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Phase I and pharmacokinetic trial of liposome-encapsulated doxorubicin

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Abstract. A total of 21 patients with advanced cancer were entered into a phase I study to determine the maximum tolerable dose (MTD) of liposome-encapsulated doxorubicin (LED) given weekly for 3 consecutive weeks at doses of 20, 30, or 37.5 mg/m^2 per week. For a comparison of the pharmacokinetic behavior of LED with that of standard-formulation doxorubicin, 13 patients received a dose of standard-formulation doxorubicin 2 weeks prior to the first dose of LED. All doses were given by 1-h infusion through a central vein. Toxicity was evaluated in 22 courses delivered to 17 patients. The MTD with this schedule was 30 mg/m^2 per week $\times 3$. The single patient treated at 37.5 mg/m^2 weekly could not complete the entire course due to myelosuppression. At the dose of 30 mg/m^2 per week, three of eight patients had grade ≥ 3 leukopenia. Other toxicities included mild to moderate thrombocytopenia, nausea, vomiting, fever, alopecia, diarrhea, fatigue, stomatitis, and infection. At the dose of 30 mg/m^2 per week, the total doxorubicin AUC and peak total doxorubicin concentrations in plasma were 8.75 ± 8.80 μM h (mean $\pm$ SD) and 3.07 ± 1.45 μM, respectively, after LED administration. The total doxorubicin AUC and peak total doxorubicin concentrations in plasma were 3.92 ± 2.47 μM h and 2.75 ± 2.70 μM, respectively, after the infusion of standard-formulation doxorubicin. The total body clearance of doxorubicin was 18.42 ± 11.23 l/h after the infusion of LED and 31.21 ± 15.48 l/h after the infusion of standard-formulation doxorubicin. The mean elimination half-lives of doxorubicin were similar: 8.65 ± 5.16 h for LED and 7.46 ± 5.16 h for standard-formulation doxorubicin. Interpatient variability in pharmacokinetic parameters as demonstrated by the percentage of coefficients of variation was 33%–105%. There was no relationship between the percentage of WBC decrease or the duration of WBC suppression and the total doxorubicin or doxorubicinol AUC. There was no correlation between the duration of leukopenia and drug exposure as reflected by the AUC of liposome-associated doxorubicin. LED can be given in doses similar to those of standard-formulation doxorubicin and produces acute toxicities similar to those caused by standard doxorubicin.

Introduction

The potential of liposomes as drug carriers in cancer chemotherapy has attracted considerable interest in recent years and has been the subject of a number of reviews [9, 16]. Researchers have investigated the usefulness of liposome encapsulation of doxorubicin as a means of ameliorating its toxicities while maintaining or improving its antitumor effect [2, 4, 5, 10, 14, 18, 19]. Preclinical studies with liposomes of various compositions and sizes have suggested that encapsulation of doxorubicin in liposomes results in less cardiotoxicity, equivalent antitumor activity, and prolonged circulation of the drug. The mechanism of these actions is unknown. Degradation of the liposome and liberation of doxorubicin could occur intra- or extracellularly. Liposomes could also act as slow-release reservoirs. The pharmacokinetics, antitumor activity, and toxicity vary with the size and composition of the liposome carrier [3, 7, 15].

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Abbreviations: MTD, maximum tolerable dose; LED, liposome-encapsulated doxorubicin; AUC, area under the plasma concentration $\times$ time curve; WBC, white blood cell count; PLT, platelet count; ECOG, Eastern Cooperative Oncology Group; EKG, electrocardiogram; MUGA, multigated nuclide scan; CLTB, total body clearance; PC, phosphatidylcholine; PG, phosphatidylglycerol; PEG-DSPE, polyethylene glycol conjugated to distearoyl phosphatidylethanolamine; HSPC, hydrogenated soy phosphatidylcholine; chol, cholesterol

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We performed a phase I trial of a new liposome-encapsulated doxorubicin (LED) formulation. Our study used egg PC/chol liposomes with a diameter of less than 1 μm. Encapsulation of doxorubicin, accomplished at the clinical site, was based on the movement of lipophilic cations across membranes in the presence of a pH gradient [13]. This method overcomes a number of potential pharmaceutical problems: (1) doxorubicin needs to be trapped in the liposome only for hours rather than for the much longer period required for preformulated preparations, (2) over 90% of the free doxorubicin is entrapped, and (3) only relatively small amounts of biodegradable lipids are necessary. A limitation of previous studies of LED formulations was the inability to compare the pharmacokinetic behavior of LED with that of standard-formulation doxorubicin in the same patient. Consequently, we gave the same dose of standard-formulation doxorubicin prior to LED to a cohort of patients so as to compare directly the pharmacokinetic behavior of the two formulations. In addition, we attempted to ascertain how much of the delivered LED dose was liposome-associated and, therefore, possibly not bioavailable. We also attempted to correlate drug exposure with toxicity.

