Breast Cancer: Targets and Therapy

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REVIEW

New approaches in the management of advanced breast cancer – role of combination treatment with liposomal doxorubicin

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Abstract: Metastatic breast cancer (MBC) remains a major cause of morbidity and mortality in women worldwide. For three decades doxorubicin, alone or in combination with other cytotoxic agents, has been a mainstay of systemic therapy for MBC. However, its use is limited by cumulative cardiotoxicity. More recently liposomal formulations of doxorubicin have been developed which exhibit equal efficacy but reduced cardiotoxicity in comparison to conventional doxorubicin. The novel toxicity profile of liposomal doxorubicins has prompted their evaluation with various cytotoxic agents in patients with MBC. In addition, their favorable cardiac safety profile has prompted re-evaluation of concomitant therapy with doxorubicin and trastuzumab, a regimen of proven efficacy in MBC but previously considered to be associated with significant cardiotoxicity. We review clinical trial data addressing combination therapy with both pegylated and non-pegylated liposomal doxorubicin in patients with MBC.

Keywords: breast cancer, anthracycline, liposome-encapsulated doxorubicin, pegylated liposomal doxorubicin, cardiotoxicity

Introduction

Systemic therapy of advanced breast cancer

Despite advances in adjuvant therapy, a significant proportion of women diagnosed with early breast cancer will ultimately relapse with metastatic disease.[1] In addition, 4% to 10% of women will present with metastatic disease at the time of initial diagnosis.[2] The management of metastatic breast cancer (MBC) is based on a number of tumor-related characteristics including anatomical sites of disease, hormonal sensitivity of the tumor, and Her2 status and may include hormonal, cytotoxic and molecularly targeted therapies. Although randomized comparisons of cytotoxic chemotherapy versus observation are lacking, survival benefit can be inferred from a variety of studies which compare a more effective with a less effective regimen. For example, overall survival benefits have been demonstrated for docetaxel and capecitabine versus capecitabine alone in anthracycline pre-treated patients[3] and for gemcitabine and paclitaxel versus paclitaxel alone as first-line therapy.[4] Nevertheless, the aim of systemic therapy for advanced disease remains palliative rather than curative. Against this background treatment related toxicity and patient quality of life are major considerations. Importantly, none of these studies prospectively compared combination chemotherapy with the same agents administered as sequential monotherapies. However, in the E1193 trial, patients with MBC were randomized to receive concomitant doxorubicin and paclitaxel versus receiving the same drugs sequentially with cross-over occurring at the time of progression.[5] While the overall response rate (ORR) and time to progression (TTP)

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were higher in patients receiving concomitant combination therapy there was no difference in overall survival (OS). The higher response rates achievable with combination chemotherapy therefore support this approach in patients who are symptomatic or who have organ-threatening visceral disease where it is imperative to achieve maximum cytoreduction. However, where minimization of toxicity is more important, a sequential monotherapy approach may be adopted.

The anthracyclines, a class of anti-tumor antibiotics, are DNA intercalating agents which act primarily by inhibiting topoisomerase II. Anthracyclines are amongst the most active single agents in breast cancer. For example, non-liposomal doxorubicin (hereafter referred to as doxorubicin), can result in objective response rates of around 40% when used as a single agent in MBC and forms the backbone of many adjuvant combination regimens.[5,6] Toxicities include myelosuppression, alopecia, emesis and, importantly, cardiotoxicity which is a major limiting factor in its use. Epirubicin is a second generation anthracycline which is less cardiotoxic on a milligram per milligram basis although this benefit may be negated by the higher doses required for equivalent anti-tumor efficacy.[7]

Cardiotoxicity of anthracyclines

The cardiotoxic effects of doxorubicin were noted early in its development with descriptions of transient electrocardiographic changes and congestive cardiac failure.[8] It is now appreciated that anthracyclines may cause acute, chronic and late cardiac toxicity. Acute cardiotoxicity, manifesting as transient ECG changes, arrhythmias and rarely myocarditis, occurs within 24 hours and is reversible. Subacute and chronic toxicity form a continuum manifesting months to years after exposure and are characterized by irreversible myocardial damage. Specific ultra-structural and histological changes such as myofibrillar disarray and myocyte necrosis are identifiable on endomyocardial biopsy.[9,10] Ultimately this myocardial damage leads to progressive dilated cardiomyopathy and clinical congestive cardiac failure. The cardiotoxic effects of anthracyclines appear, at least in part, to be distinct from their antitumor activity and primarily relate to increased oxidative stress and to alterations in calcium and iron homeostasis.[11]

The major determinant of chronic anthracycline-related cardiotoxicity is the lifetime cumulative dose received. Currently, the generally accepted safe maximum cumulative dose of doxorubicin is 450 to 500 mg/m^2, based on data suggesting a 7% incidence of congestive heart failure (CHF) after exposure to 550 mg/m^2.[12] However, contemporary data suggest clinically significant cardiotoxicity may be more common and occur with lower exposure than previously thought. Specifically, an analysis of 630 patients treated with doxorubicin across three clinical trials identified cardiac events (defined as a decline in absolute value ≥20% in left ventricular ejection fraction [LVEF] from baseline, a decline in absolute value ≥10% in LVEF from baseline and to below the institution's LLN, a post-baseline decline in absolute value ≥5% in LVEF below the institution's LLN, or the occurrence of CHF on study) in 5% of patients after 400 mg/m^2, 26% after 550 mg/m^2 and 48% after a dose of 700 mg/m^2.[13] Epirubicin is less cardiotoxic on a mg/mg basis with a recommended maximum cumulative dose of 900 mg/m^2 and similar risk factors.[14,15]

In addition to cumulative anthracycline dose, other risk factors for the development of cardiotoxicity include age,[13,16] female sex,[17] pre-existing heart disease or hypertension,[12,18] overweight (body mass index >27 kg/m^2),[19] cardiac irradiation,[20] and peak plasma level as determined by rate of infusion.[21] Moreover, there appears to be significant inter-individual variation in the development of cardiotoxicity in patients with otherwise similar risk factor profiles suggesting a gene-environment interaction.[12,22] Gene polymorphisms which may influence anthracycline metabolism, cardiac cell survival and response to oxidative stress and cardiac remodeling in women receiving adjuvant anthracyclines are under prospective evaluation in the UK BetterCare trial.[23]

A variety of strategies have been proposed to mitigate anthracycline-related cardiotoxicity.[7] These include proactive management of cardiac risk factors such as hypertension, monitoring of cardiac function, limitation of cumulative anthracycline dose and consideration of liposomal doxorubicin in patients with increased cardiac risk. Dexrazoxane, an iron-chelating agent which can reduce oxidative stress, is approved for the prevention of chronic cumulative cardiotoxicity caused by anthracycline use in advanced and/or metastatic cancer patients after previous anthracycline containing treatment. A recent Cochrane meta-analysis identified a statistically significant benefit in favor of dexrazoxane for the occurrence of heart failure (relative risk [RR] 0.29, 95% confidence interval [CI] 0.20 to 0.41).[24] No difference in response rate or survival was identified. Current ASCO guidelines recommend consideration of dexrazoxane for patients with metastatic breast cancer who have received more than 300 mg/m^2 of doxorubicin in the metastatic setting and who may benefit from continued doxorubicin-containing therapy.[25]

In this review we will consider the safety and efficacy of liposomal doxorubicin-based combination therapies in the management of patients with MBC.

