REVIEW ARTICLE

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A Comparison of Liposomal Formulations of Doxorubicin with Drug Administered in Free Form

Changing Toxicity Profiles

Dawn N. Waterhouse,[1,2] *Paul G. Tardi*,[2] *Lawrence D. Mayer*[2,3] and *Marcel B. Bally*[1,2]

1 Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, British Columbia, Canada
2 Department of Advanced Therapeutics, British Columbia Cancer Research Centre, Vancouver, British Columbia, Canada
3 Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada

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Abstract

The anthracycline antibiotic doxorubicin has wide activity against a number of human neoplasms and is used extensively both as a single agent and in combination regimens. In addition to the use of free, unencapsulated doxorubicin, there are two US Food and Drug Administration approved liposomal formulations of doxorubicin currently available, with several additional liposomal formulations being researched either in the laboratory or in clinical trials. The two approved liposomal formulations of doxorubicin have significantly different lipid compositions and loading techniques, which lead to both unique pharmacokinetic and toxicity profiles, distinct from those of the unencapsulated form.

This article discusses the toxicities associated with the free form of doxorubicin, as well as those associated with the two most common liposomal formulations, namely Doxil®[1] and Myocet™. One of the key toxicity issues linked to the use of free doxorubicin is that of both an acute and a chronic form of cardiomyopathy. This is circumvented by the use of liposomal formulations, as these systems tend to sequester the drug away from organs such as the heart, with greater accumulation in liver, spleen and tumours. However, as will be discussed, the liposomal formulations of doxorubicin are not without their own related toxicities, and, in the case of Doxil®, may be associated with the unique toxicity of palmar-plantar erythrodysaesthesia. Overall, the use of liposomal doxorubicin allows for a greater lifetime cumulative dose of doxorubicin to be administered, however acute maximal tolerated doses differ significantly, with that of Myocet™ being essentially equivalent to free doxorubicin, while higher doses of Doxil® may be safely administered.

This review highlights the differences in both toxicity and pharmacokinetic properties between free doxorubicin and the different liposomal formulations, as have been determined in pre-clinical and clinical testing against a number of different human neoplasms. The need for further testing of the liposomal formulations prior to the replacement of free doxorubicin with liposomal doxorubicin in any established combination therapy regimens, as well as in combination with the newer therapeutics such as monoclonal antibodies is also discussed.

Doxorubicin is the best known and most widely used member of the anthracycline antibiotic group of anticancer agents. It was first introduced in the 1970s and has been valuable in the treatment of both haematological and solid tumours. Despite the introduction of many anthracycline analogues designed to be safer and more effective than doxorubicin, this drug continues to be a mainstay of drug cocktails used in the management of most solid tumours. The therapy-limiting toxicity for this drug is cardiomyopathy, which may lead to congestive heart failure (CHF) and death. Approximately 2% of patients who have received a cumulative (lifetime) doxorubicin dose of 450 to 500 mg/m^2 will experience this condition. Due to the cardiotoxicity concerns, a cumulative dose exceeding 400 to 500 mg/m^2 with the 21-day regimen and 700 mg/m^2 with the weekly regimen is not recommended. Recently, this toxicity has been highlighted in clinical studies evaluating the use of doxorubicin with a humanised monoclonal antibody targeting the oncoprotein HER-2/neu, referred to as trastuzumab (herceptin). Combinations of trastuzumab and doxorubicin provide particularly promising therapeutic effects, but exacerbate cardiac-related toxicities.

The toxicity profile of conventional doxorubicin has prompted considerable effort in identifying new analogues or different drugs which maintain the clinical efficacy of doxorubicin, while reducing cardiotoxicity. Some success has been attained with the use of the anthracyclines epirubicin and idarubicin, as well as with a similar drug, the dihydroxyanthracenedione derivative mitoxantrone. Although these drugs are being considered more frequently in combination chemotherapy protocols, doxorubicin remains the predominantly utilised anthracycline.

A different approach to ameliorating doxorubicin-related toxicity is to use drug carriers, which engender a change in the pharmacodistribution of the drug, resulting in reduced drug concentrations in the heart. Examples of these carrier systems would include lipid-based (liposome) formulations

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as well as various types of polymer delivery systems. The most advanced technologies are those relying on liposomes to effect a beneficial change in doxorubicin biodistribution, with two formulations approved for clinical use. For this reason, this review will focus on liposomal delivery systems. In this regard, it is important to remember that doxorubicin, administered in free form, exhibits many adverse effects other than cardiotoxicity. Similar to other anticancer drugs targeting proliferating cell populations, doxorubicin causes significant gastrointestinal toxicity, with nausea, vomiting and diarrhoea being common soon after therapy, and stomatitis occurring within 7 to 10 days of administration. It is therefore critical to have an understanding of both the beneficial and adverse effects of liposomal formulations of doxorubicin if its use is being considered as an alternative to the free drug.

Doxorubicin was successfully encapsulated into liposomes in the late 1970s.[1,2] The liposome formulations were found to maintain the anticancer activity of the free drug in mice, while at the same time decreasing the associated cardiotoxicity. Over the past several years, liposomal formulations of doxorubicin have been developed and evaluated in clinical trials. The two most advanced formulations are Doxil® (Caelyx®) and Myocet™ (formerly known as TLC D-99 and Evacet™). Liposomal encapsulation of doxorubicin serves to extend the circulation longevity of the drug, as well as to substantially alter its pharmacodynamic properties.

This article provides a comprehensive review of the observed adverse effects of liposomal formulations of doxorubicin. Emphasis is placed on the two formulations that have been approved for clinical use. These two formulations are, as outlined in this review, significantly different from each other and clinicians contemplating their use should try to understand their differences.

1. Chemical Structure and Molecular Activity of Doxorubicin

The anthracycline antibiotic doxorubicin is one of the most important and widely used anticancer agents. Produced by *Streptomyces peucetius*, doxorubicin has broad activity against a range of human neoplasms, including breast, ovarian, stomach, bladder and bronchogenic carcinomas, leukaemias and lymphomas, and soft tissue sarcomas. The anthracyclines have tetracycline ring structures with the sugar daunosamine attached by glycosidic linkage. Cytotoxic agents of this class have quinone and hydroquinone moieties on adjacent rings that permit them to function as electron-accepting and electron-donating agents (see fig. 1).

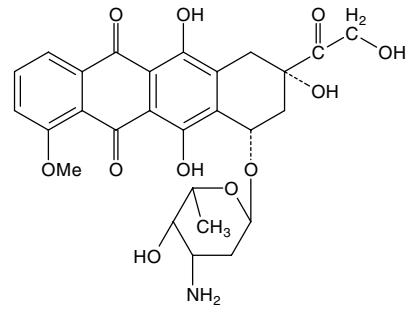

Fig. 1. Chemical structure of doxorubicin.

