Breast Cancer - Targets and Therapy

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REVIEW

Anticancer and cardio-protective effects of liposomal doxorubicin in the treatment of breast cancer

This article was published in the following Dove Press journal:
Breast Cancer - Targets and Therapy

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Abstract: Breast cancer (BC) is a highly prevalent disease, accounting for the second highest number of cancer-related mortalities worldwide. The anthracycline doxorubicin (DOX), isolated from *Streptomyces peucetius* var. *caesius*, is a potent chemotherapeutic drug that is successfully used to treat various forms of liquid and solid tumors and is currently approved to treat BC. DOX exerts its effects by intercalation into DNA and inhibition of topoisomerases I and II, causing damage to DNA and the formation of reactive oxygen species (ROS), resulting in the activation of caspases, which ultimately leads to apoptosis. Unfortunately, DOX also can cause cardiotoxicity, with patients only allowed a cumulative lifetime dose of 550 mg/m^2. Efforts to decrease cardiotoxicity and to increase the blood circulation time of DOX led to the US Food and Drug Administration (FDA) approval of a PEGylated liposomal formulation (L-DOX), Doxil® (known internationally as Caelyx®). Both exhibit better cardiovascular safety profiles; however, they are not currently FDA approved for the treatment of metastatic BC. Here, we provide detailed insights into the mechanism of action of L-DOX and its most common side effects and highlight results of its use in clinical trials for the treatment of BC as single agent and in combination with other commonly used chemotherapeutics.

Keywords: doxil, caelyx, breast cancer, anti-tumor activity, cardiotoxicity

Introduction

Breast cancer (BC) is the second most frequent cause of cancer-related deaths in women worldwide. It is a heterogeneous disease composed of multiple subtypes with distinct pathological features and clinical implications. Although men are affected, to a lesser degree, the most significant risk factors are gender (women) and older age. Other risk factors include obesity, estrogen exposure, alcohol consumption, and a family history.[1] Over the past 2 decades, accumulating evidence, both clinical and experimental, has suggested that BCs with different histopathological and biological features exhibit distinct behaviors that lead to different treatment responses and, therefore, should be given different therapeutic strategies.[2] On this basis, at diagnosis, BC patients are systematically tested for the presence of receptors, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), in order to explore tailored treatment options with molecularly targeted therapies. However, for patients who are triple negative (ER-, PR-, and HER2-), those who have innate or acquired resistance to targeted therapies, and patients whose disease has metastasized, traditional treatment options including surgery, radiotherapy, and chemotherapy are favored.

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http://dx.doi.org/10.2147/BCTT.S170239

Anthracycline-based chemotherapy with doxorubicin (DOX) is one of the most efficacious anticancer agents for both early- and late-stage BCs.[3] DOX's mechanism of action (Figure 1) on cancer cells begins with its passive diffusion through the phospholipid bilayer membrane of malignant cells into the cytoplasm, where DOX is converted into a semiquinone and generates reactive oxygen species (ROS), causing free radical formation and oxidative stress. In the cytosol, DOX enters the mitochondria causing DNA damage and energetic stress. As a result, the mitochondria release the cytochrome *C* protein, triggering the caspase cascade leading to cell death. From the cytosol, DOX translocates into the nucleus where it intercalates between double-stranded DNA helices and inhibits the enzymes topoisomerases I and II. The resulting damage to DNA leads to free radical generation, alkylation, and activation of the p53 pathway, hence inhibiting cell proliferation and inducing apoptosis. DOX can also hyperactivate the nuclear enzyme poly ADP ribose polymerase (PARP)-1, hence depleting the cell's energy, thereby resulting in autophagy.[4–6]

