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Breast Cancer Res Treat (2010) 122:169–176
DOI 10.1007/s10549-010-0860-9

CLINICAL TRIAL

Maintenance treatment with Pegylated liposomal doxorubicin versus observation following induction chemotherapy for metastatic breast cancer: GEICAM 2001-01 study

Emilio Alba · Manuel Ruiz-Borrego · Mireia Margelí · Álvaro Rodríguez-Lescure · Pedro Sánchez-Rovira · Amparo Ruiz · Jose Ramón Mel-Lorenzo · Manuel Ramos-Vázquez · Nuria Ribelles · Elisa Calvo · Antonio Casado · Antonia Márquez · David Vicente · José Angel García-Sáenz · Miguel Martín

Received: 6 November 2009 / Accepted: 17 March 2010 / Published online: 2 April 2010

Abstract This randomized multicenter phase III trial evaluated the role of maintenance therapy with pegylated liposomal doxorubicin (PLD) after induction chemotherapy in patients with metastatic breast cancer (MBC). Patients without disease progression following first-line induction chemotherapy consisting of three cycles of doxorubicin (75 mg/m^2) followed by three cycles of docetaxel (100 mg/m^2) both every 21 days, were randomized to PLD (40 mg/m^2) every 28 days for six cycles or to observation. Time to progression (TTP) was the primary endpoint. 288 patients were enrolled and received induction first-line chemotherapy. One hundred and fifty-five achieved response or stable disease and were randomized to maintenance PLD ($n = 78$) or observation ($n = 77$). With a median follow-up of 20 months from randomization (range 1–56), disease progression occurred in 94% of patients. PLD significantly improved TTP by 3.3 months (8.4 vs. 5.1 months; hazard ratio [HR] = 0.54, 95% CI: 0.39 to 0.76, $P = 0.0002$) compared with observation. Overall survival was not significantly prolonged with PLD (24.8 vs. 22.0 months, respectively; HR = 0.86, 95% CI: 0.58–1.27, $P = 0.44$). PLD-induced toxicity was mild and manageable with up to 5% of patients experiencing grade 3/4 non-hematologic events (fatigue, mucositis, palmar-plantar erythrodysesthesia). Grade 3/4 neutropenia occurred in 12% of patients;

This study was conducted on behalf of the Spanish Breast Cancer Research Group (GEICAM)

Presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1–5, 2007, Chicago, IL, USA; and the European Society of Medical Oncology (ESMO), Stockholm, Sweden, September 15, 2008.

E. Alba (✉) · N. Ribelles · A. Márquez
Department of Medical Oncology, Hospital Clínico Universitario Virgen de la Victoria, Colonia Santa Inés s/n, 29010 Malaga, Spain
e-mail: ealbac@uma.es

M. Ruiz-Borrego · E. Calvo · D. Vicente
Department of Medical Oncology, Hospital Universitario Virgen del Rocío, Sevilla, Spain

M. Margelí
Department of Medical Oncology, Hospital Universitario Germans Trias I Pujol, Badalona, Barcelona, Spain

Á. Rodríguez-Lescure
Department of Medical Oncology, Hospital General de Elche, Elche, Alicante, Spain

P. Sánchez-Rovira
Department of Medical Oncology, Complejo Hospitalario de Jaén, Jaén, Spain

A. Ruiz
Department of Medical Oncology, Instituto Valenciano de Oncología, Valencia, Spain

J. R. Mel-Lorenzo
Department of Medical Oncology, Complejo Hospitalario Xeral Calde, Lugo, Spain

M. Ramos-Vázquez
Department of Medical Oncology, Centro Oncológico de Galicia, A Coruña, Spain

A. Casado · J. A. García-Sáenz · M. Martín
Department of Medical Oncology, Hospital Clínico Universitario San Carlos, Madrid, Spain

two patients developed febrile neutropenia. This phase III trial demonstrated that maintenance chemotherapy with PLD is well tolerated and offers improved TTP in patients with MBC following first-line chemotherapy.