The precise mechanism of action of doxorubicin is not understood, however it is known to intercalate between DNA base pairs, resulting in DNA synthesis inhibition and DNA-dependent RNA synthesis inhibition due to template disordering and steric obstruction. Intercalation leads to single and double strand breaks as well to as exchange of sister chromatids. Scission of DNA is believed to be mediated through the action of topoisomerase II or by the iron-catalysed generation of free radicals, both hydrogen peroxide and hydroxyl, which are highly destructive to cells. Doxorubicin also induces the formation of covalent topoisomerase II-DNA complexes, resulting in inhibition of the religation portion of the ligation-religation reaction in replicating DNA. Although it is active throughout the cell cycle, the maximal toxicity occurs during the DNA synthesis (S) phase. At low concentrations of drug, cells will continue through the S phase, and die in the G_2 phase.[3]

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2. Doxorubicin-Induced Toxicities

2.1 Cardiomyopathies

The clinical activity of doxorubicin, as with other anthracyclines, is limited by cardiomyopathy. This, in turn, is related to the total cumulative dose of the drug and is principally due to free radical damage to myocytes.[4,5] Two types of cardiomyopathies may occur: acute or chronic.

The acute form of cardiomyopathy occurs immediately after or during a single dose or course of therapy, and is characterised by abnormal electrocardiographic changes, including ST-T wave alterations, prolongation of the QT interval and arrhythmias, and acute but reversible reduction in ejection fraction. Damage occurs due to build-up of the anthracycline within the heart muscle, DNA intercalation and free radical formation, which result in damage to myocardial cells. This in turn leads to the drug-induced release of histamines and other vasoactive agents, all resulting in a cascade of events culminating in further myocardial cell damage.[5] Acute myocarditis may be ameliorated by a slower drug infusion, an observation that is consistent with the belief that acute cardiotoxicity is a consequence of peak drug concentrations obtained after bolus administration.[4,6]

The most common cardiomyopathy is a chronic, cumulative dose-related toxicity manifested by CHF that is unresponsive to digoxin (digitalis).[4] The typical clinical presentation of chronic cardiomyopathy is similar to that of CHF secondary to systolic myocardial dysfunction; including tachycardia, dilation of the heart, fatigue, pulmonary and venous congestion, poor perfusion, and pleural effusion[7] associated with biventricular failure. Pathologically, this is caused by lysis of both the thick and thin myofilaments leading to myofibrillar loss, and dilatation of the sarcoplasmic reticulum, resulting in vacuolisation of myocytes.[4] It is probable that there is successively incomplete recovery from each acute insult of doxorubicin administration, thus leading to progressive deterioration of cardiac function, and chronic cardiomyopathy.[4]

Anthracyclines have also been documented to cause late-onset cardiac toxicity, with onset of CHF up to 15 years after the actual treatment.[7] Administration of the iron chelator dexrazoxane may alleviate some of these problems, by reducing the available iron for complexing with doxorubicin. This drug is now being included more routinely in anthracycline-containing regimens.[8]

Several factors are known to aggravate the cardiotoxicity of doxorubicin. These include prior mediastinal or chest wall irradiation, administration of high doses of cyclophosphamide or another anthracycline, age <4 or >70 years, prior history of heart disease, hypertension, and female gender.[6,9] In the presence of these factors, the total cumulative dose of doxorubicin is typically reduced from 500 to 450 mg/m^2.

2.2 Other Toxicities

The typical, acute dose-limiting toxicity for doxorubicin is myelosuppression, typically leucopenia and thrombocytopenia. This is usually a transient phenomenon, with the leucocyte nadir observed within 10 to 14 days of treatment, and recovery to normal cellularity by 21 days.[10] In severe cases, this may lead to neutropenic fever and sepsis, requiring hospitalisation. Mucositis, including both stomatitis and pharyngitis, which may lead to ulceration has been associated with continuous infusion of doxorubicin. Interestingly, this same form of toxicity is often seen with the use of liposomal doxorubicin administered as a bolus, perhaps indicating a slow release process in the intravascular compartment.[11]

An almost universal occurrence of alopecia accompanies treatment with conventional doxorubicin.[12] This is typically evident 3 to 4 weeks after initiation of therapy, with regrowth occurring 2 to 5 months after therapy, or in some cases, during therapy. Acute nausea and vomiting are also very common with doxorubicin, and many patients require the use of antiemetics to control these adverse effects. Rare doxorubicin-induced toxicities include ulceration and necrosis of the colon, and neuropathy.

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As excretion of doxorubicin is mostly through the bile, liver function will have direct impact on the pharmacokinetics of the drug. For this reason, it is important to monitor bilirubin levels during administration of doxorubicin, with special care being warranted when the drug is used to treat patients with hepatic dysfunction.[13]

3. Liposomal Doxorubicin

The encapsulation of drugs in liposomes alters the pharmacokinetic and biodistribution properties of the entrapped agents.[11,14] The nature and extent of these alterations depends on the lipids used in the liposome formulation (phospholipid acyl chain length and charge), as well as the overall size and lipid proportion of the administered liposomes.[15] For example, the inclusion of cholesterol in liposome formulations has been shown to prevent lipoprotein-induced vesicle destabilisation and concomitant release of the encapsulated drug.[16,17] This leads to increased circulation longevity of the drug and enhanced bioavailability. When negatively charged phospholipids such as phosphatidylserine are included in the formulation, liposomes are rapidly cleared from the circulation by the cells of the mononuclear phagocyte system.[18] Rapidly cleared formulations may still affect drug parameters, such as reduced cardiotoxicity with doxorubicin.[19]

The primary aim of doxorubicin encapsulation in liposomes has been to decrease nonspecific organ toxicity. Liposomes are able to direct the doxorubicin away from sites with tight capillary junctions such as the heart muscle and the gastrointestinal tract. They instead accumulate within organs rich in cells of the mononuclear phagocyte system (MPS). It should be noted however, that liposomal doxorubicin affects the cells of the MPS such that they can not accumulate further liposomal systems. Although this 'MPS toxicity' has been noted in animals, as measured by a change in liposome elimination profiles, similar effects have not been observed in humans. Regardless, MPS toxicity may be of some concern in individuals with an increased risk of opportunistic infections, such as those with AIDS, particularly because of the depletion of liver macrophages, which have been shown in animal models to take up to 2 weeks to be restored.[20]

Liposomal formulations containing polyethylene glycol (PEG)-modified lipids have an even greater blood circulation time as a result of diminished liposome-cell interactions, however these formulations have also been shown to exhibit MPS toxicities.