However, the potential therapeutic benefits of DOX are limited by the risk of cardiotoxicity, which has been evidently related to its lifetime cumulative dose.[7–9] To overcome this hurdle, the liposomal DOX (L-DOX) formulation was developed in order to reduce DOX-associated cardiotoxicity while preserving its antitumor efficacy.[10] The L-DOX formulation encapsulates DOX within a phospholipid bilayer that is coated with methoxypolyethylene glycol (Figure 2). The PEGylation protects the liposomes from recognition by the mononuclear phagocyte system (MPS) and allows a longer circulation time in the bloodstream while reducing the exposure of free DOX circulating in the plasma. Biodistribution studies have shown that L-DOX has the ability to deposit and/or penetrate tumors and release DOX.[11] Although the mechanism of release of DOX from its liposomes is still unknown, a 10-fold higher exposure of L-DOX than DOX is observed in metastatic BC tissue as compared to healthy breast tissue,[12] which is explained by the enhanced permeability retention effect.[13] This indicates that a therapeutic approach with L-DOX is more targeted compared to DOX. A differential pharmacokinetic (PK) characteristic between the two formulations includes a decreased clearance (CL), a smaller volume of distribution, and a longer half-life for L-DOX compared to DOX as a result of the sequestration of liposomes, due to their increased size, in the sinusoidal lumen of the liver, which limits their flow from the fenestrations of the lumen into the hepatocytes as compared to free DOX. This is also believed to contribute to reduced hepatic extraction of L-DOX compared to DOX as a single agent.[14] The latter being primarily metabolized in the liver to the major cytotoxic metabolites: doxorubicinol and cytotoxic aglycones. The PK properties of L-DOX as compared to DOX are summarized in Table 1.

The use of DOX as a stand-alone treatment has shown effectiveness in overall survival and response rate and time to disease progression.[15] Its limitations are seen in its effect on healthy cells and the resulting adverse effects, with the most significant being cardiotoxicity. The comparison of safety profiles between DOX and L-DOX is summarized in Table 2 with the most common side effect for L-DOX being palmar–plantar erythrodysesthesia, a skin toxicity that can be managed with supportive care, unlike cardiotoxicity, which is significantly more prevalent for DOX.[16] Although the mechanism of DOX-induced cardiotoxicity is not fully understood, its administration is dose limited. It was shown that the risk of DOX-induced cardiotoxicity increases with the increase in its cumulative lifetime dose to becoming irreversible (ie, cardiomyocytes death) when the latter reaches 450–550 mg/m^2.[17] The other major cardiotoxic effects of DOX are the occurrence of congestive heart failure (CHF) in >20% of the treated patients.[8] Additional but less detrimental adverse reactions include nausea, vomiting, gastrointestinal problems, neurological symptoms, and cutaneous injuries at the site of injection.[4]

While L-DOX has proven to be advantageous over DOX as a single agent, it is only indicated in the treatment of metastatic BC in combination with docetaxel,[18] although it is frequently utilized as adjuvant therapy in metastatic BC.[19] The comparative anticancer efficacies of these two drugs in addition to their use in combination with other anticancer agents in BC continue to be investigated.[20] Table 3 summarizes the main findings of trials assessing regimens containing L-DOX. These trials evaluated the efficacy of several combinations in varied patient populations including both locally advanced and metastatic BCs as well as the elderly and in patients with previously treated BCs. Overall, L-DOX was effective and well tolerated in the majority of trials, making it a feasible treatment option when combined with other chemotherapeutics. In the present work, we sought to investigate L-DOX's efficacy on BC and its potential associated cardiac toxicity when combined with other chemotherapeutic or targeted therapy, with the goal of showcasing the beneficial effect of L-DOX over DOX on BC therapy and cardiac function.