Keywords Breast cancer-advanced/metastatic · Pegylated liposomal doxorubicin · Maintenance therapy · Induction chemotherapy

Introduction

Metastatic breast cancer is moderately sensitive to chemotherapy. Forty to sixty percent of patients obtain a response with first-line chemotherapy, but most of them have disease progression early after treatment interruption [1]. Although the role of maintenance therapy in MBC is still undefined, its goal is to prolong the primary therapy benefit and improve disease control, while maintaining an acceptable quality of life. To date, eight out of nine randomized trials of standard versus extended duration chemotherapy in MBC patients have consistently demonstrated a progression-free survival (PFS) advantage favoring extended duration therapies [2–10]. Unfortunately, these trials have failed to demonstrate a consistent benefit in overall survival (OS), and the additional cycles of chemotherapy were often associated with a significant increase in toxicity. A meta-analysis of these trials revealed a significant ($P = 0.01$), although modest reduction in the mortality hazard with longer periods of chemotherapy [11]. This meta-analysis supports prolonged treatment in patients with MBC in the absence of disease progression or unacceptable toxicity. However, in a phase III trial, the administration of maintenance paclitaxel in patients achieving disease control after six to eight courses of first-line anthracycline + paclitaxel combination chemotherapy did not improve PFS, compared with patients who did not receive maintenance paclitaxel [10]. As such, the optimal duration of chemotherapy for the first-line treatment of MBC is still under debate.

Anthracyclines, including epirubicin and doxorubicin, are among the most active therapeutic agents for breast cancer. Although they are considered key components of breast cancer treatment, their toxicity profiles often preclude their long-term use. New anthracycline analogs and novel formulations have been developed to overcome these drawbacks [12, 13].

Pegylated liposomal doxorubicin (PLD; Caelyx, Schering-Plough, Kenilworth, NJ, USA) is a novel formulation of doxorubicin in a liposome matrix encased in polyethylene glycol [12, 13]. It is designed to concentrate preferentially in tumor tissue in order to circumvent toxicity associated with the conventional anthracyclines while maintaining, or possibly improving their efficacy [12, 13]. Results from a randomized phase III trial demonstrated PLD to have similar efficacy and more importantly, a significantly reduced risk of cardiac toxicity when compared with conventional doxorubicin as first-line therapy in patients with MBC [14]. Studies have not demonstrated a significant relationship between the cumulative dose of PLD and the incidence of cardiotoxicity [14–17].

The induction chemotherapy regimen (three cycles of doxorubicin followed by three cycles of docetaxel) administered in this particular trial (2001-01) is an established GEICAM standard first-line MBC regimen. In a previous phase III trial conducted by our group (GEICAM 9903), sequential versus concomitant administration of doxorubicin and docetaxel were compared as first-line therapy for MBC [18]. Both arms demonstrated similar antitumor efficacy. However, the sequential administration was associated with less hematologic toxicity and was considered the preferred treatment arm. Hence, this sequential regimen was selected as the standard arm for future GEICAM trials. We designed a phase III trial (GEICAM 2001-01) to compare maintenance therapy with PLD versus observation following induction treatment for MBC.

Patients and methods

Patient eligibility

Patients with newly diagnosed MBC were eligible if they fulfilled the following criteria: response or stable disease (measured by the standard Response Evaluation Criteria In Solid Tumors [RECIST]) following induction chemotherapy with sequential doxorubicin and docetaxel; at least 18 years of age; an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; normal cardiac function confirmed by a baseline left ventricular ejection fraction (LVEF) >50%, measured by MUGA or cardiac sonography (or above the institution's lower limit of normal if different from 50%); adequate bone marrow reserve (WBC $\geq 4 \times 10^9$/l, neutrophils $\geq 2 \times 10^9$/l platelets $\geq 100 \times 10^9$/l, and hemoglobin ≥ 10 g/dl); adequate hepatic and renal function. Written informed consent, including anticipated patient cooperation with treatment and follow-up, was obtained and documented before performing any protocol-specific procedure.

