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Polyethylene Glycol-Liposomal Doxorubicin

A Review of its Use in the Management of Solid and Haematological Malignancies and AIDS-Related Kaposi's Sarcoma

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Data Selection

Sources: Medical literature published in any language since 1983 on pegylated-liposomal-doxorubicin, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International Limited). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'pegylated-liposomal-doxorubicin' or 'doxil' or 'dox SL'. EMBASE search terms were 'pegylated-liposomal-doxorubicin' or 'DOX-SL' or 'doxil'. AdisBase search terms were 'pegylated-liposomal-doxorubicin' or 'doxil' or 'dox-SL'. Searches were last updated 20 August 2002.

Selection: Studies in patients with ovarian cancer, breast cancer, multiple myeloma, non-Hodgkin's lymphoma or Kaposi's sarcoma who received polyethylene glycol-liposomal doxorubicin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Polyethylene glycol-liposomal doxorubicin, pegylated-liposomal doxorubicin, ovarian cancer, breast cancer, multiple myeloma, non-Hodgkin's lymphoma, Kaposi's sarcoma, pharmacodynamics, pharmacokinetics, therapeutic use, adverse events.

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Summary

Abstract

Polyethylene glycol (PEG)-liposomal doxorubicin is a formulation of the anthracycline doxorubicin in which the drug is encapsulated in PEG-coated liposomes. This alters the pharmacokinetic properties of doxorubicin, prolonging circulation time and enhancing localisation to tumours.

In a large randomised trial, intravenous PEG-liposomal doxorubicin was at least as effective as topotecan in patients with ovarian cancer refractory or sensitive to first-line platinum-based chemotherapy. Overall response rates of patients with ovarian cancer refractory to platinum- and paclitaxel-based chemotherapy who received the drug ranged from 18.3 to 27.6% in noncomparative clinical trials.

PEG-liposomal doxorubicin also has antitumour activity in patients with metastatic breast cancer pretreated with other chemotherapeutic agents. Overall response rates were similar in patients with pretreated metastatic breast cancer who had received PEG-liposomal doxorubicin or two comparator salvage chemotherapy regimens (vinorelbine or mitomycin C plus vinblastine) in an interim analysis of a large randomised study.

In patients with advanced AIDS-related Kaposi's sarcoma, PEG-liposomal doxorubicin monotherapy produced overall response rates ranging from 46 to 77% in randomised trials. The drug was significantly more effective than

bleomycin plus vincristine alone or in combination with standard doxorubicin, as measured by tumour response.

As a replacement for standard doxorubicin in commonly used combination therapies, PEG-liposomal doxorubicin has shown activity in multiple myeloma and aggressive non-Hodgkin's lymphoma in small, preliminary trials.

The most common adverse events associated with PEG-liposomal doxorubicin are myelosuppression, palmar-plantar erythrodysaesthesia, stomatitis and nausea. These can be managed by delaying or reducing dosages. Although preliminary trials are promising, the relative cardiotoxicity of PEG-liposomal doxorubicin compared with the standard formulation has not been clearly established.

Conclusions: Monotherapy with PEG-liposomal doxorubicin is effective as a second-line chemotherapy in patients with platinum-refractory ovarian cancer and in patients with metastatic breast cancer. However, as with all chemotherapeutic agents, the benefits of treatment need to be weighed against the agent's tolerability profile. Strong comparative data have helped to establish PEG-liposomal doxorubicin as the first-line treatment option in patients with advanced Kaposi's sarcoma. Anticancer activity has also been observed in studies conducted in small numbers of patients with multiple myeloma or non-Hodgkin's lymphoma receiving PEG-liposomal doxorubicin instead of standard doxorubicin in combination regimens, although further data are needed to confirm the clinical relevance of these findings.

Pharmacodynamic Properties

Polyethylene glycol (PEG)-liposomal doxorubicin consists of doxorubicin entrapped in PEG-coated liposomes. The antitumour activity of doxorubicin may arise mainly from interference with the topoisomerase II-DNA complex, resulting in fragmented DNA; other intracellular damage is caused by free radicals formed when the drug is metabolised. The latter mechanism is thought to be responsible not only for the antitumour activity of doxorubicin but also for adverse effects such as cardiotoxicity.

PEG-liposomal doxorubicin was more effective than standard doxorubicin against human ovarian carcinoma xenografts in mice. The liposomal formulation has also demonstrated activity *in vitro* against a range of different human tumour cell cultures including breast, ovarian and lymphoma tumour cell types. Higher concentrations of PEG-liposomal doxorubicin than standard doxorubicin were required to inhibit tumour cell proliferation for all cell lines. PEG-liposomal doxorubicin also strongly inhibits the *in vitro* growth of human Kaposi's sarcoma spindle cells and Kaposi's sarcoma lesions.

Pharmacokinetic Properties

PEG-liposomal doxorubicin has a different pharmacokinetic profile from that of standard doxorubicin, including a longer circulation time, slower clearance, smaller volume of distribution and a larger area under the plasma concentration-time curve (AUC). In addition, PEG-liposomal doxorubicin delivers 5.2 to 11.4 times more doxorubicin to Kaposi's sarcoma lesions than does the same dose of standard doxorubicin.

The plasma concentration profile of PEG-liposomal doxorubicin over a dose range of 10 to 20 mg/m^2 was reported to be linear, while an increase in dose to 50 mg/m^2 was associated with a nonlinear profile. After administration of PEG-liposomal doxorubicin 20 and 50 mg/m^2, the AUC for doxorubicin was 564 and 902 mg • h/L, respectively, and the peak plasma doxorubicin concentration was 8.6 or 10.1 and 21.2 mg/L, respectively.

Limited data suggest that PEG-liposomal doxorubicin preferentially accumulates in tumour tissue because it has a prolonged circulation time. Once trapped in the tumour tissue interstitial fluid, the liposomes are thought to slowly release doxorubicin which can then enter and damage tumour cells. After PEG-liposomal doxorubicin administration, doxorubicin concentrations were about 10 to 20 times higher in Kaposi's sarcoma lesions or bone metastases than in normal skin or tumour-free muscle, respectively.

Doxorubicin metabolites (e.g. doxorubicinol) were detected at low concentrations in urine, but were not detected or were detected in low concentrations in plasma after administration of PEG-liposomal doxorubicin. Clearance of single-dose PEG-liposomal doxorubicin 25 to 50 mg/m^2 administered intravenously was independent of dose. Bile is likely to be the major route of doxorubicin excretion after administration of PEG-liposomal doxorubicin, based on results from animal studies.

The effect of hepatic dysfunction on PEG-liposomal doxorubicin pharmacokinetics has not yet been established. However, one study found no significant differences in volume of distribution and plasma clearance between patients with hepatocellular carcinoma receiving single-dose PEG-liposomal doxorubicin 20 or 30 mg/m^2 intravenously and historical controls.

Clinical Efficacy

Ovarian cancer: In a large randomised study, PEG-liposomal doxorubicin 50 mg/m^2 once every 4 weeks was at least as effective as topotecan 1.5 mg/m^2 daily for 5 days every 3 weeks in 254 patients with ovarian cancer refractory to first-line platinum-based chemotherapy (overall response rates 12.3 *vs* 6.5%). The two treatments also produced similar rates of objective tumour response in 220 patients with disease sensitive to first-line platinum-based therapy (28.4 *vs* 28.8%) in the same study; however, patients receiving PEG-liposomal doxorubicin had significantly longer progression free- and overall survival times.

In subgroup analyses of noncomparative studies, PEG-liposomal doxorubicin 40 or 50 mg/m^2 every 3 to 5 weeks produced overall response rates of 8.3 to 36.4% in 21 to 82 patients with ovarian cancer refractory or resistant to platinum- and paclitaxel-based chemotherapy.

In small, noncomparative studies, the drug has also shown efficacy in combination with topotecan, ifosfamide or gemcitabine in patients with recurrent or persistent ovarian cancer following platinum-based (and sometimes paclitaxel-based) therapy, and in combination with paclitaxel and carboplatin in chemotherapy-naïve patients with advanced ovarian cancer.

Advanced breast cancer: PEG-liposomal doxorubicin has antitumour activity in patients with metastatic disease that has already been treated with other chemotherapeutic agents. Overall response rates were similar in patients with pretreated metastatic breast cancer receiving PEG-liposomal doxorubicin 50 mg/m^2 every 4 weeks or two comparator salvage chemotherapy regimens (vinorelbine or mitomycin C plus vinblastine) [13 *vs* 15%; no statistical comparison reported] in a randomised, large study (n = 301) published as an abstract. The combinations of PEG-liposomal doxorubicin and paclitaxel or vinorelbine in previously treated patients produced promising overall response rates of 48% and 18 to 36%, respectively, in small studies (n ≤ 35).

Of 71 patients 28.2% experienced responses with PEG-liposomal doxorubicin in a multicentre study (39% of patients in this study were pretreated with chemotherapy).

Kaposi's sarcoma: In randomised trials, PEG-liposomal doxorubicin monotherapy 20 mg/m^2 every 2 to 3 weeks produced overall response rates of 46 to 77% in 126 to 258 patients.

The drug was significantly more effective than the commonly used regimen of bleomycin plus vincristine and standard doxorubicin (ABV). In two studies, PEG-liposomal doxorubicin 20 mg/m^2 every 2 to 3 weeks also produced a greater response than bleomycin plus vincristine (BV). This response was only significantly greater in the larger of these studies. There was a trend towards longer mean duration of survival in patients receiving PEG-liposomal doxorubicin than those receiving BV (239 *vs* 160 days) and a similar median duration of survival to ABV (approximately 160 days).

Alone and in combination with BV (DBV), PEG-liposomal doxorubicin produced similar overall response rates in chemotherapy-naïve patients; an interim analysis of this study determined that significantly fewer patients had died while receiving PEG-liposomal doxorubicin than while receiving DBV (18 *vs* 28%).

PEG-liposomal doxorubicin also has advantages over ABV in terms of improvements in health-related quality of life, and over both ABV and BV in reducing disfiguring characteristics and pain of indicator lesions.

Haematological malignancies: Substituting PEG-liposomal doxorubicin for standard doxorubicin in a vincristine, standard doxorubicin plus dexamethasone (VAD) regimen produced enough activity in small numbers of elderly patients with multiple myeloma to justify further studies of this regimen.

When substituted for standard doxorubicin in the commonly used standard doxorubicin plus cyclophosphamide, vincristine and methylprednisolone (CHOP) regimen, PEG-liposomal doxorubicin produced responses in all eight of the elderly patients with aggressive non-Hodgkin's lymphoma receiving treatment. In other preliminary data, PEG-liposomal doxorubicin monotherapy produced overall response rates of 80 and 83% in patients with refractory non-Hodgkin's lymphoma.

Tolerability

Preliminary results from a trial in 509 patients with metastatic breast cancer found a significantly lower risk of cardiac adverse events in patients receiving PEG-liposomal doxorubicin compared with standard doxorubicin.

Of 66 patients with solid tumours from pooled tolerability data who had received a cumulative dosage of >400 mg/m^2 and had their left ventricular ejection fraction (LVEF) measured at baseline and follow-up, 12% experienced cardiotoxicity in the form of a decrease in LVEF of ≥20% from baseline or a change to <45%. Cardiotoxicity was also experienced by 1.4 to 3.4% of 45 to 132 patients with ovarian or breast cancer who received cumulative doses of PEG-liposomal doxorubicin ranging from 45 to 1301 mg/m^2. 1.7 to 4.3% of patients with Kaposi's sarcoma who received PEG-liposomal doxorubicin 20 mg/m^2 every 2 or 3 weeks experienced cardiac-related adverse events thought to be possibly or probably related to PEG-liposomal doxorubicin. Significantly fewer cardiac histopathological changes were observed with a mean cumulative PEG-liposomal doxorubicin dose of 623 mg/m^2 than in a historical patient group matched for cumulative dose who received standard doxorubicin.

The most common adverse events (grade I to IV severity) associated with PEG-liposomal doxorubicin as monotherapy in 512 patients with ovarian cancer were palmar-planter erythrodysaesthesia (PPE) [46.1%], stomatitis (38.9%) and nausea (38.1%) in pooled data. Reported haematological events included leuco-

penia (33.2%), anaemia (32.2%), neutropenia (31.6%), and thrombocytopenia (10.7%).

Haematological adverse events and alopecia were significantly less likely to occur with PEG-liposomal doxorubicin than with topotecan in patients with relapsed ovarian cancer in a randomised trial; however, PPE and stomatitis were significantly more common with PEG-liposomal doxorubicin than with topotecan.

The tolerability profile of PEG-liposomal doxorubicin in patients with Kaposi's sarcoma differs from that in patients with solid tumours, possibly because of differences in dosages and concomitant therapies.

Myelosuppression is the dose-limiting adverse event experienced by patients with Kaposi's sarcoma receiving PEG-liposomal doxorubicin; myelosuppression occurred in about 50% of patients in pooled tolerability data. Leucopenia was the most frequent event; neutropenia, thrombocytopenia and anaemia were also common.

PEG-liposomal doxorubicin appears to have similar overall incidences of adverse events as BV and ABV. However, PEG-liposomal doxorubicin was associated with less constipation and paraesthesia than BV and less nausea and/or vomiting, alopecia and peripheral neuropathy than ABV, but more leucopenia and opportunistic infections than BV and more mucositis and/or stomatitis than ABV.

Dosage and Administration

In the US, PEG-liposomal doxorubicin is indicated for the treatment of metastatic ovarian carcinoma that has progressed during paclitaxel- and platinum-based chemotherapy regimens or within 6 months of completing these treatments, and for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed during prior combination therapy, or in patients intolerant to such therapy. In Europe, the drug is indicated for the treatment of advanced ovarian cancer that has failed platinum-based chemotherapy regimens and the treatment of AIDS-related Kaposi's sarcoma as either first- or second-line therapy. However, in these countries the drug is not to be used in the treatment of Kaposi's sarcoma that may be treated effectively with local therapy or systemic interferon-α. PEG-liposomal doxorubicin has not yet been approved for the treatment of metastatic breast cancer, multiple myeloma or non-Hodgkin's lymphoma.

The recommended dosage of PEG-liposomal doxorubicin in patients with ovarian cancer is 50 mg/m^2 administered intravenously once every 4 weeks. The drug should be administered by infusion at an initial rate of 1 mg/min, which can be increased if no infusion-related adverse events occur so that administration is completed in 1 hour. PEG-liposomal doxorubicin 20 mg/m^2 as a 30-minute intravenous infusion once every 2 to 3 weeks is recommended for patients with Kaposi's sarcoma. In both cancer types, treatment should continue for as long as patients respond satisfactorily and can tolerate therapy.

A delay or reduction of dosage is recommended if patients develop adverse events such as PPE, haematological adverse events or stomatitis. Precautions taken to avoid cardiotoxicity when administering standard doxorubicin should also be followed with PEG-liposomal doxorubicin. The cardiac function of patients receiving PEG-liposomal doxorubicin should be carefully monitored.