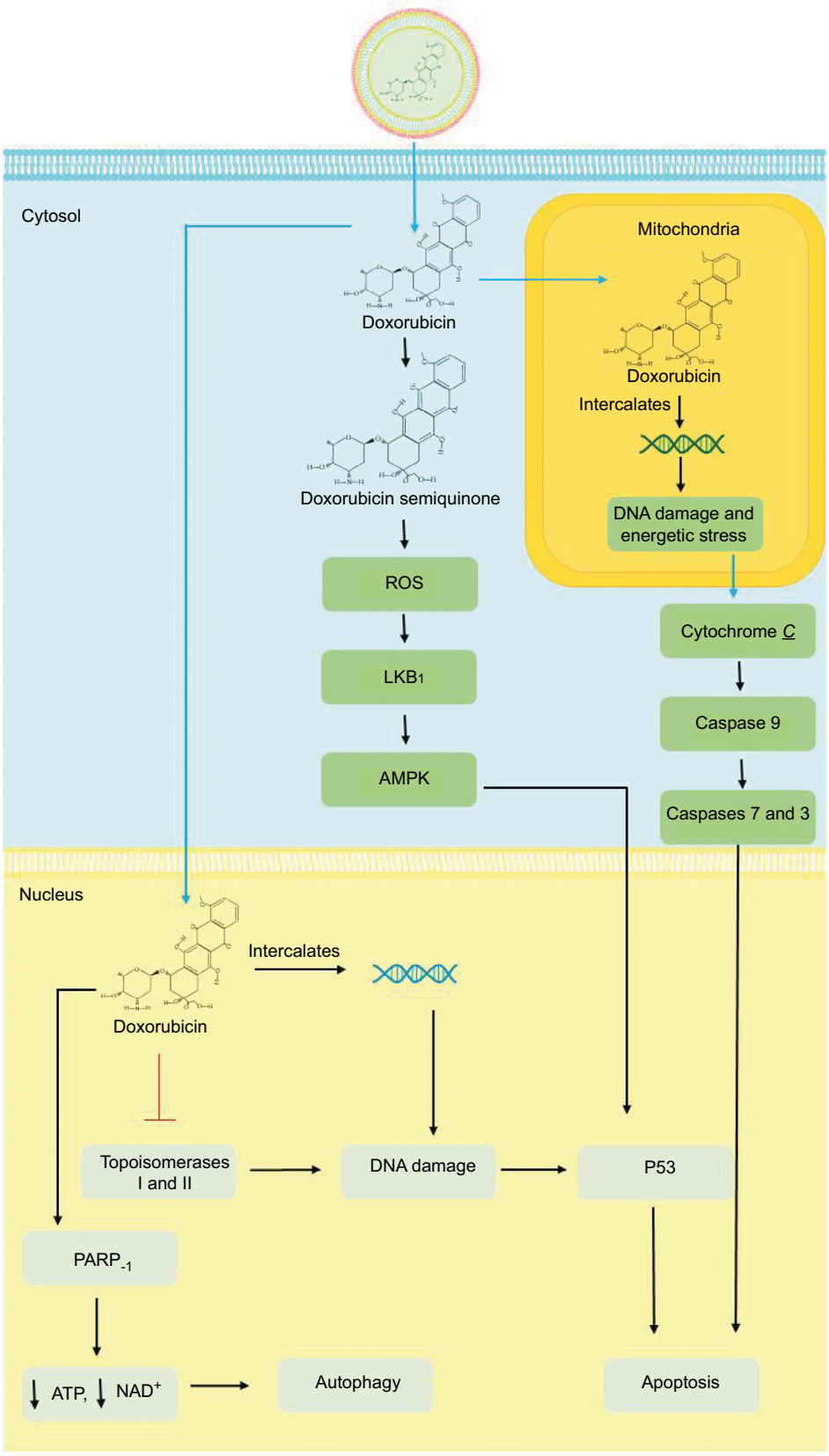

Figure 1 Mechanism of action of DOX and L-DOX.
Notes: Once L-DOX diffuses across the phospholipid bilayer of malignant cells, free DOX is released and it can be converted into a semiquinone or translocate into the nucleus or mitochondria. Conversion of DOX to a semiquinone causes the formation of ROS. DOX can also translocate to the nucleus where it intercalates between strands of DNA, inhibits topoisomerases I and II and activates PARP-1. In the mitochondria, DOX intercalates between strands of mitochondrial DNA and leads to the release of cytochrome *C* and the activation of caspases. Ultimately, damage to nuclear and mitochondrial DNA as well as that caused by ROS leads to apoptosis.
Abbreviations: DOX, doxorubicin; L-DOX, liposomal DOX; PARP, poly ADP ribose polymerase; ROS, reactive oxygen species.

