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Cardiac Safety with High Cumulative Dose of Pegylated Liposomal Doxorubicin in Patients with Metastatic Breast Cancer Previously Treated with Conventional Anthracyclines

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Abstract

Introduction: The treatment of metastatic breast cancer (MBC) is still challenging. Many studies documented the efficacy of pegylated liposomal doxorubicin (PLD) in patients with MBC, but there is a limited data about the cardiac safety with high cumulative dose (HCD) of PLD. **Aim of the work:** We conducted this trial to outline the cardiac safety of HCD of PLD in patients with MBC who previously received conventional anthracyclines. **Methods:** During the period of nine years (January 2011 to December 2019). We extracted the data of the patients with MBC receiving PLD at Medical Oncology Department, South Egypt Cancer Institute, Assiut University. These included patients' demographics and therapeutic data including the full data of PLD, prior conventional anthracyclines, prior trastuzumab, and prior radiotherapy. Also, data about comorbidities as well as cardiac and other toxicities of PLD were obtained. The data was analysed using SPSS v. 21. **Results:** For all 81 eligible patients, the mean age was 43.9 years (±standard deviation (SD) 13.2). The mean cumulative dose of PLD was 378.4 mg/m^2 (± SD of 250.2) and a range of 100 - 1200 mg/m^2. About thirty-one (38.3%) patients received high cumulative dose (400 mg/m^2 or more), while the remaining 50 patients did not. The decline in left ventricular ejection fraction (LVEF) was relatively rare; and of low grade. Grade 2 decline in LVEF occurred in only two patients who received high cumulative dose of PLD, and only one patient who did not reach HCD ($p = 0.555$). Grade 3 or 4 decline in LVEF did not occur in patients either with or without HCD. Regarding other toxicities, there was a significant increase in incidence of all grades palmar plantar erythrodysesthesia (PPE) in patients who received HCD of PLD when compared to those who did not reach

the HCD (38.7% versus 16% respectively; p = 0.021). **Conclusion:** Our study concluded that the use of PLD seems to be a justified agent in the treatment of MBC who previously treated by conventional anthracyclines in the adjuvant, metastatic or both settings, even in patients reaching the cumulative dose of conventional anthracycline.

Keywords

Metastatic Breast Cancer, Pegylated Liposomal Doxorubicin, High Cumulative Dose, Cardiac Toxicity

1. Introduction

Globally, breast cancer is the most common cancer diagnosed in women [1]. At initial presentation, about 17% have advanced stage [2]. The treatment of this advanced stage is still challenging [3]. The primary goal of that treatment is finding a tool with higher, or at least equal efficacy and lower toxicity [3].

There is no standard of care for management of the metastatic breast cancer (MBC). However, chemotherapy is a treatment option for many patients with MBC [4]. Anthracyclines and taxanes are the most effective cytotoxic agents in treatment of MBC [4]. The use of the anthracyclines is limited by their cumulative doses regarding the cardiac toxicity [5] [6] [7]. This problem is greatly resolved by invention of pegylated liposomal doxorubicin (PLD) by capsulation of doxorubicin with polyethylene glycol-coated liposome [8] [9]. By this modification, PLD has limited penetration into cardiac muscle, resulting in lesser cardiac toxicity when compared with conventional anthracyclines [8] [9].

Although many studies documented the efficacy of PLD in patients with MBC, there is a limited data about the cardiac safety with high cumulative dose (HCD) of PLD [6] [7] [8] [10] [11]. Kesterson *et al.* published a retrospective chart review showing that the cumulative doses of PLD ≥ 400 mg/m^2 are not associated with clinically evident cardiac toxicity in patients with gynecologic malignancies. However, they assessed the cardiac toxicity in patients without prior exposure to anthracyclines [12].

We conducted this trial to outline the cardiac safety of HCD of PLD in patients with MBC who previously received conventional anthracyclines.

