Single-agent treatment with pegylated liposomal doxorubicin for metastatic breast cancer

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Anthracyclines and taxanes are among the most active substances used in the treatment of metastatic breast cancer (MBC). Their frequent use in the adjuvant setting and in cumulative toxicities including cardiotoxicity, however, often limit their use in MBC. The trend towards the use of adjuvant trastuzumab-containing regimens, which can also produce cardiotoxicity, adds further support to the need for effective agents with improved tolerability in the metastatic setting. Pegylated liposomal doxorubicin (PLD) can be an effective alternative to conventional anthracyclines for certain women with MBC. In phase III clinical trials, PLD was as effective as doxorubicin and produced significantly less cardiotoxicity in women with MBC. The incidences of myelotoxicity, nausea/vomiting, and alopecia were also lower with PLD, whereas hand–foot syndrome and stomatitis occurred more frequently. Phase II and III trials conducted in women with MBC support the use of PLD monotherapy in patients relapsing after adjuvant anthracycline-containing therapy, in heavily pretreated patients with taxane-refractory disease, in patients with cardiovascular risk factors (e.g. hypertension and mediastinal irradiation), in elderly patients, and in patients for whom specific acute doxorubicin toxicities, such as alopecia, are particularly worrying. *Anti-Cancer Drugs* 19:1–7 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Anthracyclines and taxanes are among the most active of cytotoxic agents available for the treatment of metastatic breast cancer (MBC). In metastatic disease, anthracycline-containing regimens produce significant increases in response rate, median time to disease progression (TTP), and median overall survival relative to non-anthracycline-containing regimens [1,2]. As anthracyclines are widely used in the adjuvant setting, their clinical utility in MBC might, however, be limited owing to toxicity, particularly the potentially irreversible cardiotoxicity associated with cumulative doses. Recent data suggest that the risk for developing cardiotoxicity arises at cumulative doses that are much lower than those historically reported [3–6]. In a recent series of 630 doxorubicin-treated patients, Swain *et al*. [3] reported that the rate of congestive heart failure (CHF) was 5% at the cumulative dose of 400 mg/m^2, rising markedly to 16% at 500 mg/m^2, 26% at 550 mg/m^2, and 48% at 700 mg/m^2. Epirubicin is also cardiotoxic, with a cumulative risk of cardiotoxicity of 4% at a cumulative dose of 900 mg/m^2, increasing exponentially to 15% at a cumulative dose of 1000 mg/m^2 [6]. In addition to cumulative dose, other risk factors for anthracycline-induced cardiotoxicity include prior or concomitant chest irradiation, hypertension, cardiac disease, significant hepatic dysfunction, age above 65 years, and female sex [2,3,7]. Even with long anthracycline-free intervals, the repeated use of conventional anthracyclines in these settings is limited by cumulative toxicity [8,9].

The use of adjuvant anthracyclines in women with human epidermal growth factor receptor 2-positive breast cancer presents special challenges, because the addition of trastuzumab to adjuvant regimens containing conventional doxorubicin further increases the risk of cardiotoxicity [10]. Women with human epidermal growth factor receptor 2-positive breast cancer often experience particular benefit from an anthracycline [11,12]; nevertheless, conventional anthracyclines might not be an option in women who relapse after adjuvant therapy that includes a conventional anthracycline and trastuzumab.

Liposomal forms of doxorubicin offer an attractive alternative to conventional doxorubicin in some women with MBC. The liposome carries the drug into the central compartment and delivers it to the tissues, with the tissue-distribution patterns depending on the formulation being used. The slow release of doxorubicin from the liposome blunts doxorubicin peak concentrations and associated adverse events while maintaining the area under the curve. Pegylated liposomal doxorubicin (PLD) (Doxil; Tibotec Therapeutics, New Jersey, USA; Caelyx; Schering Plough Corporation, New Jersey, USA) is enclosed in liposomes on which a polymeric coat of polyethylene glycol has been grafted, which further prolongs the circulation time. A nonpegylated liposomal formulation (Myocet; Elan Pharmaceuticals, California, USA) is also available. These two formulations have dramatically different plasma pharmacokinetic and

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tissue-distribution patterns and different dosing and safety profiles [13]. They are not bioequivalent.

Both liposomal forms of doxorubicin have been shown to offer similar antitumor efficacy and lower cardiotoxicity, compared with conventional doxorubicin [14,15]. Moreover, when PLD is combined with trastuzumab, the risk of cardiotoxicity seems to be minimal [16]. Although there is general agreement that data are supportive for PLD, questions remain regarding the equivalent efficacies of nonpegylated liposomal doxorubicin and conventional doxorubicin [17].