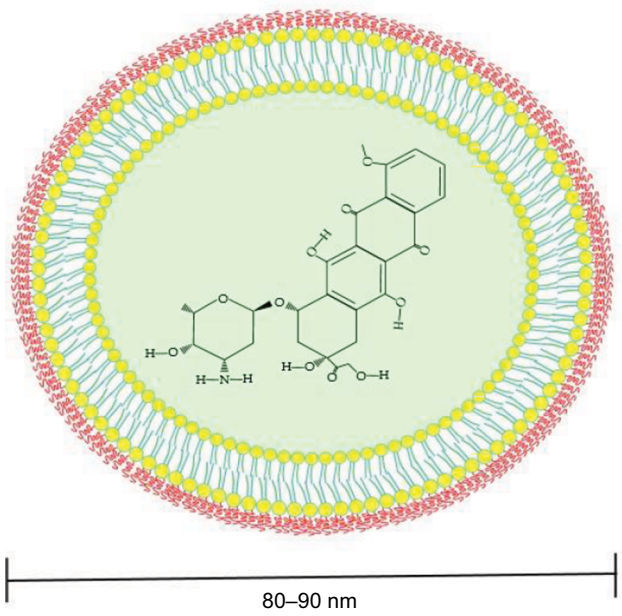

Figure 2 PEGylated liposomal DOX (Doxil®).
Notes: DOX is surrounded by a phospholipid bilayer (liposome) that is coated with methoxypolyethylene glycol. Enclosing DOX in a liposome helps decrease systemic side effects while PEGylation protects the liposomes from recognition by the mononuclear phagocyte system and increases its circulation time.
Abbreviation: DOX, doxorubicin.

Methods

A literature search was conducted on PubMed, Google Scholar, and ClinicalTrials.gov using the following main keywords: liposomal DOX, Doxil® and BC, Caelyx® and BC, and Doxil® or Caelyx® and combinations in BC, to obtain relevant publications evaluating the safety and efficacy of L-DOX in the treatment of breast tumors. Additionally, information regarding the PK and safety profiles of L-DOX and conventional DOX was acquired mainly from drug monographs. Publications assessed in this review included Phases II and III clinical trials of patients with BC, ranging from early to metastatic stages. No particular preference was given in regard to BC subtype, and the only criteria that needed to be met for combinations were the use of L-DOX in at least one arm with at least one additional agent.

Results

Tables 1 and 2 highlight the disparity in PK parameters and toxicity profiles between L-DOX and DOX. These can be attributed to differences in the formulation of the two agents, with the encapsulation of free DOX into a phospholipid bilayer

Table 1 Pharmacokinetic properties of DOX and L-DOX

Parameter (unit)	Definition	DOX, min–max[35]	L-DOX, average ± SD[36]
CL (mL/min/m^2)	Plasma clearance	324–809	0.683±0.066
$T_{1/2}$ (h)	Half-life	20–48	55±4.8
V_d (L/m^2)	Volume of distribution	809–1,214	2.72±0.12
F_b (%)	Fraction bound to plasma proteins	75[a]	Not determined

Note: [a]Data shown as average.
Abbreviations: CL, clearance; DOX, doxorubicin; L-DOX, liposomal DOX; SD, standard deviation.

Table 2 Comparison of use, efficacy, and safety profiles of DOX and L-DOX

Criteria	DOX[16,21,23]	L-DOX[16,22,24]
Indications	Label: leukemia, bladder cancer, breast cancer, gastric cancer, sarcomas, small cell lung cancer among others	Label: Kaposi's sarcoma, multiple myeloma, and ovarian cancer
	Off label: biliary tract cancer, endometrial cancer, Kaposi's sarcoma, malignant melanoma	Off label: use for breast cancer, cutaneous T-cell lymphoma
Maximum dose limits	Lifetime: up to 550 mg/m^2 IV	50 mg IV weekly
	Up to 450 mg IV if previous mediastinal radiation	Safety and efficacy have not been established in children and adolescents
Black box warnings	Bone marrow suppression, cardiotoxicity, extravasation	Cardiotoxicity and infusion-related reactions
Adverse effects	Cardiotoxicity	Palmar–plantar erythrodysesthesia
	Nausea/vomiting	Nausea/vomiting
	Alopecia	Alopecia
	Leukopenia/neutropenia	Cardiotoxicity
	Palmar–plantar erythrodysesthesia	Leukopenia/neutropenia

Abbreviations: DOX, doxorubicin; L-DOX, liposomal DOX; IV, intravenous.

Table 3 Clinical trials with L-DOX in combination with other chemotherapeutics in breast cancer