Ineligibility criteria included the following: a history of cardiac disease (class II or greater on the New York Heart Association (NYHA) scale) with congestive heart failure (CHF); hypersensitivity to anthracycline therapy or a history of severe hypersensitivity reactions to products containing Cremophor® EL; pregnancy or breast feeding; male gender; prior radiation therapy to more than one-third of

the bone marrow or within 4 weeks before enrollment; symptomatic brain metastases; concurrent treatment for any other primary tumor except for basal or squamous cell carcinoma of the skin, or carcinoma in situ; uncontrolled bacterial, viral, or fungal infection; any condition (medical, social, or psychological) that could prevent adequate follow-up.

Trial design and treatment

This randomized, multicenter, phase III trial was conducted in 15 sites throughout Spain. The study was coordinated by the Spanish Breast Cancer Research Group (GEICAM, *Grupo Español de Investigación en Cáncer de Mama*). The primary endpoint of this trial was to compare time to progression (TTP) between treatment arms. Secondary endpoint was defined as the correlation of molecular markers (XPD polymorphism, tubulin_III overexpression and ERCC-1 overexpression) with response to induction therapy. Overall survival was not considered to be an endpoint in this trial. This trial was conducted in accordance with the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, current Spanish guidelines, and with the approval of the appropriate ethical review boards. The study was registered at www.clinicaltrials.gov (identifier code = NCT00128778).

Eligible patients received induction treatment with the standard six-cycle sequential GEICAM 9903 regimen. This regimen consisted of three cycles of doxorubicin 75 mg/m^2 administered intravenously over 15 min every three weeks followed by three cycles of docetaxel 100 mg/m^2 administered intravenously over 1 h every 3 weeks. Both agents were given on day 1 of a 21-day cycle. Patients who had received prior anthracyclines in the adjuvant setting received two cycles of doxorubicin followed by four cycles of docetaxel. Patients who achieved a response (complete or partial) or stable disease following the induction chemotherapy were randomly assigned to PLD at a dose of 40 mg/m^2 every 28 days for six cycles, or to observation. Patients randomized to PLD received premedication with dexchlorpheniramine maleate (5 mg intravenously), ondansetron (8 mg intravenously 1 h before chemotherapy), and dexamethasone (20 mg intravenously). If palmar-plantar erythrodysesthesia (PPE; hand-foot syndrome) occurred, patients received dexamethasone 8 mg orally on days 1–5 and 4 mg orally on days 6–7.

Doses adjustments were based on the most severe toxicity observed in the previous cycle. Before day 1 of each cycle, patients had to have an adequate absolute neutrophil and platelet count. Patients with grade 4 neutropenia or thrombocytopenia received 75% of the previous dose. For PPE grade $\geq$2, PLD was delayed for up to 2 weeks, and once recovered to grade 0–1, resumed at 75% of previous dose. PLD was reduced by 75% in case of bilirubin 2–3 mg/dl and to 50% in case of non-related elevation greater than 3 mg/dl. For mucositis grade 1 or 2, PLD was delayed till recovery and then resumed at 75% of previous dose. Patients were not allowed to receive concurrence endocrine and/or bisphosphonate therapy.

Trial assessments and follow-up

Response to induction chemotherapy was assessed 6 weeks after the last chemotherapy dose. Following randomization, patients in both treatment arms were monitored every 28 days for 6 months. Assessment continued from 6 months to 2 years at 3-month intervals until disease progression. Medical history, physical examination (including weight and ECOG performance status), routine laboratory tests, as well as toxicity assessment were done at each clinical visit. Tumor measurement was evaluated with the same radiological procedures used when assessing response to induction therapy. Cardiac assessments (LVEF measurements using echocardiography or MUGA) were performed at baseline (prior to maintenance therapy), at cycle 3, cycle 6, and every 6 months thereafter.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC criteria, version 2).

