adjuvant hormonal therapy	17 (50)
First-line hormonal therapy	21 (62)
Adjuvant chemotherapy	13 (38)
Anthracyclines	9 (26)
No anthracyclines	4 (12)
Sites of disease	
Liver	11 (32)
Bone	17 (50)
Lung	9 (26)
Node	10 (29)
Pleura	3 (9)
Skin	2 (6)
Breast (contralateral)	2 (6)
Number of involved sites	
1	7 (20)
2	17 (50)
3	10 (29)

The median number of metastatic sites was 2 (range 1–3) and the main sites were: bone in 17 (50%) of patients, liver in 11 (32%), lymph nodes in 10 (29%) and lung in 9 (26%). The main comorbidities recorded were: hypertension in 9 (26%) patients, chronic bronchopulmonary disease in 4 (12%) and diabetes mellitus in 6 (17%).

Clinical activity evaluation

All patients included in the study were assessable for response. The median follow-up time was 12 months. Three (9%) CRs and 14 (42%) PRs have been achieved with an overall response rate (CR + PR) of 50% (95% CI 36–66%).

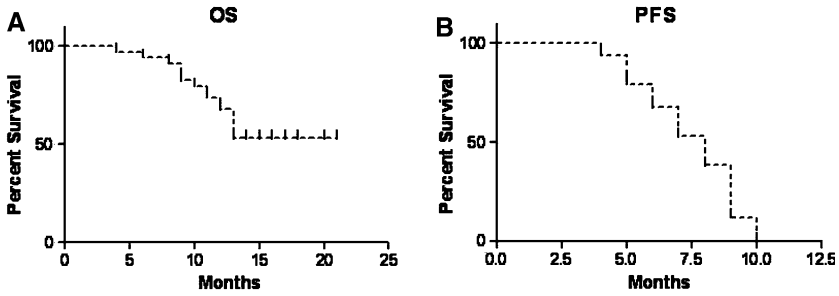

Fig. 1 Kaplan–Meier plots representing the overall survival (**a**) and the progression-free survival (**b**) of the patients enrolled in the study

In addition, nine patients (26%) obtained SD so that the clinical benefit (CR + PR + SD lasting ≥12 weeks) accounts for 77% (95% CI 62.7–88.9%). Interestingly, 1 CR, 3 PRs and 2 SDs were obtained in patients who have performed anthracycline-based adjuvant chemotherapy. Another CR and two PRs were obtained in patients who have performed not anthracycline-based adjuvant chemotherapy. At the time of the analysis, eight patients had progressed (23%). Three out of eight patients who progressed have been pre-treated with anthracyclines and another patient who progressed was pre-treated with no-nanthracyclines-containing chemotherapy. The median TTP, calculated by Kaplan–Meier plot, was 8 months (mean 7.44, 95% CI 6.7–8.0) and the median overall survival was 13 months (mean 13.11, 95% CI 11.8–14.3) (Fig. 1). Interestingly, the patient with CR has maintained the response for 15 months and is still alive after 20 months.

Toxicity evaluation

A total of 195 cycles of the combination have been administered, with a median of 5 per patient. Hematological side effects of all grades were the toxicities most commonly observed. In particular, five patients (14.7%) displayed grade 3 neutropenia and four (11.7%), grade 4. Febrile neutropenia (FN), defined as grade 4 neutropenia with fever >38°C, was reported in three (9%) patients (Table 2). In all cases FN appeared after the sixth cycle. The mean duration of neutropenia was 3 days (2–7 days). FN was treated with intramuscle and oral antibiotics only in one and hospitalization was never required. These patients required a delay of the therapy of 1 week without any dose reduction. The median duration of treatment delay was 4 days (range 4–7) and the median time interval between chemotherapy courses was 25 days (range 25–30).

Interestingly, no patient required discontinuation of the therapy. Thrombocytopenia and anemia occurred in 15 (44.1%) and 14 (41.2%) patients, respectively, but their severity was of grade 3 in only three and two of them, respectively (Table 2). Among the non-hematological toxicities, gastrointestinal disorders were the most frequent.