Drugs	Clinical trial	Main findings	References
PLD and bevacizumab - 20 mg/m^2 PLD and 10 mg/kg bevacizumab given days 1 and 15 of 4-week cycle	Phase II	46% of patients had grade three toxicities ORR: 21% Median PFS: 5.7 months Median OS: 15.9 months Severe cardiotoxicity in one patient 4.7 months after treatment	37
PLD and bortezomib - 1.3 mg/m^2 bortezomib days 1, 4, 8, and 11 and 30 mg/m^2 PLD day 4 of 21-day cycle	Phase II	ORR: 8% Median OS: 4.3 months Median TTP: 1.3 months No cardiotoxicity reported despite prior anthracycline use in 77% of patients	38
PLD and carboplatin (+ trastuzumab if HER2+) 30 mg/m^2 PLD and carboplatin AUC = 5 mg*min/mL day 1 of 21-day cycle If HER2+ also got 8 mg/kg loading dose of trastuzumab and then 4 mg/kg days 1 and 15 of 28-day cycle	Phase II	PLD/carboplatin 1A: taxane naive ORR: 31% Median PFS: 8 months 1B: taxane pretreated ORR: 31% Median OS: 13 months Median PFS: 5 months PLD/carboplatin/trastuzumab ORR: 56% Median OS: 33 months Median PFS: 10 months No clinically significant cardiotoxicity. Declines in LVEF of at least 15% in two patients in arm 1A and one patient in trastuzumab arm	39
PLD, cisplatin, infusional 5-FU, and trastuzumab 25 mg/m^2 PLD, 60 mg/m^2 cisplatin day 1 and 200 mg/m^2 5-FU as a continuous infusion days 1–21 of 21-day cycle 8 mg/kg trastuzumab loading dose then 6 mg/kg on day 2 of cycle	Phase II	Clinical response rate: 94% 2-year DFS: 94% No relevant cardiotoxicity – two patients had asymptomatic, transient declines in LVEF of at least 20%, but absolute LVEF was maintained above 50% in both cases	31
PLD and cyclophosphamide Cohort I: 50 mg/m^2 PLD day 1 and 100 mg/m^2 cyclophosphamide orally days 1–14 (28-day cycle) Cohort II: 30 mg/m^2 PLD and 600 mg/m^2 cyclophosphamide day 1 of 21-day cycle Cohort III: 35 mg/m^2 and 600 mg cyclophosphamide day 1 of 21-day cycle	Phase II	Objective response: 51% Clinical benefit rate (complete response + partial response + stable disease): 86% Median DOR: 35.1 weeks Median time-to-tumor progression: 34.4 weeks No clinical cardiotoxicity or significant declines in median LVEF following treatment	40
PLD and cyclophosphamide (in elderly patients between 65–75 years old) - 40 mg/m^2 PLD and 500 mg/m^2 cyclophosphamide day 1 of 4-week cycle	Phase II	Objective response rate: 28.6% Median PFS: 8.8 months Median OS: 20.3 months Mucositis, myelosuppression in the elderly No reported cardiac toxicity or significant changes in LVEF	41
PLD, cyclophosphamide, and 5-FU - 40 mg/m^2 PLD, 500 mg/m^2 cyclophosphamide, and 500 mg/m^2 5-FU on day 1 of 21-day cycle	Phase II	ORR: 41.9% Median PFS: 8.2 months Median OS: 36.6 months No significant changes in LVEF, even after prior anthracycline exposure	42
PLD, cyclophosphamide, and paclitaxel - 35 mg/m^2 PLD, 600 mg/m^2 cyclophosphamide every 4 weeks, and 80 mg/m^2 paclitaxel weekly	Phase II	Overall pCR: 32% Radiological ORR: 26% 5-year PFS: 58% 5-year OS: 62% No significant declines in LVEF or ECG changes; five cardiac events reported	43

(*Continued*)

Table 3 (*Continued*)