1. Liposomal Delivery of Doxorubicin

Doxorubicin, one of the first identified anthracyclines, is a cytotoxic antibiotic with an established place in the treatment of breast cancer and proven efficacy in other tumour types including lung, stomach, ovary and thyroid, and sarcomas of osteogenic and soft tissues.[1-4] However, the use of doxorubicin, as for other anthracyclines such as epirubicin and daunorubicin, is limited by adverse events associated with the drug. Notably, it can cause the development of a cumulative, dose-related, diffuse cardiomyopathy which can lead to congestive heart failure.[4-7] By improving the delivery of doxorubicin to tumour tissues, for example by encapsulating the drug in liposomes, it may be possible to retain or improve the efficacy of doxorubicin treatment while minimising toxicity problems.

Early liposomal formulations of doxorubicin tended to leak drug while circulating. Additionally, they were cleared rapidly from the bloodstream by the reticuloendothelial system (RES) which recognises plasma proteins (opsonins) that attach to liposomes.[8] Since then, variations on the liposomal formulation of doxorubicin have been produced in an attempt to improve on the limitations of early products. One such formulation, polyethylene glycol (PEG)-liposomal doxorubicin (Doxil®, Caelyx®**1**), the focus of this review, consists of doxorubicin entrapped as a precipitate in the aqueous interior of PEG-coated liposomes (figure 1).[9] PEG molecules are thought to 'sterically stabilise' liposomes by reducing the attachment of plasma proteins and lipoproteins, thereby reducing their clearance from the bloodstream by the RES and prolonging liposomal circulation.[9,10]

The use of PEG-liposomal doxorubicin in the management of AIDS-related Kaposi's sarcoma has been previously reviewed in *Drugs*.[1] This review updates the previous one and also looks at the use of this formulation in the management of patients with solid tumours of the ovary or breast, and haematological malignancies, specifically multiple myeloma and non-Hodgkin's lymphoma.

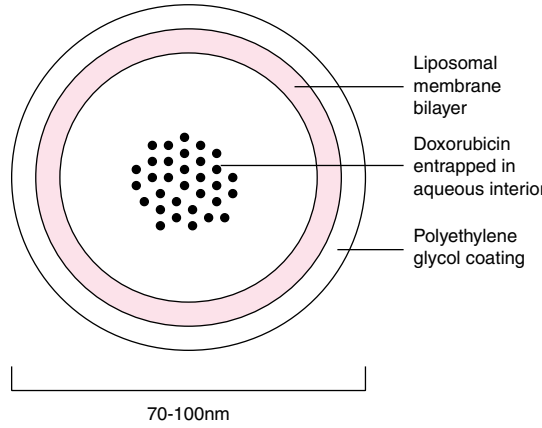

Fig. 1. Schematic representation of a polyethylene glycol-coated doxorubicin-containing liposome. The liposomes are microscopic vesicles composed of a lipid bilayer made up of hydrogenated soy phosphatidylcholine, cholesterol and polyethylene glycol diasteroyl phosphatidylethanolamine combined in an approximate molar ratio of 55:40:5.[1]

2. Pharmacodynamic Properties

This section briefly summarises the pharmacodynamics of PEG-liposomal doxorubicin in human tissues. The pharmacodynamics of the standard formulation of doxorubicin are not presented here, but are comprehensively reviewed elsewhere.[2,3]

2.1 Mechanism of Action

The main mechanism of action of doxorubicin is thought to be intercalation of the doxorubicin aglycone group between adjacent DNA base pairs. This action deforms the DNA so that the double-stranded DNA breakages, created by topoisomerase II to relax DNA supercoils, are not resealed. The resulting DNA fragmentation leads to cell death.[1,3,11-13] *In vitro*, free doxorubicin has a strong inhibitory effect on DNA synthesis in human lung carcinoma cells [50% inhibitory concentration (IC_{50}) of 0.04 μmol/L], whereas PEG-liposomal doxorubicin inhibits DNA synthesis in

1 Use of tradenames is for product identification only and does not imply endorsement.

these cells to a lesser extent (IC_{50} of about 3.0 μmol/L).[14]

Doxorubicin is also thought to indirectly cause intracellular damage when it is metabolised. During metabolism of doxorubicin, free radicals are formed which can cause damage to various intracellular components, including mitochondrial, cellular and nuclear membranes, sarcoplasmic reticulum and DNA.[6] This mechanism may be responsible not only for the antitumour activity of doxorubicin but also for associated adverse effects such as cardiotoxicity (section 5.1).[5-7]

PEG-liposomal doxorubicin induced the expression of monocyte chemoattractant protein-1 in Kaposi's sarcoma cell cultures.[15] The movement of increased numbers of phagocytic cells into Kaposi's sarcoma lesions may also contribute to the antitumour activity of the drug.[15]

2.2 Antitumour Activity

PEG-liposomal doxorubicin has demonstrated activity against human xenografts in mice,[16] human tumour cell cultures *in vitro*,[17,18] and Kaposi's sarcoma lesions in humans.[15] Antitumour activity has also been widely observed in rodent tumour models,[19-25] but these are not reviewed here.

2.2.1 Solid and Haematological Malignancies

PEG-liposomal doxorubicin has antitumour activity both in human ovarian carcinoma xenografts in mice and in human breast, ovarian, lymphoma and multiple myeloma tumour cell lines *in vitro*.

The incidence of human ovarian carcinoma xenografts present 42 days after being implanted subcutaneously in mice was significantly ($p < 0.05$) lower in animals treated with intravenous PEG-liposomal doxorubicin 6 or 9 mg/kg (17 and 15%) than with the standard formulation of doxorubicin 6 or 9 mg/kg (60 and 65%) or placebo saline solution placebo (56%).[16] After a 70-day observation period, all ten mice with intraperitoneal human ovarian carcinoma xenografts receiving PEG-liposomal doxorubicin were free of tumours, whereas eight of ten mice receiving placebo had tumours. Six of ten mice receiving standard doxorubicin died with bloody peritoneal exudate before day 26; however, by day 70, none of the four remaining mice receiving standard doxorubicin had developed tumours.

Two *in vitro* studies demonstrated that PEG-liposomal doxorubicin has cytotoxic activity in a range of different human tumour types including breast, ovarian, lymphoma[17] and multiple myeloma cell lines.[18] However, higher concentrations of PEG-liposomal doxorubicin than standard free doxorubicin were required to inhibit tumour cell proliferation for all the cell lines examined (499 to 28 500 μg/L *vs* 7.9×10^{-4} to 102.3 μg/L, respectively; $p < 0.001$,[17] statistical significance not reported in one study[18]).

2.2.2 AIDS-Related Kaposi's Sarcoma

PEG-liposomal doxorubicin 0.01 to 1 mg/L strongly inhibited the *in vitro* growth of Kaposi's sarcoma spindle cells and fibroblasts derived from patients with AIDS, compared with drug-free control cultures.[15] Similarly, histological examination of biopsies of AIDS-related Kaposi's sarcoma lesions from eight patients that had regressed with six cycles of intravenous PEG-liposomal doxorubicin 20 mg/m^2 once every 3 weeks revealed an absence of Kaposi's sarcoma spindle cells from the upper and lower epidermal layers compared with biopsies of lesions before treatment.[15]

3. Pharmacokinetic Properties

This overview of the pharmacokinetic properties of PEG-liposomal doxorubicin draws upon previous reviews published in *Drugs*,[1,8] and also incorporates relevant information provided by more recent studies.[26-34] One pharmacokinetic study of PEG-liposomal doxorubicin has been performed in patients with hepatic dysfunction.[35] No pharmacokinetic data are available in patients with renal impairment [creatinine clearance of <1.8 L/h (<30 ml/min)], and the manufacturer does not recommend a dose modification for PEG-liposomal doxorubicin in this patient group (section 6).[36]

Table I summarises the results of pharmacokinetic investigations of PEG-liposomal doxorubicin administered intravenously in patients with solid

Table I. Pharmacokinetic properties of single-dose polyethylene glycol-liposomal doxorubicin administered as an intravenous infusion in 16 patients with solid tumours[a][37] or 18 to 42 patients with AIDS-related Kaposi's sarcoma.[32,38] Values relate to total plasma doxorubicin

Parameter (unit)	Dose (mg/m^2)	Value(s)[b]	Reference
C_{max} (mg/L)	20	8.6, 10.1	32,38
	50	21.2	37
$C_{KS[72]}$ (μg/g)	20	1.6	38
AUC_∞ (mg • h/L)	20	564	32
	50	902	37
V_{ss}	20	2.9 L/m^2	32
	50	5.9 L	37
V_c (L/m^2)	20	2.3	32
V_p (L/m^2)	10-40	1.1	38
CL	20	0.058 $L/h/m^2$	32
	50	0.09 L/h	37
$t_{½1}$ (h)	20	4.5	32
	50	1.4	37
$t_{½2}$ (h)	20	53.3	32
	50	45.9	37

a Tumours include breast cancer (n = 6), non-small cell lung cancer (n = 3), ovarian cancer (n = 3), mesothelioma (n = 2), soft-tissue sarcoma (n = 1) and pancreatic cancer (n = 1).

b Mean values were reported in one study,[37] otherwise median values were reported.[32,38]

AUC_∞ = area under the plasma concentration-time curve from time zero to infinity; **$C_{KS[72]}$** = concentration in Kaposi's sarcoma lesions 72 hours after administration; **CL** = total body clearance from plasma; **C_{max}** = peak plasma concentration; **$t_{½1}$** = first-phase half-life; **$t_{½2}$** = second-phase half-life; **V_c** = apparent volume of the central compartment; **V_p** = apparent volume of the peripheral compartment; **V_{ss}** = apparent volume of distribution at steady state.

tumours (including breast and ovarian) or Kaposi's sarcoma. No data are available on the pharmacokinetic profile of PEG-liposomal doxorubicin in patients with haematological malignancies. Plasma concentrations reported in this section relate to total doxorubicin concentrations rather than those of free or liposomal encapsulated drug, unless otherwise stated.

3.1 Compared with Standard Formulation of Doxorubicin

The pharmacokinetic profile of PEG-liposomal doxorubicin is substantially different from that of standard free doxorubicin (reviewed by Gabizon and Martin[8] and Coukell and Spencer[1]).

After administration of PEG-liposomal doxorubicin 25 or 50 mg/m^2, plasma concentrations of liposome-encapsulated doxorubicin were nearly identical to concentrations of total doxorubicin over a period of 168 hours.[37] This suggests that very little doxorubicin circulates as free drug and most of the drug stays encapsulated in liposomes while in plasma.

PEG-liposomal doxorubicin 50 mg/m^2 has a slower total body clearance from plasma than standard free doxorubicin administered at the same dose (0.09 *vs* 25.3 L/h).[37] In addition, less PEG-liposomal than standard doxorubicin is cleared by the kidney (mean fraction of dose recovered in urine within 24 hours of injection: 2.5 *vs* 11%).[37] The size of the liposomes (70 to 100nm in diameter[1]) is thought to prevent the drug from being filtered by the glomeruli as readily as standard free doxorubicin,[39] since glomeruli prevent filtration of all particles with an average size greater than 16nm.[40] This may also explain why PEG-liposomal doxorubicin 50 mg/m^2 has a longer circulation time [second-phase half-life ($t_{½2}$) of 45.9 *vs* 10.4 hours] and a larger area under the plasma concentration versus time curve (AUC_∞) than the standard formulation (902 *vs* 3.5 mg • h/L).[37]

Liposomes are restricted mainly to the intravascular space, therefore, the PEG-liposomal doxorubicin has a smaller apparent volume of distribution at steady state than the standard formulation (4.1 *vs* 25.4L).[37] The higher volume of distribution of standard free doxorubicin means that it is widely distributed through all tissues of the body.[41]

These properties and the irregular and incomplete nature of blood vessels in tumours[42] (which makes them more permeable than those in normal tissues) allow PEG-liposomal doxorubicin to accumulate preferentially in tumour tissue (section 3.2.2). Doxorubicin concentrations in Kaposi's sarcoma lesions are 5.2 to 11.4 times greater after PEG-liposomal doxorubicin than after the same dose of standard free doxorubicin when measured 72 hours after administration.[38] No direct comparisons of the distribution of standard free and

PEG-liposomal doxorubicin in other tissues are currently available.

3.2 Overview of Pharmacokinetic Properties

3.2.1 Plasma Concentrations

The pharmacokinetics of PEG-liposomal doxorubicin over a dose range of 10 to 20 mg/m^2 were reported to be linear,[32,38] while an increase of dose to 50 mg/m^2 was associated with nonlinear pharmacokinetics.[43] The AUC_∞ for the 20 and 50 mg/m^2 doses was 564 and 902 mg • h/L, and the peak plasma doxorubicin concentration (C_{max}) was 8.6 or 10.1 and 21.2 mg/L, respectively.[32,37,38] One study reported mean values;[37] the others reported median values[32,38] (table I).