Statistical considerations

The trial was designed to detect a hazard ratio of 0.6 for TTP with maintenance PLD. Based on our previous experience, a median TTP of 10.5 months in the observation arm was selected [18]. Assuming that TTP would conform to an exponential distribution, at least 77 patients per group were required to provide 80% power using a significance level (alpha) of 0.01 (one-sided).

The analysis of this endpoint was performed on the intention-to-treat population, defined as the randomized patients analyzed in the assigned treatment group regardless of whether or not treatment was received. Estimated median TTP was calculated using the Kaplan–Meier method and was compared between treatment arms using the log-rank test at a one-sided 1% significance level, with associated confidence intervals (95% CI). The Cox proportional hazard model was used to adjust the treatment effect for potential confounding factors.

Results

Patient recruitment and characteristics

A total of 288 patients were registered over a 56-month period and received induction therapy with doxorubicin

and docetaxel. Of these, 155 patients were randomly assigned to receive PLD maintenance therapy ($n = 78$) or observation ($n = 77$). Exclusions for patient enrollment into the randomized phase of the trial included disease progression or death, patient refusal, toxicity, and logistical or scheduling reasons (Fig. 1).

Patient and disease characteristics were well balanced between the two groups (Table 1). The median age of the patients was 56 years (range 30–78), with an ECOG performance status of 0 or 1 in >90%. Around 30% of the patients were stage IV at diagnosis. Approximately, three-quarters of the patients had hormone-receptor-positive tumors, and half of them had dominant visceral disease. A similar number of patients in both arms had received prior adjuvant therapy (chemotherapy or hormonal treatment), with approximately one-third of them having received prior anthracyclines.

More patients in the observation arm (70%) achieved an objective response (partial + complete) to induction therapy compared with patients randomized to receive PLD (53%). This difference in response was almost statistically significant ($P = 0.055$). From the 37 patients with stable disease after induction therapy in the experimental arm, 6 (16%) achieved an objective response during the maintenance phase.

Of the 78 patients randomized to receive maintenance treatment with PLD, 39 (50%) completed all six cycles. Disease progression, occurring in 54% of patients, was the main reason for treatment discontinuation. Eight patients discontinued due to toxicity and 10 due to other reasons (mainly patient decision). A total of 339 cycles were administered, with a median number of 6 (range 0–6; Table 2). Median relative dose intensity of PLD was 97%. Dose delays were documented in 46 cycles (14%) and dose reductions in 12 cycles (4%).

Efficacy

With a median follow-up of 20 months from randomization (range 1–56), disease progression was documented in 94% ($n = 146$) of patients (analysis performed August 2009). The median TTP from randomization was 8.4 months (95% CI: 7.05–9.72) in patients receiving maintenance PLD vs. 5.1 months (95% CI: 3.52–6.60) in the observation arm. This 3.3-month improvement was statistically significant with a hazard ratio of 0.54 (95% CI: 0.39 to 0.76, $P = 0.0002$.

As depicted in Fig. 2, 28 patients in the PLD arm and 50 in the observation arm progressed during the first 6 months post-randomization, while 41 and 23 patients, respectively, progressed during the period of 6–24 months. Several baseline covariates (ECOG performance status, response to induction therapy, age, hormonal status, location of metastatic sites, and treatment arm) were studied using the Cox proportional hazard model (Table 3a). Two covariates were independent predictors of TTP: visceral disease