Regardless of whether the enhanced circulation time of liposomal doxorubicin is due to subtle changes in lipid composition, effects on MPS cell function, or the use of PEG-modified lipids, increased circulation longevity of the liposomes allows enhanced extravasation across the leaky endothelium of solid tumours, providing a local depot for drug release.[21]

In order for liposomal formulations of doxorubicin to present a therapeutic advantage over the free agent, they must be able to enhance antitumour activity at the maximal tolerated dose (MTD) without a concurrent increase in toxicity. The increased accumulation of liposome-encapsulated doxorubicin in tumours, and the decreased accumulation in sensitive nontarget organs, can enhance the therapeutic index of the drug, but it is argued here that the primary benefits occur as a consequence of reduced toxicity rather than enhanced therapeutic potency. Such conclusions have been reached on the basis of data obtained in animal models of cancer and current Good Laboratory Practices toxicity studies. The real beneficial effects of liposome encapsulation on doxorubicin's therapeutic index will only be appreciated after extensive clinical studies beyond those conducted to date. In this regard, it is notable that arguments in support of clinical use of the two approved liposomal formulations of doxorubicin are different. Advocates of one formulation highlight improved antitumour activity while advocates of the other emphasise reduced toxicity.

As suggested earlier, there have been several formulations of liposomal doxorubicin reported in the literature,[19,22-23] however only a few formulations have undergone the extensive safety and

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clinical efficacy testing necessary to support market approval. One carrier is comprised of egg phosphatidylcholine and cholesterol (Myocet™), and was given community marketing authorisation from the European Commission in August 2000 for the treatment of metastatic breast cancer. The other utilises pegylated lipids, and has been used in the US since 1995 under the brand name Doxil® and is marketed in Canada and Europe as Caelyx® (see table I). This pegylated formulation is comprised of hydrogenated soya phosphatidylcholine, cholesterol and PEG-modified phosphatidylethanolamine.

In preclinical and phase I studies, Myocet™ was shown to have a circulation half-life of approximately 3 times that of free doxorubicin,[24] although these data were derived from a large range of α plasma elimination half lives. In addition, the encapsulation of doxorubicin in liposomes was associated with decreased toxicity of the drug, notably decreased cardiomyopathy and gastrotoxicity.[25,26] The Myocet™ formulation employs an active entrapment process for doxorubicin, where liposomes are prepared in an acidic buffer (pH 4.0 300mM citrate), then sodium carbonate is added to increase the pH outside the liposomes to approximately 7.3. When these liposomes are combined with doxorubicin and heated briefly, the doxorubicin crosses the lipid bilayer and becomes protonated in the liposome interior. Once doxorubicin becomes protonated it has difficulty crossing the lipid bilayer which results in trapping efficiencies of over 99%.[24]

The Doxil® liposomal formulation contains the inert hydrophilic polymer PEG. This PEG moiety is linked to a distearoyl phosphatidylethanolamine lipid anchor, which extends out from the liposomal surface to create a hydrated barrier or shield which protects the liposomes. It has been argued that the steric barrier provided by surface-grafted PEG inhibits protein binding, in particular those serum proteins known to act as opsonins, which bind foreign particulates and promote their recognition by cells of the MPS.[27] However, the most compelling evidence regarding the mechanism of PEG is that which demonstrates inhibition of surface-surface interactions.[28] The Doxil® formulation is also loaded with doxorubicin in an active fashion using a $(NH_4)_2SO_4$ gradient across the lipid bilayer to draw the drug to the liposomal interior, where it then precipitates with sulphate.

In the absence of entrapped doxorubicin, these liposomes have a different biodistribution pattern from liposomes without PEG-modified lipids. They have a tendency to decrease accumulation in the liver and spleen and reduce the plasma elimination rate. In the presence of entrapped doxorubicin, the difference in pharmacokinetic and biodistribution characteristics of PEG liposomes and the egg phosphatidylcholine/cholesterol liposome are less dramatic because of the doxorubicin-induced MPS blockade previously discussed.

The most significant difference between Doxil® and Myocet™ is related to liposome-mediated changes in doxorubicin plasma elimination rate. Although some investigators attribute reduced doxorubicin elimination rate to the use of pegylated lipids, it is evident from numerous studies that the difference

Table I. Liposomal doxorubicin formulations

Formulation	Doxorubicin to lipid ratio (wt/wt)	Liposome size (nm)	Brand/trade name(s)	Indication
HSPC/cholesterol/MPEG-DSPE (55/40/5 molar ratio)	0.4 : 1.0	<100	Doxil®/Caelyx®	AIDS-related Kaposi's sarcoma; ovarian cancer refractory to paclitaxel- and platinum-based chemotherapy
EPC/cholesterol (55/45 molar ratio)	0.27 : 1.0	180	TLC-99/Evacet™/Myocet™	Metastatic breast cancer (Europe)

DSPE = distearoyl phosphatidylethanolamine; **EPC** = egg phosphatidylcholine; **HSPC** = hydrogenated soybean phosphatidylcholine; **MPEG** = methoxy polyethylene glycol.

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is due primarily to changes in doxorubicin release rates from the liposomes.[29] The Myocet™ formulation releases more than half of its associated doxorubicin within 1 hour of intravenous administration and more than 90% of its entrapped contents within 24 hours. In contrast, saturated liposomal lipid formulations comparable to the hydrogenated soya phosphatidylcholine/cholesterol/PEG lipid formulation release less than 10% of their encapsulated doxorubicin 24 hours after intravenous administration.[11]

Differences in doxorubicin release from liposomes following intravenous injection are reflected in rates of doxorubicin clearance, biodistribution, antitumour activity and toxicity. The Doxil® formulation exhibits enhanced drug delivery to sites of tumour growth when compared to the Myocet™ formulation. Both formulations enhance disease site delivery when compared to equivalent doses of free doxorubicin.[11,15]

As one may anticipate, changes in drug release will be reflected in the toxicity profile of the liposomal formulation. In animal models, Myocet™ is more acutely toxic than Doxil®. Importantly, both drug formulations buffer the acute cardiotoxicity of doxorubicin. Liposome-mediated changes in drug circulation time are, however, also responsible for nonspecific distribution of the liposomal drug. In the case of Doxil®, enhanced retention can account for increases in the accumulation of doxorubicin in the skin and this may, in turn, be a cause of the dose-limiting toxicity associated with use of Doxil® in humans.[30-32]