Sequential single-agent chemotherapy is an attractive option for many patients with MBC and might result in prolonged palliation. Although combination chemotherapy produces higher response rates in this setting, compelling data [1,18] to suggest that this translates into a survival benefit are few. The National Comprehensive Cancer Network recommends either combination therapy or sequential single-agent treatment for MBC, with both conventional doxorubicin and PLD being recommended single-agent therapies [18].

PLD is indicated for the treatment of ovarian cancer and Kaposi's sarcoma in both the United States and the European Union. In the European Union, PLD is also indicated for monotherapy of MBC, in cases having an increased risk for cardiotoxicity. This article reviews the results of clinical trials of single-agent PLD in the treatment of MBC.

Phase II clinical trials in metastatic breast cancer

The activity of PLD monotherapy for the treatment of MBC has been demonstrated in numerous phase II clinical trials (Table 1) [19–25]. Responses have been observed in chemotherapy-naive patients, previously treated patients (including treatment with anthracyclines and/or taxanes), and elderly patients. In less heavily pretreated patients, objective responses have been reported in approximately 15–30% of patients, with clinical benefit in 52–86% of patients [19–23]. Moreover, when response was assessed specifically in patients with anthracycline-pretreated disease, PLD demonstrated response rates as high as *22%* [20,24,25].

PLD monotherapy was generally tolerated well by women with MBC. Complete alopecia was rare. Hand–foot syndrome (HFS) and mucositis were schedule-dependent and dose-dependent, respectively. HFS usually occurred after two or more courses of therapy, and was less frequent with monthly dosing than with dosing every 3 weeks (Q3W). Although grade 3 HFS was not uncommon, grade 4 events were rare. Studies [*22*,24,26] in breast and ovarian cancer demonstrated a substantially reduced incidence of HFS when PLD was administered at an overall dose intensity of 10 mg/m^2/week (i.e. 40 mg/m^2, Q4W) rather than at 12.5 mg/m^2/week (i.e. 50 mg/m^2, Q4W).

Taken together, the results of these phase II trials show that regimens consisting of PLD 40, 45, or 50 mg/m^2 (Q4W) are safe for second-line and salvage use in women with MBC and that they produce high rates of clinical benefit.

Anthracycline-resistant metastatic breast cancer

In a small trial [25] conducted in women with anthracycline-resistant MBC, PLD was well tolerated, but had limited activity. Rivera *et al.* [25] evaluated PLD in patients who had either progressed during anthracycline therapy or relapsed within 6 months of completing anthracycline-based adjuvant therapy. Eleven patients were treated: the first seven received 50 mg/m^2 of PLD, Q4W, and four received 60 mg/m^2 of PLD, Q4W, in an effort to increase efficacy. The trial was, however, discontinued, as no responses were seen. Two patients had a minimal response to therapy, and two had disease stabilization (clinical benefit rate = 36%).

Elderly patients with metastatic breast cancer

Although limited, the data on the safety and efficacy of PLD in elderly women with MBC are thought-provoking. Results from a phase II trial conducted by the European Organisation for Research and Treatment of Cancer have been recently published [21]. A total of 116 patients aged 65 years and above, who had either refused anthracycline treatment or had a medical contraindication to anthracyclines, were randomized to PLD either at 50 mg/m^2 (Q4W) or at 60 mg/m^2 (Q6W). The two regimens seemed to be equally effective, producing response rates of *29–31%*. Consistent with the toxicity analysis by Lyass *et al.* [20], the incidence of grade 3/4 mucositis was greater in the 60-mg/m^2 dose group (35 versus 14%). Efficacy and safety reported in these elderly patients are comparable with the efficacy and safety reported in other phase II and III studies [14,19–25] of PLD monotherapy, suggesting that PLD can be a useful alternative in elderly patients with MBC.