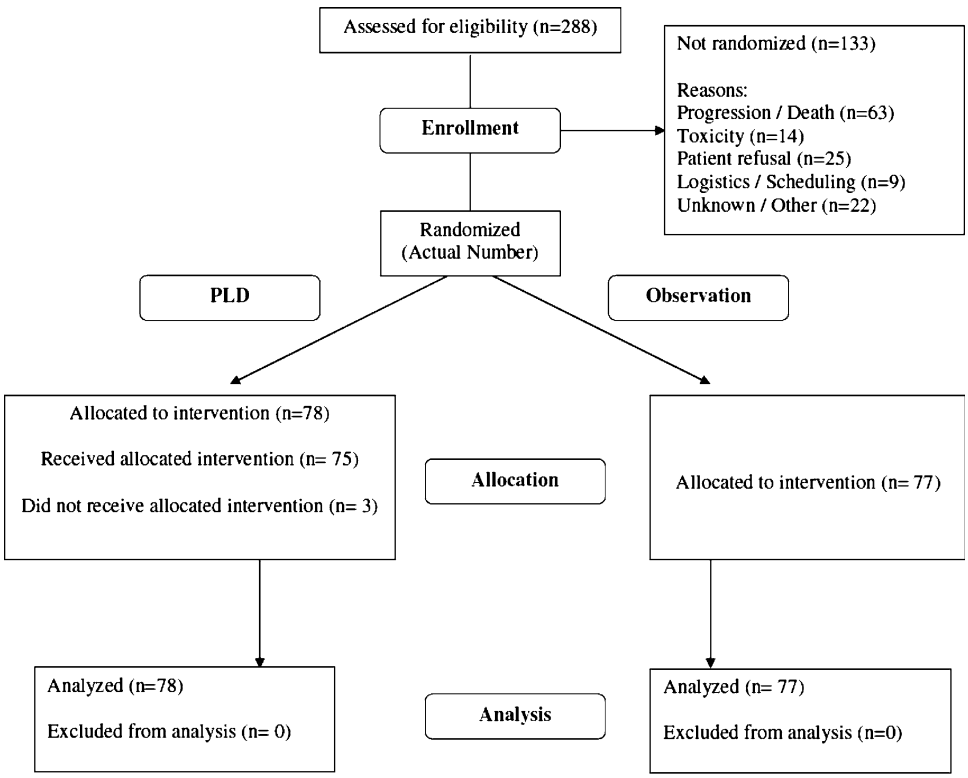


Fig. 1 GEICAM 2001-01 flowchart

Table 1 Patient baseline, disease characteristics and prior therapy

Characteristic	PLD ($n = 78$)		Observation ($n = 77$)	
	No. of patients	%	No. of patients	%
Age, years				
Median	58		55	
Range	(30–76)		(34–78)	
ECOG PS				
0	45	58	43	56
1	20	26	28	36
2	5	6	2	3
Unknown	8	10	4	5
Hormonal status				
ER+ and/or PR+	53	68	56	73
ER− and/or PR−	17	22	15	19
Unknown	8	10	6	8
Dominant site of disease				
Visceral	46	59	43	56
Non-visceral	31	40	31	40
Unknown	1	1	3	4
Disease stage at diagnosis				
I–III	57	73	54	70
IV	21	27	23	30
Prior (neo-) adjuvant therapy				
Chemotherapy	48	62	44	57
Hormonal therapy	33	42	32	42
Prior adjuvant anthracycline	23	30	27	35
Response status at randomization				
Complete response	3	4	7	9
Partial response	38	49	47	61
Stable disease	37	47	23	30

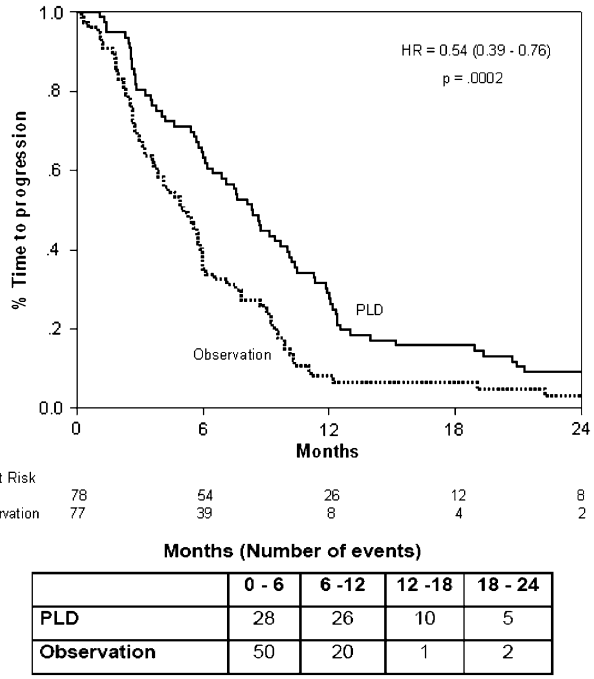
ECOG Eastern Cooperative Oncology Group, *ER* estrogen receptor, *PLD* pegylated liposomal doxorubicin, *PR* progesterone receptor, *PS* performance status