Table 2 Toxicity by patients and by cycle according to the NCI-CTC

Adverse event	By cycle		
	Overall incidence *N* (%)	Grade 3 *N* (%)	Grade 4 *N* (%)
Neutropenia	109 (59)	21 (10)	10 (5)
Anemia	70 (36)	13 (6)	1 (0.5)
Thrombocytopenia	36 (18)	9 (5)	–
Infection	8 (4)	2 (1)	–
Nausea	112 (57)	1 (0.5)	1 (0.5)
Vomiting	72 (37)	8 (4)	1 (0.5)
Diarrhoea	34 (17)	6 (3)	–
Stomatitis	61 (31)	12 (6)	–
Alopecia	NA	NA	NA
Phlebitis	2 (1)	1 (0.5)	–
Arrhytmia	2 (1)	–	–
Headache	26 (13)	7 (3)	–
Hand-foot syndrome	10 (5)	2 (1)	–

The total number of chemotherapy cycles administered to the patients was 197

The number of patients who experienced nausea and vomiting was 76 and 47%, respectively, but only two and four patients displayed grade 3 or 4. Stomatitis occurred in 63% of patients and it was scored as grade 3 in only five patients (14%). Hand-foot syndrome was recorded in six patients, but only one patient had grade 3 (Table 2). Moreover, no death due to toxicity was recorded.

The study population received a median cumulative dose of PLD of 210 mg/m^2 (range 140–280). The relative dose intensity was 92% for both drugs. The median value of LVEF at the end of treatment was 61% as compared to 62% at baseline (paired Student *t* test, not significant). Nine patients presented a LVEF decrease after the treatment. Two out of these nine patients have been previously exposed to anthracycline, other three had a history of hypertension under pharmacological control and other two had diabetes treated with oral hypoglycemic agents. However, only in two cases a decrease to <50% was observed (44 and 46% after four and six cycles respectively). Only in one of these patients the extent of the

reduction was 15%, but it did not require PLD dose reduction. In one patient a recovery to normal values after the cessation of therapy was recorded, while in the other one a residual decrease 12 months after the suppression of treatment was found. Interestingly, these two patients had diabetes and hypertension, respectively, as co-morbidities. Two patients showed grade 2 arrhythmia, but chemotherapy was never withheld.

Quality of life evaluation

Thirty-one patients completed at least one questionnaire at baseline and 26 of them filled in the quality of life (QoL) questionnaire until the sixth cycle regularly and correctly. The rate of completed questionnaires decreased as follows: first evaluation 91%, second evaluation 85%; third evaluation 73%, fourth evaluation 73%. The reasons for the lack of compliance include patient's refusal (3 cases), disease progression (3) and toxicity (1). Throughout the six courses of treatment, the score of the EORTC-C30 showed no significant changes. Consequently, based on the EORTC-C30 criteria, QoL, was not affected by the treatment course. The cognitive and emotional scores worsened; as far as symptom scores are concerned, an improvement of fatigue and pain was observed. Only 27 patients recorded the ADL and IADL questionnaires at the baseline and after six courses. After six cycles, IADL indexes increased in 4/27 patients (15%), remained stable in 20/27 (74%) and decreased in 3/27 (11%). Regarding ADL scores, after six cycles, they improved in 2/27 (7%) patients, did not change in 24/56 (89%), and worsened in 1/27 (4%). After six chemotherapy cycles, IADL and ADL indexes improved or kept unchanged in 89 and 96% of evaluable cases, respectively. No significant correlation was observed between ADL and IADL indexes after chemotherapy and the response to the treatment. Moreover, both IADL and ADL changes were not statistically significant ($P > 0.05$).