Patients and methods

Eligibility criteria. Patients eligible for study had to have histological proof of a malignant solid tumor for which conventional therapy had either failed or was unavailable. Patients had to have recovered from all toxicities of prior treatment and were required to have received no radiation or chemotherapy within 4 weeks of entry (8 weeks for drugs with delayed toxicity such as nitrosoureas or mitomycin C). A minimal life expectancy of 12 weeks and an ECOG performance status of ≤ 2 were required. Patients must have had adequate bone marrow function (WBC, $\geq 3{,}500$ cells/μl; PLT, $\geq 100{,}000$/μl), adequate liver function (bilirubin, ≤ 1.5 mg/dl), and adequate renal function (serum creatinine, ≤ 1.5 mg/dl). All patients signed an informed consent form approved by the Institutional Review Boards of the University of Maryland and the National Cancer Institute. Patients with evidence of congestive heart failure or a prior history of life-threatening cardiac arrhythmia, prior anthracycline treatment, or treatment with >100 mg/m^2 mitoxantrone and evidence of congestive heart failure were excluded. Pregnant patients and patients with an allergy to eggs were excluded. Sexually active fertile patients must have consented to the use of effective birth control, and sexually active fertile women must have had a negative serum pregnancy test prior to drug administration.

Prior to each course, a history and physical examination were performed and the tumor size was assessed, if possible. Baseline determinations of serum electrolytes, urea nitrogen, creatinine, bilirubin, calcium, phosphorus, and magnesium; liver-function studies, urinalysis; chest X-rays; and EKGs were obtained within 1 week of study entry. A MUGA scan was done if clinically indicated. Toxicity assessment (graded with the scale developed by the Cancer Therapy Evaluation Program, National Cancer Institute, USA), history, physical examination, and baseline serum studies were repeated weekly.

Drug formulation, availability, and purity. Drug and LED kits were supplied by the Division of Cancer Treatment, National Cancer Institute, which was responsible for purity and stability. The LED kits consisted of a three-vial system designed for entrapment of doxorubicin at the clinical site. Briefly, an appropriate amount of 0.9% sodium chloride for injection was injected into a vial containing 20 or 50 mg doxorubicin (Adria Laboratories, Columbus, Ohio, USA): lactose: methyl paraben in a weight ratio of 1 : 5 : 0.1 and the vial was shaken to dissolve the doxorubicin. Liposome vehicle was prepared by mixing an appropriate volume of 0.5 *M* sodium carbonate (pH 10.8–12.0) with egg PC/chol liposomes measuring <1 μm in diameter (100 mg total lipid/ml 300 m*M* citric acid buffer, pH 3.7–4.5). An appropriate volume of the vehicle was then mixed with the prepared doxorubicin solution, shaken vigorously for 10 s, heated for 1 min in a 55°–60° C water bath, and shaken again for 10 s. This procedure was repeated twice. The mixture was heated at 55°–60° C for an additional 7 min and again shaken vigorously. The solution was protected from light and used within 8 h of preparation. This method of preparation has been reported to entrap >90% of the free doxorubicin [13]. The final concentrations of lipid and doxorubicin in the preparation were 7 and 2 mg/ml, respectively.