2. Patients and Methods

2.1. Study Design

The data were extracted from the medical hospital records of patients with evidence of MBC during the period of nine years (January 2011 to December 2019) treated at Medical Oncology Department, South Egypt Cancer Institute, Assiut University. The inclusion criteria included the evidence of MBC, received PLD, age of 18 years old or more, no evidence of heart failure before treatment, frequent assessments by echocardiography were present. These data included the

age of the patient, Eastern Cooperative Oncology Group (ECOG) performance status, height, weight, medical comorbidities (*i.e.* diabetes mellitus and hypertension), type of previously received conventional anthracycline and its cumulative dose, prior exposure to trastuzumab, prior exposure to locoregional radiotherapy to left breast cancer, the cumulative dose and number of cycles of PLD, left ventricular ejection fraction (LVEF) as measured by echocardiography (baseline and follow up measurements), and manifestations of congestive heart failure (CHF). Body mass index (BMI) was calculated from patient's height and weight to outline whether the patient was obese (BMI ≥ 30 kg/m^2) or not.

2.2. Patients Stratification

Patients were grouped according to age group (less than 65 years and 65 years or more according to definition of World Health Organization of the elderly), ECOG performance status (grade 0/I and grade II), obesity (obese or not), medical comorbidities (No, diabetes mellitus, hypertension or both diabetes mellitus and hypertension),prior conventional anthracyclines (doxorubicin or epirubicin), cumulative dose of prior conventional anthracyclines in mg/m^2, prior exposure to trastuzumab (yes or no), prior exposure to locoregional radiotherapy to left breast cancer (yes or no), the cumulative dose of PLD in mg/m^2, degree of the cumulative dose (high ≥ 400 mg/m^2 versus not high, based on definition reported by Kesterson *et al.* [12]), grades of the decline in LVEF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [13], grades of congestive heart failure according to the CTCAE 4.03 [13].

2.3. Grades of the Decline in LVEF According to CTCAE 4.03 [13]

Grade 1: not applicable;

Grade 2: Resting ejection fraction (EF) 40% - 50%; or 10% - 19% drop from baseline;

Grade 3: Resting ejection fraction (EF) 20% - 39%; >20% drop from baseline;

Grade 4: Resting ejection fraction (EF) < 20%;

Grade 5: not applicable.

2.4. Grades of the Heart Failure According to CTCAE 4.03 [13]

Grade 1: Asymptomatic with cardiac imaging abnormalities;

Grade 2: Symptoms with mild to moderate activity or exertion;

Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated;

Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support);

Grade 5: Death.

2.5. Treatment Plan and Assessment of Cardiac Function

PLD was given as 50 mg/m^2 as a 30- or 60-minute intravenous infusion on day 1,

repeated every 28 days. The medical history and clinical examination were taken every visit specially cardiac symptoms and signs suggesting cardiac failure and other toxicity. Baseline echocardiography was done, then every 3 - 4 courses of PLD. Treatment was continued until maximum response, unacceptable toxicity, or patient refusal to continue.

2.6. Statistical Analysis

The primary endpoint was PLD-related cardiotoxicity though outlining the grades of the decline of LVEF and grades of heart failure. This assessment is based on the Common Terminology Criteria for Adverse Events (CTCAE 4.03) [13]. The secondary endpoint were PLD-related other toxicities. Shapiro-Wilk test was used to define the normality of distribution of our sample. Univariate analysis was used through the presentation of continuous variables as mean ± standard deviation. Categorical variables (nominal and ordinal) are presented as frequency and percentage. Bivariate analysis was done to compare categorical variables using Chi-Square test or Fisher Exact test when appropriate. A p-value less than 0.05 is considered as a cut off of significance. SPSS version 21.0 (SPSS Inc. Chicago, IL, USA) was used in the storage and analysis of data [14].

3. Results

3.1. Patients' Flow Chart

CONSORT diagram (**Figure 1**) shows flow of the examined and the analyzed cases through this retrospective trial. During a period of nine years (January 2011 to December 2019), eighty-one patients met our eligibility criteria.