This Doxil®-specific toxicity, observed as palmar-plantar erythrodysaesthesia (PPE), can be considered a new doxorubicin toxicity attributable specifically to the use of the Doxil® formulation. PPE is a painful, desquamating dermatitis which primarily affects the hands and feet but can also affect other skin areas such as the perineum as a result of pressure and friction.[31] This appears to be a toxicity unique to liposomes containing pegylated lipids, as it was not observed in the Myocet™ trials. Importantly, this toxicity does not necessitate a decrease in the total cumulative dose of the Doxil® formulation. The maximal tolerated acute dose of Doxil® is somewhat lower than that of free doxorubicin because of PPE for patients treated at short dose intervals of 3 weeks, and because of mucositis at high doses. The plasma half-life of Doxil® in humans ranges from approximately 45 hours[11] to up to 70[31] or 90 hours.[32]

4. Phase I Trials of Liposomal Doxorubicin

4.1 Egg Phosphatidylcholine/ Cholesterol Formulation

In an initial phase I clinical trial, Myocet™ was administered as a single 1 hour infusion at doses of 20, 30, 45, 60, 75 and 90 mg/m^2 every 3 weeks, or daily at dosages of 20, 25, and 30 mg/m^2/day for 3 days to patients with solid tumours.[24] The dose-limiting toxicity in this study was leucopenia, with leucocyte and platelet nadirs occurring 10 to 15 days after treatment. Leucopenia was most marked with the single doses of Myocet™ 90 mg/m^2; three recipients (33%) experienced grade IV leucopenia. Following dose reduction, full recovery of white blood cell counts occurred by day 20 in all patients. This leucopenia was similar to that seen with free doxorubicin at the same dosage schedule.[33]

For the daily Myocet™ injections, 25 mg/m^2 was found to be the MTD, and for the injections every 3 weeks, 90 mg/m^2 was considered the MTD. Only one patient had a total cumulative dose of >400 mg/m^2, but this was due to pretreatment with 480 mg/m^2 anthracycline. This patient had a total cumulative dose of 750 mg/m^2, and did not demonstrate altered left ventricle ejection fraction after treatment with liposomal doxorubicin. Therefore, this study was not able to demonstrate the potential for increased cumulative doses and an associated reduction in chronic dose-related cardiomyopathies.

Nonhaematological toxicities included fever, chills and rigors in most patients, as well as mild nausea and vomiting. The fever, chills and rigors appeared to be unique to the use of the liposomal drug and it has been speculated that this toxicity may be due to direct effects of the liposomal drug

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on immune cells.[24] Alopecia was present at doses of 45 mg/m^2 or greater with the injections every 3 weeks, and one patient receiving the daily dose schedule had severe alopecia.

The delayed pyrexia (often associated with chills) observed following Myocet™ administration was seen in virtually all patients, however, this did not appear to be dose-related and resolved without the need for supportive care.[24] It was surmised that the pyrexia might have been due to macrophage activation/toxicity by Myocet™. The other toxicity of note in this trial was that of a general malaise in a significant number of patients at a dose level of greater than 30 mg/m^2, beginning on days 7 to 10 after treatment. This toxicity resolved by day 20.[24]

Myocet™ has also been tested in a phase I trial in soft tissue sarcomas,[34] using the results from solid tumour trials as a reference. The dose ranged from 75 mg/m^2 to 120 mg/m^2 every 2 to 3 weeks, with a limit of 600 mg/m^2 for the total cumulative dose. Patients were given granulocyte colony-stimulating factor to minimise haematological toxicity. Overall, a total of ten patients (35%) required hospitalisation for neutropenic fever at some point during therapy, and dose-limiting thrombocytopenia occurred at 120 mg/m^2. Nonhaematologic toxicities occurred at all dose levels and included fatigue (severe at 105 and 120 mg/m^2), mucositis, nausea and vomiting (mostly grade 2, but one patient had grade 4), as well as a 100% incidence of alopecia. No patients in this trial had a cumulative doxorubicin dose of greater than 600 mg/m^2, and none developed symptoms of CHF or had a decrease in left ventricular ejection fraction.[34]

In another phase I trial of doxorubicin 30 mg/m^2 per week, egg phosphatidylcholine/cholesterol liposomes caused dose-limiting leucopenia. As noted in the above trials, a number of patients (three of 21) developed severe nausea and vomiting. Mild nausea and vomiting were common in the remainder of the patients as were mild to moderate stomatitis.[35]

4.2 Pegylated Formulation

Early studies with Doxil® administered at 50 mg/m^2 every 21 to 28 days[11] showed frequent nausea, similar to that observed with the administration of conventional doxorubicin. This nausea, however, was quite mild (WHO grade 1 and 2) and was accompanied by only sporadic vomiting. Stomatitis was present in five of 15 patients treated at this dosage level, occurring 7 to 14 days after treatment, and was worse (grade 3 to 4) in patients with a history of heavy pretreatment chemotherapy. This is contrasted with the complete absence of stomatitis in a group of seven patients receiving conventional doxorubicin at the same dosage. Myelosuppression was found to be minimal (grade 1 to 2) with no associated fever in the Doxil®-treated group, as compared with grade 1 to 3 in three out of four patients treated with equivalent amounts of free doxorubicin. Also observed in this study were infusion reactions in several patients, consisting of dyspnoea and facial flushing, which were attributable to Doxil®. This type of reaction to Doxil® infusion has also been noted by other investigators as have chest pain, difficulty in swallowing, hypotension and/or back pain.[36] These toxicities are resolved by discontinuing or reducing the rate of infusion.

Uziely et al.,[37] in two phase I clinical trials in patients with refractory cancers, found the major clinical adverse events associated with Doxil® therapy to be mucositis in the form of stomatitis-pharyngitis (dose related) and skin toxicity in the form of PPE (schedule related). This was dose limiting following three or more courses given at 60 mg/m^2. These trials also indicated that lengthening the treatment interval is important in reducing the incidence of PPE. For example, all four patients receiving three or more courses of 60 mg/m^2 every 3 weeks showed signs of PPE, while only two of nine patients exhibited PPE after receiving the same dose every 4 weeks. No cardiotoxicity was noted (as determined by nuclear angiocardiography of left ventricular ejection fraction) for patients given greater than or equal to 450 mg/m^2. Some of these patients received a total cumulative dose of 840 mg/m^2. Of note in this trial was that leucopenia was not a dose-limiting toxicity. The MTD for Doxil® was 50 mg/m^2 when administered once every 3

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weeks, lower than that of free doxorubicin (60 to 75 mg/m^2), because of mucositis. The calculated dosage intensity was found to be 15 mg/m^2/week, which is about 25% lower than that of free doxorubicin.[37]

4.3 Cardiolipin/Phosphatidylcholine/Cholesterol/Stearylamine Formulation

Although Doxil® and Myocet™ have advanced most in terms of their development as drugs for treatment of human disease, other liposomal formulations have been tested in humans and it is of interest to consider the phase I data obtained with these other formulations.