Drug administration. At 2 weeks prior to the planned administration of the first dose of LED, patients received standard-formulation doxorubicin at the same dose as that of the planned weekly LED infusion. After 2 weeks, if WBC, PLT, and liver-function values had recovered to at least the eligibility levels, patients received LED at 20, 30, or 37.5 mg/m^2 per week. This allowed each patient to serve as his own control for pharmacokinetics studies. After the MTD, defined as the dose that resulted in reversible grade ≥ 3 toxicity in at least two patients at a given dose, had been reached in this initial schedule, an additional seven patients received LED alone at 30 mg/m^2 per week. This was done to exclude any possible contribution to the MTD by the myelosuppressive effect of the initial dose of standard-formulation doxorubicin. All drug was infused through a free-flowing central venous catheter over 1 h. The initial dose of LED for each patient was delivered during an overnight hospital admission. Other doses were given on an outpatient basis. Doses were not escalated or decreased in a given patient, but doses were delayed if the WBC was $\leq 2{,}000$ cells/μl or the PLT was $\leq 75{,}000$/μl. Patients had their temperature and blood pressure recorded every 6 h during the 24 h after the initial dose of LED and did not receive prophylactic antiemetics prior to the initial dose. Drug courses were repeated every 28 days, provided that the patient had recovered from previous drug-induced toxicity.

Pharmacokinetics. Blood samples were obtained before treatment and at the following times after the initiation of the infusion of standard-formulation doxorubicin and the first weekly dose of LED: 0.5, 1.0, 1.08, 1.17, 1.33, 1.5, 2, 4, 6, 9, 13, 17–19, 24, 48, and 72 h. Plasma was immediately separated from whole blood by centrifugation for 10 min at 1,000 *g*. For patients treated at or above the 30-mg/m^2 weekly dose, a 0.25- to 1.0-ml aliquot of each plasma sample was applied to a carboxylic acid column that had previously been conditioned with sequential washes of methanol and 10 m*M* potassium phosphate buffer (pH 7.0). Free and liposome-associated doxorubicin were separated by the method of Thies et al. [20]. Drug associated with liposomes was eluted with 1.5 ml 10 m*M* phosphate buffer (pH 7.0). After the column had been washed with 1 ml 0.1 *N* HCl, free drug was eluted with 1 ml methanol : 0.1 *N* HCl (9 : 1, v/v). Samples were then stored at –20° C until analysis.

Determination of doxorubicin and doxorubicinol was accomplished by high-performance liquid chromatography (HPLC) [1]. Briefly, 1 ml plasma or carboxylic acid column eluate was mixed with 15 μl 4′-epidoxorubicin (2 μg/ml) internal standard. Doxorubicin was extracted with 2 ml chloroform : isopropanol (1 : 1, v/v) and an excess of ammonium sulfate. HPLC was performed with an Alltech (Alltech Associates, Deerfield, Ill., USA) C_{18} Econosil column with a 10-μm particle size, a length of 25 cm, and an internal diameter of 4.6 mm. The mobile phase consisted of acetonitrile: 0.32 *M* *O*-phosphoric acid (27 : 73, v/v) pumped at a flow rate of 1 ml/min. Fluorescence detection was accomplished with an excitation wavelength of 470 nm and an emission wavelength of >500 nm. With this method, good separation of doxorubicin, doxorubicinol, and internal standard was achieved with retention times of 12.5, 7, and 15 min, respectively. The limit of detection of doxorubicin was 0.1 n*M*. Doxorubicin pharmacokinetics were modeled as a two-compartment model with the PCNONLIN pharmacokinetic modeling package (Statistical Consultants, Inc., Lexington, Ky., USA). Doxorubicinol AUCs were determined with the trapezoidal rule as implemented by the MLAB computer modeling package [11].

Table 1. Patients' characteristics

Number of patients entered	21
Number of patients evaluable	17
Male	10
Female	7
Median age	60 (range, 22–77) years
Median performance status (ECOG)	1 (range, 0–2)
Tumor type (evaluable patients):	
Colorectal carcinoma	4
Squamous head and neck carcinoma	3
Hepatocellular carcinoma	2
Mesothelioma	2
Other:	6
(1 each: cervical carcinoma, osteosarcoma, adenocarcinoma of unknown primary, non-small-cell lung carcinoma, endometrial carcinoma, adenocarcinoma of the esophagus)	
Prior therapy:	
None	2
Chemotherapy	6
Radiation	1
Both	8

Table 2. Leukocyte toxicity observed with LED

Dose (mg/m^2 weekly)	Number of patients/ courses	WBC toxicity grade				
		0	1	2	3	4
20[a]	3/3	1	1	1	0	0
30[a]	8/11	2	2	2	2	0
30	5/6	1	1	0	3	0
37.5[a]	1/2	0	0	0	0	1

[a] Standard-formulation doxorubicin was given 2 weeks prior to administration of the first course of LED