Randomized phase II trial comparing pegylated liposomal doxorubicin with docetaxel

The taxanes paclitaxel and docetaxel are highly active in patients with breast cancer. Docetaxel produces significantly superior relapse-free survival relative to conventional doxorubicin as a first-line treatment for patients with anthracycline-naive MBC [27]. An ongoing randomized phase II clinical trial [28] is evaluating the safety and effectiveness of PLD relative to weekly docetaxel in the first-line setting. Patients with MBC are being randomized either to PLD at 40 mg/m^2 (Q4W) or to docetaxel at 36 mg/m^2 on days 1, 8, and 15 (Q4W), with

Table 1 Response and clinical benefit rates in phase II noncomparative trials of PLD single-agent therapy for metastatic breast cancer

Study	Population	Sample size (evaluable, number of patients)	PLD regimen	Outcomes	% (*n*)	ORR in anthracycline-pretreated population
Ranson *et al.* [19]	First-line or first anthracycline-containing regimen for MBC	71 (64)	60 mg/m^2 Q3W, reduced to 45 mg/m^2 Q3W, and then extended to 45 mg/m^2 Q4W	ORR	31% (20)	NA
				CR	6% (4)	
				PR	25% (16)	
				SD	31% (20)	
				CBR	62% (40)	
Lyass *et al.* [20]	Previously treated for MBC ($\leq$ 2 prior regimens)	45	35–45 mg/m^2 Q3W	ORR	20% (9)	22%[a]
			50–60 mg/m^2 Q4W	CR	4% (2)	
			65–70 mg/m^2 Q5–6W	PR	16% (7)	
				SD	31% (14)	
				CBR	64% (29)[a]	
Coleman *et al.* [21]	Elderly ($\geq$ 65 years) patients presenting with refusal/contraindication to anthracycline	116 (95)	Randomized to 50 mg/m^2 Q4W or 60 mg/m^2 Q6W	ORR	29–31%	NA
				CR	0	
				PR	29–31%	
				SD	33–43%	
Al-Batran *et al.* [22]	Previously treated MBC	46	40 mg/m^2 Q4W	ORR	13% (6)	NA
				CR	2% (1)	
				PR	11% (5)	
				SD	35% (16)	
				CBR	52% (24)	
Mlineritsch *et al.* [23]	Second-line MBC (first palliative anthracycline regimen)	30 (29)	45 mg/m^2 Q4W	ORR	31% (9)	NR
				CR	0	
				PR	31% (9)	
				SD	55% (16)	
				CBR	86% (25)	
Al-Batran *et al.* [24]	Previously treated MBC	79	50 mg/m^2 Q4W	ORR	13% (10)	13%
				CR	1.3% (1)	
				PR	11.4% (9)	
				SD	28% (22)	
				CBR	24%[b]	
Rivera *et al.* [25]	Anthracycline-resistant MBC	11	50–60 mg/m^2 Q4W	ORR	0	0%
				CR	0	
				PR	0	
				SD	18% (2)	
				CBR	36% (4)[c]	

CBR, clinical benefit rate (ORR + SD); CR, complete response; MBC, metastatic breast cancer; NA, not available; NR, not reported; ORR, overall response rate (CR + PR); PLD, pegylated liposomal doxorubicin; PR, partial response; Q3W, dosing every 3 weeks; Q4W, dosing every 4 weeks; SD, stable disease.
[a]Includes six patients with clinical improvement greater than SD but less than PR.
[b]Clinical benefit for $\geq$ 6 months.
[c]Includes two patients with a minimal response.

crossover to the alternate regimen at progression or after eight cycles. Patients should have completed adjuvant chemotherapy at least 6 months before treatment, and the cumulative doxorubicin dose must be less than 300 mg/m^2. Interim results ($n = 73$) showed that the response rates to PLD and docetaxel were similar (17 and 22%, respectively). Median progression-free survival (PFS) and median survival time (MST) were longer with PLD (PFS: 6.9 versus 5.4 months; MST: 15.8 versus 13.6 months, respectively). With weekly docetaxel dosing, the hematologic toxicity profiles were similar. In each arm, 14% of the patients experienced grade 3/4 neutropenia, and approximately 30% required cytokine support. Grade 3 fatigue, arthralgia, and nausea were more common with docetaxel (30, 11, and 16%, respectively) than with PLD (3, 3, and 6%, respectively). Hospitalizations were also more common in the docetaxel arm (35 versus 17%, respectively). Grade 3/4 HFS and stomatitis were more common with PLD (11 and 14%, respectively; 5% incidence of each in the docetaxel arm). Overall, these interim data are encouraging, and they further support the activity of PLD in the first-line setting.