PEG-coated liposomes have a prolonged plasma circulation time compared with conventional liposomes (without PEG) because they are not taken up as readily by the RES. In one study, 16 to 22% of intravenous radiolabelled PEG-coated liposomes (without doxorubicin) were taken up by the RES in ten patients with solid tumours,[44] whereas about 70% of conventional radiolabelled liposomes were taken up by the RES.[45]

3.2.2 Distribution

After a single dose of PEG-liposomal doxorubicin, the first phase of distribution half-life ($t_{½1}$) [from plasma into the tissue] of doxorubicin was short (median 4.5[32] and mean 1.4[37] hours with 20 and 50 mg/m^2 doses, respectively) [table I]. The $t_{½}$ of the following phase of distribution ($t_{½2}$) of doxorubicin after administration of PEG-liposomal doxorubicin was longer (median 53.3[32] and mean 45.9[37] hours with 20 and 50 mg/m^2, respectively; table I). Clearance of PEG-liposomal doxorubicin from plasma was independent of dose within the dose range of 25 to 50 mg/m^2.[37]

Preliminary data suggest that PEG-liposomal doxorubicin preferentially localises in tumour tissues (section 3.1). Ten to 20 times higher doxorubicin concentrations were measured in Kaposi's sarcoma lesions than in normal skin 48 to 96 hours after administration of a single dose of PEG-liposomal doxorubicin 20 mg/m^2 in 24 patients with AIDS-related Kaposi's sarcoma (figure 2).[46] Similarly, in two patients with metastatic breast cancer who received PEG-liposomal doxorubicin 35 or 50 mg/m^2, the concentration of doxorubicin in bone metastases was about ten times greater than in tumour-free muscle in both patients (tissue samples were taken 6 or 12 days after drug administration).[29] PEG-liposomal doxorubicin has also been found to localise in brain tumour tissue in a patient with a primitive cerebral neuro-ectodermal tumour who received PEG-liposomal doxorubicin 40 and 50 mg/m^2 3 weeks apart.[30]

Once delivered to the tumour tissue interstitial fluid, the liposomes are thought to leak doxorubicin slowly, probably through the continued leakage of doxorubicin from intact liposomes and possibly as a result of catabolism by enzymes such as phospholipases or engulfment or destruction by tissue macrophages.[47,48] The free doxorubicin can subsequently diffuse into tumour cells.[47] Several *in vitro* experiments support this idea. When PEG-liposomal doxorubicin was incubated in physiological buffer, slow drug leakage occurred over 24 hours.[14] Fluorescent micrographs from two patients with metastatic breast cancer showed that doxorubicin from the liposomal formulation loc-

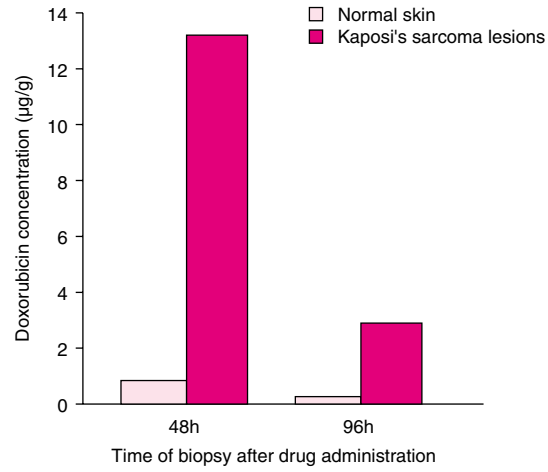

Fig. 2. Doxorubicin concentrations in normal skin and Kaposi's sarcoma lesions from 24 patients with AIDS-related Kaposi's sarcoma who received a single dose of intravenous polyethylene glycol-liposomal doxorubicin 20 mg/m^2.[46]

alised in the nuclei of tumour cells,[29] whereas gold-labelled PEG-coated liposomes were found in the interstitial space, but not in the tumour cell cytoplasm of tumour tissue in implanted murine colon carcinoma.[49] After human lung carcinoma cells were incubated with PEG-liposomal doxorubicin, doxorubicin was mainly detected in the nuclei of the cells, and was also associated with mitochondria.[14]

The extent to which PEG-liposomal doxorubicin binds to plasma proteins has not yet been determined, although the plasma protein binding of standard doxorubicin is about 70%.[43]

3.2.3 Metabolism and Elimination

Limited data is available regarding the metabolism and elimination of PEG-liposomal doxorubicin; however, it appears that it is partially metabolised, with bile being the major route of doxorubicin excretion and urine the major route of liposome excretion.[31,37,48]

No doxorubicin metabolites were detected in plasma after administration of PEG-liposomal doxorubicin 10 to 50 mg/m^2 in patients,[37,38] and in another study, doxorubicinol (the major metabolite of doxorubicin) was detected at very low concentrations in plasma (≤0.026 mg/L) after administration of PEG-liposomal doxorubicin 10 or 20 mg/m^2.[32] Doxorubicin metabolites were detected in small quantities in urine after administration of PEG-liposomal doxorubicin 50 mg/m^2.[37]

A terminal elimination phase (from tissue into plasma) was not detected, possibly because the high concentrations of liposomal-associated drug may have masked low plasma concentrations of free doxorubicin during terminal clearance.[37]

Animal studies have shown that some doxorubicin is excreted in urine, but bile is the major route of doxorubicin excretion after PEG-liposomal doxorubicin administration.[48] The major metabolite of doxorubicin, doxorubicinol, was present in urine, plasma and bile after administration of PEG-liposomal doxorubicin. Doxorubicinol concentrations were approximately 0.5% of PEG-liposomal doxorubicin concentrations and kinetics of the metabolite paralleled those of PEG-liposomal doxorubicin in these animal studies.[48]

After administration of radiolabelled PEG-liposomes containing diethylenetriaminepentacetic acid, 4 to 28% of the injected radioactivity associated with the liposomes was excreted in the urine within 96 hours of administration to patients with solid tumours (n = 17).[31] However, since whole liposomes are too large to be excreted in urine, the liposomes are metabolised before excretion. The lipid components of the liposomes are ubiquitous dietary lipids, administered at a fraction of the normal concentrations in the body and are probably metabolised by standard metabolic pathways; the PEG component of the liposomes is thought to be excreted unchanged.[48]

3.3 Special Patient Groups

3.3.1 In Patients with Hepatic Dysfunction

One small study suggests that the pharmacokinetics of PEG-liposomal doxorubicin are unchanged in patients with hepatic dysfunction. The pharmacokinetics of a single intravenous dose of PEG-liposomal doxorubicin 20 or 30 mg/m^2 in ten patients with hepatocellular carcinoma, hepatic dysfunction and elevated serum bilirubin concentrations (0.7 to 40 mg/L) were compared with those of PEG-liposomal doxorubicin (dosage not reported) in 41 historical control patients with normal serum bilirubin concentrations.[35] Only values from patients with hepatic dysfunction were reported. No significant differences in median steady-state volume of distribution (3.31 L/m^2), total plasma clearance (0.046 L/h/m^2), $t_{½1}$ (3.29 hours) or $t_{½2}$ (49.7 hours) were observed (p values not reported). However, in the absence of more conclusive evidence, the dosage of PEG-liposomal doxorubicin should be reduced in patients with elevated serum bilirubin concentrations as for standard doxorubicin (section 6).[43]

3.3.2 Patients Receiving Other Antineoplastic Agents

In two small studies, the clearance of PEG-liposomal doxorubicin was found to be higher when administered in combination with other antineo-

plastic agents than when administered alone.[33,34] When compared with the results of a single-agent PEG-liposomal doxorubicin study, a 40% higher clearance was observed when PEG-liposomal doxorubicin 40 mg/m^2 (day 1) in combination with vincristine 1.4 mg/m^2 (day 1) and dexamethasone 40mg (days 1 to 4 and 15 to 18) were administered to some of 19 patients with multiple myeloma (exact number of patients and routes of administration not reported).[34] In the second study,[33] PEG-liposomal doxorubicin 25 mg/m^2 (day 1) plus cyclophosphamide 2000 mg/m^2 intravenously (days 1 and 2), vinorelbine 30 mg/m^2 intravenously (day 1) and prednisone 100mg orally (days 1 to 5) were administered to five patients with non-Hodgkin's lymphoma. The clearance of PEG-liposomal doxorubicin was approximately 5.5 times greater than when administered as monotherapy (0.44[33] *vs* 0.08 L/h[37]). Pharmacokinetic values in this study were calculated by use of a noncompartment model for continuous infusion.[33]

4. Clinical Efficacy

This section reviews the efficacy of PEG-liposomal doxorubicin in ovarian cancer and breast cancer in randomised and noncomparative studies, and updates the previous review of PEG-liposomal doxorubicin in the management of AIDS-related Kaposi's sarcoma published in *Drugs*.[1] Preliminary evidence of the efficacy of the drug in multiple myeloma and non-Hodgkin's lymphoma is also reviewed. A number of trials presented in this section are small and published as abstracts; thus, some details on the methodology of these studies are lacking. PEG-liposomal doxorubicin and other drugs used in the trials reported here were administered by intravenous infusion as a single dose during each treatment cycle unless otherwise stated. AIDS-related Kaposi's sarcoma is referred to as Kaposi's sarcoma in this review.

The efficacy of PEG-liposomal doxorubicin has also been investigated in a number of indications not discussed in this review. These include head and neck cancer,[50-53] hepatocellular cancer,[54] prostate cancer,[55,56] soft-tissue sarcoma,[57] glioma[58,59] and mesothelioma.[60,61]

4.1 Ovarian Cancer

Ovarian cancer is one of the most common gynaecological cancers and, of these, has the highest incidence of mortality, in part because ovarian cancer is often not detected until at an advanced stage.[62,63]

PEG-liposomal doxorubicin has been evaluated as monotherapy or as part of combination therapy in women with recurrent epithelial ovarian cancer (aged 25 to 87 years). All but one trial[64] reviewed here were noncomparative. One study was conducted in previously untreated patients (aged 27 to 64 years) with advanced ovarian cancer.[65]

Tumour response was assessed by use of Southwest Oncology Group (SWOG) standard response criteria[66] in five studies.[64,67-70] One study measured changes in plasma cancer antigen (CA)-125 levels (Rustin criteria[71]) and two studies combined adaptations of SWOG and Rustin criteria.[72,73] Health-related quality of life was assessed in one trial by use of the European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QOL) questionnaire.[64] One study is available as an abstract and did not define response criteria.[74]

4.1.1 In Previously Treated Patients

Monotherapy

A variety of definitions have been used to describe the response of ovarian cancer to previous chemotherapy treatments in clinical trials; however, it is generally defined as refractory (no response), resistant (progressing 0 to 6 months after treatment) or sensitive (relapsing or progressing after a treatment-free interval of >6 months).[75]

PEG-liposomal doxorubicin was at least as effective as topotecan in the treatment of patients with ovarian cancer that was refractory (defined in this study as progression during treatment, stable disease or relapse within 6 months after treatment) or sensitive to first-line platinum-based chemotherapy in a randomised, nonblind multicentre

trial.[64] The overall response rates with PEG-liposomal doxorubicin 50 mg/m^2 every 4 weeks and topotecan 1.5 mg/m^2 daily for 5 days every 3 weeks did not differ significantly in 254 patients with disease refractory to first-line platinum-based therapy (12.3 *vs* 6.5%, respectively) [table II].[64] The median progression-free and overall survival times (primary endpoints) also did not differ significantly between treatments (9.1 *vs* 13.6 weeks and 35.6 *vs* 41.3 weeks).[64]

In 220 patients with disease sensitive to first-line platinum-based therapy, PEG-liposomal doxorubicin and topotecan produced similar overall response rates (28.4 *vs* 28.8%) [table II]; however, median progression-free and overall survival times were significantly longer with PEG-liposomal doxorubicin [28.9 *vs* 23.3 weeks (p = 0.037) and 108 *vs* 71.1 weeks (p = 0.008), respectively]. No significant differences between treatment groups were found 12 weeks after study entry in the scores of any domains in the EORTC-QOL questionnaire.[64] At the time of analysis, 103 PEG-liposomal doxorubicin recipients and 86 topotecan recipients were still alive.

Similar results were seen in noncomparative studies (including two retrospective studies[70,72]); PEG-liposomal doxorubicin 40 or 50 mg/m^2 every 3 to 5 weeks produced overall response rates of 8.3 to 28.5% in trials in 28 to 82 previously-treated patients with ovarian cancer (table III).[67-70,72-74]

In subgroup analyses of these trials, patients with disease refractory or resistant to previous platinum therapy (n = 21 to 82)[68-70,72,73] had an 8.3 to 36.4% overall response to therapy with PEG-liposomal doxorubicin. Patients who were sensitive to previous treatment with platinum-based therapy were not included in most trials; however, in one study it was observed that 19 patients who were sensitive to treatment with platinum-based therapy had a greater response to treatment with PEG-liposomal doxorubicin than platinum-resistant or -refractory patients (36.8 *vs* 27.2%).[68] Despite this, the probability of treatment failure or survival at 1 year was not significantly different between groups.[68]

The median overall survival time in noncomparative studies was ≥8 to 15 months, with a median duration of progression-free survival of 3 to 5.7 months and a median duration of response of 3.5 to 13.2 months.[67-70,72-74]

Combination Therapy

PEG-liposomal doxorubicin in combination with topotecan, ifosfamide or gemcitabine had antineoplastic activity in patients with recurrent or persistent ovarian cancer following platinum-based (and sometimes paclitaxel-based) therapy in a number of small, noncomparative trials presented as abstracts. Only two studies specified when disease had progressed in relation to pre-

Table II. Randomised, nonblind, multicentre comparison of polyethylene glycol-liposomal doxorubicin (LD) and topotecan (TP) as monotherapy in previously treated patients with ovarian cancer that had recurred or failed first-line, platinum (PT)-based therapy.[64] Drugs were administered intravenously

Dosage regimen (mg/m^2) [mean no. of cycles]	Responsiveness to first-line, PT-based therapy (no. of intent-to-treat patients)	Response rate (% of patients)				Median progression-free survival (wk)	Median overall survival (wk)
		OR	CR	PR	SD		
LD 50 once every 4wk [4.9]	refractory[a] (130)	12.3	0.8	11.5	27.7	9.1	35.6
	sensitive[b] (109)	28.4	7.3	21.1	37.6	28.9*	108.0*
TP 1.5/d × 5 every 3wk [5.7]	refractory[a] (124)	6.5	0.8	5.6	42.7	13.6	41.3
	sensitive[b] (111)	28.8	9.0	19.8	37.8	23.3	71.1

a The disease was considered to be PT-refractory if it progressed during or stabilised or relapsed within 6mo after completing initial PT-based therapy.

b The disease was considered to be PT-sensitive if patients experienced a progression-free survival interval of >6mo after completing first-line PT-based chemotherapy.

CR = complete response; **OR** = overall response (CR + PR); **PR** = partial response; **SD** = stable disease; * p < 0.04 *vs* TP.

Table III. Noncomparative trials of polyethylene glycol-liposomal doxorubicin (LD) monotherapy in previously treated patients with recurrent ovarian cancer (n ≥28). Drugs were administered intravenously once during each cycle unless otherwise indicated and the response rate was calculated using the number of patients enrolled as the denominator

Reference (no. of previous chemotherapy regimens)	No. of evaluable patients (no. enrolled)	LD dosage regimen (mg/m^2) [no. of cycles]	Response rate (% of patients)					Median PFS (mo)	Median OS (mo)
			OR	CR	PR	SD	PD		
Arcuri et al.[74]a (NR)	28 (28)	50 every 4wk [range 1-6, median 3.5]	28.5	7.1	21.4	39.2	32	3	8.5+
Campos et al.[72]b (2-9)	71 (72)	40 every 4wk [range 1-12]	26.4[c]	4.2[c]	22.2[c]	16.7	54.2	5.3	13.9
Gordon et al.[69] (1-3)	89 (90)	50 every 4wk [mean 4.4]	16.7	1.1	15.6	40.0	21.1	4.8	NR
Israel et al.[73] (1-6)	21 (48[d])	50 every 3-4wk [NR]	8.3	2.1	6.3	NR	NR	3	10
Muggia et al.[67] (1-4)	35 (35)	40-50 every 3-5wk [NR]	25.7	2.9	22.9	NR	NR	5.7	11
Rose et al.[70]b (1-7)	76 (78[e])	40 or 50 every 4wk [NR]	9.0	2.6	6.4	47.4	41.0	4	8+
Safra et al.[68] (1-9)	48 (52[f])	40-60 every 3-4wk [range 1-26]	30.8[g]	3.8	26.9[g]	42.3	26.9	5.2[h]	15

a Available as an abstract.

b Retrospective analysis.

c Complete response in this study included a reduction in CA-125 levels of <35 U/ml for ≥30 days and partial response included a reduction in CA-125 levels of >50%.

d 21 patients had measurable disease and 27 had evaluable disease on CT scan and elevated serum CA-125.

e In this study, 65 patients had ovarian cancer, 11 had peritoneal cancer and 2 had tubal cancer.

f Patients from three trials.

g Includes four patients (7.7%) who experienced a CA-125 PR (defined as a reduction of ≥50% in CA-125 level with no greater than a 10% change in subsequent consecutive measures for at least 4 weeks).

h Time to treatment failure.