3.2. Patients' Demographics and Disease Characteristics

On initial statistical assessment, we found that our sample was normally distributed (Shapiro-Wilk test is not significant, $p = 0.076$). **Table 1** illustrates the patients' demographics and disease characteristics. The mean age at the time PLD initiation was 43.9 years with the standard deviation of 13.2 years. About one-tenth (9.9%) of our sample were elderly (65 or more years old). Twenty-one patients were hypertensive, while seven patients were diabetic. Only three cases had both hypertension and diabetes mellitus (DM). The majority (93.8%) had ECOG performance status grade II. About one-fifth (21%) of the subjects had a history of prior exposure to trastuzumab. Regarding the prior anthracyclines, less than half (39.5%) of the cases received doxorubicin (mean cumulative dose ± SD: 253.1 ± 25.2 mg/m^2), whereas the remaining cases (60.5%) received epirubicin (mean cumulative dose ± SD: 588.0 ± 97.3 mg/m^2). The mean number of PLD cycles was 7.57 (range 2 - 24). The mean cumulative dose of PLD was 378.4 mg/m^2 (±SD of 250.2) and a range of 100 - 1200 mg/m^2. With taking of 400 mg/m^2 as the cutoff of the HCD of PLD, thirty-one (38.3%) patients received HCD of PLD (400 mg/m^2 or more), while the remaining 50 patients did not.

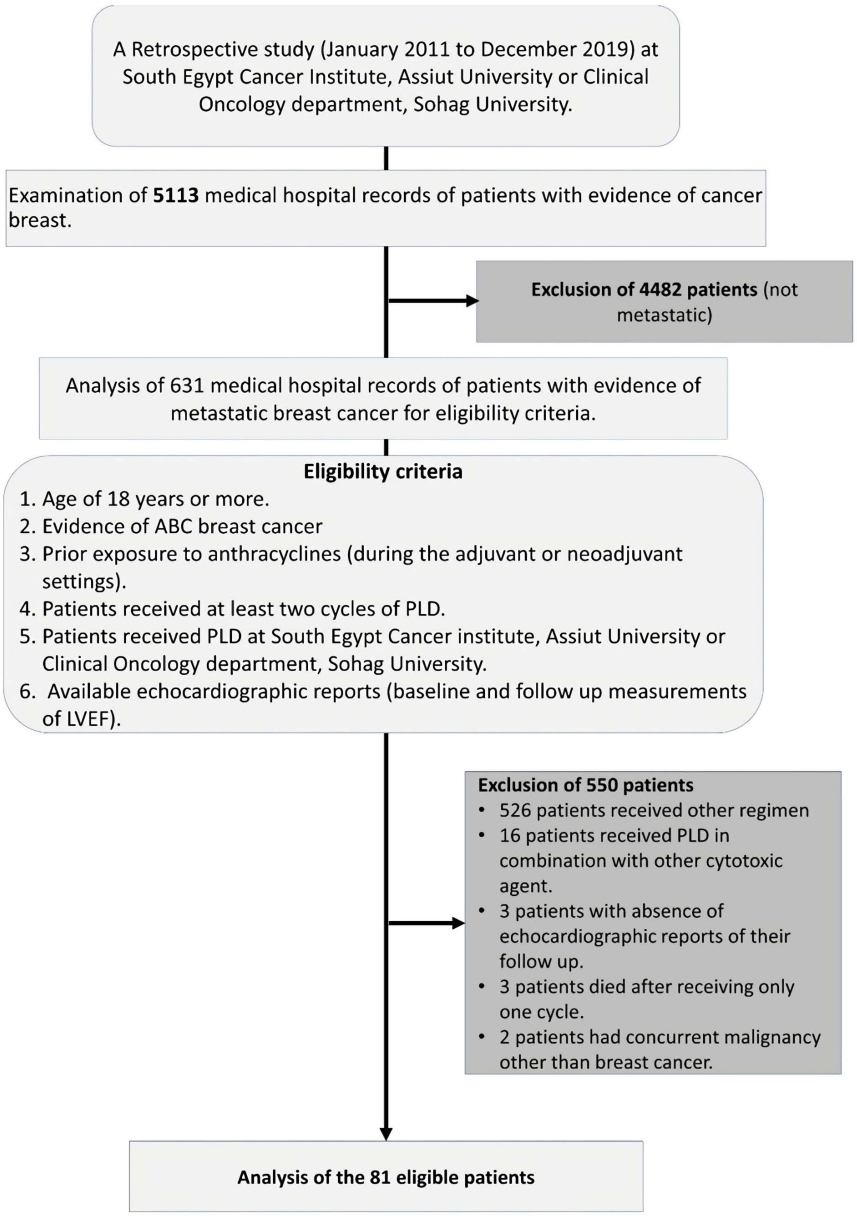

Figure 1. CONSORT diagram.