Table 3. Nonhematologic toxicity observed with LED

Toxicity	Grade				
	0	1	2	3	4
Nausea/vomiting	7	6	1	3	0
Fever	7	1	9	0	0
Infection	14	0	0	3	0
Mucositis	14	1	1	1	0
Diarrhea	15	1	0	0	1
Alopecia	14	1	2	0	0

Results

Patient's characteristics

Characteristics of the patients enrolled in the study are shown in Table 1. Four patients were not evaluable for toxicity. One patient received only 10 min of standard-formulation doxorubicin before therapy was discontinued because the results of coagulation studies revealed disseminated intravascular coagulopathy. A second patient received a dose of standard-formulation doxorubicin and one dose of LED but developed severe hip pain from metastatic disease and had to be removed from study for radiation therapy. A third patient, who had hepatoma, developed liver failure from progressive disease after receiving two doses of LED. A fourth patient, who also had hepatoma, developed cholangitis, thought to be disease-related, after receiving two doses of LED and had to be removed from study.

Toxicity

The MTD of LED given as a 1-h infusion weekly for 3 weeks was 30 mg/m^2 per week. Although wide interpatient variability was observed, WBC toxicity was dose-related and dose-limiting (Table 2). The single patient treated at a dose of 37.5 mg/m^2 weekly could not complete the planned 3-week course due to severe leukopenia. At the dose of 30 mg/m^2 per week, two of eight patients who had received a dose of standard-formulation doxorubicin prior to LED had at least grade 3 leukopenia. A second cohort of patients was treated at 30 mg/m^2 per week without the initial dose of standard-formulation doxorubicin. Three of five patients treated with LED alone at 30 mg/m^2 weekly had at least grade 3 leukopenia. A leukopenia-related delay in the weekly $\times 3$ treatment occurred in one patient after two LED doses at 37.5 mg/m^2 per week. One patient (at 30 mg/m^2 per week) had LED discontinued after the second dose of course 2 due to the development of pneumonia during a period of neutropenia (WBC nadir, 2,400 cells/μl). Thrombocytopenia was mild. Only one patient (at a dose of 30 mg/m^2 per week) developed grade ≥ 2 thrombocytopenia.

Anemia was common. Many patients had lower than normal hemoglobin levels prior to entering the study; therefore, the percentage of decrease in hemoglobin ([pretreatment hemoglobin – nadir hemoglobin/pretreatment hemoglobin] $\times 100$) was calculated for each course. The median (range) percentage of decrease in hemoglobin was 12.5% (range, 4%–31%) at 20 mg/m^2 per week, 13.8% (range, 0–31.5%) at 30 mg/m^2 per week with a prior dose of standard-formulation doxorubicin, and 22.6% (range, 3.7%–31.4%) at 30 mg/m^2 per week without prior dosing with standard-formulation doxorubicin. The percentage of decrease in hemoglobin was 31% and 32% in the single patient (two courses) treated at a dose of 37.5 mg/m^2 per week.

Other severe toxicities (Table 3) were observed in three patients who developed severe nausea and vomiting at a dose of 30 mg/m^2 per week. Fever of up to grade 2 (approximately 39° C) was observed in ten patients within 24 h of the LED infusion. Three patients developed fevers while granulocytopenic: one developed *Klebsiella* pneumonia; one had grade 3 mucositis and grade 4 diarrhea; and one had fever that resolved on the administration of broad-spectrum antibiotics, although no definite source of infection was documented. All of these patients had received LED at a dose of 30 mg/m^2 per week. Alopecia, mild to moderate stomatitis, mild to moderate nausea and vomiting, and reactivation of oral herpes simplex infection were also seen in a minority of patients. No hepatic or renal toxicity was observed. One patient experienced severe

Table 4. Pharmacokinetic parameters expressed as mean values ± standard deviation of the mean