Randomized phase III clinical trials of pegylated liposomal doxorubicin for metastatic breast cancer

The largest phase III trial to date was conducted in Europe, and it included 509 women previously untreated for metastatic disease. The study [14] compared PLD with conventional doxorubicin in women with stage IIIB/IV disease. Prior adjuvant chemotherapy was allowed, if

the chemotherapy-free interval exceeded 12 months and if the prior cumulative doxorubicin dose did not exceed 300 mg/m^2. Patients were randomized to PLD at 50 mg/m^2 (Q4W) or conventional doxorubicin at 60 mg/m^2 (Q3W). Left ventricular ejection fraction (LVEF) was evaluated using sequential multigated blood pool imaging (multiple-gated acquisition) scans. The trial was designed to demonstrate the noninferiority of PLD with respect to PFS.

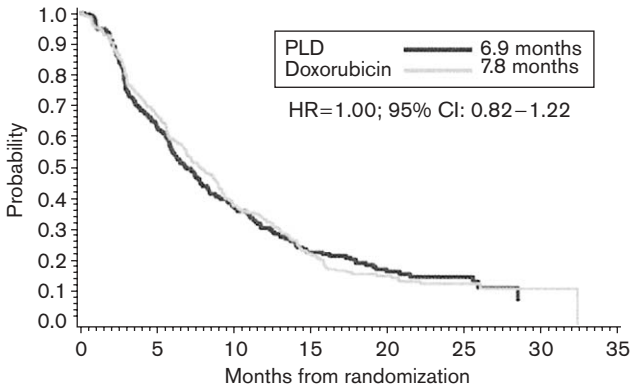
Most patients had visceral disease (nearly 60%) and many had more than two sites of metastatic disease (30%). Most had not received anthracyclines in the adjuvant setting (15% in the PLD arm and 16% in the doxorubicin arm). Nearly half had presented cardiac risk factors at baseline, which included the following: (i) prior mediastinal irradiation (4 and 3%, respectively), (ii) hypertension (12 and 17%, respectively), (iii) age 65 years or above (15 and 13%, respectively), or (iv) two or more of these factors combined (17 and 15%, respectively) [14].

The results demonstrated that PLD is as effective as conventional doxorubicin for the first-line treatment of women with MBC. The median PFS was 6.9 months in the PLD arm and 7.8 months in the doxorubicin arm [hazard ratio (HR) = 1.00; 95% confidence interval (CI) for HR: 0.82–1.22], consistent with the noninferiority of PLD as hypothesized in the protocol (Fig. 1). The treatment effect was consistent across known prognostic factors, including age, menopausal status, performance status, sites of metastatic disease, use of prior therapy (including anthracyclines), estrogen-receptor status, and disease-free interval. Overall survival was similar, with an MST of 21 months with PLD and 22 months with doxorubicin [14].

Despite the similarities in the baseline cardiac risk factors, there was a significant reduction in the risk of cardiotoxicity with PLD (Table 2). Patients receiving PLD had a median cumulative anthracycline exposure of 398 mg/m^2 (including prior therapy); patients receiving doxorubicin had a median exposure of 421 mg/m^2. Ten patients in the PLD arm and 48 patients in the doxorubicin arm experienced a decrease in the LVEF of more than 20%, the protocol-specified definition of cardiotoxicity. Of these, none of the patients in the PLD group became symptomatic, whereas 10 patients in the doxorubicin arm developed symptoms of CHF. Two patients in each group developed clinical CHF without a corresponding decrease in LVEF [14].

The incidence of several other expected anthracycline toxicities was lower with PLD as well. Pronounced or total alopecia occurred in 7% of the patients who received PLD versus 54% who received doxorubicin. All grades of nausea (37 versus 53%) and vomiting (19 versus 31%) were less frequent with PLD than with doxorubicin, as was antiemetic use (72 versus 83%, respectively).

Fig. 1



Progression-free survival in a phase III trial of first-line pegylated liposomal doxorubicin (PLD) versus doxorubicin. HR, hazard ratio; CI, 95% confidence interval. Reprinted from [14] with permission.

Table 2 Cardiotoxicity associated with PLD and doxorubicin in the phase III trial of first-line therapy for MBC [14]

	No. of patients (%)		
	PLD		Doxorubicin
Overall analysis			
Patients with cardiotoxicity[a]	10/254 (3.9%)	HR=3.16 ($P<0.001$)	48/255 (18.8%)
With signs and symptoms of CHF	0/254		10/255 (3.9%)
Without signs and symptoms of CHF	10/254 (3.9%)		38/255 (14.9%)
Patients with signs and symptoms of CHF only	2/254 (0.8%)		2/255 (0.8%)
Subgroup analyses			
Cardiotoxicity among patients with prior anthracycline exposure	1/38 (2.6%)	HR=7.27 (95% CI: 0.93–56.8)	11/40 (27.5%)
Cardiotoxicity among patients with baseline cardiac risk factors	5/122 (4.1%)	HR=2.7 (95% CI: 1.01–7.18)	21/121 (17.3%)

[a]Defined as $\geq$ 20% decrease in LVEF.
CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio, LVEF, left ventricular ejection fraction; MBC, metastatic breast cancer; PLD, pegylated liposomal doxorubicin.