Table 2 Dose administration

	PLD ($n = 78$)
Cycles (n)	339
Mean	4.9
Median (range)	6 (0–6)
Patients completing all planned cycles	39 (50%)
Discontinuation reason	
PD or death	21 (54%)
Toxicity	8 (20%)
Other (e.g. patient choice)	10 (26%)

PD progressive disease, *PLD* pegylated liposomal doxorubicin

(HR = 1.8; $P = 0.001$) and treatment with PLD (HR = 0.53; $P = 0.0002$) (Table 3b). Overall survival (Fig. 3) was not significantly prolonged by PLD maintenance therapy, compared to the observation arm (24.8 vs. 22.0 months, respectively; HR = 0.86, 95% CI: 0.58–1.27, $P = 0.435$).



Months (Number of events)

	0 - 6	6 -12	12 -18	18 - 24
PLD	28	26	10	5
Observation	50	20	1	2

Fig. 2 Time to disease progression (TTP)

Molecular markers data are not available at the present time and will be disclosed in a separate publication.

Safety

Most of the treatment-related adverse events associated with PLD maintenance therapy were mild-to-moderate (grade 1 or 2) in severity (Table 4). Grade 1/2 neutropenia and anemia occurred in 35 and 32% of patients treated with PLD and approximately 10% in the observation arm. Grade 3/4 neutropenia was experienced by 12% of PLD-treated patients, with only two patients developing febrile neutropenia. Almost all cases of non-hematologic toxicity were limited to grade 1 or 2. Grade 3/4 fatigue and mucositis occurred in only 3 and 5% of PLD-treated patients. Grade 3 PPE occurred in 4% of PLD-treated patients. One severe infusion reaction was reported.

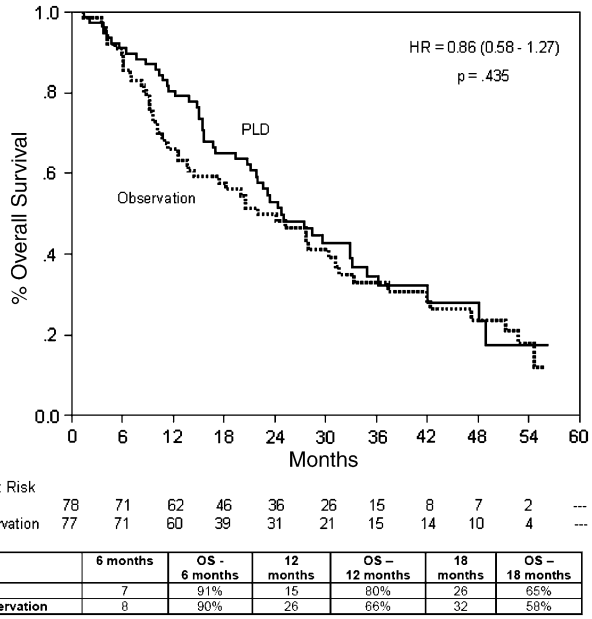
The median LVEF after three cycles and at the end of treatment was similar in both treatment arms; 61/60/61.50% with PLD and 63/67/60% with observation. After three treatment cycles decreases in LVEF $\geq$10% were noted in three patients, two treated with PLD and one in the observation arm. LVEF decreased below 50% (to 48 and 43%) in the two PLD-treated patients, both recovered to normal limits 6 months later. At the end of treatment