Dose (mg/m² weekly)	[Peak] (μ*M*)	$t^1/_2\alpha$ (h)	$t^1/_2\beta$ (h)	AUC (μ*M* h)	CLTB (l/h)	Vd (l)
Total doxorubicin (standard formulation):						
20	2.0±1.6	0.3±0.4	21.3±19.5	17 ±22	41.7±33.8	16.7±11.4
30	2.8±2.7	0.1±0.02	7.5± 5.2	3.9± 2.5	31.2±15.5	5.1± 2.8
37.5[a]	1.7	0.05	9.4	3.02	37.1	5.6
Total doxorubicin (liposomal formulation):						
20[b]	2.0±0.5	0.5±0.4	11.9± 6.8	7.7± 1.5	7.2± 1.8	13.7± 2.7
30[b]	3.1±1.4	0.1±0.1	8.6± 5.2	8.8± 8.8	18.4±11.2	4.9± 2.9
30	4.7±2.2	0.2±0.1	25.1±35.5	42.6±44.4	9.8±10.7	7.1± 4.0
37.5[a]	2.3	0.2	8.0	4.9	22.8	18.4

[a] 1 patient only
[b] Standard-formulation doxorubicin was given 2 weeks prior to administration of the first dose of LED

Table 5. Comparison by dose level of the doxorubicinol AUC (mean ± SD) after the administration of standard-formulation doxorubicin and LED

Dose (mg/m²)	Doxorubicinol AUC (μ*M* h)	
	After standard formulation	After liposomal formulation
30[a]	1.42±1.81	0.95±0.99
30	N/A	0.6 ±0.7
37.5[b]	2.5	2.2

NA, Not applicable
[a] Standard-formulation doxorubicin was given 2 weeks prior to administration of the first dose of LED
[b] 1 patient only

back pain during the infusion of LED, prompting a cessation of the infusion. The pain resolved within 1 h, and the infusion was resumed without recurrence of the pain. No back pain developed during subsequent LED infusions in this patient. One patient was removed from study because of a decrease in ejection fraction as demonstrated by MUGA; however, the ejection fraction later returned to baseline.

Pharmacokinetics and pharmacodynamics

A biexponential model fit better than a triexponential model in 9 of 11 data sets in comparisons using the Akaike Information Criterion. At all doses, wide interpatient variability was observed in the parameters describing the plasma pharmacokinetics of total doxorubicin after the infusion of either standard-formulation doxorubicin or LED (Table 4). Mean peak plasma doxorubicin concentrations were not significantly different after the administration of LED as compared with the administration of standard-formulation doxorubicin. At doses exceeding 20 mg/m² per week, mean AUCs were larger for patients who received LED as compared with those who received standard-formulation doxorubicin, but the large standard deviations make it difficult for us to have confidence in this result. A comparison of these parameters for the two formulations in individual patients revealed that in two of three patients, the peak total doxorubicin concentrations in plasma and the AUCs were greater after the infusion of LED at 20 mg/m² than after the infusion of an identical dose of standard-formulation doxorubicin. At 30 mg/m², the peak total doxorubicin concentrations were greater in four of eight patients and the AUCs were greater in five of eight patients after the infusion of LED than after the infusion of an identical dose of standard-formulation doxorubicin. No definite relationship between doxorubicin clearance and dose was observed in the narrow range of doses studied.

In six patients in whom measurements of free and liposome-associated doxorubicin concentrations in plasma were performed, liposome-associated doxorubicin accounted for 49%–100% of the total doxorubicin concentrations. Plasma doxorubicinol concentrations were measured as possible markers of doxorubicin bioavailability (Table 5). Doxorubicinol was not detected at the 20-mg/m² weekly dose of either standard-formulation doxorubicin or LED. At 30 mg/m² per week, the AUC of doxorubicinol was 1.42±1.81 μ*M* h in seven patients after the administration of standard-formulation doxorubicin and 0.95±0.99 μ*M* h in the same patients following the infusion of LED (Table 5). In six patients who received LED alone, the doxorubicinol AUC ranged from 0 to 1.91 μ*M* h.

Because total granulocyte counts were not consistently available in all patients but were proportional to the WBC, the percentage of decrease in WBC was compared with measures of doxorubicin exposure. There was no relationship between the percentage of decrease in WBC and the total doxorubicin AUC. Likewise, the AUC of doxorubicinol or of total doxorubicin + doxorubicinol after the administration of LED did not correlate with the percentage of decrease in WBC. No correlation existed between the duration of WBC suppression and the AUC of either total or liposome-associated doxorubicin. The observed myelosuppression did not differ in the 14 patients who had previously received chemotherapy versus the 2 chemotherapy-naive patients.