All grades of mucositis and stomatitis were more common with PLD (PLD: 23 and 22%; doxorubicin: 13 and 15%, respectively), although the rates of grade 3/4 toxicity were similar between the arms (mucositis: 4 and 2%, respectively; stomatitis: 5 and 2%, respectively). The most frequently reported adverse event associated with PLD was HFS (48 versus 2% with doxorubicin). Most cases (81/123) were grade 1/2 in severity, and no cases of grade 4 HFS were reported. Grade 3/4 hematologic toxicity was relatively uncommon in each arm, although neutropenia (2 versus 8%) and leukopenia (1 versus 9%) were slightly more common with doxorubicin [14].

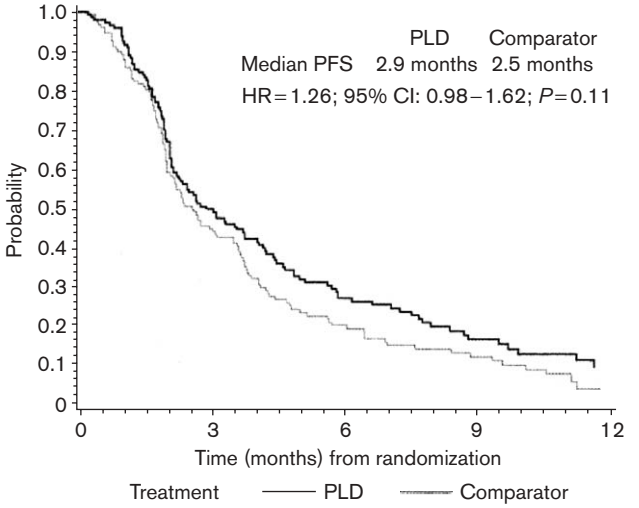
This phase III trial [14] demonstrates that PLD is as effective as doxorubicin in the first-line treatment of MBC, but has reduced rates of cardiotoxicity, myelosuppression, nausea, vomiting, and alopecia. These data formed the basis for the European approval of PLD in this setting.

A second phase III trial [26] was conducted to evaluate the safety and efficacy of PLD for the treatment of taxane-refractory MBC. A total of 301 women who had failed first-line or second-line taxane therapy were randomized to PLD at 50 mg/m^2 (Q4W; $n = 150$) versus vinorelbine (30 mg/m^2 weekly; $n = 129$) or mitomycin C with vinblastine ($n = 22$; 10 mg/m^2 on day 1, Q4W; 5 mg/m^2 on days 1, 14, 28, and 42, every 6–8 weeks; respectively). The choice between comparators was at the investigators' discretion. All patients had failed prior taxane therapy; failure of taxane therapy was defined as disease progression during or within 6 months of the last taxane dose. The trial was designed to detect a 50% improvement in PFS in the intent-to-treat (ITT) population [29].

The majority of the patients had visceral disease (63 and 66%, respectively) and two or more sites of metastases (65 and 64%, respectively). Most had received prior anthracycline therapy (83% in each group), and 37% overall had primary anthracycline-resistant disease. Anthracycline resistance was defined as progression while receiving an anthracycline-based regimen for metastatic disease or within 6 months of completing a course of an anthracycline-based regimen, either in the adjuvant or in the metastatic setting [29].

PFS was increased with PLD in the ITT analysis, but the results were not statistically significant (Fig. 2). Median PFS was 2.9 months with PLD and 2.5 months in the control arm (HR = 1.26, 95% CI: 0.98–1.62, $P = 0.11$). The results were similar in the protocol-eligible patient subgroup. Median PFS was significantly longer in the PLD versus the control arm, in patients ($n = 44$) who had not received prior anthracycline therapy (5.8 versus 2.1 months; HR = 2.40, 95% CI: 1.16–4.95, $P = 0.01$).

