Direct Comparison of Liposomal Doxorubicin with or without Polyethylene Glycol Coating in C-26 Tumor-bearing Mice: Is Surface Coating with Polyethylene Glycol Beneficial?1

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ABSTRACT

Sterically stabilized liposome is characterized by a surface coating of polyethylene glycol (PEG) or other polymers that can reduce opsonization of the liposome by plasma proteins. It has a higher plasma area under the concentration-time curve (AUC), which is believed to correlate with better therapeutic efficacy. However, the presence of large molecules on the liposomal surface may reduce the interactions of liposomes with cells and hinder entry of liposomes into the tumor tissue. Using a stable liposomal system composed of distearoyl phosphatidylcholine/cholesterol, we examined the effect of PEG (M, 2000) on the pharmacokinetics and on the efficacy of liposomal doxorubicin with C-26 syngeneic tumor model in BALB/c mice. The plasma AUC of liposomal doxorubicin with 6 mol-% PEG-modified distearoylphosphatidylethanolamine (PEG-DSPE) was approximately twice that of liposomal doxorubicin without PEG at various dosages, regardless of whether the mice were tumor-bearing. Paradoxically, the group of mice treated with liposomal doxorubicin without PEG had higher tumor doxorubicin concentrations. The 72-h tumor AUC was 1.44 times that of liposomal doxorubicin with 6% PEG-DSPE. The tumor-accumulation efficiency (AUCTumor/AUCPlasma) of liposomal doxorubicin without PEG was 0.87, and this was more than twice that of the liposomal doxorubicin with 6% PEG-DSPE (0.31). At a dose of 10 mg/kg, although both liposomal groups were better than the free drug group in terms of clinically relevant parameters, including toxicity, tumor shrinkage, and survival, there was no difference between the two liposomal drug groups. In this stable liposome system, surface coating with PEG offered no benefit for liposomal doxorubicin in the C-26 tumor model. To enhance the therapeutic index of liposomal doxorubicin, simply increasing plasma AUC by surface coating with PEG may not be satisfactory.

INTRODUCTION

Liposomal drug delivery systems have been studied extensively to increase the therapeutic index of chemotherapy. Conventional liposomes, composed of natural phospholipids mixed with varying amounts of cholesterol, are removed from circulation by the RES within a few minutes to a few hours, subsequent to the acquisition of opsonins from plasma (1–3). Because of this short circulation half-life, the use of conventional liposome has limited clinical applications.

The fact that some polymers, such as PEG, GMI ganglioside, and cerebroside sulfate, are able to inhibit opsonization of the liposomes by plasma proteins and to increase the half-life of liposomal drugs (4–6) has renewed activity in the area of liposomal drug-delivery systems (5, 7, 8). Prolonged circulation of liposomes has been linked to better therapeutic efficacy of liposomal anthracyclines, possibly related to increased accumulation of drug-loaded liposomes in tumor tissue (9, 10).

However, the presence of large molecules such as PEG on the liposomal surface may reduce the interactions of liposomes with cells and hinder entry of liposomes into the tumor tissue (11, 12), thereby possibly reducing the accumulation of liposomal drugs in the tumor tissue. A recent report, in which a maximal tolerated dose of liposomal doxorubicin (55 mg/kg) was used to study the accumulation of drug in the tumor, demonstrated that the use of PEG-modified liposomes may be of little advantage in terms of maximizing drug accumulation in tumor sites (11). These data further raised the question of whether PEGylation is beneficial for cancer therapy.

In addition, the use of phospholipid with a high transition temperature is also necessary for prolongation of circulation time of liposomal drugs (13). At doses of 55 mg/kg, DSPC/cholesterol liposomal doxorubicin with PEG only has a 1.5-fold increase in plasma AUC compared with the PEG-free liposomal...
doxorubicin (11, 12). Could a liposomal drug composed of phospholipid with a higher transition temperature, such as DSPC (14–16), even without PEG coating have antitumor activity equivalent to or better than a sterically stabilized one? At a commonly used dose for therapeutic study, 10 mg/kg, we directly compared the pharmacokinetic and therapeutic effects of liposomal doxorubicin with the same lipid components but with different PEG percentages to explore the necessity of PEGylation.