Liposomal doxorubicin

There are two commercially available liposomal formulations of doxorubicin: liposome-encapsulated doxorubicin (LED; Myocet®; Cephalon Ltd, UK) and pegylated liposomal doxorubicin (PLD; Caelyx®; Schering-Plough Ltd, UK; Doxil®; Ortho Biotech, New Jersey, USA). The encapsulation of doxorubicin within a lipid bilayer to form a liposome causes two fundamental alterations in its pharmacokinetics. First, due to their large size liposomes are unable to efficiently cross endothelium with intact tight junctions but rather will preferentially accumulate within tumors which typically have an abnormal "leaky" vasculature.[26] Second, due to slow release from the liposome, peak plasma concentrations of bioactive free drug are reduced. Both of these alterations would be predicted to improve the therapeutic index of doxorubicin. A further modification, the grafting of a polyethylene glycol coat to the outer surface of the liposome ("pegylation"), inhibits interaction with plasma proteins and prevents uptake of the liposome by cells of the reticulo-endothelial system. In consequence pegylation results in a significantly prolonged half-life. Pegylated and non-pegylated liposomal doxorubicin have distinct pharmacokinetic and pharmacodynamic profiles and are not bioequivalent.

Pegylated liposomal doxorubicin

Unlike conventional doxorubicin which shows extensive tissue distribution, PLD has a volume of distribution close to the blood volume (Table 1).[27–29] The clearance of PLD is reduced approximately 250-fold and the area under the concentration-time curve dramatically increased in comparison with doxorubicin. As a result the toxicity profile of PLD is closer to that of doxorubicin administered by continuous infusion than it is to doxorubicin administered by the more common bolus method.[30] Thus, myelosuppression, alopecia and cardiotoxicity are reduced but mucositis and palmar-plantar erythrodysesthesia (PPE), a toxicity rarely encountered with bolus doxorubicin, are increased. Preferential delivery of PLD to tumor tissue has been confirmed in animal models as well as in biopsy studies in patients with MBC and Kaposi's sarcoma.[29,31,32]

The efficacy and safety of PLD monotherapy was evaluated in 2 phase III studies in patients with advanced breast cancer. O'Brien et al randomized 509 women with stage IIIb/IV disease to first-line PLD 50 mg/m^2 every 4 weeks (n = 254) or doxorubicin 60 mg/m^2 every 3 weeks (n = 255).[33] Prior adjuvant chemotherapy including anthracyclines was allowed provided the chemotherapy-free interval was greater than 12 months and the cumulative dose of prior doxorubicin did not exceed 300 mg/m^2. Progression-free survival (PFS; 6.9 vs 7.8 months; HR 1.0; 95% CI 0.82 to 1.22), overall survival (OS; 21 vs 22 months; HR = 0.94; 95% CI 0.74 to 1.19), and ORR (33% vs 38%) were comparable but PLD was associated with significantly less cardiotoxicity (defined as a decrease of ≥20% from baseline if within normal range or ≥10% if LVEF became abnormal or CHF). Specifically, 10 patients treated with PLD experienced cardiac events in comparison to 48 patients treated with doxorubicin (HR 3.16; 95% CI 1.58 to 6.31). This included 10 cases of symptomatic CHF in the doxorubicin arm with no symptomatic CHF seen in the PLD arm. In the subgroup of patients who had received prior anthracyclines, the risk of a cardiac event was 7-fold higher for those patients receiving doxorubicin versus PLD. As expected, non-cardiac toxicities also differed between the two treatment arms. PLD was associated with less alopecia (7% vs 54%), vomiting (19 vs 31%) and neutropenia (4% vs 10%) but with increased stomatitis (22% vs 15%) and PPE (48% vs 2%). On the basis of these results PLD was approved in Europe as monotherapy for patients with MBC where there is an increased cardiac risk.

A second phase III trial evaluated PLD (50 mg/m^2 every 28 days) in 301 patients with taxane-refractory MBC and suggested similar efficacy to a comparator regimen of either vinorelbine of vinblastine plus mitomycin C.[34] Cardiac toxicity (defined as either a decrease of ≥15 points from baseline or a ≥5-point decrease from baseline with a level below the LLN) was observed in 22 patients, none of whom developed symptomatic CHF. The most frequent grade 3/4 toxicities observed in patients receiving PLD were PPE (19%),

Table 1 Pharmacokinetics of non-liposomal and liposomal doxorubicin formulations

	Doxorubicin	Liposome-encapsulated doxorubicin	Pegylated liposomal doxorubicin
Volume of distribution	700 to 1100 L/m^2	34 L/m^2	1.93 L/m^2
Clearance	24 to 73 L/h/m^2	3 L/h/m^2	0.030 L/h/m^2
Terminal half-life	30 hours	16 hours	73.9 hours

stomatitis (5%), vomiting (4%), nausea (3%) and fatigue (3%). Alopecia occurred in only 3% of patients.

Liposome-encapsulated doxorubicin

Pharmacokinetic analyses of LED indicate higher plasma levels of total doxorubicin (free and encapsulated) with a lower volume of distribution and lower clearance in comparison to non-liposomal doxorubicin (Table 1).[35–38] As with PLD, experimental data exist to support the hypothesis of enhanced accumulation within tumors.[39]

The clinical relevance of these pharmacokinetic (PK) differences is supported by data from three phase III trials, all of which demonstrated comparable efficacy with reduced toxicity for LED in comparison to non-liposomal doxorubicin. Harris et al randomized 224 patients with MBC to first line LED (n = 108) or non-liposomal doxorubicin (n = 116).[40] Exclusion criteria included cumulative anthracycline dose >300 mg/m^2, LVEF <50%, history of significant cardiac disease and adjuvant chemotherapy within the previous 6 months. Both LED and non-liposomal doxorubicin were dosed at 75 mg/m^2 every 3 weeks. Cardiotoxicity (defined as LVEF decline on multi-gated acquisition scan [MUGA] scanning of 20 or more units from baseline to a final value ≥50%, or by 10 or more units to a final value <50%, or onset of CHF) was observed in 13% of patients treated with LED (including 2 cases of symptomatic CHF) compared to 29% of doxorubicin patients. Median cumulative doxorubicin dose at onset of cardiotoxicity was 785 mg/m^2 for LED versus 570 mg/m^2 for doxorubicin. The overall response rate was identical in both groups at 26% with no significant difference in median TTP. Lower rates of myelosuppression, nausea/vomiting and mucositis were recorded in the LED arm although these did not reach statistical significance.

Batist et al randomized 297 women with MBC to first-line cyclophosphamide 600 mg/m^2 with either LED 60 mg/m^2 or doxorubicin 60 mg/m^2 every 3 weeks.[41] Patients were at least 6 months from completion of adjuvant chemotherapy (adjuvant doxorubicin allowed provided cumulative dose <300 mg/m^2) and had no significant cardiac morbidity. There was no difference in efficacy with an ORR of 43% in both treatment arms. Cardiotoxicity (defined as per Harris)[40] occurred in 6% of patients in the LED arm compared to 21% in the doxorubicin arm. Again there was a trend for reduced rates of common toxicities. On the basis of this pivotal trial, LED was licensed for the first-line treatment of MBC in combination with cyclophosphamide.