Table 1. Patients' demographics and disease characteristics (N = 81).

Characteristic	N°	%
Age (years)		
<65 years	73	90.1
≥65 years	8	9.9
Mean	43.9	
SD	13.2	
Comorbidity		
Neither hypertension nor DM	50	61.7
Hypertension	21	25.9
DM	7	8.6
Both hypertension and DM	3	3.7

Continued

Obesity		
Not obese	48	59.3
Obese	33	40.7
ECOG PS		
0, I	5	6.2
II	76	93.8
Prior trastuzumab		
Yes	17	21.0
No	64	79.0
Prior locoregional radiotherapy to left breast		
Yes	21	25.9
No	60	74.1
Prior anthracycline-based regimen		
Doxorubicin-based	32	39.5
Epirubicin-based	49	60.5
Cumulative dose of priordoxorubicin		
Mean ± SD	253.1 ± 25.2	
Cumulative dose of prior epirubicin		
Mean ± SD	588.0 ± 97.3	
Number of PLD cycles		
Mean (Range)	7.57 (2 - 24)	
Cumulative dose of PLD (mg/m^2)		
Mean ± SD	378.4 ± 250.2	
Range	100 - 1200	
High PLD cumulative dose (≥400 mg/m^2)		
Yes	31	38.3
No	50	61.7

Abbreviations: DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group; SD, Standard deviation.

3.3. Dose-Related Cardiotoxicity of PLD

Table 2 shows that the decline in LVEF was relatively rare; and of low grade. Grade 2 decline in LVEF occurred in two patients who received HCD of PLD, and only one patient who did not reach HCD (p = 0.555). Grade 3 or 4 decline in LVEF did not occur in patients either with or without HCD. Also, there were no reported grade 3/4 congestive heart failure in both groups.

3.4. Dose-Related Other Toxicities of PLD

Regarding other non-hematological toxicities, there was a significant increase in incidence of all grades palmar plantar erythrodysesthesia (PPE) in patients received HCD of PLD when compared to those did not reach the HCD (38.7% versus 16% respectively; p = 0.021). Also, the grades 3/4 PPE significantly increased with HCD (16.1% for patients with HCD versus 2.0% for those without HCD; P = 0.028) (Table 2). In addition to previous findings, patients who received HCD of PLD experienced higher incidences of grades 3/4 stomatitis (p = 0.039), all grades constipation (p = 0.049), all grades anorexia (p = 0.004), grades 3/4 anorexia (0.028), and all grades fatigue (p = 0.007) when compared to those

Table 2. Cardiac and other Toxicties of pegylated liposomal doxorubicin in the studied patients according to its cumulative dose.

Event	All grades		P values	Grade III/IV		p values
	Cumulative dose < 400 mg/m² (n = 50)	Cumulative dose ≥ 400 mg/m² (n = 31)		Cumulative dose < 400 mg/m² (n = 50)	Cumulative dose ≥ 400 mg/m² (n = 31)	
	Number (%)	Number (%)		Number (%)	Number (%)	
Non-hematological						
Decline in LVEF	1 (2.0)	2 (6.5)	0.555	0 (0.0)	0 (0.0)	NA
Congestive heart failure	1 (2.0)	2 (6.5)	0.555	0 (0.0)	0 (0.0)	NA
PPE	8 (16.0)	12 (38.7)	0.021	1 (2.0)	5 (16.1)	0.028
Stomatitis	8 (16.0)	10 (32.3)	0.087	3 (6.0)	7 (22.6)	0.039
Mucositis	6 (12.0)	7 (22.6)	0.207	2 (4.0)	3 (9.7)	0.366
Diarrhea	6 (12.0)	7 (22.6)	0.207	3 (6.0)	2 (6.5)	1.000
Constipation	2 (4.0)	6 (19.4)	0.049	0 (0.0)	0 (0.0)	NA
Anorexia	3 (6.0)	10 (32.3)	0.004	1 (2.0)	5 (16.1)	0.028
Nausea	10 (20.0)	11 (35.5)	0.122	4 (8.0)	5 (16.1)	0.293
Vomiting	5 (10.0)	8 (25.8)	0.060	1 (2.0)	4 (12.9)	0.068
Fatigue	4 (8.0)	10 (32.3)	0.007	2 (4.0)	5 (16.1)	0.100
Hematological						
Anemia	8 (16.0)	8 (25.8)	0.281	2 (4.0)	4 (12.9)	0.196
Leukopenia	4 (8.0)	9 (29.0)	0.026	3 (6.0)	4 (12.9)	0.419
Neutropenia	3 (6.0)	5 (16.1)	0.249	0 (0.0)	4 (12.9)	0.019
Thrombocytopenia	6 (12.0)	6 (19.4)	0.365	2 (4.0)	2 (6.5)	0.635