Drugs	Clinical trial	Main findings	References
PLD, cyclophosphamide, and trastuzumab 50 mg/m^2 PLD and 600 mg cyclophosphamide every 4 weeks 4 mg/kg trastuzumab loading dose then 2 mg/kg weekly	Phase II	Objective response rate: 68.8% Median OS: 34.2 months Median TTP: 12 months No symptomatic CHF; declines in LVEF observed in eight of the 48 patients and reversed in seven patients (six of them had prior anthracycline exposure)	27
PLD, cyclophosphamide, docetaxel, and trastuzumab (if HER2+) 35 mg/m^2 PLD and 600 mg cyclophosphamide on day 1 of 21-day cycle 100 mg/m^2 docetaxel day 1 of 21-day cycle If HER2+ got 8 mg/kg loading dose of trastuzumab then 6 mg/kg day 1 of 21-day cycles	Phase II	Objective response rate: 83% pCRT: 13% Normal LVEF maintained during the study	44
PLD and docetaxel Group A: 35 mg/m^2 PLD on day 1 and 40 mg/m^2 docetaxel days 1 and 15 of 28-day cycle Group B: 30 mg/m^2 PLD day 1 and 75 mg/m^2 docetaxel day 2 (3-week cycle)	Phase II	Overall clinical benefit: 47% ORR: 49% High rates of toxicity in both groups No significant cardiotoxicity	45
PLD and docetaxel (trastuzumab if HER2+) Group A: 30 mg/m^2 PLD and 60 mg/m^2 docetaxel every 3 weeks Group B: 30 mg/m^2 PLD, 60 mg/m^2 docetaxel every 3 weeks, and 4 mg/kg trastuzumab loading dose then 2 mg/kg weekly	Phase II	PLD/docetaxel ORR: 47.4% Median PFS: 11 months Median OS: 24.6 months PLD/docetaxel/trastuzumab ORR: 45.7% Median PFS: 10.6 months Median OS: 31.8 months Higher rates of hand foot syndrome Incidence of CHF <3% and the addition of trastuzumab did not increase CHF risk	46
PLD and docetaxel vs docetaxel (in patients who experienced a relapse following adjuvant anthracycline use) - 30 mg/m^2 PLD and 60 mg/m^2 docetaxel (21-day cycle) vs 75 mg/m^2 docetaxel (21-day cycle)	Phase III	PLD/docetaxel Objective response rate: 35% Median TTP: 9.8 months Median OS: 20.5 months Docetaxel Objective response rate: 26% Median TTP: 7 months Median OS: 20.6 months No significant increase in CHF incidence or LVEF decline with the addition of PLD	47
PLD and GEM - 25 mg/m^2 PLD day 1 and 800 mg/m^2 GEM on days 1 and 8 of 21-day cycle	Phase II	ORR: 47.8% Median TTP: 7 months Median duration of clinical benefit: 8 months Mild cardiac toxicity in 4% patients; it was recovered after the end of the study	48
PLD and GEM - 24 mg/m^2 PLD day 1 and 800 mg/m^2 GEM days 1 and 8 (21-day cycle)	Phase II	ORR: 52% Median OS: 16.1 months Median TTP: 4.5 months Clinical benefit: 78% Minimal cardiotoxicity, with a transient decline in LVEF in one patient, who recovered after the end of the study	49

(*Continued*)

Table 3 (*Continued*)

Drugs	Clinical trial	Main findings	References
PLD and GEM - 25 mg/m^2 PLD and 800 mg/m^2 GEM days 1 and 8 of 21-day cycle	Phase II	ORR: 39.1% Median TTP: 11 months Overall clinical benefit: 85.9% Only one case of cardiac toxicity was observed, despite 41% of patients having undergone prior anthracycline therapy	50
PLD, GEM and docetaxel - 1,000 mg/m^2 GEM on day 1 followed by 800 mg/m^2 GEM, 75 mg/m^2 docetaxel, and 30 mg/m^2 PLD on day 8 (3-week cycles)	Phase II	ORR: 74% No cardiotoxicity was observed as per protocol-defined criteria and all patients maintained LVEF >50%	51
PLD and lapatinib - 1,250 mg lapatinib daily and 40 mg/m^2 PLD every 4 weeks	Phase II	ORR: 54% Median PFS: 5.8 months Median OS: 23.3 months No cardiac events were observed	52
PLD (low dose) and paclitaxel - 15 mg/m^2 PLD every other week and 80 mg/m^2 paclitaxel weekly	Phase II	Objective response rate: 74% 9% pathological complete response on breast and axilla 55% had breast conserving surgery No impairment of cardiac function was observed	53
PLD and paclitaxel - 30 mg/m^2 PLD and 175 mg/m^2 paclitaxel (3-week cycles)	Phase II	Objective response rate: 80% Median duration of objective response: 31 weeks Median time to treatment failure: 45 weeks Decline in LVEF was observed in eight of the 26 patients; however, no clinical signs or symptoms of cardiac toxicity/failure were observed	54
PLD and trastuzumab - 40 mg/m^2 PLD every 4 weeks and 4 mg/kg trastuzumab loading dose then 2 mg/kg weekly	Phase II	Clinical benefit: 50% Median PFS: 9.67 months Median OS: 16.23 months Three of the 16 patients developed decline in LVEF; a clinically relevant and symptomatic decrease occurred in only one patient	30
PLD and trastuzumab - 50 mg/m^2 PLD every 4 weeks and 4 mg/kg trastuzumab loading dose then 2 mg/kg weekly	Phase II	ORR: 52% Median DOR: 11.1 months Median PFS: 12 months 10% of the patients developed protocol-defined cardiotoxicity, albeit without any symptoms of CHF	28
PLD and trastuzumab - 30 mg/m^2 PLD and 8 mg/kg trastuzumab loading dose then 6 mg/kg (3-week cycles)	Phase II	ORR: 22% Median PFS: 6.5 months Median OS: 18.7 months Severe cardiotoxicity as per protocol-defined criteria was not recorded. Median LVEF was maintained at 62% throughout the study	55
PLD and VNB - 30 mg/m^2 PLD day 1 and 20 mg/m^2 VNB on days 1 and 8 (3-week cycles)	Phase II	Objective response rate: 36% Median PFS: 6.7 months Median OS: 13.2 months No cardiotoxicity was observed	56
PLD and VNB - 40 mg/m^2 PLD day 2 and 25 mg/m^2 VNB on days 1 and 15 (4-week cycles)	Phase II	ORR: 39% Median TTP: 6.5 months Median OS: 14.5 months Four of the 36 patients developed a decline in LVEF (>15%); all four had received prior anthracycline treatment. There were no clinical symptoms of cardiac failure	29
PLD and VNB - 35 mg/m^2 PLD day 1 and 30 mg/m^2 VNB day 1 (4-week cycles)	Phase II	ORR: 35% Median TTP: 7 months Median OS: 13 months Three of the 33 patients had a significant decline in LVEF (<50%); none had clinical cardiac symptoms and cardiac function recovered for two patients after cessation of treatment	57