A smaller trial randomized 167 anthracycline-naive patients with MBC to first-line cyclophosphamide 600 mg/m^2 plus LED 75 mg/m^2 versus cyclophosphamide 600 mg/m^2 plus epirubicin 75 mg/m^2 every 3 weeks.[42] There was no significant difference in the primary endpoint of ORR (46% vs 39%) although TTP was longer for LED (7.7 vs 5.6 months; $P = 0.022$). There was no significant difference in the incidence of cardiotoxicity (12% vs 10%).

Combination of PLD with cytotoxics

PLD has been studied in combination with a variety of cytotoxic agents in patients with MBC (Table 2).[43–65] All of the trials reported to date have been early phase investigatory studies with relatively small numbers of patients and should be interpreted accordingly.

PLD and paclitaxel

Paclitaxel, a microtubule-stabilizing agent originally derived from the bark of the yew *Taxus brevifolia*, has significant single agent activity in breast cancer.[81] Paclitaxel with concomitant doxorubicin represents a highly active regimen in MBC.[66,67] However, the combination of doxorubicin and paclitaxel has been associated with increased cardiotoxicity thus making PLD an attractive alternative.[68]

Vorobiof and colleagues observed a high response rate (73%; 95% CI 55% to 86%) with PLD 30 mg/m^2 and paclitaxel 175 mg/m^2 administered 3 weekly. However, this was associated with the occurrence of grade 3 PPE (blistering, ulceration or swelling interfering with walking or normal daily activities) in 30% of patients.[45] The high response rate yet poor tolerability of this regimen was supported by a second study which was terminated early due to an unacceptably high rate of PPE.[44] Interestingly a recently reported phase I study conducted in a Taiwanese population with MBC demonstrated better tolerability when paclitaxel was administered at lower doses of 150 to 160 mg/m^2 in comparison to 175 mg/m^2.[47]

Schwonzen and colleagues investigated an alternative schedule consisting of PLD 20 mg/m^2 every 2 weeks with weekly paclitaxel 80 mg/m^2. The combination demonstrated a high response rate (48%) in a heavily pre-treated population but once more this was at the cost of significant PPE and mucositis and a lower dose was recommended for further study.[43] Excessive levels of mucositis and PPE were also evident in a phase I study which explored various dose levels of weekly paclitaxel with 4-weekly PLD.[46]

The relatively high frequency of PPE and mucositis identified across these studies may result from a PK interaction previously identified when paclitaxel was combined with

non-liposomal doxorubicin. Specifically, the administration of paclitaxel prior to doxorubicin was associated with reduced elimination of doxorubicin and its metabolites and a higher incidence of cardiac failure, probably reflecting competition of the Cremaphor vehicle with doxorubicin and its metabolites for P-glycoprotein-dependent hepatobiliary excretion.[69,70] A similar PK interaction does not occur with docetaxel (which is not formulated with a Cremaphor vehicle). This PK interaction appears to be subject to a high degree of interpatient variability with up to 10-fold increases in free doxorubicin seen in some patients after administration of paclitaxel.[46] A similar pharmacokinetic interaction has also been demonstrated for PLD.[46,71] Given the short half-life of conventional doxorubicin this PK interaction may be ameliorated by administering doxorubicin prior to paclitaxel with a washout period or by increasing the duration of the paclitaxel infusion.[68] However, the long half-life of PLD limits such approaches. For example, when PLD was administered on day 1 and paclitaxel on days 1, 8 and 15, elevations in free doxorubicin concentration were shown to occur after each paclitaxel infusion.[46]

Taken together, these data indicate that the combination of PLD with paclitaxel, at least at the doses and schedules studied to date, is poorly tolerated in patients with MBC. Given the palliative aim of chemotherapy and the lack of overall survival benefit identified for conventional anthracycline/taxane combination therapy such toxicity cannot be justified.

PLD and docetaxel

Docetaxel is a semi-synthetic derivative of paclitaxel. Phase II studies in patients with MBC have evaluated both weekly and 3 weekly docetaxel in combination with PLD. Alexopoulos and colleagues administered PLD (30 mg/m^2 on day 1) and docetaxel (75 mg/m^2 on day 2) every 3 weeks to 44 patients with MBC, achieving an ORR of 64.3% (95% CI 49.8% to 78.8%).[50] This regimen was well tolerated with only 2 patients requiring dose modification for PPE and with febrile neutropenia occurring in 9% of patients. The mean reduction in LVEF from baseline was less than 4% with no patient experiencing a decrease in LVEF to less than 60%.

Morabito and colleagues conducted a phase I/II trial of PLD administered on day 1 and docetaxel on days 2 and 9 of a 3-weekly cycle. Dose-limiting toxicities (DLTs) were febrile neutropenia and PPE, identifying 35 mg/m^2 PLD/35 mg/m^2 docetaxel as the recommended phase II dose.[49] At this dose the ORR was 59.5% (95% CI 43.3% to 74.4%). This regimen was reasonably well tolerated, with stomatitis and PPE (each occurring in 14% of patients) representing the most frequent grade 3 toxicities. There were no episodes of febrile neutropenia, consistent with observations that docetaxel is less myelosuppressive when administered on a weekly schedule.[72] No cardiotoxicity was identified.

PLD and vinorelbine

Single agent vinorelbine, a vinca alkaloid and mitotic spindle poison, is widely used in MBC with ORRs of 40% to 44% in chemotherapy-naive patients and 17% to 36% in pre-treated patients.[73] It has a favorable toxicity profile including a low incidence of alopecia. In the first phase I trial of PLD with vinorelbine in patients with MBC, Burstein and colleagues attempted to administer vinorelbine on days 1 and 8 of a 4 weekly cycle.[51] This was not feasible due to myelosuppression preventing administration of the day 8 vinorelbine but an alternative day 1 and 15 regimen was better tolerated and the recommended phase 2 dose was PLD 40 mg/m^2 on day 1 and vinorelbine 30 mg/m^2 on days 1 and 15 of a 28-day cycle. The findings of a second phase I trial were consistent with a recommended phase II dose of PLD 20 mg/m^2 (days 1 and 8) and vinorelbine 30 mg/m^2 (days 1 and 8) every 4 weeks.[52] DLTs in both trials consisted of febrile neutropenia and mucositis.

In 36 women with pre-treated MBC, PLD 40 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 on days 1 and 15 of a 4-weekly cycle was associated with an ORR of 39% (95% CI 23% to 54.8%) and median TTP of 6.5 months and was well tolerated with a febrile neutropenia rate of 5% and low incidence of non-hematological toxicity.[55] The tolerability of this regimen in older patients was supported by a study which recruited 34 women ≥65 years of age (median 71; range 65 to 82) with previously untreated MBC.[57] Febrile neutropenia and grade 3 mucositis occurred in 9% and 14% of patients respectively and the ORR was 50% (95% CI 36% to 66%) with a median TTP of 8 months. In an effort to reduce toxicity further Martin and colleagues omitted the day 15 vinorelbine, evaluating PLD 35 mg/m^2 (day 1) + vinorelbine 30 mg/m^2 (day 1) every 4 weeks in 35 women, most of whom had received prior treatment for MBC. The ORR of 35% (95% CI 20% to 54%) and median TTP of 7 months compared favorably with the day 8/15 regimens although rates of grade 3 mucositis (15%) and febrile neutropenia (9%) were not appreciably lower.