Discussion

The combination PLD plus alternate intravenous and oral vinorelbine represents a step forward in the management of elderly patients with MBC and, to our knowledge, the present study represents the first experience in the treatment of a particular subset of patients often complicated by associated co-morbidities. The results obtained have completely fulfilled the objectives of the study. In fact, we have demonstrated that this combination chemotherapy regimen is highly effective and totally well tolerated in elderly patients. The consistent benefits of this treatment (51% OR rate along with a median TTP of 8 months and a median survival time of 15 months) have not been overwhelmed or limited by the onset of signs or symptoms due to toxic effects, thus allowing to maintain a high global health status of patients throughout the whole treatment. In detail, the lack of anthracycline-induced cardiac toxicity by PLD, the oral dosing of vinorelbine on day 15 which offers the opportunity of administering the drug at home avoiding the medical complications and the psychological distress associated with venous access, the good tolerability profile of the combination PLD-vinorelbine in terms of both hematological and non-hematological toxicity represent fundamental benefits which deserve to be taken into careful consideration. That the data of the present study are consistent with other experiences previously undertaken by other authors in younger patients is also worth mentioning. In a phase II study carried out by Gebbia et al. [11] in patients with MBC, the combination of PLD with intravenous vinorelbine bimonthly administered appeared very safe inducing an overall response rate of 63%. In another phase II trial conducted by Serin et al. [25] a combination of epirubicin and alternating intravenous and oral vinorelbine yielded response rates of 51%, which are exactly of the same order of those obtained in our study in elderly patients. PLD + vinorelbine regimen was also previously administered as second or third-line chemotherapy in patients with advanced breast cancer [2]. In this study, Ardavanis et al. obtained an OR rate (CR + PR) of 39% with a median TTP of 6.5 months and a median survival time of 14.2 months. Also in this case there was no clinically important cardiac toxicity or treatment-related deaths. Taking into account the different subset of treated patients and the different indication of the treatment (as second or third line) these data are in agree with the results reported in the present study [2]. It has also to be considered that in our series four out of nine patients who were pre-treated with anthracyclines recorded a clinical response after treatment with PLD + vinorelbine combination. Two additional patients had a SD. These results suggest that this combination is active also in anthracycline pre-treated patients without cumulative cardiac toxicity. Moreover, also those patients pre-treated with schedules not containing anthracyclines, were still responsive to the PLD + vinorelbine combination since three out of four patients had a CR or a PR in our series.

Our results add new information about the clinical use of PLD/vinorelbine combination in the treatment of elderly patients with MBC. In fact, we have demonstrated that it is active, safe and does not induce QoL worsening in this subset of patients. In this setting, the role of QoL cannot be underestimated: consequently, growing attention is continuously paid to patients' convenience and compliance, especially to the elderly patients who represent the fastest growing segment of the oncology population. In these patients, in fact, the choice of the chemotherapy regimen is

not only based on the biological characteristics of the tumour, but also implies a careful examination of a series of other important concomitant issues such as the clinical history of the patient, the age, the comorbidities which can be preexisting or iatrogenic, and the previous treatments. For instance, it is common knowledge that in patients in whom a standard chemotherapy with anthracycline-based regimens is not any more feasible because of previous use of these drugs either in adjuvant setting or in first line treatment of metastatic disease, or in those who cannot undergo anthracycline administration for serious comorbidity conditions, the availability of alternative drugs highly effective in controlling tumour growth, in reducing tumor-related symptoms and in preserving the best QoL represents an achievement that cannot be given up. Our results suggest that the administration of PLD can be safe in avoiding severe cardiac side effects also in patients pretreated with anthracyclines. In fact, in our series nine patients received previous anthracycline-based chemotherapy and only two of these patients experienced a slight LVEF reduction. Globally 9 out of 34 patients enrolled experienced a reduction of LVEF after the treatment and none of these patients required PLD discontinuation. It is noteworthy that the most severe cardiac side effects were obtained in two patients with a history of hypertension and diabetes, respectively.

Another advantage of this schedule is the oral administration of vinorelbine at day 15 that avoids an additional day of hospitalization for the patients with consequent reduction of psychological distress for the patients and of costs for the National Health Service [7, 17]. Finally, this schedule did not induce significant changes of QoL suggesting an optimal compliance for the patients. However, no QoL assessments were done after chemotherapy completion and data about delayed effects are not available.

To conclude, the combination PLD-alternating intravenous and oral vinorelbine appears an effective, safe and convenient therapeutic option in the first line treatment of elderly MBC patients who are refractory to hormonal therapy or have negative status for estrogen receptors expression. Moreover, the schedule can be also safely administered to patients who performed anthracycline-based chemotherapy in the adjuvant setting.

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