(*Continued*)

Table 3 (*Continued*)

Drugs	Clinical trial	Main findings	References
EPI/VNB vs PLD/VNB - 90 mg/m^2 EPI day 1 and 25 mg/m^2 VNB days 1 and 5 (21-day cycle) 40 mg/m^2 PLD day 1 and 30 mg/m^2 VNB days 1 and 15 (4-week cycles)	Phase II	EPI/VNB: ORR: 42.6% Median PFS: 10.7 months Median OS: 34.6 months PLD/VNB: ORR: 52% Median PFS: 8.8 months Median OS: 24.8 months No cases of CHF, two transient LVEF decreases in arm EPI/VNB that resolved in 2 months	58

Abbreviations: 5-FU, 5-fluorouracil; AUC, area under the concentration curve; CHF, congestive heart failure; DFS, disease-free survival; DOR, duration of response; ECG, electrocardiogram; EPI, epirubicin; GEM, gemcitabine; HER2, human epidermal growth factor receptor 2; L-DOX, liposomal doxorubicin; LVEF, left ventricular ejection fraction; ORR, overall response rate; OS, overall survival; pCR, pathological complete response; pCRT, total pathological complete response; PFS, progression-free survival; PLD, PEGylated L-DOX; TTP, time to progression; VNB, vinorelbine.

and exterior PEGylation of the liposomes providing improvements in terms of increasing the drug's half-life ($T_{1/2}$), decreasing both the volume of distribution (V_d) and plasma CL, and reducing the severity of toxicity associated with the use of anthracyclines. L-DOX's decreased CL (~0.7 vs 324–809 mL/min/m^2 for DOX) and increased $T_{1/2}$ (55±4.8 vs 20–48 h for DOX) may be attributed to decreased metabolism by the liver and MPS. L-DOX liposomes are ~80–90 nm in diameter, although some references state that the size of the molecule is ≥100 nm, a characteristic that impedes their passage across hepatic sinusoidal epithelial fenestrations and decreases their metabolism by hepatocytes. In addition, PEGylation of liposomes decreases their opsonization by immunoglobulin/complement proteins and their uptake by phagocytic cells of the MPS (eg, Kupffer cells and splenic macrophages), thus prolonging the agent's plasma circulation time.