Two phase II studies which evaluated day 1 and 8 vinorelbine have, in contrast to the Burstein study, found it feasible and well tolerated. PLD 40 mg/m^2 with vinorelbine 20 mg/m^2 was associated with a disappointing ORR of 17%

Table 2 Published trials of pegylated liposomal doxorubicin (PLD)/cytotoxic combination therapy for MBC

Agent/ Phase	Study	Population	Prior doxorubicin allowed?	Treatment (IV unless otherwise stated)	Efficacy		Selected toxicities (% pts experiencing grade 3/4)	Cardiotoxicity	Comments
					ORR	PFS/TTP			
Paclitaxel									
II	Schwonzen[43]	MBC, pretreated (n = 21)	Yes	PLD 20 mg/m^2 (d1) + paclitaxel 100 mg/m^2 (d1,8) every 2 weeks	48%	>10 mo	Alopecia (all grades) 100% Neutropenia 62% PPE 29% Neuropathy 24% Mucositis 14%	None	PLD 15 mg/m^2 (d1) and paclitaxel 80 mg/m^2 (d1/8) recommended for further based study based on actual dose delivery achieved
II	Rigatos[44]	MBC, first line (n = 24)	Yes (adjuvant)	PLD 30 mg/m^2 (d1) + paclitaxel 175 mg/m^2 (d1) every 3 weeks	70%	7 mo	Alopecia 65% PPE 47% Neutropenia 22% Neurotoxicity 22% Myalgia 22%	1 pt decreased LVEF	
II	Vorobiof[45]	MBC, first line (n = 34)	Yes (adjuvant and ≥12 mo elapsed)	PLD 30 mg/m^2 (d1) + paclitaxel 175 mg/m^2 (d1) every 3 weeks	73%	10.4 mo	Alopecia (all grds) 78% PPE 30% Leucopenia 21% Febrile neutropenia 6% Neurotoxicity 3%	Grade I/II drop in LVEF – 31% No CHF	
I	Bourgeois[46]	MBC, first line (n = 30)	Yes (adjuvant and >6 m elapsed; cumulative dose <300 mg/m^2 [or <600 mg/m^2 for epi])	Dose escalation: PLD 30–40 mg/m^2 (d1) + paclitaxel 80–100 mg/m^2 (d1, 8, 15) every 4 weeks	60%	12 mo	DLT = mucositis, PPE, febrile neutropenia	No CHF	RP2D = PLD 35 mg/m^2 + paclitaxel 80 mg/m^2
I	Hong[47]	MBC with prior anthracycline exposure in adjuvant or metastatic setting (n = 23)	Yes (mandatory)	Dose escalation: PLD 30–40 mg/m^2 (d1) + paclitaxel 150–170 mg/m^2 (d1) every 3 weeks	52%	7.9 mo	DLT = febrile neutropenia, PPE	None	RP2D = PLD 35 mg/m^2 + paclitaxel 160 mg/m^2 (d1)
Docetaxel									
I	Sparano[48]	MBC or LABC, Up to one prior non-anthracycline non-taxane regimen for metastatic disease (n = 41)	Yes (adjuvant; cumulative dose <400 mg/m^2)	Dose escalation: PLD 30–45 mg/m^2 (d1) + docetaxel 60–75 mg/m^2 (d1) every 3–4 weeks	52% (MBC) 88% (LABC)	–	DLT = febrile neutropenia, prolonged neutropenia, mucositis, infusion reaction	2 pt with LVEF decrease >10% No CHF	RP2D = PLD 30 mg/m^2 (d1) + docetaxel 60 mg/m^2 (d1)
I/II	Morabito[49]	MBC or LABC, first line (n = 57)	Yes (adjuvant and >12 mo elapsed; cumulative dose <300 mg/m^2 [or <450 mg/m^2 for epi])	RP2D = PLD 35 mg/m^2 (d1) + docetaxel 35 mg/m^2 (d2, 9) every 3 weeks	59%	9 mo	Mucositis 14% PPE 14% Neutropenia 9% Infusion reaction 7%	none	

II	Alexopoulos[50]	MBC, first line (n = 44)	Yes (adjuvant)	PLD 30 mg/m^2 (d1) + docetaxel 75 mg/m^2 (d2) every 3 weeks	64%	>17 mo	Alopecia (all grds) 95% Neutropenia 18% Febrile neutropenia 9% PPE 2% Neurotoxicity 2%	None	
Vinorelbine									
I	Burstein[51]	MBC with 0–3 prior chemotherapy regimens (n = 30)	Yes (cumulative dose ≤360 mg/m^2)	Dose escalation: PLD 30–50 mg/m^2 (d1) + vinorelbine 25–30 mg/m^2 (d1,8 or d1,15) every 4 weeks	25%	–	DLT = neutropenia, PPE, mucositis,	1 pt with asymptomatic decrease in LVEF	RP2D = PLD 40 mg/m^2 (d1) +Vinorelbine 30 mg/m^2 (d1, 15)
I/II	Gebbia[52]	MBC, first-line (n = 30)	Yes (adjuvant and ≥12 m elapsed)	Phase II dose: PLD 20 mg/m^2 (d1,15) + vinorelbine 30 mg/m^2 (d1,15) every 4 weeks	68%	>7 mo	Neutropenia 39% Mucositis 22% N/V 6%	1 pt with asymptomatic decrease in LVEF > 15% No CHF	
II	Rimassa[53]	MBC, first line (n = 23)	Yes (adjuvant and ≥12 mo elapsed; cumulative dose ≤450 mg/m^2 [or 900 mg/m^2 for epi])	PLD 40 mg/m^2 (d1) + vinorelbine 20 mg/m^2 (d1, 8) every 4 weeks	17%	10 mo	Neutropenia 74% Mucositis 30% PPE 21%	none	
II	Martin[54]	MBC with prior anthracycline exposure in adjuvant or metastatic setting (n = 35)	Yes (mandatory)	PLD 35 mg/m^2 (d1) + vinorelbine 30 mg/m^2 (d1) every 4 weeks	35%	7 mo	Alopecia (all grades) 53% Mucositis 15% Febrile neutropenia 9% PPE 6% Neurotoxicity 2%	3 pts with decline in LVEF to <50% No CHF	
II	Ardavanis[55]	MBC with prior anthracycline and taxane (n = 36)	Yes (mandatory)	PLD 40 mg/m^2 (d1) + vinorelbine 25 mg/m^2 (d1,15) every 4 weeks	39%	6.5 mo	Alopecia (all grds) 25% Mucositis 6% Febrile neutropenia 3% Thrombocytopenia 3%	Asymptomatic decrease LVEF >15 % – 11%	
II	Chow[56]	Taxane and/or anthracycline pretreated MBC (n = 25)	Yes (adjuvant or metastatic setting)	PLD 30 mg/m^2 (d1) + vinorelbine 20 mg/m^2 (d1,8) every 3 weeks	36%	6.7 mo	Neutropenia 16% Mucositis 8%	None	
II	Addeo[57]	MBC, first line, age ≥65 (n = 34)	Yes (adjuvant and ≥12 mo elapsed)	PLD 40 mg/m^2 (d1) + vinorelbine 25 mg/m^2 iv (d1), 60 mg/m^2 po (d15) every 4 weeks	50%	8 mo	Neutropenia 15% Febrile Neutropenia 9% Mucositis 6% Vomiting 4% PPE 1%	2 pt with decrease LVEF to <50%	

(*Continued*)

Table 2 (*Continued*)