Discussion

No dramatic increase in MTD was observed with the LED formulation used in the current trial as compared with the expected MTD of standard-formulation doxorubicin. Fe-

vers related to drug infusion have been observed with other liposome formulations [6]. The other nonhematologic toxicities observed in our trial were very similar to those expected for standard-formulation doxorubicin.

Given that liposomes measuring about 1 μm in diameter have been reported to concentrate in reticuloendothelial sites [3, 8], it was theoretically possible that LED might have produced myelosuppression more severe than that reported for standard-formulation doxorubicin. This did not prove to be the case, however. Other LED formulations have also been reported to have MTDs similar to that of standard-formulation doxorubicin. Rahman et al. [17] reported an MTD of 90 mg/m^2 given every 21 days in their study, which used liposomes of different lipid composition but of a size similar to that of the liposomes used in our study. Gabizon et al. [6] have reported an MTD of 120 mg/m^2 given every 21 days for smaller liposomes, measuring <0.5 μm in diameter, composed of PG/PC/chol. Doxorubicin encapsulated in very small liposomes composed of PEG-DSPE/HSPC/chol/alpha-tocopherol ("stealth" liposomes) has shown less accumulation in the reticuloendothelial system in mice [15] than other LED formulations and has a different toxicity profile as well. Most LED formulations have shown decreased uptake in the heart as compared with standard doxorubicin formulations [4, 10, 18], offering hope that longer treatment may be possible with LED than with standard-formulation doxorubicin. Our study did not have enough patients receiving significant cumulative doses of LED to enable conclusions to be drawn on cardiac toxicity. Likewise, there were too few patients who had not received previous chemotherapy for an evaluation to be made as to whether patients who had previously been treated with chemotherapy were more likely to develop severe myelosuppression.

Our studies confirm that LED therapy is associated with wide interpatient pharmacokinetic variability. LED did not consistently produce higher peak doxorubicin concentrations in plasma or greater doxorubicin AUCs than did standard-formulation doxorubicin, although higher values for these parameters were noted in about half of the patients in whom the pharmacokinetic behavior of LED was compared with that of standard-formulation doxorubicin. This observation contrasts somewhat with that of Rahman et al. [17], who reported peak plasma concentrations and AUCs for cardiolipin/PC/chol/stearylamine liposomes of similar diameter (range, 0.9–1.2 μm) that were higher than those historically reported for standard-formulation doxorubicin. However, that study did not employ the same duration of infusion for all doses and did not compare the pharmacokinetics of the LED formulation with those of standard-formulation doxorubicin in the same patient. Mean plasma doxorubicinol concentrations were not very different overall in patients after the infusion of LED as compared with those in the same patients following the administration of standard-formulation doxorubicin. This observation could imply that pharmacodynamically similar amounts of doxorubicin were available from both preparations. Measurement of the amount of doxorubicin associated with liposomes also revealed great interpatient variability and did not contribute to a greater understanding of the bioavailability of doxorubicin delivered in LED.

In our study, measures of exposure to either doxorubicin, doxorubicinol, or both could not be correlated with the degree of myelosuppression. The degree of myelosuppression observed varied widely within this patient population. Because myelosuppression was the major toxicity, it is conceivable that higher doses could be given to individual patients along with appropriate colony-stimulating factors.

It is also possible that doses of LED equivalent to those of standard-formulation doxorubicin may have therapeutic advantages, even if toxicity advantages are not observed. Several investigators [4, 5, 15, 19] have reported increased tumor uptake and/or killing with LED as compared with the standard-formulation drug. As with toxicity, this property is related to both the size and the lipid composition of the encapsulating liposome. In addition to direct antitumor effects, LED has also been reported to have improved efficacy in multidrug-resistant cells [14]. Encapsulation of doxorubicin in liposomes may also enhance the activity of host tumoricidal cells [12]. Antitumor activity has been reported for LED in a phase II trial in breast cancer patients [21].

In summary, LED composed of egg PC/chol and with a diameter of <1 μm can be given in doses similar to those of standard-formulation doxorubicin without producing significantly different toxicity. The administration of LED results in higher peak plasma doxorubicin concentrations and AUCs in some patients as compared with the administration of similar doses of standard-formulation doxorubicin. Phase II studies are needed to determine whether the antitumor activity is improved by encapsulation of doxorubicin in liposomes or whether the administration of doxorubicin in LED can allow the delivery of higher cumulative doses of doxorubicin without resulting in cardiotoxicity.

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