CA = plasma cancer antigen; **CR** = complete response; **NR** = not reported; **OR** = overall response (CR + PR); **OS** = overall survival; **PD** = progressive disease; **PFS** = progression-free survival; **PR** = partial response; **SD** = stable disease.

vious therapy (within 6[76] or 12 months[77] of previous treatment completion).

In three trials involving 10 to 21 patients, PEG-liposomal doxorubicin in combination with topotecan produced overall response rates of 19 to 35%.[76-78] In two studies, overall responses lasted for up to 11 or >26 months (median number of four cycles administered to each patient).[77,78] During each 3- or 4-week cycle, PEG-liposomal doxorubicin 25 to 40 mg/m^2 was administered once with intravenous topotecan 0.5 to 1 mg/m^2/day for 5 days[76,77] or 0.3 to 0.4 mg/m^2/day for 14 to 21 days[78] or oral topotecan 0.4 mg/m^2 twice daily for 14 days.[78]

A combination of PEG-liposomal doxorubicin 25 to 40 mg/m^2 on day 1 and ifosfamide 1700 mg/m^2/day on days 1 to 3 every 4 weeks produced a response in 5 of 14 patients.[79] The definition of response in this study included a reduction in plasma CA-125 levels of ≥50% (Rustin criteria[71]).

PEG-liposomal doxorubicin 25 or 30 mg/m^2 once every 4 weeks in combination with gemcitabine 650 or 800 mg/m^2 twice every 4 weeks produced an overall response in 6 of 14 patients who had previously received platinum-based regimens.[80]

4.1.2 In Previously Untreated Patients

PEG-liposomal doxorubicin in combination with paclitaxel and carboplatin produced an overall response rate of 67% (assessed radiologically in patients with measurable disease) or 87% (assessed by CA-125 levels) in 31 previously untreated patients with advanced ovarian cancer.[65] Patients received PEG-liposomal doxorubicin 20 to 30 mg/m^2 plus paclitaxel 135 to 175 mg/m^2 and

carboplatin (titrated to achieve an AUC of 83 to 100 mg • h/L) every 3 to 4 weeks.[65]

4.2 Advanced Breast Cancer

Breast cancer is the most common cancer in women.[81] Although ≥80% of patients in developed countries present with operable disease, approximately half of these patients eventually experience relapse.[82]

Trials of PEG-liposomal doxorubicin have been conducted in patients (aged 31 to 83 years) with metastatic or locally advanced breast cancer that has generally been previously treated with chemotherapeutic agents (section 4.2.1).[26,83-91] Most have been noncomparative; however, one nonblind trial has compared the efficacy of PEG-liposomal doxorubicin alone with that of vinorelbine or mitomycin C plus vinblastine.[83]

In addition to the studies described above, a number of studies of PEG-liposomal doxorubicin have been conducted in patients with metastatic[85,90,92-94] or locally advanced breast cancer[93] that had not been previously treated (section 4.2.2).

Where reported, World Health Organization (WHO)[95] and Eastern Cooperative Oncology Group (ECOG)[96] standard response criteria were used.

4.2.1 In Previously Treated Patients

PEG-liposomal doxorubicin has antitumour activity in patients with metastatic disease that has already been treated with other chemotherapeutic agents (table IV). In most trials, all patients had metastatic breast cancer pretreated with chemotherapy. Five of the trials presented in table IV included a small number of patients (4 to 27%) that were chemotherapy naïve.[87,89-91,97] Forty-eight to 100% of patients in four trials had previously received anthracyclines[26,83,86,88] and all patients in one trial had disease resistant to standard doxorubicin (recurrent within six months of the last dose).[84]

Overall response rates were similar in 301 patients with metastatic breast cancer receiving PEG-liposomal doxorubicin 50 mg/m^2 every 4 weeks or two comparator salvage chemotherapy regimens (13 *vs* 15%; no statistical comparison reported) in a randomised, nonblind, multicentre study.[83] Median progression-free survival times (2.9 *vs* 2.5 months) and overall survival times (10.4 *vs* 9.4 months) were also similar. All patients had failed to respond to a prior taxane-containing regimen. The comparator regimens consisted of vinorelbine or mitomycin C plus vinblastine (see table IV for dosages) which are agents that have all previously demonstrated activity in metastatic breast cancer.[98]

There was little difference in progression-free survival times between PEG-liposomal doxorubicin and the comparator chemotherapies in patients who had received previous anthracyclines (n =250) [2.43 *vs* 2.66 months, hazard ratio (HR) 1.09, 95% confidence interval (CI) 0.83 to 1.43] and in patients who were anthracycline-resistant (n = 112) [2.56 *vs* 2.37 months, HR 1.20, CI 0.8 to 1.82].[83] Patients who had not received previous anthracyclines experienced a longer progression-free survival time with PEG-liposomal doxorubicin than with the comparator chemotherapies (4.96 *vs* 1.91 months, HR 2.50, CI 1.30 to 4.82).

An overall response rate of 20% and long survival times (table IV) were seen in a small (n = 45) noncomparative study; however, the study was designed primarily to assess dose-related toxicity.[26]

No responses were experienced by 17 patients with doxorubicin-resistant metastatic cancer (previous cumulative doses ranged between 200 and 500 mg/m^2) who received PEG-liposomal doxorubicin 30 mg/m^2 every 3 weeks. 23.5% of patients had stable disease lasting from 5 to 8 months in this study, which was presented as an abstract.[84]

A small (n = 32) dose-finding study found that the maximum tolerated dose of PEG-liposomal doxorubicin in combination with paclitaxel was 30 plus 175 mg/m^2, respectively, every 3 weeks in patients with advanced breast and gynaecologic malignancies. The trial had not been completed at the time of reporting; however, 3 of the 25 patients with breast cancer had responded to treatment (one patient was chemotherapy naïve).[85] More fre-

Table IV. Polyethylene glycol-liposomal doxorubicin (LD) in patients with metastatic breast cancer who had previously received chemotherapy.[a] Drugs were administered intravenously once during each cycle unless otherwise indicated and the response rate was calculated using the number of patients enrolled as the denominator

Reference	No. of evaluable patients (no. enrolled)	Patients who received prior DX or AN (%)	Chemotherapy-naïve patients (%)	Dosage regimen (mg/m^2)	Response rate (% of patients)					Median PFS/OS (mo)
					OR	CR	PR	SD	PD	
Monotherapy										
Keller et al.[83]b,c	209 (301)	84 (AN)[d]	0	LD 50 every 4wk	13	3	10	44	44	2.9/10.4
				VR 30 every wk or MT 10 (d1) + VB 5 (d1+21) every 6-8wk	15	3	12	37	48	2.5/9.4
Lyass et al.[26]	45 (45)	71 (AN)	0	LD 35-70 every 3-6wk	20	4.4	15.6	44.4	35.6	7.5/16
Smith et al.[84]b	13 (17)	100 (DX)	0	LD 30 every 3wk	0	0	0	23.5	52.9	NR[e]
In combination with paclitaxel (PA)										
Modiano et al.[85]b	NR (25[f])	NR	11.5[g]	LD 30-50 + PA 125-200 every 3-4wk	12.0[g]	4[g]	8.0	NR	NR	NR
Schwonzen et al.[86]	21 (21)	48 (AN)	0	LD 20 (d1) + PA 100 (d1+8) every 2wk	47.6	9.5	38.1	4.8	47.6	NR/>10
In combination with vinorelbine (VR)										
Burstein et al.[87]	24 (30)	63 (DX)	24	LD 30-35 (d1) + VR 25-30 (d1+8) or (d1+15) every 4wk	20	0	20	NR	NR	NR
Martin et al.[88]b	33 (35)	100 (AN)	0	LD 35 (d1) + VR 30 (d1) every 4wk	36	3	33	36	27	NR
Rimassa et al.[89]b	22 (22)	0 (AN)	27	LD 40 (d1) + VR 20 (d1+8) every 4wk	18.2	0	18.2	54.5	NR	NR
In combination with antimetabolites										
Rivera et al.[90]	27 (27)	NR	7	LD 20-29 (d1) + GC 800 (d1+8) every 3wk or (d1+8+15) every 4wk	33.3	7.4	25.9	37.0	29.6	NR
In combination with hyperthermia (HT)										
Park et al.[91]b	20 (23[h])	NR	4	LD 45 + HT every 4wk	60	5	55	NR	NR	NR

a A small number of patients were chemotherapy naïve in some trials.[85,87,89-91]

b Abstract.

c Study was randomised, nonblind and multicentre.

d All patients in this study had disease that had failed prior taxane-containing regimens.

e Stable disease lasted for 5 to 8mo.

f Number of patients with breast cancer from a total of 32 patients (seven patients had gynaecological malignancies).

g From total evaluable patients (including gynaecological malignancies). The one patient with a CR had not received prior chemotherapy.

h Of 23 patients, 22 had received prior chemotherapy and 21 had received prior radiotherapy.

AN = anthracyclines; **CR** = complete response; **DX** = standard formulation doxorubicin; **GC** = gemcitabine; **MT** = mitomycin C; **NR** = not reported; **OR** = overall response (CR + PR); **OS** = overall survival; **PD** = progressive disease; **PFS** = progression-free survival; **PR** = partial response; **SD** = stable disease; **VB** = vinblastine;

quent administration (every 2 weeks; see table IV for dosages) produced a response in 10 of 21 patients with previously treated metastatic breast cancer and a survival time of >10 months.[86] This promising result justifies further studies to confirm the efficacy of this regimen. PEG-liposomal doxorubicin and vinorelbine produced responses in 18 to 36% of patients in three small trials;[87-89] however, only one patient had a complete response (table IV).

Thirty-three percent of patients treated with PEG-liposomal doxorubicin in combination with the antimetabolite gemcitabine had a tumour response (2 of the 27 patients having a complete response and seven patients a partial response).[90] PEG-liposomal doxorubicin 45 mg/m^2 administered in combination with hyperthermia every 4 weeks was associated with an overall response rate of 60% in patients with metastatic breast cancer of the chest wall in a small study (20 evaluable patients) available as an abstract (table IV).[91]

4.2.2 In Previously Untreated Patients

Results from a recent study presented at the 2002 annual meeting of the American Society of Clinical Oncology have shown that PEG-liposomal doxorubicin has equivalent efficacy and a reduced risk of cardiac adverse events (sections 5.1 and 5.2) compared with standard doxorubicin in the first-line treatment of metastatic breast cancer. The duration of progression-free survival in 254 patients with metastatic breast cancer randomised to receive PEG-liposomal doxorubicin 50 mg/m^2 every 4 weeks was similar to that of 255 patients receiving standard doxorubicin 60 mg/m^2 every 3 weeks (HR 1.00, 95% CI 0.82 to 1.22).[94] The length of progression-free survival and the overall response rates were not reported in the abstract.

The noncomparative studies presented here (table V) included patients with metastatic or locally advanced breast cancer who had not received prior chemotherapy with the exception of two trials[92,93] that included a small number of patients who had received prior chemotherapy. Complete dosage regimens are detailed in table V.

28.2% of 71 patients experienced responses with PEG-liposomal doxorubicin monotherapy in a noncomparative multicentre study (39% of patients in this study were pretreated with chemotherapy) [table V].[92] The median overall survival time was 7 months and the median progression-free survival time for responding patients was 9 months.

PEG-liposomal doxorubicin in combination with docetaxel or paclitaxel in small studies (n = 21 to 41) has also been effective in the first-line treatment of patients with breast cancer with promising objective response rates ranging from 56 to 71% (table V).[85,90,93]

A number of the trials reviewed in section 4.2.1 included a small number of chemotherapy-naïve patients;[85,87,89-91] however, the response rates of previously treated and untreated patients were not reported separately therefore conclusions about the efficacy of these regimens as first-line treatment can not be made.

4.3 AIDS-Related Kaposi's Sarcoma

Kaposi's sarcoma is a malignancy that commonly occurs in patients with AIDS and requires human herpes virus type 8 to develop.[1,101] At advanced stages, Kaposi's sarcoma can cause pain, bleeding, oedema, disfigurement and debilitation, thus impairing the quality of life of the patient.

Various treatment options are available to manage the disease. Local therapies, such as surgical excision, cryotherapy, photodynamic therapy, intralesional injections of chemotherapeutic agent or radiotherapy, are generally recommended for treatment of early disease confined to cutaneous lesions.[102] Advanced Kaposi's sarcoma, involving aggressive and extensive cutaneous disease, visceral disease or lymphoedema, commonly responds best to systemic therapies such as chemotherapy or interferon-α.[102]

PEG-liposomal doxorubicin has been most extensively studied in the treatment of patients with Kaposi's sarcoma. As mentioned earlier, a comprehensive review of PEG-liposomal doxorubicin in the management of Kaposi's sarcoma has been

Table V. Polyethylene glycol-liposomal doxorubicin (LD) in patients with chemotherapy-naïve[a] metastatic breast cancer.[b] Drugs were administered intravenously once during each cycle and the response rate was calculated using the number of patients enrolled as the denominator

Reference	No. of evaluable patients (no. enrolled)	Dosage regimen (mg/m^2)	Response rate (% of patients)					Median PFS/OS (mo)
			OR	CR	PR	SD	PD	
Monotherapy								
Ranson et al.[92]	64 (71[c])	LD 45-60 every 3-4wk	28.2	5.6	22.5	28.2	33.8	9[d]/7
In combination with taxanes								
Gogas et al.[99][e]	31 (35)	LD 35 + PA 175 every 3wk	71	17	54	11	6	NR
Sparano et al.[93]	38 (41[f])	LD 30-40 + DO 60-75 every 3-4wk	56	2	54	NR	NR	8/18[g]
Vorobiof et al.[100][e]	16 (21)	LD 30 + PA 175 every 3wk	63	19	44	NR	NR	NR

a In two trials a small percentage of patients had received prior treatment.[92,93]

b One study included both metastatic (n = 31) and locally advanced (n = 10) breast cancer.[93]

c Twenty-eight patients had received prior chemotherapy with a non-anthracycline-containing regimen.

d In responding patients.

e Abstract.

f Fourteen patients had received prior adjuvant therapy; nine of these had received standard doxorubicin.

g PFS/OS in patients with metastatic disease only (n = 31).