Abbreviation: PPE, palmar plantar erythrodysesthesia; LVEF, left ventricular ejection fraction.

who not reaching the HCD. From data about hematological toxicities, HCD was associated with a significant increase in the incidence of allgrades leukopenia (p = 0.026) and grades 3/4 neutropenia (p = 0.019) (Table 2). Regarding the other toxicities, there was no statistical difference between patients who received HCD of PLD and those who did not (Table 2). There was no treatment-related death.

4. Discussion

This study on a group of MBC patients who were pretreated with an anthracycline to evaluates the toxicity of anthracycline rechallenge using PLD. All patients had received conventional anthracyclines. Therefore, most patients in this study were in an advanced and palliative course of their disease when they received PLD.

Our data suggest safety profile of PLD. Results from this study showed the decline in LVEF was relatively rare. Grade 2 decline in LVEF occurred in two patients who received HCD of PLD, and only one patient who did not reach HCD (p = 0.555). Grade 3 or 4 decline in LVEF did not occur in patients either with or

without HCD. Also, there were no reported grade 3/4 congestive heart failure in both groups.

Similar to our results, a Phase III study [15] was proposed in which 301 patients with metastatic breast cancer progressing on taxanes (<6 months) were randomized to receive one of the following three alternatives: PLD 50 mg/m^2 every 4 weeks; vinorelbine 30 mg/m^2 every week; or mitomycin-C 10 mg/m^2, on days, on 1 and 28 plus vinblastine 5 mg/m^2 on days 1, 14, 28, and 42 every 6 - 8 weeks. 83% of patients had received prior anthracyclines. No patient treated with PLD showed clinical symptoms of cardiotoxicity.

In another study [16], 129 patients with metastatic breast cancer treated with PLD were analyzed. Seventy percent of patients had 2 or more cardiovascular risk factors. Despite this, only 4% of patients had some degree of cardiotoxicity and only 2 cases of clinical heart failure were reported.

Results from this study showed increase in incidence of PPE in patients received PLD, the grades 3/4 PPE significantly increased with HCD (16.1% for patients with HCD versus 2.0% for those without HCD; p = 0.028). Our finding appears to be keeping with results published by Fiegl *et al.* [16], which demonstrated that PPE was significantly more prevalent in patients who received > 3 cycles PLD compared to patients receiving only 1 - 3 cycles (22% vs 8%, p = 0.043).

In our study, in spite of thirty-one patients received HCD of PLD, the frequencies of other toxicities induced by PLD were within the range of previously published studies [17] [18] [19] [20] [21]. The typical side effects of PLD therapy (**Table 2**) appeared to be of minor relevance, probably due to the intensified management of these toxicities according to the manufacturer's recommendations and published guidelines [22].

The main limitation of this study is the retrospective nature of study. Also, there is lack of measurement of cardiac biomarker *i.e.* troponin. We would to conduct this trial prospectively with large sample size and biomarker measurement.

5. Conclusion

Our study concluded that the use of PLD even with HCD seems to be a justified agent in the treatment of MBC who previously treated by conventional anthracyclines in the adjuvant, metastatic or both settings, even in patients reaching the cumulative dose of conventional anthracycline.