Fig. 2



Progression-free survival (PFS) in a phase III trial of pegylated liposomal doxorubicin (PLD) versus comparator (vinorelbine or mitomycin plus vinblastine) in taxane-refractory metastatic breast cancer. PFS was similar for PLD and comparators. HR, hazard ratio; CI, 95% confidence interval. Reprinted from [29] with permission.

No differential benefit was observed in patients with anthracycline-resistant disease (median PFS: 2.6 months in each group). Overall survival in the ITT population and the objective response rates among eligible patients were comparable between groups (MST: 10.4 months with PLD, 9.0 months in control arm; overall response rate: 10 and 12%, respectively) [29].

The incidence of nausea, vomiting, fatigue, and asthenia was similar among the treatment arms. Patients treated with PLD experienced more HFS and stomatitis; and those treated with vinorelbine experienced more constipation, neuropathy, and neutropenia. Changes in LVEF were assessed in the PLD arm. Twenty-two patients experienced asymptomatic cardiotoxicity (defined as an LVEF decrease either of more than 15 points from baseline or of more than 5 points from baseline with a level below the lower limit of normal), although these events did not correlate with cumulative anthracycline dose [29].

Overall, this study demonstrates that PLD is a useful option in the treatment of heavily pretreated, taxane-refractory MBC. Reversible, non-life-threatening skin toxicity occurs in a significant proportion of patients treated with PLD; nevertheless, the risks of myelosuppression and neuropathy are lower for them than for those treated with vinorelbine.

More recently, the results of a multicenter phase III [30] randomized trial demonstrated that maintenance PLD after the completion of six cycles of conventional

anthracycline and taxane chemotherapy prolongs TTP. A median of six cycles of PLD was administered. Cardiotoxicity was not observed and nausea, vomiting, and alopecia were negligible. Grade 3 HFS was reported in three patients. Median TTP increased from 9.96 months in the observation arm to 16.04 months in the PLD arm ($P = 0.0001$).

Discussion and conclusion

PLD is a safe and effective alternative to conventional doxorubicin in the treatment of MBC. PLD has demonstrated activity in taxane-refractory disease and in patients who had previously responded to doxorubicin. Treatment is associated with a significantly reduced risk of cardiotoxicity relative to doxorubicin; rates of alopecia, nausea, vomiting, and myelosuppression are also significantly lower with PLD. The major side effect, HFS, is manageable, reversible, and non-life-threatening.

The reason for the differences in the safety profiles of PLD and conventional doxorubicin is related to the PLD formulation. PLD is formulated with a polyethylene glycol coating that covers a liposome bilayer containing an aqueous doxorubicin core. Liposome encapsulation alters the plasma pharmacokinetics of doxorubicin and promotes drug concentration at the tumor site. Owing to their large size, liposomes generally cannot escape the vasculature in areas with tight capillary junctions, such as muscle, skeletal, and connective tissues; however, tumor angiogenesis produces discontinuous, leaky capillaries with gaps large enough for PLD liposomes to pass through [31]. In this manner, PLD accumulates in the interstitial space between tumor cells, where the encapsulated doxorubicin is ultimately released [7]. Pegylation further extends the half-life of doxorubicin by preventing the clearance of the liposomes by the cells of the reticuloendothelial system (RES). Without pegylation, liposomes are marked by opsonins and are rapidly cleared from the circulation by the RES cells; with pegylation, opsonization is hindered and RES uptake is reduced. Indeed, the circulation half-life of PLD is 74 h, significantly longer than the 10-min circulation half-life of conventional doxorubicin and the 12-min circulation half-life of nonpegylated liposomal doxorubicin [29,32]. Nearly all of the doxorubicin (93–99%) remains encapsulated while in circulation [31]. The concentrations in tumor tissue are, however, several-fold higher than those in adjacent normal tissue. Free doxorubicin, having all the characteristics of conventionally administered doxorubicin, becomes available after the PLD enters the tissues. The results of whole-body γ-imaging studies and tissue-biopsy studies [7,33–35] demonstrate that doxorubicin preferentially accumulates in tumor tissue when administered as PLD.

Numerous clinical trials are underway to further characterize the role of PLD in the management of MBC. PLD is being studied in combination with any of these: bevacizumab, cyclophosphamide in addition to trastuzumab, bortezomib, and lapatinib. The PELICAN trial compares PLD with capecitabine as first-line therapy for MBC. The primary efficacy endpoint is TTP. The target enrollment is 346 patients.