Agent/ Phase	Study	Population	Prior doxorubicin allowed?	Treatment (IV unless otherwise stated)	Efficacy		Selected toxicities (% pts experiencing grade 3/4)	Cardiotoxicity	Comments
					ORR	PFS/TTP			
Gemcitabine									
I	Rivera[58]	MBC, first-line and pretreated (n = 27)	Yes (adjuvant or metastatic setting)	Dose escalation: PLD 20–29 mg/m^2 (d1) + gemcitabine 800–1000 mg/m^2 (d1,8) every 3 weeks	33%	–	DLT = neutropenia, thrombocytopenia	None	RP2D = PLD 24 mg/m^2 (d1) + gemcitabine 800 mg/m^2 (d1, 8)
II	Rivera[59]	MBC, first line (n = 49)	Yes (adjuvant and ≥2 mo elapsed)	PLD 24 mg/m^2 (d1) + gemcitabine 800 mg/m^2 (d1, 8) every 3 weeks	52%	4.5 mo	Neutropenia 74% Febrile neutropenia 2% Thrombocytopenia 27% N/V 11% Mucositis 8% PPE 6%	1 pt symptomatic CHF	
II	Fabi[60]	MBC, first line or pretreated (n = 50)	Yes (adjuvant or metastatic setting; cumulative dose ≤350 mg/m^2 [or 480 mg/m^2 for epi])	PLD 25 mg/m^2 (d1) + gemcitabine 800 mg/m^2 iv (d1, 8) every 3 weeks	44%	7 mo	Neutropenia 30% Febrile neutropenia 4% Mucositis 10% PPE 2%	2 pts with asymptomatic decrease LVEF >15 % No CHF	
II	Ulrich-Pur[61]	MBC, >1 prior regimen for metastatic disease (n = 34)	Yes (adjuvant or metastatic setting)	PLD 24 mg/m^2 (d1) + gemcitabine 800 mg/m^2 (d1,8) every 3 weeks	26%	7.5 mo	Neutropenia 44% Alopecia (all grds) 36% Mucositis 3% PPE 3%	No CHF	
I/II	Wong[62]	MBC, first line (n = 38)	Yes (adjuvant and ≥12 mo elapsed; cumulative dose ≤240 mg/m^2)	Phase II dose: PLD 35 mg/m^2 (d1) + gemcitabine 1200 mg/m^2 (d1, 8) every 3 weeks	83%	6.7 mo	Alopecia (all grades) 84% Mucositis 36% Neutropenia 56% Febrile neutropenia 4% PPE 4%	None	
II	Adamo[63]	MBC, first-line (n = 71)	Yes (adjuvant and >12 mo elapsed; cumulative dose ≤350 mg/m^2 [or 450 mg/m^2 for epi])	PLD 25 mg/m^2 (d1) + gemcitabine 800 mg/m^2 (d1,8) every 3 weeks	35%	11 mo	Neutropenia 25% Mucositis 11% PPE 9%	1 pt with >20% decrease in LVEF No CHF	
Cyclophosphamide									
II	Overmoyer[64]	MBC, first line (n = 51)	Yes (adjuvant and >12 mo elapsed; cumulative dose <300 mg/m^2)	(i) PLD 50 mg/m^2 (d1) + cyclophosphamide 100 mg/m^2 po (d1–14) every 4 weeks (ii) PLD 30 mg/m^2 (d1) + cyclophosphamide 600 mg/m^2 (d1) every 3 weeks	51%	7.8 mo	Alopecia (all grades) 43% Mucositis 10% Neutropenia 39% PPE 20%	Asymptomatic decline in LVEF to <50% in 1 pt No CHF	Recommended dose: PLD 30 mg/m^2 + cyclophosphamide 600 mg/m^2 (d1) every 3 weeks

				(iii) PLD 35 mg/m^2 (d1) + cyclophosphamide 600 mg/m^2 (d1) every 3 weeks			
II	Kurtz[65]	MBC, first line, age 65–75 (n = 35)	Yes (adjuvant and >12 mo elapsed; cumulative dose ≤300 mg/m^2 [or 750 mg/m^2 for epirubicin])	PLD 40 mg/m^2 + cyclophosphamide 500 mg/m^2 (d1) every 4 weeks	29%	8.8 mo	Mucositis 4 episodes PPE 1 episode	None

Abbreviations: ORR, overall response rate; PFS, progression-free survival; TTP, time to progression; MBC, metastatic breast cancer; LABC, locally advanced breast cancer; DLT, dose-limiting toxicity; R2P2D, recommended phase II dose; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; PPE, palmar-plantar erythrodysesthesia; epi, epirubicin.

in an Italian study.[53] However, an ORR of 36% (95% CI 17% to 55%) and median PFS of 6.7 months was observed in a heavily pre-treated population who received a 3-weekly regimen of PLD 30 mg/m^2 (day 1) + vinorelbine 20 mg/m^2 (days 1, 8).[56]

Across these studies there was an acceptably low rate of patients experiencing reductions in LVEF and there were no reported cases of symptomatic CHF.

PLD and gemcitabine

Gemcitabine, an anti-metabolite, is an active agent in MBC with response rates of 14% to 37% as monotherapy and up to 75% when combined with taxanes.[74] Non-overlapping toxicity profiles and alternative mechanisms of action supported the evaluation of gemcitabine in combination with anthracyclines in MBC.

Rivera and colleagues enrolled 27 patients with MBC in a phase I study which initially explored a 4-weekly cycle with gemcitabine administered on days 1, 8 and 15.[58] However, myelosuppression typically precluded administration of the day 15 gemcitabine prompting evaluation of an alternative 3-weekly schedule with gemcitabine administered on days 1 and 8. This regimen was well tolerated with neutropenia and thrombocytopenia representing DLTs and showed promising signs of activity with 2 complete and 7 partial responses. PLD 24 mg/m^2 on day 1 and gemcitabine 800 mg/m^2 on days 1 and 8 every 3 weeks were the recommended doses for further investigation.

A subsequent phase II trial tested this regimen in 49 patients with previously untreated MBC.[59] The ORR was 52% (95% CI 37% to 67%) and median TTP 4.5 months. Toxicity was primarily hematological although this translated into only 1 episode of febrile neutropenia. The incidence of grade 3/4 non-hematologial toxicity was low with PPE, mucositis and nausea/vomiting occurring in 6.3%, 8.5% and 10.6% of patients respectively. This low incidence of PPE likely reflects the lower dose of PLD administered.

Three other groups have conducted phase II trials using identical[61,63] or virtually identical[60] regimens. For example, among 71 patients with previously untreated MBC, a response rate of 39.1% (95% CI 27.1% to 50.9%) and median TTP of 11 months was observed.[63] The favorable toxicity profile was supported with only 1 case of febrile neutropenia and with grade 3/4 mucositis and PPE observed in 11.6% and 8.6% of patients respectively. In addition, 2 phase II trials have evaluated this regimen in patients pre-treated for MBC. A study conducted by Fabi et al recruited a heterogeneous

population with 46% of patients having received at least one prior chemotherapy regimen for metastatic disease.[60] Despite this an ORR of 44% (95% CI 30.2% to 57.8%) was observed. A similar toxicity profile was elicited with grade 3/4 neutropenia occurring in 30% of patients but febrile neutropenia seen in only 4%. Grade 3/4 mucositis and PPE occurred in 10% and 6% of patients respectively. The most common reasons for dose modification or delay were neutropenia and elevated transaminases. The activity of this regimen in pre-treated MBC was supported in a second trial which recruited 34 patients who had received 1 to 3 prior lines of chemotherapy for metastatic disease with most having received both anthracycline- and taxane-based regimens.[61] In this pre-treated population the ORR was 26% (95% CI 13.5% to 44.6%) and median TTP was 7.5 months. Despite prior chemotherapy myelosuppression was not significantly greater than that reported in the first-line studies and the rate of febrile neutropenia remained low. Similarly the incidence of grade 3/4 PPE and mucositis remained acceptably low (3% for both).