Table 3 Cox proportional hazard model for TTP

(a) Parameters	*N*	Univariate analysis	
		HR (95% CI)	*P*
Hormone receptors			
Positive	109		0.706
Negative	32	0.95 (0.63–1.42)	
Unknown	14	0.78 (0.44–1.40)	
Induction chemotherapy response			
Stable disease	61		0.297
Complete response	10	1.22 (0.60–2.48)	
Partial response	84	1.31 (0.93–1.84)	
ECOG			
2	7		0.138
0	88	1.90 (0.77–4.68)	
1	48	1.41 (0.56–3.55)	
Age			
<50 years	50		0.202
≥50 years	105	1.26 (0.89–1.78)	
Visceral disease			
No visceral	62		0.002
Visceral	92	1.72 (1.22–2.41)	
Treatment arm			
Observation	77		0.003
PLD	78	0.54 (0.39–0.76)	

(b) Parameters	HR (95% CI)	*P*
Visceral disease		
No visceral		0.001
Visceral	1.76 (1.25–2.46)	
Treatment arm		
Observation		0.0002
PLD	0.53 (0.38–0.75)	

Multivariate Cox multivariate model for TTP



	6 months	OS - 6 months	12 months	OS – 12 months	18 months	OS – 18 months
PLD	7	91%	15	80%	26	65%
Observation	8	90%	26	66%	32	58%

Fig. 3 Kaplan–Meier estimates of overall survival

Table 4 NCI-CTC (version 2.0) toxicity

Toxicity	% Of patients			
	PLD ($n = 78$)		Observation ($n = 77$)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hematologic				
Neutropenia	32	12	9	0
Anemia	35	0	12	0
Non-hematologic				
Nausea/vomiting	21	0	4	0
Fatigue	32	3	8	0
Alopecia	29	0	4	0
Infusion reaction	1	1	0	0
Mucositis	32	5	0	0
PPE	29	4[a]	0	0

NCI-CTC.2 National Cancer Institute Common Toxicity Criteria, version 2, *PLD* pegylated liposomal doxorubicin, *PPE* palmar-plantar erythrodysesthesia

[a] Grade 3 only

decreases in LVEF ≥10% were noted in six patients, five treated with PLD, and one in the observation arm. LVEF decreased below 50% (to 47 and 44%) in two of the PLD-treated patients, both recovered to normal limits 6 months later. No congestive heart failure (CHF) was reported.

Discussion

Standard chemotherapy has been shown to be an effective palliative treatment for most patients with advanced breast cancer. To-date, response to treatment and TTP outcomes are suboptimal; further research is warranted. The GEICAM 2001-01 trial was designed to test whether maintenance therapy after a standard first-line chemotherapy regimen in patients with MBC would have a beneficial impact on the course of disease. TTP, an appropriate and highly sensitive endpoint for advanced disease, was utilized as a primary endpoint in this study [19]. In this phase III trial, maintenance therapy comprised of six cycles of PLD monotherapy (40 mg/m^2 every 4 weeks) was associated with a significantly prolonged TTP (additional 3.3 months what reflects an improvement of 65%) in patients with MBC who demonstrated an objective response or stable disease

following first-line chemotherapy. Median OS was not statistically different between treatment arms. Of note, this trial was not powered to determine an OS advantage with maintenance therapy.

In the present GEICAM trial, toxicities associated with PLD maintenance therapy were infrequent, mild, and manageable. The hematologic toxicity observed in both treatment arms was most likely attributable to residual toxicity from the induction chemotherapy regimen. The majority of non-hematologic toxicities reported were grade 1 or 2 and, importantly, less than 5% of the patients experienced grade 3 or 4 events. We observed a low percentage (3% grade 3) of PPE using PLD 40 mg/m^2 every 4 weeks. Of note, neither clinically relevant decrease in LVEF nor CHF events were observed in patients receiving PLD treatment.