On the basis of clinical trial results, potential candidates for PLD monotherapy include patients who relapse after adjuvant anthracycline-based therapy and heavily pretreated patients with taxane-refractory disease. Anthracycline re-treatment with PLD is a viable option for patients who had received anthracyclines in the adjuvant or metastatic settings; however, it is not indicated in patients classified as being resistant to anthracycline. Anthracycline maintenance with PLD after first-line MBC treatment with doxorubicin and docetaxel might prolong the TTP. Specific patient groups, such as those with cardiovascular risk factors, the elderly, and those for whom specific acute toxicities of doxorubicin, such as alopecia, are of particular concern can also be excellent candidates for PLD.

References

1 Robert NJ, Vogel CL, Henderson IC, Sparano JA, Moore MR, Silverman P, *et al*. The role of the liposomal anthracyclines and other systemic therapies in the management of advanced breast cancer. *Semin Oncol* 2004; **31** (**6 Suppl 13**):106–146.

2 Thigpen JT. Innovations in anthracycline therapy: overview. *Community Oncol* 2005; **2** (**Suppl 1**):3–7.

3 Swain S, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer* 2003; **97**:2869–2879.

4 Von Hoff D, Layard M, Basa P, Davis HL, von Hoff AL, Rozencweig M, *et al*. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med* 1979; **91**:710–717.

5 Praga C, Trave F, Petroccione A. Anthracycline-induced cardiotoxicity and its relevance in cancer treatment. In: Nimmo WS, Tucker GT, editors. *Clinical measurement in drug evaluation*. London: Wolfe Publishing; 1991. pp. 132–142.

6 Ryberg M, Nielsen D, Skovsgaard T, Hansen J, Jensen BV, Dombernowsky P. Epirubicin cardiotoxicity: an analysis of 469 patients with metastatic breast cancer. *J Clin Oncol* 1998; **16**:3502–3508.

7 Orditura M, Quaglia F, Morgillo F, Martinelli E, Lieto E, de Rosa G, *et al*. Pegylated liposomal doxorubicin: pharmacologic and clinical evidence of potent antitumor activity with reduced anthracycline-induced cardiotoxicity [review]. *Oncol Rep* 2004; **12**:549–556.

8 Singal P, Iliskovic N. Doxorubicin induced cardiomyopathy. *N Engl J Med* 1998; **339**:900–905.

9 Pai VB, Nahata MC. Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. *Drug Saf* 2000; **22**:263–302.

10 Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, *et al*. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol* 2002; **20**:1215–1221.

11 Kim C, Bryant J, Horne Z, Geyer CE, Wickerham DL, Wolmark N, *et al*. Trastuzumab sensitivity of breast cancer with co-amplification of HER2 and cMYC suggests pro-apoptotic function of dysregulated cMYC *in vivo*. *Breast Cancer Res Treat* 2005; **94** (**Suppl 1**):S6.

12 Pritchard KI, Shepherd LE, O'Malley FP, Andrulis IL, Bramwell VH, Levine MN, for the National Cancer Institute of Canada Clinical Trials Group. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J Med* 2006; **354**:2103–2111.

13 Park JW. Liposome-based drug delivery in breast cancer treatment. *Breast Cancer Res* 2002; **4**:95–99.

14 O'Brien MER, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, *et al*., CAELYX Breast Cancer Study Group. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol* 2004; **15**:440–449.

15 Batist G, Ramakrishnan G, Rao CS, Chandrasekharan A, Gutheil J, Guthrie T, *et al*. Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. *J Clin Oncol* 2001; **19**:1444–1454.

16 Chia S, Clemons M, Martin L-A, Rodgers A, Gelmon K, Pond GR, *et al*. Pegylated liposomal doxorubicin and trastuzumab in HER-2 overexpressing metastatic breast cancer: a multicenter phase II trial. *J Clin Oncol* 2006; **24**:2773–2778.

17 Williams G, Cortazar P, Pazdur R. Developing drugs to decrease the toxicity of chemotherapy. *J Clin Oncol* 2001; **19**:3439–3441.

18 National Comprehensive Cancer Network website. Clinical practice guidelines in oncology: breast cancer v.2.2006. available at: *http://www.nccn.org/professionals/physician_gls /PDF/breast.pdf*. Accessed August 1, 2006.

19 Ranson MR, Carmichael J, O'Byrne K, Stewart S, Smith D, Howell A. Treatment of advanced breast cancer with sterically stabilized liposomal doxorubicin: results of a multicenter phase II trial. *J Clin Oncol* 1997; **15**:3185–3191.