Taken together these studies support the activity and feasibility of PLD/gemcitabine combinations in MBC including in pre-treated patients. Patient acceptability is likely to be enhanced by the low rate of alopecia.

PLD and cyclophosphamide

In 10 patients with previously untreated MBC PLD (50 mg/m^2 on d1) with oral cyclophosphamide (100 mg/m^2 on days 1 to 14 of a 4 weekly cycle) was associated with excessive toxicity, prompting Overmoyer and colleagues to investigate alternative schedules.[64] A 3-weekly regimen with PLD 30 mg/m^2 and iv cyclophosphamide 600 mg/m^2 on day 1 was reasonably well tolerated and associated with an ORR of 50%.

Kurtz has reported a phase II trial of first-line PLD (40 mg/m^2 on day 1) and cyclophosphamide (500 mg/m^2 iv on day 1) administered to 35 women with MBC aged 65 or greater.[65] The ORR was 28.6% but the incidence of grade 3/4 mucositis (11%) and neutropenia (31%) were considered high in this patient population.

Trudeau has presented the results of a phase II trial which recruited 73 women with MBC, all of whom had prior anthracycline exposure. Treatment consisted of PLD 35 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks. The regimen appeared to be well tolerated with an asymptomatic >10% decline in LVEF occurring in 9% of patients and no symptomatic CHF. The ORR was 38%, supporting the concept of anthracycline rechallenge.[75]

Combination of LED with cytotoxics

LED has been most extensively studied in combination with cyclophosphamide leading to approval of this regimen in the first-line treatment of MBC as discussed above.[41,42,76,77] However, the combination of LED with other cytotoxic agents has been less intensively studied than is the case for PLD. The early phase nature of these trials and the small numbers of patients treated should again be emphasized (Table 3).[78–80]

LED and docetaxel

Mrozeck and colleagues conducted a dose escalation study of LED on day 1 and docetaxel on days 1 and 8 of a 3-weekly cycle.[78] Dose-limiting toxicities were febrile neutropenia and mucositis. In addition 2 patients (10%) developed symptomatic CHF. The ORR of 29% was lower than that observed in similar patients with either conventional doxorubicin or PLD/docetaxel combinations and the authors did not recommend further investigation of this particular regimen.

Schmid has recently reported the results of a phase II trial evaluating 3-weekly docetaxel (75 mg/m^2) and LED (60 mg/m^2) in 51 patients with previously untreated MBC.[79] The ORR was 50% and median TTP was 10 months (95% CI 6.9 to 13.1 months). However, there was a high rate of febrile neutropenia (23.5%) consistent with the relatively high drug doses used in this combination.

LED and gemcitabine

Del Barco and colleagues encountered significant myelosuppression at an initial dose level of LED 60 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1 and 8 repeated every 3 weeks.[80] A lower dose of LED 50 mg/m^2 and gemcitabine 900 mg/m^2 was better tolerated and was associated with an ORR of 51.1% (95% CI 36% to 66%) and median time to progression of 12 months in women with previously untreated MBC or locally advanced breast cancer (LABC). Toxicity was primarily hematological with a 9% incidence of febrile neutropenia. Major non-hematological toxicities were elevated liver enzymes and stomatitis (grade 3/4: 21% and 12%, respectively).

Combination of liposomal doxorubicin with trastuzumab

Around 20% of breast cancers overexpress the human epidermal growth factor receptor 2 (Her2) and display a more aggressive phenotype.[81] The ability to directly target Her2 with trastuzumab, a humanized murine monoclonal

Table 3 Published trials of liposome-encapsulated doxorubicin (LED)/cytotoxic combination therapy for MBC

Agent/ Phase	Study	Population	Prior doxorubicin allowed?	Treatment (iv unless otherwise stated)	Efficacy		Selected toxicities (% pts experiencing grade 3/4)	Cardiotoxicity	Comments
					ORR	PFS/TTP			
Cyclophosphamide									
II	Valero[76]	MBC, first line (n = 41)	Yes	LED 60 mg/m^2 (d1) + cyclophosphamide 500 mg/m^2 (d1) + 5-FU 500 mg/m^2 (d1, 8) every 3 weeks	73%	8.4 m	Febrile neutropenia 24% Mucositis 15% Nausea/vomiting 12%	2 pts decrease LVEF below 40% No CHF	
III	Batist[41]	MBC, first line (n = 297)	Yes (adjuvant and >6 mo elapsed; cumulative dose ≤300 mg/m^2)	Cyclophosphamide 600 mg/m^2 (d1) + LED 60 mg m^2 (d1) (n = 142) OR doxorubicin 60 mg/m^2 (d1) (n = 155)	LED vs dox 43% vs 43%	LED vs dox 5.1 mo vs 5.5 m (ns)	LED vs dox Anemia 23 vs 27% Thrombocytopenia 22 vs 20% Neutropenia 61 vs 75%* Neutropenic fever 9 vs 13% Nausea/vomiting 13 vs 16% Stomatitis/mucositis 4 vs 7% Diarrhea 3 vs 8% Asthenia/fatigue 6 vs 5% Alopecia (all grds) 91 vs 95% *P* = 0.02	Protocol-defined cardiotoxicity: 6% vs 21% (*P* = 0.0001) CHF 0% vs 3% (*P* = 0.02)	
III	Chan[42]	MBC, first line (n = 160)	No	Cyclophosphamide 600 mg/m^2 (d1) + LED 75 mg/m^2 (d1) (n = 80) OR epirubicin 75 mg/m^2 (d1) (n = 80)	LED vs epi 46% vs 39% (n.s)	LED vs epi 7.7 mo vs 5.6 m (*P* = 0.02)	LED vs epi Anemia 25 vs 14% Neutropenia 87 vs 67%* Febrile neutropenia 5 vs 1% Nausea/vomiting 21 vs 19% Mucositis 7 vs 0%§ Diarrhea 1 vs 1% Asthenia/fatigue 0 vs 1% Alopecia (all grds) 87 vs 85% *P = 0.004; §P = 0.03	Protocol-defined cardiotoxicity: 11.8 vs 10.2% No CHF	
II	Giotta[77]	MBC, first line (n = 67)	Yes (adjuvant and >12 mo elapsed)	LED 60 mg/m^2 (d1) + cyclophosphamide 600 mg/m^2 (d1) every 3 weeks	64%		Leucopenia 7%		1 pt experienced asymptomatic decline in LVEF No CHF
Docetaxel									
I	Mrozek[78]	MBC, first line (n = 21)	Yes (adjuvant and >6 m elapsed; cumulative dose < ≤300 mg/m^2)	Dose escalation: LED (d1) + docetaxel (d1, 8) every 3 weeks	29%	8.8 mo	DLTs = mucositis + febrile neutropenia	1 pt asymptomatic decrease in LVEF 2 pts developed CHF	Further evaluation of this schedule not recommended

(*Continued*)