Another advantage of L-DOX is its extremely small volume of distribution in comparison to that of DOX (2.72±0.12 vs 809–1,214 L/m^2). While DOX's large V_d indicates that it can effectively distribute into all compartments of the body, its lack of selectivity for tumors means that it can cause a wide range of toxicities. In contrast, the small volume of distribution of L-DOX indicates that the drug is mostly confined into the vascular space, with little free DOX available, as the drug is contained within the liposomes and does not distribute freely to healthy tissues. The small size of L-DOX allows it to extravasate more selectively across fenestrations in the epithelium of blood vessels supplying tumors, where it releases DOX, meaning that generally the use of L-DOX is associated with milder side effects.[5,14] The classic adverse effect associated with DOX use is cardiotoxicity that can range in severity from an acute form that develops shortly after exposure to DOX to a more severe late form where patients may experience decreases in left ventricular ejection fraction (LVEF) and a subsequent diagnosis of DOX induced CHF. Furthermore, the use of DOX is limited by a cumulative lifetime dose limit of up to 550 or 450 mg/m^2 if a patient received previous mediastinal radiation. In contrast, the more common toxicities from L-DOX use include palmar–plantar erythrodysesthesia, nausea, and alopecia.[16,21–25]

Since DOX is considered one of the most effective chemotherapy drugs available, it is often added to regimens for localized or metastatic BC as first- or second-line therapy, as a part of a neoadjuvant therapy prior to surgery or as a salvage therapy. Although it is an effective agent, the risks of cardiotoxicity, particularly when combined with other medications associated with the development of CHF, such as trastuzumab and cyclophosphamide, can limit its use.[26] In the case of L-DOX, the decreased rates of cardiotoxicity due to the formulation/PK differences described in the preceding paragraph allows its inclusion in regimens where free DOX would have a high risk of cardiotoxicity. Table 3 summarizes several trials where L-DOX has been combined with other chemotherapeutics or targeted therapies. Of note, a study combining L-DOX, trastuzumab, and cyclophosphamide was one of the most effective, with an overall survival of 34.2 months and the progression-free survival (PFS) of 12 months.[27] In terms of toxicity, eight of the 48 included patients experienced asymptomatic decreases in LVEF and all but one recovered; of the affected patients, six patients had prior exposure to anthracyclines. As for the other trials included in Table 3, a majority did not find any significant changes to LVEF or high incidences of clinically relevant

cardiotoxicity; however, in several instances where mild-to-moderate cardiotoxicity was reported, it was often in patients who either had prior anthracycline exposure or were concurrently being treated with trastuzumab.[27–31]

Discussion

The decreased risk for the cardiotoxicity of L-DOX combined with its comparable efficacy to DOX in the treatment of BC has made it a suitable alternative therapy in treatment regimens that traditionally utilized conventional DOX.[16] In the in vivo setting, the prolonged systemic circulation of L-DOX due to its relatively long half-life,[32] along with its selective delivery to the tumor site due to its extravasation through leaky tumor vasculature,[33] results in a higher tumor accumulation as compared to normal tissues. In addition, circulating free-drug concentrations in plasma are reduced due to the highly stable L-DOX formulation, leading to lower cardiac tissue exposure of free-DOX, as compared to tumor tissue. Thus, the use of L-DOX would not only be able to alleviate cardiotoxicity but also to retain significant cytotoxic activity against target tumor cells, due to differences in exposure as well as relative potency of DOX in both tissue types. This is in agreement with results from a Phase III study,[16] where L-DOX was shown to be as efficacious as DOX, with significantly reduced cardiotoxicity and other adverse events, in patients with metastatic BC.

Table 3 summarizes all clinical trials for combinatorial effects of L-DOX with other chemotherapeutics and targeted agents. It is noted that practically all trials are Phase II, and the cardiotoxic events observed were either very low or not existent. In most cases where patients experienced mild-to-moderate cardiotoxicity, they were reported to have received prior anthracycline therapy or were on regimens that included trastuzumab, which is known to augment cardiotoxicity caused due to DOX.[34] Nevertheless, the cardiotoxicity observed in the case of L-DOX was significantly lower than that observed with DOX, thus establishing the cardiac safety of this formulation and supporting its clinical use.

In this work, we sought to discuss the therapeutic use of L-DOX in BC. A review of available Phase II and III trials in BC patients has demonstrated that the use of L-DOX generally causes very little cardiotoxicity, while retaining efficacy when used in combination with other chemotherapeutics. Together, this information suggests that L-DOX should continue to be evaluated in further Phase II and III trials in BC, as it remains an effective agent when combined with other chemotherapeutics and is a reasonable agent to substitute in the place of conventional DOX, particularly in patients who are at higher risk for cardiotoxicity.

Disclosure

The authors report no conflicts of interest in this work.

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