MATERIALS AND METHODS

Chemicals. Doxorubicin was obtained from Farmitalia Carlo Erba (Milan, Italy). DSPC, cholesterol, and PEG (average $M_f$ 2000)-derived DSPE (PEG-DSPE) were obtained from Avanti Polar Lipids (Alabaster, AL). The lipids were dissolved in chloroform, sealed in ampoules under argon, and stored at $-20^\circ$C before use. Cell culture materials were obtained from Life Technologies (Gaithersburg, MD). All other chemicals were obtained from Sigma Chemical Co. (St. Louis, MO).

Preparation of Doxorubicin-loaded Liposomes. Small unilamellar vesicles (size < 100 nm) were prepared by a combination of the standard thin-film hydration method and repeated extrusion as described previously (17, 18). Briefly, liposomes were composed of DSPC, cholesterol (3:2 molar ratio) with PEG-DSPE as indicated. Contents were hydrated at 55°C in ammonium sulfate solution [250 mM (NH$_4$)$_2$SO$_4$ (pH 5.0) 530 mOs] and extruded through polycarbonate membrane filters (Costar, Cambridge, MA) of 0.1 and 0.05 μm pore size using high-pressure extrusion equipment (Lipex Biomembranes, Vancouver, British Columbia) at 55°C. Doxorubicin was encapsulated by a remote loading method at a concentration of 1 mg of doxorubicin per 10 μmol of phospholipid. The final concentration of liposome was estimated by phosphate assay. After 1 ml of acidic isopropanol (81 mM HCl in isopropanol) was added to 0.2 ml of diluted drug-loaded liposomes, the amount of doxorubicin trapped inside the liposomes was determined with a spectrofluorometer (Hitachi F-4500). If required, the sample volumes were adjusted so that the doxorubicin level fell within the range of the standard curve. The resulting data were converted to doxorubicin fluorescent equivalents derived from a standard curve prepared from doxorubicin. High performance liquid chromatographic analysis of selected samples was performed to provide an indication of the amount of fluorescence that was due to nonmetabolized doxorubicin.

Pharmacokinetic analysis was done by nonlinear least squares analysis using Pkana software (MicroMath, Inc., Salt Lake City, UT). The following biexponential model was fitted to the plasma concentration-time data:

$$c_{(t)} = A_1 \cdot e^{-kt_1} + A_2 \cdot e^{-kt_2}$$

where $c_{(t)}$ is the drug concentration (Y axis) at time $t$ (X axis); $k_1$ and $k_2$ are slopes or apparent first-order elimination rate constants; and $A_1$ and $A_2$ are the $Y$-intercepts.

The AUC was calculated from the sums of the ratios $A_1/k_1$ and $A_2/k_2$. The clearance was calculated by dividing the dose by the AUC. The volume of distribution at steady state ($V_{ss}$) and mean residence time ($MRT$) were calculated using the following equations:

$$V_{ss} = \frac{\text{Dose} \cdot \text{AUMC}}{\text{AUC}^2}$$

$$MRT = \frac{\text{AUMC}}{\text{AUC}}$$

where $AUMC$ was the area under the product of $c \cdot t$ plotted against $t$ from time 0 to infinity.

Tissue Distribution. The experiment was performed 7 days after tumor implantation. At selected time points (2, 8, 24, 48, and 72 h) post i.v. injection at a dose of 10 mg/kg liposomal doxorubicin with or without PEG-modified lipid, mice were anesthetized with pentobarbital. After blood sampling, various organs including the liver, spleen, kidneys, lungs, heart, s.c. tissue, and tumor were excised immediately after perfusion with saline. Excised tissues were homogenized and subjected to acidic isopropanol extraction, and the extracted doxorubicin was measured by a spectrofluorometer (Hitachi F-4500).

Subacute Toxicity Evaluation. Tumor-free mice (five to eight mice per group) were used to test the doxorubicin-mediated toxicity. Treatment was administered as a bolus injection of 10 mg/kg equivalent amount of doxorubicin through the tail vein on days 0, 7, 14, 21, and 28 of the experiment, and the body weight of each mouse was measured. For histological changes, the mice were sacrificed by carbon dioxide on day 30, 2 days after the last injection. The organs were fixed in 10% neutral formalin and processed for light microscopy examination with H&E-phosphomolybdic acid light green stain. The
following organs were examined: heart, kidney, stomach, and testis.