For example, a phase I trial has been completed using a formulation of liposomal doxorubicin in which liposomes were formed from cardiolipin, phosphatidylcholine, cholesterol and stearylamine.[19] The liposomes were administered to 14 patients with cancers for which no curative or palliative therapy existed.[19] Liposomal doxorubicin was administered at 30, 45, 60 and 90 mg/m^2 once every 3 weeks. The limiting toxicity of the trial was found to be dose-dependent granulocytopenia. 100% of patients receiving the highest dosage developed grade 3 or 4 granulocytopenia, and two had nadirs of <100 cells/mm^3. Granulocyte and platelet nadirs occurred at days 10 to 15, and recovered by day 25 in most cases. Patients at the highest dosage level also had complete alopecia, but nausea and vomiting were relatively mild (grade 1 to 2). The investigators noted that this formulation of liposomal doxorubicin appeared to cause less sclerosing than free doxorubicin as evidenced by the lack of phlebitis associated with infusion, a lower incidence of gastrointestinal toxicity and a complete absence of stomatitis.

5. Phase II and III Trials of Liposomal Doxorubicin

Liposomal doxorubicin formulations have been tested against many different types of cancer in phase II and III trials. This review covers a few of these, with specific focus on trials involving patients with AIDS-related Kaposi's sarcoma, advanced breast cancer and ovarian cancer.

In a randomised phase III trial of patients with AIDS-related Kaposi's sarcoma, combination therapy with doxorubicin, bleomycin and vincristine (ABV) was compared with Doxil® (see table II).[36] Drugs were administered every 14 days for six cycles, with a doxorubicin dose of 20 mg/m^2 in each arm. Notably, there were six patients with acute infusion-related reactions in the pegylated liposomal doxorubicin arm compared with none in the ABV arm. Overall, the researchers presented Doxil® as being more efficacious than the ABV regimen, with an improvement in the therapeutic ratio. This was based on reduced toxicity and increased response rate (45.9% of patients for Doxil® versus 24.8% for ABV), as the survival between the groups showed no significant difference. The incidences of opportunistic infections were approximately equal in the two groups, at roughly 33%, and approximately half of all patients requiring colony-stimulating factors during treatment. The ABV arm had a four-fold higher incidence of alopecia and a two-fold higher incidence of nausea and vomiting than the Doxil® arm. The relatively low cumulative doses achieved precluded the authors from drawing any conclusions as to the risk of cardiotoxicity with the Doxil® formulation.

A meta-analysis[39] of 1716 patients with AIDS-related Kaposi's sarcoma given Doxil® every 2 to 3 weeks at 10 to 40 mg/m^2 in 10 different phase II/III studies confirmed a reduction in toxicity of Doxil® over conventional doxorubicin and found Doxil® to be well tolerated in general. Only 6% of patients experienced grade 3 or 4 leucopenia, and 6.8% experienced alopecia. Infusion reactions did occur but only in 3.3% of all patients. In spite of the large patient number analysed, only one of 82 patients who received a total cumulative doxorubicin dose of >500 mg/m^2 had any evidence of cardiomyopathy. This was a pivotal study which provided key data, leading to the US Food and Drug Administration approval of Doxil® for use in patients with AIDS-related Kaposi's sarcoma.

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Table 2 to go here

Myocet™ has also been tested in patients with AIDS-related Kaposi's sarcoma, in a phase II trial which randomised 40 patients to either 10 or 20 mg/m^2 every 3 weeks.[38] Table II highlights some of the features of this trial, in which the most notable toxicity was neutropenia, occurring in 75% of patients. At the higher dosage, a partial response rate of 24% was achieved, however, no patient achieved a complete response.

In two recently reported phase II trials of Doxil® for the treatment of hepatocellular carcinoma, two treatment schedules were explored; 30 mg/m^2 every 3 weeks[40] and 50 mg/m^2 every 4 weeks.[41] In both trials Doxil® was fairly well tolerated, however, one of these trials had no objective responses[40] and the other had only a 13.3% objective response rate (one complete response, three partial responses).[41] Toxicities included two grade 4 hypersensitivity reactions (incidence 11.8%), 11 cases of grade 3 or 4 increased liver enzymes (64.7%),[40] two grade 3 neutropenic events and seven mild cases of PPE.

Although one study[41] recommended the use of Doxil® for this type of cancer, the other study[40] did not. However, when compared with a trial of conventional doxorubicin in the treatment of hepatocellular carcinoma[42] in which the response rate was 18% (with marked myelosuppression), the results would not seem to indicate a sufficiently enhanced therapeutic index to support the use of Doxil® in this patient group. In retrospect, this is an interesting result considering it is generally believed that liposomal anticancer drug formulations enhance drug delivery to organs such as the liver and spleen. In this case however, improved drug delivery is not expressed as an enhancement of therapeutic activity, suggesting that drug distribution will also play an important role in defining both efficacy and toxicity of the liposomal anticancer drugs.

Doxil® toxicities, primarily mucocutaneous (table II), were found to be too great to warrant use of the drug in a trial of 20 patients with prostate cancer given either 45 mg/m^2 every 3 weeks or 60 mg/m^2 every 4 weeks.[32] In this trial, groups of ten and

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Table II. Toxicities and response rates for selected phase II and III trials of liposomal doxorubicin

Tumour type	Study arm	No. of patients	Mean cumulative dose in mg/m^2 (range)	Percentage of patients with						
				leucopenia	mucositis/ stomatitis	nausea/vomiting	PPE	alopecia	response (PR + CR)	Ref.
AIDS-related Kaposi's sarcoma	Doxorubicin 20 mg/m^2 + bleomycin 10 mg/m^2 + vincristine 1mg	125	79 (17-124)	34[a]	2[a]	27[a]		15[a]		36
	Doxil® 20 mg/m^2	133	120 (20-139)	27[a]	4[a]	11[a]		1[a]		
Prostate cancer	Doxil® 60 mg/m^2 every 4 weeks	10			50[b] 40[a]		44[b] 25[b]	10 (mild)	30	32
	Doxil® 45 mg/m^2 every 3 weeks	10			40[b]		75[a]			
AIDS-related Kaposi's sarcoma	Myocet™ 10 mg/m^2 every 2 weeks	19		16[a]					5	38
	Myocet™ 40 mg/m^2 every 2 weeks	21		14[a]				8 (mild)	24	

a Grade 3-4.

b Grade 1-2.

CR = complete response; **PPE** = palmar-plantar erythrodysaesthesia; **PR** = partial response.