Table 3 (*Continued*)

Agent/ Phase	Study	Population	Prior doxorubicin allowed?	Treatment (iv unless otherwise stated)	Efficacy		Selected toxicities (% pts experiencing grade 3/4)	Cardiotoxicity	Comments
					ORR	PFS/TTP			
Gemcitabine									
I/II	Del Barco[80]	MBC or LABC, first line (n = 53)	Yes (adjuvant and >12 mo elapsed; cumulative dose <300 mg/m^2 [or <500 mg/m^2 for epi])	Phase II dose: LED 55 mg/m^2 (d1) + gemcitabine 900 mg/m^2 (d1,8) every 21 days	51%	12 mo	(Phase II) Neutropenia 48% Elevated LFTs 21% Mucositis 12% Febrile neutropenia 9% Nausea 8% Diarrhea 8%	4 pts with asymptomatic decrease in LVEF No CHF	

Abbreviations: dox, doxorubicin; ORR, overall response rate; PFS, progression-free survival; TTP, time to progression; MBC, metastatic breast cancer; LABC, locally advanced breast cancer; DLT, dose-limiting toxicity; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; epi, epirubicin.

antibody, has been a major advance in the treatment of this subset of breast cancer.[81] Preclinical data which demonstrated enhanced antitumor efficacy for trastuzumab in combination with doxorubicin or paclitaxel[82] were validated clinically with the demonstration of significantly increased RR, TTP and OS for patients with MBC treated with first-line chemotherapy plus trastuzumab versus chemotherapy alone.[83] Subsequent trials established significant benefits for trastuzumab in the adjuvant treatment of Her2-positive early breast cancer.[84,85]

Whether Her2-positivity may specifically predict for anthracycline sensitivity has been an area of controversy. Retrospective analyses of certain adjuvant trials such as NSABP-B11[86] and the Canadian MA.5 trial,[87] together with a recent meta-analysis,[88] have suggested that any incremental benefit gained by the addition of anthracyclines is confined to patients with Her2-positive disease. In vitro data do not support a direct mechanistic link between Her2 overexpression and anthracycline sensitivity.[89] One interpretation has been that Her2-positivity may actually reflect co-amplification of the TOP2A gene which is situated nearby on chromosome 17 and which encodes topoisomerase 2 alpha, a major anthracycline target. Although biologically plausible, the significance of topoisomerase 2 alpha amplification remains uncertain.[90] Indeed an analysis of the NEAT and MA.5 trials presented at the 2008 San Antonio Symposium suggested that polysomy of chromosome 17, rather than Her2 or TOP2A amplification per se, may be the strongest predictor of anthracycline sensitivity.[91] At present the important question of whether patients can be selected to receive anthracyclines or not on the basis of Her2 or TOP2A amplification or chromosome 17 polysomy remains an area of intense study and debate.[92,93]

Clinical trials determined cardiotoxicity, manifesting as reduced LVEF and CHF, to be a major clinical toxicity of trastuzumab.[94] The development of dilated cardiomyopathy in mice with conditional knockout of Her2 in the myocardium confirmed a direct role for Her2 signaling in the maintenance of the myocardium.[95] The pathogenesis of trastuzumab-induced cardiotoxicity is clinically and mechanistically distinct to that of anthracyclines; it is not dose-dependent, ultra-structural signs of myocardial damage are lacking, and it is reversible with discontinuation of therapy.[96] However, trastuzumab does appear to sensitize the myocardium to anthracycline-mediated damage.[97] This was evident in the pivotal trial of trastuzumab in MBC in which an unacceptably high rate of cardiotoxicity (27%; two-thirds of which were New York Heart association Class III or IV) was evident in patients receiving concomitant trastuzumab/doxorubicin.[83] Thus, while taxane/trastuzumab combination therapy has

become standard, the concomitant administration of anthracyclines with trastuzumab has, for the most part, been avoided. However, the inherently lower cardiotoxicity of liposomal doxorubicin formulations has prompted the evaluation of both PLD[98–103] and LED[104–107] in combination with trastuzumab (Table 4).

PLD and trastuzumab

PLD at doses of 30 to 50 mg/m^2 every 3 or 4 weeks has been combined with both weekly and 3-weekly trastuzumab in a series of phase II trials. ORRs up to 52% have been reported in the first-line setting, with ORRs of 22% to 53% observed when pre-treated patients are included. For example, Chia et al conducted a phase II trial of first-line PLD (50 mg/m^2 every 4 weeks) and weekly trastuzumab in 30 patients with previously untreated MBC.[99] LVEF was assessed using serial MUGA scans performed at baseline, after every second cycle of PLD and trastuzumab, and at 4 to 6 months and 12 months post-treatment completion. The primary objective was to assess the rate of cardiotoxicity (defined as clinical signs and symptoms of CHF in association with a ≥10% decline in LVEF from baseline and a value below the LLN; a ≥15% decline from baseline in LVEF in an asymptomatic patient regardless of the absolute value; or a less than 10% decline from baseline in LVEF in an asymptomatic patient and an absolute value less than 45% on MUGA scan). The mean LVEF at baseline was 62.8% declining to 58.3% after cycle 6. There were no episodes of symptomatic CHF and no patient had a decline in LVEF to less than 40% or had a ≥10% decline in LVEF with an absolute value less than 45% during the course of the study. The protocol defined cardiotoxicity rate was 10% (95% CI 2.1% to 26.5%), leading the authors to conclude that further investigation was warranted. Similar rates of cardiotoxicity have been reported in other trials of PLD and trastuzumab with symptomatic CHF occurring infrequently. For instance, in 46 patients treated with a PLD/carboplatin/trastuzumab regimen only 1 patient experienced a decline in LVEF > 15% and there were no cases of symptomatic CHF.[101] Across the trials non-cardiac toxicity was as expected with the exception of the E3198 trial in which the addition of docetaxel was associated with an unacceptable incidence of grade III PPE.[98] Taken together these studies suggest it is safe and feasible to co-administer PLD and trastuzumab with appropriate cardiac monitoring and support further evaluation.

LED and trastuzumab

Theodoulou and colleagues presented the first data addressing the combination of LED with trastuzumab in patients with MBC and previous anthracycline exposure.[104] The cardiac safety profile was acceptable with one of 37 patients experiencing symptomatic CHF and the ORR was 57%.

Two studies which evaluated the combination of LED and docetaxel with trastuzumab were presented at the 2008 San Antonio Breast Cancer Symposium. Venturini and colleagues treated 31 anthracycline-naive women with LED 50 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks along with weekly trastuzumab.[106] The mean LVEF at baseline was 62.8 ± 7.1%, with a decrease to 60.2 ± 6.5% at cycle 2 and did not change significantly thereafter. Three patients experienced cardiotoxicity, defined as a decrease in LVEF to less than 45% or a 20% decrease in LVEF from baseline. Symptomatic CHF occurred in 1 patient. A second study, presented by Amadori, enrolled 46 women with previously untreated MBC or LABC.[105] Treatment was with LED 50 mg/m^2 on day 1 and docetaxel 30 mg/m^2 on days 2 and 9 every three weeks together with weekly herceptin. Again the incidence of cardiotoxicity was acceptable with 2 patients experiencing a fall in LVEF below 50% and 2 patients a decrease ≥15% with respect to baseline. There were no cases of symptomatic CHF. Both trials reported similar response rates (65% and 57% respectively).