Ethical Approval

This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C. and Parkin, D.M. (2010) Estimates of Worldwide Burden of Cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer*, **127**, 2893-2917. https://doi.org/10.1002/ijc.25516

[2] Iqbal, J., Ginsburg, O., Rochon, P.A., Sun, P. and Narod, S.A. (2015) Differences in Breast Cancer Stage at Diagnosis and Cancer-Specific Survival by Race and Ethnicity in the United States. *The Journal of the American Medical Association*, **313**, 165-173. https://doi.org/10.1001/jama.2014.17322

[3] Hayes, D. (2009) An Overview of Treatment for Locally Advanced Recurrent, and Metastatic Breast Cancer. *UpToDate*, **9**, 66-72.

[4] Gralow, J.R. (2005) Optimizing the Treatment of Metastatic Breast Cancer. *Breast Cancer Research and Treatment*, **89**, S9-S15. https://doi.org/10.1007/s10549-005-0143-z

[5] Al-Batran, S.E., Bischoff, J., von Minckwitz, G., Atmaca, A., Kleeberg, U., Meuthen, I., Morack, G., Lerbs, W., Hecker, D., Sehouli, J., Knuth, A. and Jager, E. (2006) The Clinical Benefit of Pegylated Liposomal Doxorubicin in Patients with Metastatic Breast Cancer Previously Treated with Conventional Anthracyclines: A Multicentre Phase II Trial. *British Journal of Cancer*, **94**, 1615-1620. https://doi.org/10.1038/sj.bjc.6603158

[6] Rafiyath, S.M., Rasul, M., Lee, B., Wei, G., Lamba, G. and Liu, D. (2012) Comparison of Safety and Toxicity of Liposomal Doxorubicin vs. Conventional Anthracyclines: A Meta-Analysis. *Experimental Hematology & Oncology*, **1**, 10. https://doi.org/10.1186/2162-3619-1-10

[7] McGowan, J.V., Chung, R., Maulik, A., Piotrowska, I., Walker, J.M. and Yellon, D.M. (2017) Anthracycline Chemotherapy and Cardiotoxicity. *Cardiovascular Drugs and Therapy*, **31**, 63-75. https://doi.org/10.1007/s10557-016-6711-0

[8] Xing, M., Yan, F., Yu, S. and Shen, P. (2015) Efficacy and Cardiotoxicity of Liposomal Doxorubicin-Based Chemotherapy in Advanced Breast Cancer: A Meta-Analysis of Ten Randomized Controlled Trials. *PLoS ONE*, **10**, e0133569. https://doi.org/10.1371/journal.pone.0133569

[9] Simunek, T., Sterba, M., Popelova, O., Adamcova, M., Hrdina, R. and Gersl, V. (2009) Anthracycline-Induced Cardiotoxicity: Overview of Studies Examining the Roles of Oxidative Stress and Free Cellular Iron. *Pharmacological Reports*, **61**, 154-171. https://doi.org/10.1016/S1734-1140(09)70018-0

[10] Rivera, E. (2003) Liposomal Anthracyclines in Metastatic Breast Cancer: Clinical Update. *Oncologist*, **8**, 3-9. https://doi.org/10.1634/theoncologist.8-suppl_2-3

[11] Harbeck, N., Saupe, S., Jäger, E., Schmidt, M., Kreienberg, R., Müller, L., Otremba, B.J., Waldenmaier, D., Dorn, J., Warm, M., Scholz, M., Untch, M., de Wit, M., Barinoff, J., Lück, H.J., Harter, P., Augustin, D., Harnett, P., Beckmann, M.W. and Al-Batran, S.E. (2017) A Randomized Phase III Study Evaluating Pegylated Liposomal Doxorubicin versus Capecitabine as First-Line Therapy for Metastatic Breast Cancer: Results of the PELICAN Study. *Breast Cancer Research and Treatment*, **161**, 63-72. https://doi.org/10.1007/s10549-016-4033-3

[12] Kesterson, J.P., Odunsi, K. and Lele, S. (2010) High Cumulative Doses of Pegylated Liposomal Doxorubicin Are Not Associated with Cardiac Toxicity in Patients with Gynecologic Malignancies. *Chemotherapy*, **56**, 108-111. https://doi.org/10.1159/000312644

[13] https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[14] IBM Corp Released (2013) IBM SPSS Statistics for Windows. Version 22.0. IBM, Armonk, NY.