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five patients were randomised to each dosage, with five and two patients, respectively, requiring dose reductions because of toxicity. There was a high incidence of severe (grade 4) skin toxicity with the shorter dosage schedule, and only grade 1 or 2 PPE with the longer schedule. PPE appeared after a minimum of two courses and precluded further patients being accrued on the shorter schedule. There were 4 reported cases of stomatitis which represented 26.7% of the patient group, and all required a dose reduction. The condition developed 10 to 15 days after the first Doxil® course and lasted for 5 to 10 days. Myelosuppression was mild, and alopecia was seen in only one patient at the higher dose. There were no reported instances of CHF or decreases in left ventricular ejection fraction, even at the highest cumulative dose of 540 mg/m^2.[32]

This reduction in cardiotoxicity was also noted in a retrospective analysis of eight phase I and II trials of Doxil®,[43] in which only two of 34 patients with no prior doxorubicin treatment and a median cumulative Doxil® dose of 654 mg/m^2 (range 500 to 1450 mg/m^2) had a decrease in left ventricular ejection fraction of greater than 10%.

5.1 Advanced Breast Cancer

Approximately 1 in 9 women will develop breast cancer in their lifetime if they live to the age of 85 years. Currently, anthracycline-containing combination therapy is the standard of care for this disease, although there is much excitement in the areas of the taxanes and monoclonal antibodies.[44] These are attractive agents for combination therapy due to minimal overlapping toxicities with anthracyclines. In clinical trials of advanced breast cancer, the objective response rates for conventional doxorubicin treatment are approximately 42 and 30% in untreated and previously treated patients, respectively.[45]

5.1.1 Pegylated Formulation

There have been several recently reported trials of Doxil® in the treatment of advanced breast cancer.[31,46-47] In one of these trials,[31] Doxil® was used as a single agent at several doses and schedules (see table III) in order to explore the effect of these parameters on toxicity and pharmacokinetics. All patients in this trial had failed one or more lines of chemotherapy, but had prior doxorubicin therapy of <400 mg/m^2. This trial demonstrated a fairly high incidence of mucositis which was prevented in further courses by dose reduction. The peak plasma concentration of doxorubicin was correlated with both the incidence of mucositis and the leucocyte nadir. As in other Doxil® trials, there was a high incidence of PPE, which was determined to be strongly correlated to the plasma half-life of the drug after the first, second or third cycles, therefore prompting a recommendation for a dosage intensity of 10 to 12 mg/m^2/week. Importantly, there was only one instance of CHF in this trial, which occurred in a patient who had had prior mitoxantrone therapy and radiotherapy to the mediastinum. Otherwise, no patients had a greater than 15% decrease in left ventricular ejection fraction as determined by multiple-gated acquisition (MUGA) scan, even with cumulative doses of Doxil® up to 1500 mg/m^2.

In a trial of Doxil® in combination with paclitaxel[46] (table III) with a dosage intensity of 11.25 mg/m^2/week, which is within the suggested range of the above-mentioned trial,[31] there was also a high incidence (33%) of grade 3 or 4 mucositis as well as a 33% incidence of neutropenia, including one case of febrile neutropenia. No patients had CHF. There was a 50% incidence of grade 3 or 4 PPE.

A recent trial[47] tested the combination of Doxil® with vinorelbine. In this trial, the dosage intensity was 10 mg/m^2/week, with a schedule of 40 mg/m^2 every 4 weeks. The incidence of mucositis was somewhat lower (18.2%) than in the previous 2 trials, as was that of PPE (13.6%). Neutropenia was similar to that seen in other advanced breast cancer Doxil® trials.[31] Despite the relatively low toxicities and absence of any CHF, the investigators could not support the use of Doxil® in combination with vinorelbine in advanced breast cancer due to the disappointingly low objective response rate (four of 22 patients had a partial response and none had a complete response).

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This is in contrast to the previously mentioned trials of Doxil® in advanced breast cancer where a response occurred in 9 out of 45 patients (2 complete responses)[46] and 9 out of 18 patients (2 complete),[31] respectively. Of the trials (table III) which reported on alopecia, this adverse effect was found to be minimal or absent.[30,31] Infusion reactions were noted in 11.1%[47] and 4.2%[30] of administrations, including two allergic reactions to Doxil® infusion in the 1997 study.[30]

5.1.2 Egg Phosphatidylcholine/ Cholesterol Formulation

Myocet™ has been developed as a drug for use in the treatment of metastatic breast cancer. Table III lists two trials of Myocet™ reported in 1999, one of which was in combination with cyclophosphamide and fluorouracil,[48] and the other in which Myocet™ was administered with colony-stimulating factor[48] due to the high dose employed (135 mg/m^2 every 3 weeks). Each of these trials noted almost complete incidence of grade 3 or 4 neutropenia (95 and 98%, respectively), which was similar to the results reported in a phase III trial of free doxorubicin in combination with taxol or cyclophosphamide.[50] These studies reported a 27% and 48% incidence of anaemia, respectively. This toxicity was also noted in a Doxil® trial with a mean incidence of 14%.[31]

This high dose intensity trial of Myocet™ was associated with a 13.5% incidence of CHF, with one death following a cumulative dose of 1035 mg/m^2. For those patients experiencing CHF, the minimal cumulative Myocet™ dose was 525 mg/m^2. As this dose only resulted in a response rate of 45%, which was only marginally superior to that of free doxorubicin, the investigators determined that this dose was not justifiable.

In the combination trial,[48] three patients were withdrawn due to a decrease in the baseline left ventricular ejection fraction. There was also a 100% incidence of neutropenia with 24% of these cases being febrile. Alopecia was complete in this trial, similar to that seen with conventional doxorubicin. Despite the similar or increased toxicities, a high response rate of 73% was reported (68% partial response, 5% complete response). Neither of the Myocet™ trials had any incidence of PPE.

Results from more recent trials of Myocet™ administered either as a single agent or in combination with cyclophosphamide for the first-line treatment of metastatic breast cancer showed a decrease in cardiotoxicity compared with that of conventional doxorubicin from 26 to 10%, respectively, in at-risk patients.[51] Moreover, the total cumulative dose of anthracycline at onset of cardiotoxicity was increased from 570 mg/m^2 with conventional doxorubicin, to 895 mg/m^2 with Myocet™. In the same trial, Batist et al.[52] observed a reduction in cardiotoxicity from 39% in the conventional doxorubicin arm to 22% in patients treated with Myocet™ who had received prior adjuvant doxorubicin therapy. There was no appreciable difference in other toxicities associated with the use of free drug versus liposomal doxorubicin in this trial.

5.1.3 Doxorubicin in Combination with Trastuzumab

Trastuzumab is a humanised monoclonal antibody that selectively targets the HER-2/neu protein, a 185kDa transmembrane receptor tyrosine kinase. The HER-2/neu gene is amplified and/or overexpressed in a variety of human tumours, and is associated with poor prognosis in prostate,[53] ovarian[54] and breast cancer.[55] As a single agent, trastuzumab exhibits modest antineoplastic activity but appears to have greater potential when used in combination with established chemotherapeutics.