CR = complete response; **DO** = docetaxel; **NR** = not reported; **OR** = overall response (CR + PR); **OS** = overall survival; **PA** = paclitaxel; **PD** = progressive disease; **PFS** = progression-free survival; **PR** = partial response; **SD** = stable disease.

previously published in *Drugs*.[1] This review focuses on data from trials comparing PEG-liposomal doxorubicin with various combination therapies and updates results from trials that had not been completed at the time of publishing the previous review. A summary of these trials, including complete dosage regimens, is provided in table VI.[103-106] Noncomparative data are not reviewed here except for a study which included data from a subgroup of 28 patients who had previously relapsed while receiving standard doxorubicin[107] and a study reporting long-term treatment data.[108] Studies[49,104,106,107] assessed response using criteria based on that of the AIDS Clinical Trials Group, defined by Krown et al.[109] A health-related quality-of-life assessment of one study[104] (published separately[110]) was conducted using a previously validated, AIDS-modified questionnaire.[111]

Where reported, the baseline severity of Kaposi's sarcoma was advanced,[103,104,107,108] mostly advanced[106] or moderate/severe.[105] Mean and median baseline CD4+ helper T lymphocyte counts ranged from 10 to 75 cells/μl.[104,106-108] Trial participants were predominantly male. Reported concomitant medication included antiretroviral therapies, antimicrobial prophylaxis, antiviral therapies and/or antifungal medication.[104,106,108] Most patients had ≥24 mucocutaneous lesions at baseline and 19 to 21% of patients had >50 lesions.[104,106]

4.3.1 Response and Survival

PEG-liposomal doxorubicin 20 mg/m^2 administered as monotherapy every 2 or 3 weeks for up to six cycles produced overall response rates ranging from 46 to 88% in studies involving 79 to 258 patients (table VI).[103-106] The duration of response reported for PEG-liposomal doxorubicin was 90 to 142 days.[104-106] The overall response rate reported for previously untreated patients in one study was 77% (n = 62).[103]

PEG-liposomal doxorubicin is at least as effective as bleomycin plus vincristine (BV) at producing a response according to results from two comparative studies.[105,106] In two other randomised studies, PEG-liposomal doxorubicin produced a significantly higher overall response rate than standard doxorubicin plus BV (ABV)[104] and a similar

response rate to BV plus PEG-liposomal doxorubicin (DBV).[103]

In one study (n = 241), PEG-liposomal doxorubicin 20 mg/m^2 as monotherapy every 2 or 3 weeks produced a significantly higher overall response than BV (59 *vs* 23%; p < 0.001).[106] In a smaller study published as an abstract (n = 79), PEG-liposomal doxorubicin 20 mg/m^2 every 2 weeks produced a larger response than BV (88 *vs* 64%; statistical analysis not reported).[105] There was no significant difference in mean duration of response between treatment groups in the larger study,[106] although PEG-liposomal doxorubicin produced a longer mean duration of response than BV in the smaller study (statistical analysis not reported) [table VI].[105] PEG-liposomal doxorubicin also produced a longer mean duration of survival than BV in the smaller study (239 *vs* 160 days; statistical analysis not reported).[106]

Compared with ABV, PEG-liposomal doxorubicin 20 mg/m^2 every 2 weeks produced a significantly greater overall response [46% (CI 37 to 54%) *vs* 25% (CI 17 to 32%); p < 0.001] (table VI).[104] The median durations of response (table VI) and survival (approximately 160 days for both groups) were similar between groups (statistical significance not reported).

PEG-liposomal doxorubicin 20 mg/m^2 every 2 weeks produced a similar overall response rate to DBV in 126 chemotherapy-naïve patients (77 *vs* 80%; statistical analysis not reported) in a study presented as an abstract (table VI).[103] The median time to disease progression or death was also similar between treatment groups (29 and 32 weeks, respectively). A scheduled interim analysis show-

Table VI. Summary of comparative trials of polyethylene glycol-liposomal doxorubicin (LD) monotherapy in patients with AIDS-related Kaposi's sarcoma. Drugs were administered intravenously once during each cycle unless otherwise indicated

Reference (study design)	No. of patients (no. of previous chemotherapy regimens)	Dosage regimen (mg/m^2 unless otherwise stated) [no. of cycles]	Response rate (% of patients)					Median duration of response (days)
			OR	CR	PR	SD	PD	
Compared with LD plus bleomycin (BM) and vincristine (VC)								
Mitsuyasu et al.[103]a,b (r,nb)	62[c] (0)	LD 20 every 2wk [NR]	77.4	8.1	69.4	NR	NR	NR
	64[c] (0)	LD 20 + BM 10 + VC 1mg every 2wk [NR]	79.7	7.8	71.9	NR	NR	NR
Compared with DX plus BM and VC								
Northfelt et al.[104] (r,nb,mc)	133[d] (≥0)	LD 20 every 2wk [mean 5.2]	45.9*	0.8[e]	45.1*	52.6	1.5	90.0
	125[d] (≥0)	DX 20 + BM 10 + VC 1mg every 2wk [mean 3.8]	24.8	0.0	24.8	67.2	8.0	92.0
Compared with BM plus VC								
Rizzardini et al.[105]a,b (NR)	34[c] (NR)	LD 20 every 2wk [6]	88.2	5.9[e]	82.4	5.9	5.9	101 (mean)
	45[c] (NR)	BM 15 + VC 1.4mg every 2wk [6]	64.4	0.0	64.4	22.2	13.3	86 (mean)
Stewart et al.[106] (r,nb,mc)	121[d] (≥0)	LD 20 every 3wk [≤6][f]	58.7*	5.8[e]	52.9	38.0	0.0	142.0
	120[d] (≥0)	BM 15 + VC 1.4-2.0mg every 3wk [≤6][f]	23.3	0.8[e]	22.5	67.5	4.2	123.0

a Statistical analysis not reported for response data[103] or all data.[105]

b Abstract.

c Evaluable patients.

d Enrolled patients.

e CR without confirmation by biopsy on a representative lesion.

f Granulocyte colony-stimulating factor was administered as required. Most patients also received concomitant antiretroviral therapy on commencement of LD therapy.

CR = complete response; **DX** = standard formulation doxorubicin; **mc** = multicentre; **nb** = nonblind; **NR** = not reported; **OR** = overall response (CR + PR); **PD** = progressive disease; **PR** = partial response; **r** = randomised; **SD** = stable disease; * p < 0.001 *vs* comparator.

ed a trend towards better survival with PEG-liposomal doxorubicin than DBV (18 *vs* 28%); however, this did not reach statistical significance (p = 0.079).

Nine of 28 patients who had received PEG-liposomal doxorubicin 20 mg/m^2 every 3 weeks and who had previously relapsed while receiving standard doxorubicin experienced a partial response for a median duration of 127 days. Fourteen patients had stable disease and five had disease progression. The mean time to treatment failure was 148 days.[107]

In a long-term noncomparative study, 52 patients received PEG-liposomal doxorubicin 20 mg/m^2 every 2 to 4 weeks for a mean of 22.8 cycles (median observation period of 71 weeks).[108] The overall response rate was 65.4% (complete response 9.6%; partial response 55.8%); 19.2% of patients had stable disease and 15.4% had progressive disease.

4.3.2 Quality of Life and Clinical Benefits

PEG-liposomal doxorubicin was better than ABV and BV at improving some aspects of quality of life and/or producing clinical benefits in patients with Kaposi's sarcoma.

The effect of PEG-liposomal doxorubicin compared with ABV on health-related quality of life was assessed in one randomised study[104] (section 4.3.1) and published separately.[110] The questionnaire that was used contained 22 items covering nine domains;[111] higher scores indicated better health. Assessments were made only in symptomatic patients who completed all or parts of the questionnaire (73 to 93 patients who received PEG-liposomal doxorubicin and 61 to 89 patients who received ABV).[110]

From baseline to the end of treatment (approximately 21 days after the last chemotherapy cycle) patients receiving PEG-liposomal doxorubicin improved significantly ($p \leq 0.01$) in four domains (pain, cognitive functioning, social functioning and health distress).[110] Patients receiving ABV deteriorated significantly (p = 0.004) in one domain (energy/fatigue). No statistically significant changes were reported in the rest of the domains with either treatment.

In comparisons between the two treatments, changes were statistically similar in seven domains. Improvements were significantly better with PEG-liposomal doxorubicin in pain and energy/fatigue than with ABV ($p \leq 0.01$). In patients who completed the questionnaires, significantly more of those who received PEG-liposomal doxorubicin achieved a clinically significant change in the overall quality-of-life domain score (change of ≥10 on a scale from 0 to 100) than those who received ABV (65 *vs* 43%; p = 0.0008). The duration of response was longer in patients receiving PEG-liposomal doxorubicin than ABV; approximately 40% of the patients receiving PEG-liposomal doxorubicin who had achieved a clinically significant change in overall quality-of-life score had maintained this response for 70 days compared with none of the patients responding to ABV treatment.

The quality of everyday life for a patient with Kaposi's sarcoma can be improved by reducing disfiguration and pain caused by the disease. Therefore this section also looks at change in clinical benefit data such as Karnofsky performance status, lesion flattening, nodularity, oedema, colour and lesion-associated pain reported in two randomised trials.[104,106] Five indicator cutaneous lesions were identified on each patient and assessed subjectively on a 2- to 4-point scale.[104,106]

There was no appreciable change from baseline in mean Karnofsky status in patients receiving ABV or those receiving PEG-liposomal doxorubicin,[104] but PEG-liposomal doxorubicin was significantly better than ABV at flattening indicator lesions ($p < 0.001$) and at changing the colour of indicator lesions from red or purple to brown (considered less disfiguring) [$p < 0.002$]; both treatments reduced lesion-associated pain with 83 and 78% of PEG-liposomal doxorubicin- and ABV-treated patients free from pain at the end of treatment.[104] PEG-liposomal doxorubicin was significantly better than BV at reducing the thickness and nodularity of indicator lesions, at reduc-

ing oedema, at fading indicator lesion colour to brown and at reducing lesion-associated pain ($p < 0.003$ for all comparisons).[106]

4.4 Haematological Malignancies

4.4.1 Multiple Myeloma

Multiple myeloma constitutes about 10% of all haematological malignancies.[112] Although it is treatable and chemotherapy has significantly improved the median survival time of patients, multiple myeloma is rarely curable.[113]

At present, only small (n <30) preliminary, noncomparative trials have investigated the efficacy of PEG-liposomal doxorubicin in patients with multiple myeloma.[34,114-116] All but one[114] of these trials were published in abstract form as interim analyses. Details on duration of response, time to disease progression and survival were not reported.

Substituting PEG-liposomal doxorubicin for standard doxorubicin in a vincristine plus doxorubicin and dexamethasone (VAD) regimen was effective in the treatment of 12 patients with multiple myeloma. Eight patients receiving the regimen (PEG-liposomal doxorubicin 40 mg/m^2 and vincristine 2 mg/m^2 administered once every 4 weeks in combination with oral dexamethasone 40mg administered 12 times every 4 weeks) had no detectable paraprotein in the serum or urine and <5% bone marrow plasma cells at the end of treatment; a further three patients had a partial response (<50% of baseline paraprotein and <5% bone marrow plasma cells).[114] Of note, patients included in the trial who had received prior standard VAD therapy (n = 3) had an improved response following treatment with the PEG-liposomal doxorubicin containing regimen.

In a trial in 26 patients with newly diagnosed multiple myeloma, the same regimen resulted in complete remission in three patients and an objective response in nine patients.[115] Ten patients had a minor response and four had stable disease. In a follow-up trial to examine the efficacy of this regimen in patients who had failed prior treatment, 4 out of 12 patients (four of whom had received VAD) had an objective response to treatment with a further four and three patients having a minor response or stable disease, respectively.[116] Both of these trials used the ECOG multiple myeloma response criteria.[115,116]

In a trial using a lower dosage (PEG-liposomal doxorubicin 40 mg/m^2 plus vincristine 1.4 mg/m^2 once every 4 weeks in combination with oral dexmethasone 40mg administered eight times every 4 weeks) eight of nine patients who were previously untreated or responsive to prior treatment had a complete (no detectable paraprotein) or partial (≥25% decrease in paraprotein) response; five of nine patients who had relapsed or been resistant to prior treatment had a partial response.[34]

4.4.2 Non-Hodgkin's Lymphoma

The most common type of lymphoid malignancy is non-Hodgkin's lymphoma, a heterogeneous group of lymphomas with varying clinical presentations and responsiveness to treatment.[117,118] Treatment depends on the histological subtype and stage of the disease; therefore accurate classification is essential. The objective of treatment of many non-Hodgkin's lymphomas is curative rather than palliative; about 50 to 60% of patients with the disease survive for at least 5 years with modern treatment.[117,119] However, age is a poor prognostic factor for non-Hodgkin's lymphoma.[120]

The limited data in this section are taken from three small, noncomparative trials (n = 5 to 8), two of which were published as abstracts.[121,122]

When substituted for standard doxorubicin in the commonly used standard doxorubicin plus cyclophosphamide, vincristine and methylprednisolone (CHOP) regimen, PEG-liposomal doxorubicin 20 mg/m^2 demonstrated activity in elderly patients (aged 77 to 81 years) with aggressive non-Hodgkin's lymphoma. An overall response lasting ≥6 months was experienced by all eight patients receiving this regimen in a small trial (whether patients were previously treated or not was not reported).[121]

Four out of five[122] and five out of six[123] patients (aged 40 to 78 years) with relapsed or refrac-

tory B cell or cutaneous T cell lymphomas experienced an overall response with PEG-liposomal doxorubicin 20 to 40 mg/m^2 as monotherapy every 3 or 4 weeks in two trials. Stable[122] and progressive[123] disease were reported in one patient each.

5. Tolerability

The tolerability profile of PEG-liposomal doxorubicin in patients with solid tumours and those with Kaposi's sarcoma differ because of the different doses used for each patient group and also because patients with Kaposi's sarcoma receive many concurrent therapies. Therefore, in this section the adverse events occurring with PEG-liposomal doxorubicin in these patient groups are reviewed separately, except for cardiotoxicity (section 5.1), which is reviewed using evidence from both patient groups.

Data presented are predominantly taken from revised prescribing information,[36] two large randomised trials in patients with Kaposi's sarcoma (n = 241 and 258)[104,106] and a large randomised trial in patients with ovarian cancer (n = 474).[64] Data are also sourced from a long-term noncomparative trial in 52 patients with Kaposi's sarcoma,[108] a noncomparative trial in 71 patients with breast cancer[92] and from three studies in patients with breast cancer who received PEG-liposomal doxorubicin in combination with paclitaxel (n = 21),[86] docetaxel (n = 41)[93] or gemcitabine (n = 27) [see tables IV and V for dosage details].[90]

The only tolerability data available in patients with haematological malignancies who received PEG-liposomal doxorubicin are from very small studies (n = 5 to 26) and are therefore not included here.