[15] Keller, A.M., Mennel, R.G., Georgoulias, V.A., Nabholtz, J.M., Erazo, A., Lluch, A., Vogel, C.L., Kaufmann, M., von Minckwitz, G., Henderson, I.C., Mellars, L., Alland, L. and Tendler, C. (2004) Randomized Phase III Trial of Pegylated Liposomal Doxorubicin versus Vinorelbine or Mitomycin C plus Vinblastine in Women with Taxane-Refractory Advanced Breast Cancer. *Journal of Clinical Oncology*, **22**, 3893-901. https://doi.org/10.1200/JCO.2004.08.157

[16] Fiegl, M., Mlineritsch, B., Hubalek, M., Bartsch, R., Pluschnig, U. and Steger, G.G. (2011) Single-Agent Pegylated Liposomal Doxorubicin (PLD) in the Treatment of Metastatic Breast Cancer: Results of an Austrian Observational Trial. *BMC Cancer*, **11**, 373. https://doi.org/10.1186/1471-2407-11-373

[17] Mlineritsch, B., Mayer, P., Rass, C., Reiter, E., Russ, G., Vesenmayer, G., Oberaigner, W. and Hausmaninger, H. (2004) Phase II Study of Single-Agent Pegylated Liposomal Doxorubicin HCl (PLD) in Metastatic Breast Cancer after Firstline Treatment Failure. *Onkologie*, **27**, 441-446. https://doi.org/10.1159/000080363

[18] Huober, J., Fett, W., Nusch, A., Neise, M., Schmidt, M., Wischnik, A., Gerhardt, S., Goehler, T., Lück, H.J. and Rost, A. (2010) A Multicentric Observational Trial of Pegylated Liposomal Doxorubicin for Metastatic Breast Cancer. *BMC Cancer*, **10**, 2. https://doi.org/10.1186/1471-2407-10-2

[19] Coleman, R.E., Biganzoli, L., Canney, P., Dirix, L., Mauriac, L., Chollet, P., Batter, V., Ngalula-Kabanga, E., Dittrich, C. and Piccart, M. (2006) A Randomised Phase II Study of Two Different Schedules of Pegylated Liposomal Doxorubicin in Metastatic Breast Cancer (EORTC-10993). *European Journal of Cancer*, **42**, 882-887. https://doi.org/10.1016/j.ejca.2005.12.011

[20] Lorusso, D., Di Stefano, A., Carone, V., Fagotti, A., Pisconti, S. and Scambia, G. (2007) Pegylated Liposomal Doxorubicin-Related Palmar-Plantar Erythrodysesthesia ('Hand-Foot' Syndrome).

[21] Perez, A.T., Domenech, G.H., Frankel, C. and Vogel, C.L. (2002) Pegylated Liposomal Doxorubicin (Doxil) for Metastatic Breast Cancer: The Cancer Research Network, Inc., Experience. *Cancer Investigation*, **20**, 2-29. https://doi.org/10.1081/CNV-120014883

[22] Von Moos, R., Thuerlimann, B.J., Aapro, M., Rayson, D., Harrold, K., Sehouli, J., Scotte, F., Lorusso, D., Dummer, R., Lacouture, M.E., Lademann, J. and Hauschild, A. (2008) Pegylated Liposomal Doxorubicin-Associated Hand-Foot Syndrome: Recommendations of an International Panel of Experts. *European Journal of Cancer*, **44**, 781-790. https://doi.org/10.1016/j.ejca.2008.01.028

Abbreviations

MBC: metastatic breast cancer
BMI: body mass index
CHF: congestive heart failure
CTCAE: Common Terminology Criteria for Adverse Events
DM: diabetes mellitus
ECOG: Eastern Cooperative Oncology Group
HCD: high cumulative dose
LVEF: left ventricular ejection fraction
PLD: pegylated liposomal doxorubicin
PPE: palmar-plantar erythrodysesthesia
SD: standard deviation