At the time of trial initiation, questions remained regarding the optimal duration of chemotherapy for patients with metastases in the absence of disease progression. Irrespective of a lack of corroborating evidence, national and international guidelines have supported the use of chemotherapy until disease progression in the absence of unacceptable toxicity in this setting [20]. Several trials over the past two decades have demonstrated consistent prolongation of progression-free survival (PFS); however, a survival benefit or quality of life (QoL) advantage has been infrequently documented. These studies have supported the use of more protracted chemotherapy regimens [2, 4–7, 9]. Results of a meta-analysis demonstrated a modest, but statistically significant survival advantage for patients randomized to longer versus shorter treatments [11]. While these data support a continuation of chemotherapy in patients with an absence of either disease progression or unacceptable toxicity, these studies utilized older cytotoxic regimens. Since then, new cytotoxic agents and novel formulations of existing drugs have been adapted into use in clinical practice, expanding the management of MBC patients.

Though paclitaxel has demonstrated efficacy in the MBC setting, its use as maintenance therapy (8 weeks) following induction with an anthracycline-taxane regimen was not associated with an improvement in PFS in a phase III trial [10].The lack of benefit of maintenance paclitaxel may have been attributed to the concurrent use of hormonal therapy, paclitaxel schedule, or activity of first-line regimen utilized. GEICAM initiated the 2001-01 trial with PLD, a novel liposomal anthracycline formulation, as maintenance therapy because of its proven antitumor efficacy, safety profile, and established role in the first-line treatment of MBC [14]. Conventional anthracyclines such as doxorubicin and epirubicin are integral components in the management of women with breast cancer. However, they are of limited use because of the increasing risk of cardiotoxicity when cumulative exposure increases. In our trial, PLD was demonstrated to be a well-tolerated monotherapy that delayed disease progression. The main treatment effect with PLD was observed during treatment as evidence by the increased number of progressions after the 6-month PLD treatment period.

In conclusion, evidence from this trial shows that maintenance therapy with six cycles of PLD significantly improves TTP and is well tolerated. A sequential induction regimen of three cycles of doxorubicin followed by three cycles of docetaxel with subsequent maintenance PLD is a new therapeutic option for patients with MBC who have not progressed on first-line chemotherapy.

Acknowledgements The author thanks Andrés Hernando for his help in the conduction of the trial, Maribel Casas and Maria José Escudero for the statistical analyses and Dra. Eva Carrasco and Dr. Peter R. Turner for the editorial assistance. This work was research supported by Spanish Breast Cancer Research Group (GEICAM) and this study was supported in part by Schering Plough Corporation.

Conflict of interest statement None of the co-authors has any involvement that can be construed as a conflict of interest. The funding bodies were not involved in the collection and interpretation of the data, or in the decision to publish.

Appendix

See Table 5.

Table 5 List of participating centers and investigators

Center	Principal investigators
Hospital Clínico Universitario Virgen de la Victoria	Emilio Alba
Hospital Universitario Virgen del Rocío	Manuel Ruiz-Borrego
Hospital Clínico Universitario San Carlos	Miguel Martín
Hospital Universitario Germans Trias i Pujol	Mireia Margelí
Hospital General de Elche	Álvaro Rodríguez-Lescure
Complejo Hospitalario de Jaén	Pedro Sánchez-Rovira
Instituto Valenciano de Oncología	Amparo Ruiz
Complejo Hospitalario Xeral Calde	Jose Ramón Mel-Lorenzo
Centro Oncológico de Galicia	Manuel Ramos-Vázquez
Fundación Hospital de Alcorcón	Carlos Jara
Hospital Univeristario Marqués de Valdecilla	José Manuel López-Vega
Hospital Universitario Miguel Servet	Antonio Antón
Hospital Universitario Puerta de Hierro	Ricardo Cubedo
Complejo Hospitalario Juan Canalejo	Lourdes Calvo
Hospital Municipal de Badalona	Isabel Moreno

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