The prescribing information reports tolerability data pooled from clinical trials in 876 patients with solid tumours, including a subset of 512 patients with ovarian cancer, and patients with Kaposi's sarcoma (number of patients not reported).[36] Patients with solid tumours received PEG-liposomal doxorubicin 50 mg/m^2/cycle and patients with Kaposi's sarcoma received 20 mg/m^2/cycle (cycle lengths not reported).

Adverse events associated with PEG-liposomal doxorubicin in clinical trials were assessed for severity using the US National Cancer Institute common toxicity criteria[64,86,90,92,106] or standard WHO criteria[104] where severity ranges from grade I (mild) to grade IV (life-threatening). The prescribing information defined adverse event severity in terms of grades I to IV for palmar-plantar erythrodysaesthesia (PPE), adverse haematological events (absolute neutrophil and platelet counts) and stomatitis (section 6).[43]

5.1 Cardiac Events

High peak plasma concentrations and lifetime cumulative doses of standard doxorubicin are thought to be important factors contributing to the cardiotoxicity of the drug.[1,8] The risk of developing impaired myocardial function is estimated to be 5 to 8% at a total cumulative dose of 450 mg/m^2; above this level, incidences of congestive heart failure increase.[124] PEG-liposomal doxorubicin may be less cardiotoxic than standard doxorubicin since very little doxorubicin circulates freely in plasma after PEG-liposomal doxorubicin administration (section 3.1), and the liposomal formulation may not as readily traverse the continuous capillaries in myocardial tissue.[8] Preliminary results presented at the 38th annual meeting of the American Society of Clinical Oncology demonstrated that patients with metastatic breast cancer receiving standard doxorubicin 60 mg/m^2 every 3 weeks (n = 255) were at a significantly higher risk of developing a cardiac adverse event than patients receiving PEG-liposomal doxorubicin 50 mg/m^2 every 4 weeks (n = 254) [hazard ratio 3.2, p = 0.0006].[94] However, experience with large cumulative doses of PEG-liposomal doxorubicin are limited, therefore current prescribing information recommends adherence to the warnings relating to cardiac toxicity for the standard formulation of doxorubicin[43] and PEG-liposomal doxorubicin must be considered to have a similar risk of cardiomyopathy as standard doxorubicin.[36]

According to pooled data, the incidence of clinically significant cardiac dysfunction was low in

774 patients with solid tumours who had received cumulative doses of PEG-liposomal doxorubicin of up to 944 mg/m^2 (incidence not reported).[36] Of 66 patients who had received a cumulative dose of >400 mg/m^2 and had left ventricular ejection fraction (LVEF) measured at baseline and follow-up, 12% had a decrease in LVEF of ≥20% from baseline or a change to <45%. One patient (1.5%) discontinued treatment because of clinical symptoms of congestive heart failure.

Cardiotoxicity (measured as a decrease in LVEF of >10,[92] ≥15[26] or ≥20%[64,69] or congestive heart failure[26]) was experienced by 1.4 to 3.4% of 45 to 132 patients with ovarian or breast cancer who received PEG-liposomal doxorubicin 35 to 70 mg/m^2 as monotherapy every 3 to 6 weeks; cumulative doses of PEG-liposomal doxorubicin ranged from 45 to 1301 mg/m^2.[26,64,69,92]

The median change in LVEF was –2% (range –15 to +9%) in a retrospective analysis of 41 patients with solid tumours (about 75% with ovarian or breast cancer) who had received cumulative PEG-liposomal doxorubicin doses of ≥500 mg/m^2.[125] Although this change was statistically significant compared with baseline ($p = 0.009$), it was not considered clinically significant (defined as a >10% change). No relationship between cumulative PEG-liposomal doxorubicin dose and change from baseline in LVEF was found in two studies.[64,125]

In randomised trials in patients with Kaposi's sarcoma, the percentage of patients experiencing a ≥20% reduction in LVEF appeared to be lower with PEG-liposomal doxorubicin than with ABV (4.3 *vs* 9.1%, statistical analysis not reported).[104] However, cardiotoxicity appeared to be more common with PEG-liposomal doxorubicin than with BV (1.7 *vs* 0.8%, statistical analysis not reported).[106]

In a preliminary study, PEG-liposomal doxorubicin produced significantly fewer cardiac histopathological changes than standard doxorubicin in patients with Kaposi's sarcoma.[126] The median endomyocardial biopsy score from the ten patients who had received a mean cumulative dose of intravenous PEG-liposomal doxorubicin of 623 mg/m^2 was significantly lower than the median biopsy score from ten historical patients (with various types of cancer) matched by cumulative standard doxorubicin dose (mean 565 mg/m^2) [0.3 *vs* 3.0; $p = 0.002$]. In an extension of the cardiac biopsy study, four patients with either breast or ovarian cancer who had received cumulative doses of PEG-liposomal doxorubicin ranging from 730 to 1680 mg/m^2 were enrolled.[36] Two patients had mild cardiotoxicity and two had normal myocardial ultrastructural morphology.

5.2 In Patients with Solid Malignancies

The percentage of overall discontinuations due to adverse events associated with PEG-liposomal doxorubicin was similar to that associated with topotecan in 474 patients with relapsed ovarian cancer (18 *vs* 16%).[64] No deaths related to treatment occurred with PEG-liposomal doxorubicin, whereas three (1.7%) occurred with topotecan.

The most common adverse events associated with PEG-liposomal doxorubicin as monotherapy in patients with ovarian cancer were PPE, stomatitis and nausea.[36]

5.2.1 Palmar-Plantar Erythrodysaesthesia and Other Mucocutaneous Adverse Events

PPE or hand-foot syndrome is a dermatological adverse event characterised by swelling, pain, erythema and sometimes desquamation of the skin in pressure-sensitive areas such as the palms and soles, and is commonly associated with PEG-liposomal doxorubicin.[42] The mechanism by which PEG-liposomal doxorubicin causes PPE is currently unknown, but it is thought that breakage of small capillaries as a result of pressure may lead to extravasation of liposomes. This in turn would lead to prolonged drug exposure and the symptoms of PPE in these areas.[127]

According to pooled tolerability data, 46.1% of patients with ovarian cancer developed PPE (figure 3); 20.1% experienced events of grade III or IV severity and <5% discontinued treatment permanently because of PPE.[36] PPE usually developed after two or three cycles of therapy. 38.9% of patients experienced stomatitis; 8.8% experienced

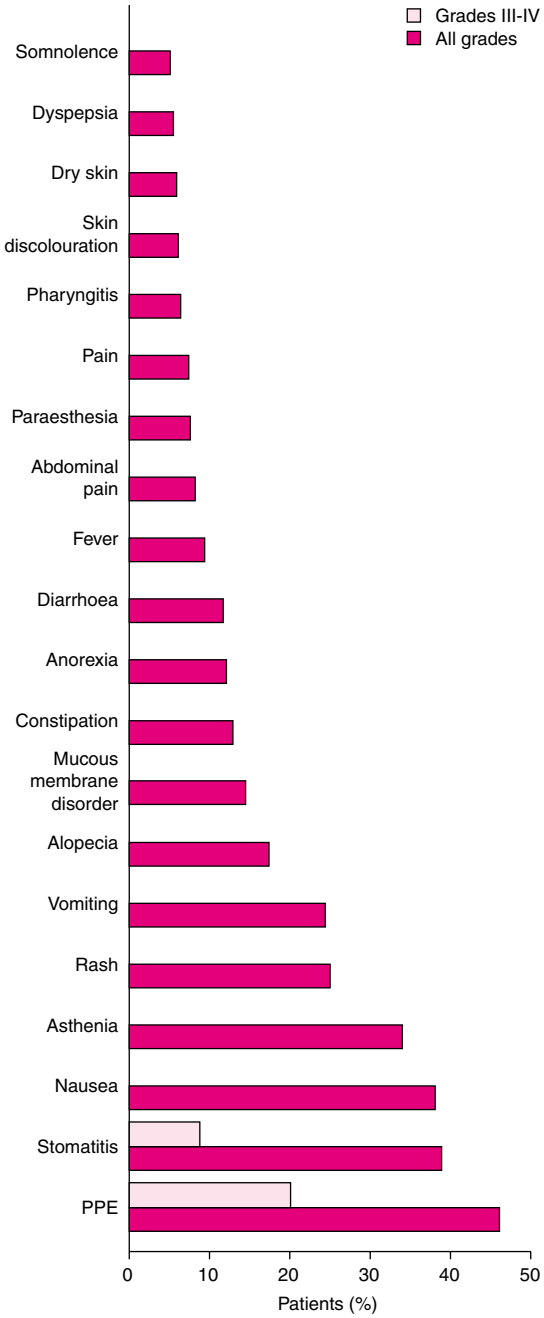

Fig. 3. Incidence of drug-related nonhaematological adverse events experienced by ≥5% of 512 patients with ovarian cancer who received polyethylene glycol-liposomal doxorubicin 50 mg/m^2 (cycle length or number not reported; pooled tolerability data).[36] Incidences of grade III and IV adverse events were available only for stomatitis and palmar-plantar erythrodysaesthesia (PPE).

stomatitis of grade III or IV and <1% of patients discontinued treatment because of stomatitis.

In a randomised trial, the incidence of PPE (49% grades I to IV; 23% grade II or IV; figure 4) in patients with relapsed ovarian cancer receiving PEG-liposomal doxorubicin (n = 239) was similar to that in pooled data, with 3.8% of patients discontinuing therapy because of PPE.[64] In contrast, no grade III or IV PPE was experienced by 235 patients receiving topotecan in this trial ($p < 0.001$ *vs* PEG-liposomal doxorubicin) and only 1% experienced grade I to II PPE. Significantly more patients receiving PEG-liposomal doxorubicin developed grade III or IV stomatitis than patients receiving topotecan (8 *vs* 0.4%; $p < 0.001$) [fig. 4]. However, grade III or IV alopecia was significantly less common with PEG-liposomal doxorubicin than topotecan (1 *vs* 6%; $p = 0.007$).

34 and 31% of 71 patients with breast cancer receiving PEG-liposomal doxorubicin monotherapy (45 to 60 mg/m^2 every 3 to 4 weeks) experienced grade III or IV PPE and mucositis, respectively, in a noncomparative trial.[92]

PPE may be managed by delaying or reducing dosages (see section 6). Concurrent administration of oral pyridoxine 50 to 150 mg/day has been used for the prophylaxis and treatment of PPE.[36] With coadministration of pyridoxine 200 mg/day, no PPE greater than grade I severity was experienced by 13 patients with multiple myeloma receiving PEG-liposomal doxorubicin 40 mg/m^2 every 4 weeks in combination with vincristine and dexamethasone.[116] Concomitant dexamethasone and pyridoxine may also lower the incidence of PPE caused by PEG-liposomal doxorubicin.[128] PPE can develop despite administration of oral pyridoxine 150 mg/day concurrently with PEG-liposomal doxorubicin;[129] topical dimethyl sulfoxide four times daily for 14 days resolved grade III PPE that developed in two patients who had received oral pyridoxine and PEG-liposomal doxorubicin.

In a combination study, PPE (any grade) occurred in 29% and mucositis (grade III) occurred in 14% of patients receiving paclitaxel plus PEG-liposomal doxorubicin.[86] The dosage of PEG-

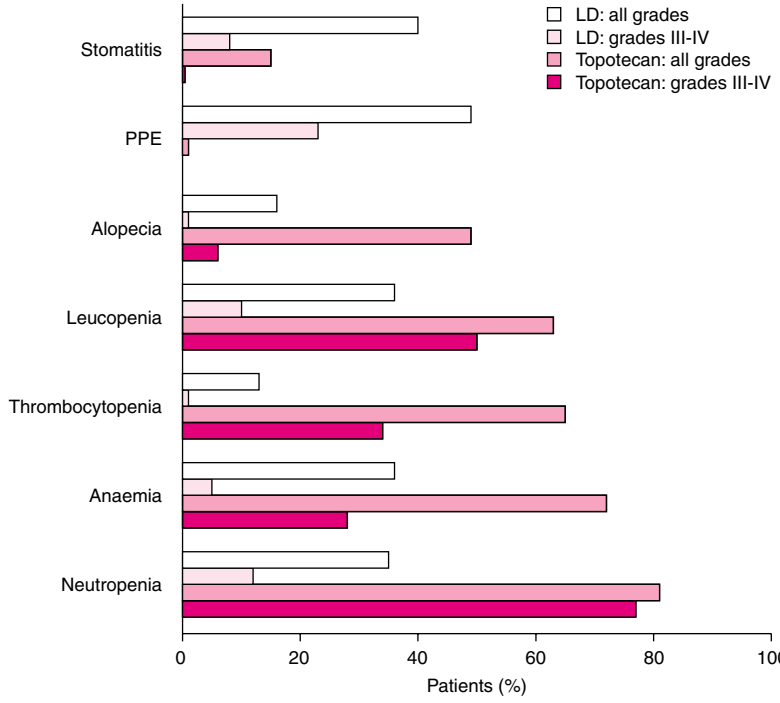

Fig. 4. Tolerability of polyethylene glycol-liposomal doxorubicin (LD) compared with that of topotecan in patients with ovarian cancer. 474 women with cancer that recurred after or did not respond to first-line platinum-based chemotherapy received LD 50 mg/m^2 once every 4 weeks or topotecan 1.5 mg/m^2 five times every 3 weeks in a randomised, multicentre study.[64] Incidences of all adverse events were significantly different between treatment groups ($p < 0.01$), and 29.1% (LD) or 4.6% (topotecan) of patients received granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor. **PPE** = palmar-plantar erythrodysaesthesia.

liposomal doxorubicin was reduced in five patients because of PPE. PPE and stomatitis (grade III) both developed in 13% of patients receiving docetaxel plus PEG-liposomal doxorubicin.[93] After one cycle of PEG-liposomal doxorubicin plus gemcitabine, 4% of patients had experienced stomatitis.[90]

5.2.2 Haematological Events

Pooled data from trials in patients with ovarian cancer found the following frequency of haematological events (grade I to IV severity): leucopenia (33.2%), anaemia (32.2%), neutropenia (31.6%), and thrombocytopenia (10.7%) [figure 5].[36] In most patients, the severity of these events was grade I or II. Less than 5% of patients required growth factor support and about 15% required transfusion support. In a trial in 71 patients with breast cancer receiving PEG-liposomal doxorubicin monotherapy, 27% and 3% experienced grade III or IV neutropenia and thrombocytopenia, respectively.[92]

Incidences of haematological adverse events (neutropenia, anaemia, thrombocytopenia and leucopenia) were significantly lower with PEG-liposomal doxorubicin than with topotecan when considering adverse events of all grades or just grades III and IV ($p < 0.001$ for all comparisons) in patients with relapsed ovarian cancer (figure 4).[64] Therefore, more topotecan than PEG-liposomal doxorubicin recipients received granulocyte colony-stimulating or granulocyte-macrophage colony-stimulating factor (29.1 *vs* 4.6%), erythropoietin (23.1 *vs* 6.3%), blood transfusions (57.8 *vs* 14.9%) or dose modifications (78.3 *vs* 57.3%).