In a 1998 trial[56] involving 469 women with HER-2/neu overexpressing breast cancer, cardiac dysfunction was observed in 27% of patients receiving concurrent doxorubicin and cyclophosphamide (AC) plus trastuzumab compared with 8% of those receiving AC alone. Despite the increased toxicity and lack of a significant increase in objective response rate (56% with AC plus trastuzumab, 42% for AC alone; $p = 0.02$), the time to progression of disease increased to 7.8 months from 6.1 months when the trial included trastuzumab, leading the investigators to conclude that anthracyclines are beneficial in regimens containing trastuzumab

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Table III. Clinical trial results for liposomal doxorubicin in advanced breast cancer

Treatment	Dose (mg/m^2)	No. of patients	Median cumulative dose in mg/m^2 (range)	Percentage of patients with						No. of patients		Ref.
				mucositis (grade 3-4)	PPE (grade 3-4)	neutropenia (grade 3-4)	anaemia (grade 3-4)	alopecia	CHF	CR	PR	
Cardiolipin/ phosphatidylcholine/ cholesterol/ stearylamine formulation	75 every 3 weeks 60 every 3 weeks	16 4	120 - 880	10 (mild stomatitis)				100.0[a]	5.0[b]	5	6	23
Caelyx®	45 every 3 weeks	26	179 (45-399)	19.2[c]	46.2	23.1		7[d]		4	16	30
	45 every 4 weeks	32		31.3[c]	15.6	25.0						
	60 every 3 weeks[e]	13		53.9[c]	53.9	38.5						
Myocet™ + cyclophosphamide + fluorouracil	60 every 3 weeks + 500 on day 1 every 3 weeks + 500 on days 1 and 8 every 3 weeks	41	528 (108-962)	15.0	0	95.0	26.8		2.4	2	28	48
Myocet™ + G-CSF	135 every 3 weeks	52	405 (135-1065)	40.4	0	98.0	48.1		13.5[f]	3	21	49
Doxil®	35 every 3 weeks	11	227.5 (70-665)	36.4[g]	72.3[h]		0	0		1	1	31
	45 every 3 weeks	5	220 (90-720)	20.0	40.0[h]		20.0	0			1	
	50 every 4 weeks	5	180 (100-365)	80.0	20.0[h]		40.0	20.0[i]				
	60 every 4 weeks	6	425 (60-1140)	83.3	33.3[h]		16.7	0			2	
	65 every 5 weeks	6	270 (65-455)	66.7	16.7[h]	16.7[i]	0	0				
	70 every 6 weeks	12	385 (70-770)	83.3	33.3[h]	16.7[i]	8.3	16.7[i]		1	3	
Doxil® + paclitaxel	45 every 4 weeks + 80 weekly	18	45-515[k]	33.3	50.0				0	2	7	46
Caelyx® + vinorelbine	40 every 4 weeks + 20 on days 1 and 8 every 4 weeks	22		18.2	13.6	18.2			0		4	47

a Usually complete.

b Prior 300 mg/m^2 antracycline treatment.

c Grade 3.

d Grade 1.

e Dose reduction to 45 mg/m^2 required.

f One death at accumulative dose of 1035 mg/m^2.

g Includes grade 2 toxicity data.

h Includes grade 2 PPE.

i Grade 1 or 2.

j Heavily pretreated with anthracycline.

k Reflects the total cumulative doxorubicin dose (conventional plus Doxil®).

CHF = congestive heart failure; **CR** = complete response; **G-CSF** = granulocyte colony-stimulating factor; **PPE** = palmar-plantar erythrodysaesthesia; **PR** = partial response.

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but that the increased cardiotoxicity needs to be addressed.

Several studies are currently being planned or are underway to assess whether there is any pharmacokinetic interaction between trastuzumab and doxorubicin that could explain the increased cardiac toxicity (see table IV). Clinical trials examining the combination of trastuzumab with a liposomal formulation of doxorubicin have also been initiated, and the results of such studies may provide additional clinical niches where the toxicity profiles of liposomal doxorubicin formulations may provide significant therapeutic benefits.

5.2 Ovarian Cancer

Ovarian cancer represents the leading cause of death from gynaecologic cancers in North America and Europe. This is largely because of the advanced stage of the disease with which many patients present. Currently, combined cisplatin and paclitaxel therapy is the standard care for these women, with the recent inclusion of liposomal doxorubicin for platinum- and paclitaxel-refractory disease.

Table V outlines a few studies with Doxil® in the treatment of refractory ovarian cancer. These studies were important in the approval of Doxil® for refractory ovarian cancer. A phase II trial reported in 1997[60] was initiated based on an 8-month partial response in an ovarian cancer patient with massive liver involvement in a phase I trial, and also to confirm activity noted in animal xenograft models of human ovarian cancer. This trial utilised Doxil® at a dose of 50 mg/m^2 every 3 weeks, which led to dose reductions and or delays in several patients, primarily due to stomatitis and PPE. Subsequent trials have either used a 4-weekly schedule,[61,62] or both a lower dose of 40 mg/m^2 and a 4-weekly schedule[63], in order to ameliorate these toxicities.

Having been granted US FDA approval as an agent for the treatment of platinum- and paclitaxel-refractory ovarian cancer, a further trial is investigating the use of Doxil® in combination with paclitaxel.[64] Early results from this trial indicate that the nonhaematological toxicities of Doxil® may be more pronounced, but that this toxicity is acceptable. An ongoing phase III trial is assessing activity of Doxil® in comparison with topotecan for the treatment of patients with relapsed ovarian cancer.[65] Preliminary results from this trial show favourable Doxil® activity, as compared with topotecan, thus increasing the arsenal of drugs available for this patient population.

6. Conclusions

There are several toxicities unique to liposomal formulations of doxorubicin. These toxicities vary according to the specific lipid composition of the liposomes, and the tissue distribution attained. For instance, the use of doxorubicin in pegylated liposomes (Doxil®/Caelyx®) is associated with a higher incidence of PPE than that of free doxorubicin. This specific toxicity is insignificant in the cardiolipin/phosphatidylcholine/cholesterol/stearylamine or Myocet™ liposomes.