20 Lyass O, Uziely B, Ben-Yosef R, Tzemach D, Heshing NI, Lotem M, *et al*. Correlation of toxicity with pharmacokinetics of pegylated liposomal doxorubicin (Doxil) in metastatic breast carcinoma. *Cancer* 2000; **89**: 1037–1047.

21 Coleman RE, Biganzoli L, Canney P, Dirix L, Mauriac L, Chollet P, *et al*. A randomised phase II study of two different schedules of pegylated liposomal doxorubicin in metastatic breast cancer (EORTC-10993). *Eur J Cancer* 2006; **42**:882–887.

22 Al-Batran S-E, Meerpohl HG, von Minckwitz G, Atmaca A, Kleeberg U, Harbeck N, *et al*. Reduced incidence of severe palmar–plantar erythrodysesthesia and mucositis in a prospective multicenter phase II trial with pegylated liposomal doxorubicin at 40 mg/m^2 every 4 weeks in previously treated patients with metastatic breast cancer. *Oncology* 2006; **70**:141–146.

23 Mlineritsch B, Mayer P, Rass C, Reiter E, Russ G, Vesenmayer G, *et al*. Phase II study of single-agent pegylated liposomal doxorubicin HCl (PLD) in metastatic breast cancer after first-line treatment failure. *Onkologie* 2004; **27**:441–446.

24 Al-Batran SE, Bischoff J, von Minckwitz G, Atmaca A, Kleeberg U, Meuthen I, *et al*. The clinical benefit of pegylated liposomal doxorubicin in patients with metastatic breast cancer previously treated with conventional anthracyclines: a multicentre phase II trial. *Br J Cancer* 2006; **94**: 1615–1620.

25 Rivera E, Valero V, Esteva FJ, Syrewicz L, Chrisofanilli M, Rahman Z, *et al*. Lack of activity of stealth liposomal doxorubicin in the treatment of patients with anthracycline-resistant breast cancer. *Cancer Chemother Pharmacol* 2002; **49**:299–302.

26 Rose PG. Pegylated liposomal doxorubicin: optimizing the dosing schedule in ovarian cancer. *Oncologist* 2005; **10**:205–214.

27 Chan S, Friedrichs K, Noel D, Pinter T, van Belle S, Vorobiof D, *et al*., for the 303 Study Group. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1999; **17**:2341–2354.

28 Yardley DA, Shipley DM, Greco FA, Montes I, McCarty M, Hainsworth JD, *et al*. Phase II randomized trial of pegylated liposomal doxorubicin versus weekly docetaxel with subsequent crossover as first-line chemotherapy for metastatic breast cancer. Poster presentation at the *27th Annual San Antonio Breast Cancer Symposium*, December 8–11, 2004. Poster 5057.

29 Keller AM, Mennel RG, Georgoulias VA, Nabholtz J-M, Erazo A, Lluch A, *et al*. Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. *J Clin Oncol* 2004; **22**: 3893–3901.

30 Alba E, Ruiz-Borrego M, Martin M, Margeli M, Rodriguez-Lescure P, Sánchez-Rovira P, *et al*. Prolongation of TTP by maintenance therapy with PLD in a multicenter phase III randomized trial following standard chemotherapy for MBC: GEICAM 2001-01 study. *J Clin Oncol* 2007; **25** (**18 Suppl**):1007.

31 Allen TM, Martin FJ. Advantages of liposomal delivery systems for anthracyclines. *Semin Oncol* 2004; **31** (**Suppl 13**):5–15.

32 Conley BA, Egorin MJ, Whitacre MY, Carter DC, Zuhowski EG, Van Echo DA. Phase I and pharmacokinetic trial of liposome-encapsulated doxorubicin. *Cancer Chemother Pharmacol* 1993; **33**:107–112.

33 Vail DM, Amantea MA, Colbern GT, Martin FJ, Hilger RA, Working PK. Pegylated liposomal doxorubicin: proof of principle using preclinical animal models and pharmacokinetic studies. *Semin Oncol* 2004; **31** (**Suppl 13**): 16–35.

34 Gabizon A, Shmeeda H, Barenholz Y. Pharmacokinetics of pegylated liposomal doxorubicin: review of animal and human studies. *Clin Pharmacokinet* 2003; **42**:419–436.

35 Symon Z, Peyser A, Tzemach D, Lyass O, Sucher E, Shezen E, *et al*. Selective delivery of doxorubicin to patients with breast carcinoma metastases by stealth liposomes. *Cancer* 1999; **86**:72–78.