The most common adverse events observed in studies of PEG-liposomal doxorubicin in combination with paclitaxel, docetaxel, vinorelbine or gemcitabine in patients with breast cancer were haematological. In combination with paclitaxel, PEG-liposomal doxorubicin produced grade III or IV neutropenia in 62% of 21 patients[86] and in combination with docetaxel it produced grade III or IV neutropenia in 60%, febrile neutropenia in 13% and anaemia in 13% of 15 patients.[93] Grade IV neutropenia occurred in 15 of 33 patients receiving PEG-liposomal doxorubicin in combination with vinorelbine (three patients had neutropenic fever).[88] PEG-liposomal doxorubicin in combination with gemcitabine produced grade III or IV neutropenia and thrombocytopenia in 48 and 26%, respectively, of 27 patients (the dose-limiting adverse events) but neutropenic complications did not occur.[90]

5.2.3 Hypersensitivity Reactions

Infusion-related events were experienced by 12.2% of 876 patients with solid tumours receiving PEG-liposomal doxorubicin, primarily during the first infusion (pooled tolerability data).[36] These events included allergic reaction, anaphylactic reaction, asthma, face oedema, hypotension, vasodilation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, nausea, dizziness, dyspnoea, pharyngitis, rash, pruritus, sweating, and injection site reaction.

Three percent of 71 patients with breast cancer who received PEG-liposomal doxorubicin as an infusion over 1 hour developed allergic responses (urticarial rash, flushing, back and chest pain) requiring discontinuation from the first infusion and withdrawal from further treatment.[92]

In patients with breast cancer receiving a combination of docetaxel and PEG-liposomal doxorubicin, infusion reactions of up to grade IV occurred in six out of 11 patients who received PEG-liposomal doxorubicin at a rate of 0.25 L/h.[93] Only one of 30 patients developed an infusion reaction while receiving PEG-liposomal doxorubicin using a modified infusion schedule (initial rate 0.01 L/h, doubled every 5 to 10 minutes until the rate reaches 0.25 L/h). No patients developed an infusion or hypersensitivity reaction related to docetaxel.

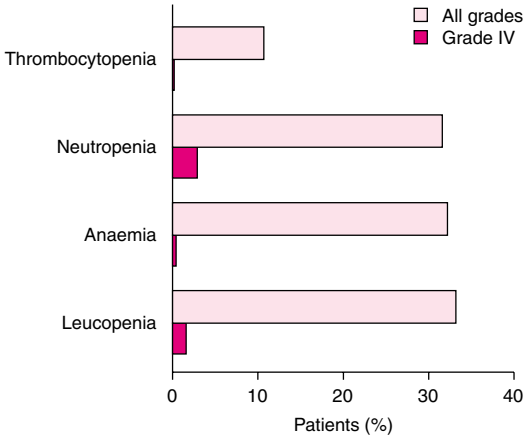

Fig. 5. Incidence of haematological adverse events in patients with ovarian cancer. 512 patients received polyethylene glycol-liposomal doxorubicin 50 mg/m^2 (cycle length or number not reported; pooled tolerability data).[36] Growth factor and transfusion support were required in <5 and ≈15% of patients, respectively.

5.2.4 Other Adverse Events

In pooled tolerability data, 38.1% of patients with ovarian cancer receiving PEG-liposomal doxorubicin reported nausea (figure 3).[36] Other gastrointestinal events that occurred in >5% of patients include vomiting (24.4%), constipation (12.9%), diarrhoea (11.7%), pharyngitis (6.4%) and dyspepsia (5.5%) [figure 3].

In general, adverse events related to the nervous system were not of major concern with administration of PEG-liposomal doxorubicin as monotherapy, although drug-related paraesthesia occurred in 7.6% of patients according to pooled tolerability data.[36] 38% of patients who received PEG-liposomal doxorubicin in combination with paclitaxel experienced peripheral sensoral neuropathy of up to grade III in severity[86] and 27% of patients who received PEG-liposomal doxorubicin in combination with docetaxel experienced neurosensory adverse events (grade I or II).[93]

Clinically significant laboratory abnormalities reported in patients with ovarian cancer (n = 410) included increases in bilirubin (5%) and serum creatinine levels (5%) [pooled data].[36] Increases in aspartate aminotransferase levels and observations of sepsis related to leucopenia were infrequent (<1%).

Nonhaematological adverse events reported in pooled data and occurring in ≥5% of patients with refractory ovarian cancer are shown in figure 3.[36]

5.3 In Patients with AIDS-Related Kaposi's Sarcoma

Myelosuppression is the dose-limiting adverse event experienced by patients with Kaposi's sarcoma receiving PEG-liposomal doxorubicin.[36] Leucopenia was the most frequent event in trials (pooled tolerability data); neutropenia, thrombocytopenia and anaemia were also common.[36] Incidences for each event were not reported but myelosuppression in general occurred in about 50% of patients.[36]

Other adverse events occurring in ≥5% of patients from pooled data include: nausea, asthenia, alopecia, fever, diarrhoea, infusion-associated acute reactions, stomatitis and respiratory events.[36] Respiratory adverse events may be related to opportunistic infections as a result of HIV-induced immunodeficiency; commonly opportunistic infections in patients receiving PEG-liposomal doxorubicin included candidiasis, cytomegalovirus, herpes simplex, *Pneumocystis carinii* and *Mycobacterium avium* complex.[36]

The most common adverse events in a long-term study of PEG-liposomal doxorubicin were also haematological.[108] Leucopenia was reported in 79%, neutropenia in 77% and anaemia in 60% of 52 patients who received PEG-liposomal doxorubicin once every 2 to 4 weeks for a mean of 22.8 cycles.

According to pooled tolerability data, 5 to 10% of patients with Kaposi's sarcoma experienced infusion-associated reactions, including flushing, shortness of breath, facial oedema, headache, tightness in the chest and throat, chills, back pain and hypotension.[36]

Clinically significant laboratory abnormalities occurred frequently (≥5%) in clinical studies and included increases in alkaline phosphatase, aspartate aminotransferase and bilirubin levels.[36] Reductions in haemoglobin levels and platelet numbers were reported in <5% of patients and observations of sepsis related to leucopenia in <1%. Some of the abnormalities reported may have been related to underlying HIV infection.

In the long-term study, 33% of patients experienced an increase in liver function values and seven patients (13%) stopped receiving treatment for >8 weeks because of abnormal liver function tests.[108]

5.3.1 Comparative Studies

The overall incidences of adverse events associated with PEG-liposomal doxorubicin and BV or ABV did not appear to differ.[104,106] However, fewer early withdrawals due to adverse events occurred with PEG-liposomal doxorubicin than with BV (10.7 *vs* 26.7%, statistical analysis not reported)[106] and there were differences between regimens with regard to specific events. PEG-liposomal doxorubicin was associated with significantly less constipation (1.7 *vs* 10.8%) and paraesthesia (3.3 *vs* 14.2%) than BV ($p < 0.01$),[106] and significantly less grade III or IV nausea and/or vomiting (15 *vs* 34%), alopecia (1 *vs* 19%) and peripheral neuropathy (numbers of patients not reported) than ABV ($p < 0.001$).[104] However, PEG-liposomal doxorubicin was associated with significantly more opportunistic infections (49.6 *vs* 30.0%) than BV ($p < 0.002$)[106] and grade III or IV mucositis and/or stomatitis (5 *vs* 2%) than ABV ($p = 0.026$).[104]

With regard to myelosuppression, PEG-liposomal doxorubicin produced a significantly higher incidence of leucopenia than BV (71.9 *vs* 50.8%; $p < 0.001$) and a nonsignificantly higher incidence of anaemia (18.2 *vs* 15.0%) and thrombocytopenia (14.9 *vs* 11.7%).[106] The drug produced a slightly lower, but not statistically different, incidence of grade III or IV leucopenia (36 *vs* 42%), anaemia

(9.8 *vs* 11.2%) and thrombocytopenia (3 *vs* 5.6%) than ABV.[104]

Fewer early withdrawals due to adverse events occurred with PEG-liposomal doxorubicin than with DBV (6 *vs* 25%, statistical analysis not reported), and the median time until the occurrence of the first adverse event of grade III or IV was significantly longer with PEG-liposomal doxorubicin than DBV (10 *vs* 7 weeks; $p < 0.01$).[103]

6. Dosage and Administration

Indications for PEG-liposomal doxorubicin differ slightly between countries. In the US, PEG-liposomal doxorubicin is indicated for the treatment of metastatic ovarian carcinoma that progressed while patients were receiving both paclitaxel- and platinum-based chemotherapy regimens or within 6 months of completing these treatments.[43] The drug is also approved in the US for the treatment of patients with AIDS-related Kaposi's sarcoma that had not responded to, or were intolerant of, prior combination chemotherapy.[43]

In the UK, the drug is indicated for the treatment of advanced ovarian cancer that failed first-line platinum-based chemotherapy, and AIDS-related Kaposi's sarcoma in patients with a CD4+ helper T lymphocyte count of <200 cells/μl and extensive or visceral disease.[36] In Kaposi's sarcoma, it can be used either as first-line systemic chemotherapy or second-line chemotherapy in patients that were resistant to, or intolerant of, a previous chemotherapy combination (including a vinca alkaloid, bleomycin and/or an anthracycline).[36] However, the drug is not to be used to treat Kaposi's sarcoma that may be treated effectively with local therapy or systemic interferon-α.[36]

PEG-liposomal doxorubicin is not currently approved for the treatment of metastatic breast cancer, multiple myeloma or non-Hodgkin's lymphoma.

For the treatment of ovarian carcinoma, PEG-liposomal doxorubicin 50 mg/m^2 should be administered as an intravenous infusion once every 4 weeks.[36,43] PEG-liposomal doxorubicin must not be administered as a bolus injection or an undiluted solution or administered intramuscularly or subcutaneously.[36,43] The drug should be administered at an initial rate of 1 mg/min, then if no infusion-related adverse events occur, the infusion rate can be increased so that administration is completed in 1 hour.[36,43]

In patients with Kaposi's sarcoma, PEG-liposomal doxorubicin 20 mg/m^2 should be administered as an intravenous infusion over 30 minutes once every 3 weeks in the US[43] or once every 2 to 3 weeks in the UK.[36]

In both indications, treatment should continue until disease progresses or the patient can no longer tolerate therapy.[36,43] A minimum of four cycles of treatment is recommended in the US for ovarian cancer[43] and 2 to 3 months of treatment are recommended in the UK to achieve a therapeutic response in patients with Kaposi's sarcoma.[36]

If symptoms of an infusion reaction occur, the infusion should be immediately discontinued, appropriate premedications such as antihistamines, corticosteroids and/or adrenaline should be administered and then the infusion can be restarted at a slower rate.[36]

Adverse events may be managed by delaying, reducing or suspending dosages; dosage modifications are summarised in tables VII and VIII. Recommendations vary slightly between countries

Table VII. Recommended modifications to the dosage of polyethylene glycol-liposomal doxorubicin based on the occurrence of adverse haematological events[36,43]

Toxicity grade[a]	Signs and symptoms at time of next scheduled treatment cycle	Dosage modification by event type
I	ANC 1.5-<2; PLT 75-150	None
II	ANC 1-<1.5; PLT 50-<75	Wait until ANC ≥1.5 and PLT ≥75, then administer 100% of dose
III	ANC 0.5-<1; PLT 25-<50	
IV	ANC <0.5; PLT <25	Wait until ANC ≥1.5 and PLT ≥75, then administer 75% of dose or 100% of dose with cytokine support

a Grade 0 indicates no toxicity, grade IV indicates severe toxicity.

ANC = absolute neutrophil count (× 10^9 cells/L); **PLT** = platelet count (× 10^9 cells/L).

Table VIII. Recommended modifications to the dosage of polyethylene glycol-liposomal doxorubicin based on the occurrence of palmar-plantar erythrodysaesthesia (PPE) or stomatitis[36,43]

Toxicity grade[a]	Signs and symptoms at time of next scheduled treatment cycle		Dosage modification		
	PPE	stomatitis	UK[36]		US[43]
			4 or 5wk after prior dose	6wk after prior dose	
I	Mild symptoms which do not interfere with daily activities	Painless ulcers, erythema or mild soreness	Administer 100% of dose unless patient has experienced prior grade III or IV toxicity, in which case, wait an additional wk	Administer 75% of dose; return to original dose interval[b]	Administer 100% of dose unless patient has experienced prior grade III or IV toxicity, in which case, delay treatment by ≤2wk and administer 75% of dose; return to original dose interval
II	Erythema, desquamation or swelling which interfere with, but do not prevent, normal physical activity; small blisters or ulcerations <2cm in diameter	Painful erythema, oedema or ulcers, but able to eat	Wait an additional wk then administer 100% of dose	Administer 75% of dose; return to original dose interval[b]	Delay treatment by ≤2wk or until resolved to grade 0-I and administer 100% of dose. Discontinue if after 2wk no resolution occurs
III	Blistering, ulceration or swelling which interfere with normal physical or daily activities; cannot wear regular clothing	Painful erythema, oedema or ulcers, and unable to eat	Wait an additional wk then administer 100% of dose	Discontinue	Delay treatment by ≤2wk or until resolved to grade 0-I then administer 75% of dose and return to original dose interval. Discontinue if no resolution occurs after 2wk
IV	Diffuse or local process causing infectious complications, hospitalisation or bedridden state	Requirement for parenteral or enteral nutrition support			

a Grade 0 indicates no toxicity; grade IV indicates severe toxicity.

b Or discontinue treatment per physician's assessment (stomatitis only).

with regard to stomatitis and PPE (table VIII).[36,43] Once a dosage has been reduced, it should not be increased at a later time.[43] Pretreatment with or coadministration of antiemetics should be considered in patients with ovarian cancer.[43] Careful haematological monitoring must be performed frequently during administration (including white blood cell, neutrophil and platelet counts).[36,43] Caution must be used when coadministering any cytotoxic agents, especially myelotoxic agents, or drugs known to interact with standard doxorubicin.[36,43]

The risk of cardiac events with PEG-liposomal doxorubicin has not yet been adequately evaluated (section 5.1).[43] Thus, precautions taken when administering the standard formulation doxorubicin should also be followed when administering PEG-liposomal doxorubicin, such as excluding patients at high risk of cardiotoxicity.[36,43] Only when the benefits of treatment outweigh the risks should patients with a history of cardiovascular disease receive PEG-liposomal doxorubicin.[36,43] Acute left ventricular failure is more likely to occur in patients who have received a total cumulative doxorubicin dose of >550 mg/m^2 or in patients who have received mediastinal radiation or therapy with other potentially cardiotoxic agents than those who have not.[43]