Patients are more likely to develop PPE after multiple doses of liposomal doxorubicin (Doxil®), indicating that this condition arises as a result of

Table IV. Proposed/current trials to assess the combination of doxorubicin with other drugs including trastuzumab

Trial	Proposed by
Doxorubicin + cyclophosphamide, paclitaxel ± trastuzumab in HER-2/neu-positive patients	National Surgical Adjuvant Breast and Bowel Project (Protocol B-31)[57]
Doxorubicin + cyclophosphamide, weekly paclitaxel ± trastuzumab during paclitaxel ± trastuzumab following paclitaxel ± dexrazoxane during doxorubicin + cyclophosphamide	Cancer and Leukemia Group B (Protocol CLB-49808)[58]
Doxorubicin + cyclophosphamide, weekly paclitaxel OR trastuzumab during and after paclitaxel	North Central Cancer Treatment Group (Protocol NCCTG-N9831)[59]

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Table V. Phase II trial results for liposomal doxorubicin (Doxil)® in ovarian cancer

Dose (mg/m^2)	No. of patients	Median cumulative dose in mg/m^2 (range)	No. of patients with								
			mucositis/ stomatitis (grade 3-4)	PPE (grade 3-4)	neutropenia (grade 3-4)	anaemia (grade 3-4)	alopecia	cardiotoxicity	PR	CR	Ref.
50 every 3 weeks	35		5	10	7		0	0	8	1	60
50 every 4 weeks	89	150 (50-808)	5	18	14	12	8 (mild)	1	14	1	62
50 on day 1; cycle 2, 3 weeks later, then every 4 weeks	50[a]		5		19	7		0	3[b]	1[b]	61
40 every 4 weeks	49	80 (40-480)	0 (4 grade 2)	0	1		Minimal	1[c]	1		63

a Number for ovarian cancer patients only.

b Among 21 patients with evaluable disease.

c Greater than 10% decrease in baseline ejection fraction.

CR = complete response; **PPE** = palmar-plantar erythrodysaesthesia; **PR** = partial response.

cumulative skin damage when the concentration of liposomal drug is maintained over a certain threshold. Because the pegylated liposomes are very stable in plasma and retain drug for extended time periods following administration, it is likely that most of the administered dose will reach the tissues in an intact liposomal form. Based on results obtained in clinical trials, the incidence of PPE can be decreased by increasing the time interval between doses.[30-32,37] The alleviation of skin toxicity with longer periods between doses may be related to the keratinocyte turnover and epidermal transit time which is approximately 3 weeks. Therefore a break of 4 weeks between Doxil® administration would allow time for recovery, whereas at 3 weeks the skin may still be in a sensitive phase.

The pegylated liposomal doxorubicin formulation has also been associated with a higher degree of mucositis than has conventional doxorubicin. This is particularly true for stomatitis.[30-32,46-47] It is conceivable that a slow release of doxorubicin takes place in the intravascular compartment which mimics a protracted infusion of free doxorubicin.[30] The reasoning for this increased toxicity may be extrapolated from the reason given for increased skin toxicity; namely, that of increased accumulation of intact liposomal drug in sites with relatively high degrees of vascularity. The liposomes localised in these tissues can provide a depot for drug release. In general, pegylated liposomal doxorubicin increases mucous membrane and skin toxicities, however, these increases in toxicity are greatly offset by the reduction in cardiotoxicity afforded by this liposomal preparation. This formulation also provides a marked reduction in other toxicities including nausea, vomiting, myelosuppression and alopecia.

The Myocet™ formulation of egg phosphatidylcholine/cholesterol has a toxicity profile that is distinct from Doxil®. Most notable is the absence of PPE and a reduced incidence of mucositis in the form of stomatitis or pharyngitis. This formulation is comparable to free doxorubicin when toxicities are represented by the occurrence of alopecia and the marked level of neutropenia. Neutropenia, however, can be effectively managed through use of granulocyte colony-stimulating factor. At a dose of 60 mg/m^2 Myocet™ every 3 weeks, there was a reported 95% incidence of grade 3 or 4 neutropenia[48] versus only 38.5% in a trial with Doxil® at the same dose and schedule.[30] Despite this high level of dose-limiting myelosuppression, Myocet™

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does allow a higher total cumulative dose of doxorubicin than free doxorubicin without a concomitant increased risk of cardiomyopathy. In a recently reported trial comparing conventional doxorubicin to Myocet™ in the treatment of metastatic breast cancer, cardiotoxicity was lower in the liposomal arm and occurred after a lifetime dose of 785 mg/m^2 compared with 570 mg/m^2 for free doxorubicin.[51-52] This is important considering the use of Myocet™ does not require a change in administration schedules, as indicated with the use of Doxil®.

The reduction in cardiotoxicity demonstrated by both Doxil® and Myocet™, as determined by clinical evidence of cardiomyopathy (MUGA scans or biopsy), may be attributed to the ability of these liposomal drug formulations to target the drug away from sensitive cardiac muscle. Several trials of liposomal doxorubicin formulations have reported total cumulative doses of over 1000 mg/m^2 without any evidence of cardiotoxicity. It remains to be seen if the incidence of cardiotoxicity can be reduced even further with the addition of cardioprotective agents such as dexrazoxane to the chemotherapeutic regimens.

The results of the trials mentioned in this review, and many others, clearly indicate that the encapsulation of doxorubicin into liposomes is an active step in ameliorating the cardiotoxic effects of this anthracycline. Work is underway to study the liposomal doxorubicin formulations in currently accepted combination chemotherapy regimens in order to optimise scheduling and dose.

Liposomal doxorubicin formulations may, in the future, play an important role in those regimens which include paclitaxel or docetaxel. Several groups have reported high response rates with doxorubicin/paclitaxel combinations. Unfortunately, this is often accompanied with high rates of CHF due to pharmacokinetic interference of doxorubicin elimination by paclitaxel.[44,66] There is a strong likelihood that the use of liposomal doxorubicin formulations in combination with paclitaxel will be able to reduce this toxicity while maintaining the efficacy of the combination and allowing for higher cumulative doxorubicin doses.[66] Another interesting combination treatment with liposomal doxorubicin is with the monoclonal antibody, trastuzumab. A trial of Myocet™ in conjunction with this antibody for first-line treatment of metastatic or locally advanced breast cancer has been planned to evaluate the safety and efficacy of the combination, with specific focus on a reduction in the cardiotoxicity associated with the combination of conventional doxorubicin and trastuzumab.

As a final note, despite the reduced toxicities associated with the use of liposomal doxorubicin, clinical trials to date have not identified a clear survival advantage for these formulations over the use of free doxorubicin. Ultimately, the use of these liposomal drugs will rely on an improvement in the therapeutic index over that of the free drug as represented by reduced mortality. This will hopefully be achieved when using the liposomal drugs in appropriate combinations with other drugs as highlighted above.

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Correspondence and offprints: Dr *Dawn N. Waterhouse*, Department of Advanced Therapeutics, British Columbia Cancer Research Centre, 601 West 10th Avenue, Vancouver, British Columbia, Canada V5Z 1L3.
E-mail: dsaxon@bccancer.bc.ca

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