Cortes has recently reported the results of a Spanish trial in which 69 women with locally advanced or MBC were treated with LED (50 mg/m^2) every 3 weeks together with weekly paclitaxel (80 mg/m^2) and trastuzumab.[107] Asymptomatic protocol-defined cardiotoxicity (decline in LVEF ≥ 10% resulting in LVEF < 50%; LVEF < 40%; any absolute decline ≥20%) was observed in 12 patients but there were no cases of symptomatic CHF. The regimen appeared highly active with response rates of 100% in LABC and 96% in MBC. On this basis the Spanish Breast Cancer Cooperative Group have initiated a phase III trial to compare LED, paclitaxel and trastuzumab versus paclitaxel and trastuzumab alone in the first-line treatment of MBC.

Conclusions and future perspectives

Both PLD and LED have demonstrated equivalent efficacy and reduced cardiotoxicity in comparison to conventional doxorubicin in patients with MBC. This has prompted their evaluation both as monotherapies and in combination with a range of cytotoxics as described above. At present LED with cyclophosphamide is the only approved liposomal doxorubicin-based combination. The further development of PLD or LED-based combination therapy is particularly attractive in certain clinical situations:

- In patients who would be denied further anthracycline-based therapy at the time of progression based on prior

Table 4 Trials of liposomal doxorubicins and trastuzumab for MBC

Agent/ Phase	Study	Population	Prior doxorubicin allowed?	Treatment (iv unless otherwise stated)	Efficacy		Selected toxicities (% pts experiencing grade 3/4)	Cardiotoxicity	Comments
					ORR	PFS/TTP			
PLD									
II	Wolff[98]	Her2 +ve and –ve MBC (n = 26)	No	PLD 30 mg/m^2 (d1) + docetaxel 60 mg/m^2 (d1) every 3 weeks with weekly trastuzumab 4 mg/kg loading dose then 2 mg/kg thereafter if Her2 +ve	Not reported		PPE 40%	No grade 3 or 4 cardiotoxicity	Regimen not feasible due to rate of PPE
II	Chia[99]	Her2 +ve MBC, first line (n = 30)	Yes (adjuvant; cumulative dose ≤300 mg/m^2 [or 720 mg/m^2 for epi])	PLD 50 mg/m^2 (d1) every 4 weeks and weekly trastuzumab 4 mg/kg loading dose then 2 mg/kg thereafter	52%	12 mo	PPE 30% Neutropenia 27% Mucositis 3%	3 pts experienced asymptomatic decline in LVEF > 15%	
II	Andreopoulou[100]	Her2 +ve MBC, first line or pretreated (n = 12)	Yes (adjuvant or metastatic setting)	PLD 30 mg/m^2 (d1) every 3 weeks + weekly trastuzumab 4 mg/kg loading dose then 2 mg/kg thereafter	0%	–	Neutropenia 17% Hypersensitivity 17% Mucositis 8% Rash 8%	4 pts experienced grade 2/3 LVEF decrease	
II	Collea[101]	Her2 +ve and –ve MBC, ≤1 prior regimen for MBC (n = 129)	Yes (adjuvant and >1 year elapsed)	PLD30 mg/m^2 (d1) and carboplatin AUC = 5 (d1) every 28 days (Arm 1) + trastuzumab 8 mg/kg loading dose then 4 mg/kg on (d1),15 thereafter (Her2 +ve pts;Arm 2)	Arm 1/Arm 2 30%/53%	Arm 1/Arm 2 5.4 mo/ 10.1 mo	Arm 1/Arm 2 Neutropenia 25%/35% N/V 2%/9% Mucositis 1%/2%	1 pt in Arm 2 >15% decrease in LVEF. No CHF	Grade 2 alopecia rare (<6.5%)
II	Christodoulou[102]	Her2 +ve MBC, prior taxane for adjuvant or metastatic disease (n = 37)	Yes (adjuvant)	PLD 30 mg/m^2 (d1) + trastuzumab 8 mg/kg loading dose then 6 mg/kg thereafter every 3 weeks	22%	6.5 mo	Hypersensitivity 5% PPE 3%	2 pts experienced grade 1 cardiotoxicity	
II	Stickeler[103]	Her2 +ve MBC, first and second line (n = 16)	Yes (adjuvant or metastatic; cumulative dose ≤400 mg/m^2 [or ≤600 mg/m^2 for epi])	PLD 40 mg/m^2 (d1) every 4 weeks + weekly trastuzumab 4 mg/kg loading dose then 2 mg/kg thereafter	33%	9.7 mo	Hypersensitivity 12% PPE 6%	2 pts with asymptomatic decrease in LVEF; 1 pt symptomatic CHF	
LED									
I/II	Theodoulou[104]	Her2 +ve MBC, first or second line (n = 37)	Yes (adjuvant or metastatic; cumulative dose ≤400 mg/m^2)	LED 60 mg/m^2 (d1) every 3 weeks and weekly trastuzumab 4 mg/kg loading dose then 2 mg/kg thereafter	58%	–	Nausea 5.4% Febrile neutropenia 2/203 cycles	1 pt asymptomatic decline in LVEF; 1 pt CHF	

II	Venturini[106]	Her2 +ve MBC, first line (n = 31)	No	LED 50 mg/m^2 (d1) and docetaxel 75 mg/m^2 (d1) every 3 weeks and trastuzumab 4 mg/kg loading then 2 mg/kg weekly	65%	13 mo	Incidence not reported	3 pts with decrease in LVEF to less than 45% or a 20% decrease in LVEF from baseline; 1 pt with CHF
I/II	Cortes[107]	Locally advanced and MBC, Her2 +ve (n = 69)	No	Phase II dose: LED 50 mg/m^2 (d1) + paclitaxel 80 mg/m^2 (d1, 8, 15) every 3 weeks + herceptin 4mg/kg loading then 2 mg/kg weekly	98%	22.1 mo (MBC pts)	Febrile neutropenia 20.4% Mucositis 7.4% Diarrhea 7.4%	17% asymptomatic declines in LVEF No CHF

Abbreviations: ORR, overall response rate; PFS, progression-free survival; TTP, time to progression; MBC, metastatic breast cancer; LABC, locally advanced breast cancer; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; PPE, palmar-plantar erythrodysesthesia; epi. epirubicin.

cumulative exposure to conventional anthracyclines. Both PLD and LED are active in patients with progression of disease occurring at least 6–12 months after prior anthracycline therapy.[33,34,108,109] The ability to maximize the therapeutic benefit of anthracyclines by re-challenging appropriate patients has increased in significance with the rising proportion of patients receiving both anthracyclines and taxanes in the adjuvant setting.

- In combination with Her2-directed therapies. The phase I/II trials discussed above have provided reassuring cardiac safety data for the combination of liposomal anthracyclines with trastuzumab although randomized phase III data are not yet available. Her2 can also be targeted with lapatinib, a small-molecule tyrosine kinase inhibitor, and investigation of this agent with PLD is ongoing.

Finally, the attraction of liposomal anthracyclines in the adjuvant setting, where minimization of late toxicity is crucial, is evident. Indeed, the data elicited in the metastatic setting lend clear support to the evaluation of adjuvant liposomal doxorubicin-based combination therapy. This may be of particular interest in the setting of Her2-positive breast cancer, an area to be addressed by the Breast Cancer Adjuvant Caelyx Herceptin (BACH) study.[82]

Disclosures

The authors disclose no conflicts of interest.

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