The cardiac function of patients receiving PEG-liposomal doxorubicin should be carefully monitored by use of routine frequent electrocardiogram monitoring or LVEF evaluation.[36,43] The LVEF

needs to be measured before therapy starts and periodically during treatment, including before each additional administration of PEG-liposomal doxorubicin that exceeds a cumulative dose of 450 mg/m^2.[36] If cardiomyopathy is suspected, an endomyocardial biopsy should be carried out to provide the most definitive confirmation. Patients with possible cardiac injury should receive PEG-liposomal doxorubicin only when the benefits of treatment outweigh the risks.[36,43]

There is some evidence to suggest that the pharmacokinetics of PEG-liposomal doxorubicin are not changed in patients with hepatic dysfunction (section 3.3.1). However, in the absence of conclusive evidence, the manufacturer recommends that the dosage of PEG-liposomal doxorubicin be reduced in patients with elevated serum bilirubin levels as summarised in table IX.[36,43] Recommendations vary slightly between countries. Dose modification should not be required in patients with impaired renal function; however, no pharmacokinetic data are available in patients with a creatinine clearance of <1.8 L/h.[36]

The tolerability and efficacy of PEG-liposomal doxorubicin have not been established in patients aged <18 years.[36]

Contraindications to the use of PEG-liposomal doxorubicin include breast feeding and previous hypersensitivity events caused by conventional formulations of doxorubicin or components of the PEG-liposomal doxorubicin formulation.[36,43] PEG-liposomal doxorubicin is embryotoxic in animals. Women capable of bearing children should avoid pregnancy while receiving PEG-liposomal doxorubicin.[36,43]

Table IX. Recommended modifications to the dosage of polyethylene glycol-liposomal doxorubicin in patients with impaired hepatic function[a,36,43]

Serum bilirubin levels (mg/L)	Dosage modification (% of full dose)			
	UK[36]			US[43]
	dose 1	dose 2[b]	subsequent doses[b]	
12-30	75	100	100	50
>30	50	75	100	25

a Hepatic function should be evaluated before administration of polyethylene glycol-liposomal doxorubicin using conventional clinical laboratory tests.

b If previous dose is tolerated without an increase in serum bilirubin or liver enzyme levels.

7. Place of Polyethylene Glycol-Liposomal Doxorubicin in the Management of Solid and Haematological Malignancies and AIDS-Related Kaposi's Sarcoma

Standard doxorubicin is a well established chemotherapeutic agent in the treatment of many cancers; however, adverse events, particularly cardiotoxicity, limit the usefulness of the drug (section 1). By encapsulating the drug in liposomes, it may be possible to retain or improve the efficacy of doxorubicin while minimising adverse events. Early liposomal formulations were cleared rapidly from the bloodstream by the RES and thus had limited utility as therapeutic agents. The improved PEG-coated liposome formulation reviewed here is cleared at a slower rate (section 3.2.2). It has a substantially different pharmacokinetic profile from that of standard free doxorubicin, with a slower clearance and longer circulation time (section 3.1). Importantly, preliminary data also suggest that the PEG-liposomes preferentially localise in tumour tissue.

PEG-liposomal doxorubicin has been investigated in a number of different cancer types, both as monotherapy and in combination with other chemotherapeutic agents. These combination regimens, predominantly investigated in patients with metastatic breast cancer or haematological malignancies, often contain PEG-liposomal doxorubicin as a replacement for the standard formulation of doxorubicin in a commonly used regimen. As yet, the benefits of the PEG-liposomal formulation over standard doxorubicin have not been clearly established.

Ovarian Cancer

An important group in which PEG-liposomal doxorubicin has been evaluated is patients with refractory epithelial ovarian cancer. Paclitaxel plus cisplatin or carboplatin is recommended as first-line treatment for advanced ovarian cancer by the

US National Comprehensive Cancer Network[130] and has been reported to produce overall response rates of 73 to 75%.[131,132] Patients who experience progression while receiving initial therapy are recommended to receive supportive care, salvage therapy or to participate in a clinical trial.[130] Single-agent salvage therapy is recommended for disease that relapses less than 6 months after stopping initial therapy. Patients with disease that relapses greater than 6 months after stopping initial therapy are recommended to receive paclitaxel and/or platinum therapy or a salvage regimen.

No single chemotherapeutic agent is considered the treatment of choice for recurrent ovarian cancer in the guidelines. Agents listed as acceptable salvage options include PEG-liposomal doxorubicin, topotecan, gemcitabine, vinorelbine, oral etoposide, altretamine and ifosfamide.[130]

A number of clinical trials have demonstrated the activity of a variety of single agents and combination regimens in the treatment of relapsed ovarian cancer; some general observations regarding these studies have been noted (reviewed by Gibbs & Gore[133]). Response rates for all agents tend to be higher in patients with platinum-sensitive disease. Combination regimens are not clearly more effective than single-agent therapies, and in large trials in platinum- or paclitaxel-resistant disease, response rates range from about 15 to 25% and do not vary much between agents.[133]

On the basis of results from a large multicentre, randomised trial (section 4.1.1), PEG-liposomal doxorubicin monotherapy can be considered an effective second-line treatment option in patients with relapsed ovarian cancer refractory to platinum-based therapy.[64] PEG-liposomal doxorubicin was at least as effective as topotecan in the treatment of patients with ovarian cancer refractory or sensitive to first-line platinum-based chemotherapy. Furthermore, the adverse effects profile of PEG-liposomal doxorubicin differed from that of topotecan with a higher incidence of PPE and stomatitis than topotecan but fewer potentially fatal haematological adverse effects. An independent report by the National Institute for Clinical Excellence concluded that, based on the results from clinical trials and a cost-minimisation analysis combined with the relative ease of administration, PEG-liposomal doxorubicin may be the chemotherapy of choice for many, but not all, patients with advanced ovarian cancer for whom first-line treatment has failed.[75]

The efficacy of PEG-liposomal doxorubicin combination chemotherapy in the treatment of ovarian cancer has not been established.[36] However, PEG-liposomal doxorubicin in combination with topotecan, ifosfamide or gemcitabine has been found to have antineoplastic activity in patients with recurrent ovarian cancer in a number of small, noncomparative trials presented as abstracts (overall response rates of 19 to 43%; section 4.1.1). Response criteria differed between studies and few studies specified when disease had progressed in relation to previous therapy.

In patients with advanced ovarian cancer who had not been previously treated with chemotherapy, PEG-liposomal doxorubicin in combination with paclitaxel and carboplatin produced an 83% overall response rate (section 4.1.2).[134] This result justifies further studies comparing this regimen with the established first-line therapy of paclitaxel plus cisplatin or carboplatin.

Advanced Breast Cancer

The overwhelming majority of patients receiving treatment for metastatic breast cancer die of their disease; therefore palliation of symptoms and increasing the duration of high-quality life are the main goals of therapy in this group.[135,136] Chemotherapy, although widely used, is a problematic treatment option because any response achieved must be balanced against potentially severe adverse effects.[82] The use of relatively well-tolerated hormonal therapies is preferred to cytotoxic therapy,[137] therefore chemotherapy is recommended only for the treatment of hormone-refractory or life-threatening metastatic breast cancer.[98,135,137]

The optimal second-line regimen for metastatic breast cancer has not been established, but the anthracyclines (standard doxorubicin) and the

taxanes (paclitaxel, docetaxel) are widely recognised as the most active agents clinically.[138] Doxorubicin was regarded as the most active agent in metastatic breast cancer until recently, producing an average overall response rate of 34% as second-line treatment.[139] A trial comparing standard formulation and PEG-liposomal doxorubicin in patients with metastatic breast cancer demonstrated similar efficacy between the treatments (section 4.2.2); however, treatment with PEG-liposomal doxorubicin was associated with a significantly lower risk of cardiac adverse effects (section 5.1).[94] In recent phase III trials, docetaxel demonstrated greater efficacy as second-line therapy than standard formulation doxorubicin, as well as methotrexate plus fluorouracil and mitomycin plus vinblastine;[140] however, no direct comparisons have been made with PEG-liposomal doxorubicin.

A wide variety of single-agent or combination regimen options are in use as second-line therapies; there is no clear advantage with single-agent or combination chemotherapy.[98] Mitomycin, mitoxantrone, gemcitabine, cisplatin, etoposide and vinorelbine are other agents often used when the disease progresses further.[136]

According to the US National Comprehensive Cancer Network practice guidelines for breast cancer (updated in 2002),[141] the preferred first-line chemotherapy for metastatic breast cancer is an anthracycline-based regimen, a taxane or a combination of cyclophosphamide plus methotrexate and fluorouracil (CMF). Preferred second-line chemotherapy should include a taxane if the first-line therapy was anthracycline-based, or an anthracycline-based therapy or CMF if the first-line therapy was a taxane; capecitabine, fluorouracil, vinorelbine and mitoxantrone are also active.[141]

Monotherapy with PEG-liposomal doxorubicin 50 mg/m^2 every 4 weeks has demonstrated antitumour activity in patients with metastatic disease who have been previously treated with other chemotherapeutic agents (13% response rate with an average survival time of 10.4 months).[83] These results were similar to those achieved in 150 patients receiving two comparator salvage chemotherapy regimens consisting of vinorelbine or mitomycin C plus vinblastine (no statistical comparison reported). The fully published results of this trial are awaited with interest.

Regimens in which PEG-liposomal doxorubicin has been administered in combination with paclitaxel, vinorelbine, gemcitabine or hypothermia have produced promising results in previously treated patients with breast cancer (table IV); however, to date trials have been small and non-comparative and further studies are needed.

As first-line chemotherapy, PEG-liposomal doxorubicin has demonstrated significant antitumour activity in preliminary trials. In combination with docetaxel or paclitaxel, 56 to 71% of patients with metastatic breast cancer responded to treatment (table V).

AIDS-Related Kaposi's Sarcoma

Before the introduction of PEG-liposomal doxorubicin, BV and ABV were the principal combination chemotherapeutic regimens used as first-line treatment of life-threatening or visceral disease.[102,142] Bleomycin and vincristine in combination or as single agents are less myelosuppressive than ABV and are widely used to treat patients with leucopenia.[142] Other single-agent chemotherapies that have shown usefulness as systemic therapy include oral etoposide, teniposide, paclitaxel and vinorelbine;[102,142] however, no studies comparing the efficacy of these agents with ABV, BV or PEG-liposomal doxorubicin in Kaposi's sarcoma have been published.

According to two large randomised studies in patients with advanced Kaposi's sarcoma, PEG-liposomal doxorubicin is more effective than the principal combination chemotherapeutic regimens of ABV and BV in eliciting a response and has also demonstrated a trend towards improved patient survival versus BV (section 4.3.1).[104,106] PEG-liposomal doxorubicin was also better than ABV and BV at improving some aspects of quality of life and reducing disfiguring characteristics and pain (section 4.3.2).[110] The drug continues to be effective during long-term administration.[108]

Although direct comparisons with other single-agent treatments with efficacy in this disease (such as paclitaxel) are warranted, the findings above have helped to establish PEG-liposomal doxorubicin as the preferred first-line chemotherapeutic agent for extensive Kaposi's sarcoma.[142]

Haematological Malignancies

The standard first-line chemotherapeutic regimen for multiple myeloma is currently oral or intravenous melphalan plus oral prednisone.[112,113] This regimen is well tolerated and produces consistent results. In multiple myeloma resistant to alkylating agents, combinations of VAD or VAD plus carmustine are commonly used.[112] In patients with advanced stage non-Hodgkin's lymphoma, CHOP is considered to be the standard first-line therapy.[119]

The risk of cardiotoxicity with the standard doxorubicin-based VAD and CHOP regimens may be reduced by replacing doxorubicin with PEG-liposomal doxorubicin. Data are limited, but anticancer activity has been observed in studies conducted in small numbers of patients receiving PEG-liposomal doxorubicin instead of standard doxorubicin in the VAD and CHOP regimens (section 4.4). The clinical importance of these results have not yet been established.

Tolerability

The most common dose-limiting adverse events in patients with Kaposi's sarcoma are haematological, with leucopenia being the most frequent event in pooled tolerability data.[36] The most common events in patients with ovarian cancer are PPE, stomatitis and nausea.[43] Recommendations from the manufacturer to delay or reduce the next drug dose if these events occur[43] may help to reduce or minimise subsequent adverse effects. Of interest is the possibility that pyridoxine may help to manage PPE,[116] although further data are required to confirm this observation.

Overall discontinuations due to adverse events were similar with PEG-liposomal doxorubicin and topotecan in patients with ovarian cancer (section 5.2). Incidences of haematological adverse events and alopecia were significantly lower with PEG-liposomal doxorubicin than with topotecan (sections 5.2.1 and 5.2.2), but grade III or IV PPE and stomatitis were significantly more common with PEG-liposomal doxorubicin (section 5.2.1).

Haematological adverse events and alopecia are significantly less likely to occur with PEG-liposomal doxorubicin than with topotecan in patients with relapsed ovarian cancer; however, PPE and stomatitis are significantly more common with PEG-liposomal doxorubicin than topotecan (section 5.2).[64]

Cardiotoxicity, a well-recognised adverse event associated with the anthracyclines, is clearly a point of interest for the PEG-liposomal formulation of doxorubicin. PEG-liposomal doxorubicin is associated with cardiotoxicity in some patients; incidence rates of up to 3.4% have been reported with the formulation in clinical trials, and in pooled tolerability data, 12% of 66 patients who had received a cumulative dosage of >400 mg/m^2 experienced cardiotoxicity (section 5.1). Preliminary results from a large comparative trial of standard formulation doxorubicin and PEG-liposomal doxorubicin in patients with metastatic breast cancer indicate that the standard formulation is associated with a significantly higher risk of cardiac events than PEG-liposomal doxorubicin (section 5.1).[94] However, current recommendations regarding the maximum cumulative dosage of doxorubicin are the same for both formulations.

Conclusion

PEG-liposomal doxorubicin is effective as a second-line chemotherapy in patients with platinum-refractory ovarian cancer and in patients with metastatic breast cancer. As with all chemotherapeutic agents, the benefits of treatment need to be weighed against the agent's tolerability profile; however, the PEG-liposomal formulation of doxorubicin has an improved tolerability profile compared with the standard formulation. Preliminary trials of this drug in combination with other chemotherapeutic agents have been promising and further studies are warranted.

Strong comparative data have helped to establish PEG-liposomal doxorubicin as the first-line

treatment option in patients with advanced Kaposi's sarcoma. Anticancer activity has also been observed in studies conducted in small numbers of patients with multiple myeloma or non-Hodgkin's lymphoma receiving PEG-liposomal doxorubicin instead of standard doxorubicin in standard combination regimens, although further data are needed to confirm the clinical relevance of these findings.

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