Therapeutic Studies. Therapeutic experiments started 4 days after tumor implantation in the groin of the right hind limb. Animals (groups of 10) were treated with free doxorubicin or the liposomal doxorubicin at a dose of 10 mg/kg weekly through the tail vein on days 4, 11, 18, and 25 after tumor implantation. The survival time of each mouse was recorded, and the study was repeated three times. The increase in median survival was expressed as \((T/C)^2\times100\%), where \(T\) is the median survival days of treated mice, and \(C\) is the median survival days of control mice.

Statistics. The difference in drug concentrations between liposomal doxorubicin with or without PEG was assessed with an unpaired \(t\) test. Mean AUCs were calculated based on mean values obtained for individual time points, where means were derived from at least three animals. Because individual animals were required to generate each data point and subsequent sampling over time was not possible, the difference in mean AUC could potentially be examined with a nonlinear mixed effects model. Unfortunately, we were not able to carry out this type of test because the required software was not available. The body weight changes in all groups were evaluated with one-way ANOVA, all pairwise multiple comparison procedure such as a Dunn’s method or Tukey test depending on the normality. The differences in survival curves were evaluated by the Breslow test and the Mantel-Cox test using the BMDP software.

RESULTS

The Effect of PEG on the Plasma Pharmacokinetics in Non-Tumor-bearing BALB/c Mice. To explore the relationship between the amount of PEG and pharmacokinetic properties, plasma doxorubicin concentrations in BALB/c mice were determined after i.v. injection of 6 mg/kg DSPC/cholesterol liposomal doxorubicin with varying percentages of PEG-modified lipid (Fig. 1). In agreement with previously published data (19), the amount of free doxorubicin in plasma was negligible (<1% of total doxorubicin) compared with that of the drug encapsulated in liposome. The pharmacokinetic parameters of these liposomal drugs are listed in Table 1. The initial concentrations and \(t_{1/2}\) increased with the percentage of PEG linearly. The AUC and MRT also increased as the percentage of PEG was increased. The clearance was slower and the \(V_{ss}\) was smaller for liposomes with higher percentages of PEG, but both plateaued at 3% PEG and did not further decrease with 6% PEG. From this analysis, PEGylation decreased the volume of distribution, slowed the elimination of liposomal doxorubicin, and thereby increased the AUC, but the effect seemed to plateau between 3 and 6%. Further increases in PEG percentage may not alter the pharmacokinetic property of the DSPC/cholesterol liposome system significantly.

The effect of dosage on pharmacokinetic properties of liposomal doxorubicin was also examined (Fig. 1; Table 1). The \(t_{1/2}\) of liposomal doxorubicin without PEG-modified lipid was prolonged, and the clearance diminished considerably when the dosage was increased from 6 mg/kg to 10 mg/kg. With the increase in dosage, the plasma AUC of liposomal doxorubicin without PEG-DSPE increased 2.41-fold. The pharmacokinetic properties of liposomal doxorubicin with 6% PEG-DSPE were less influenced by the dosage, and the AUC increased 2.25-fold.

Pharmacokinetics of Liposomal Doxorubicin in C-26 Tumor-bearing BALB/c Mice. Seven days after C-26 tumor implantation, the plasma doxorubicin concentrations in tumor-bearing BALB/c mice were studied after injection of 10 mg/kg of liposomal doxorubicin. The pharmacokinetics, regardless of PEGylation, were different from those in non-tumor-bearing mice (Fig. 2; Table 1). Compared with tumor-free mice, the plasma doxorubicin concentrations fell more
For liposomal doxorubicin without PEG, the clearance increased by approximately half and the \( t_{1/2} \) decreased by more than half, but the change in \( V_{ss} \) was slight. For liposomal doxorubicin with 6% PEG-DSPE, the effect of tumor-bearing status on pharmacokinetics was less marked, although the trend was similar.

The amount of doxorubicin in organs was determined at various time points after i.v. injection of 10 mg/kg liposomal doxorubicin into C-26 bearing BALB/c mice. In the RES, including the liver and spleen, the group without PEG had higher tissue drug concentrations than the group with PEG (Table 2). The biggest difference was observed in the spleen, with an AUC ratio of 2.61. In the heart, lung, and s.c. tissue, the differences between liposomal doxorubicin with or without PEG-modified lipid were small.

The tumor drug concentrations peaked at 24 h for both liposomal drugs and then decreased slowly over time (Fig. 2). At 24, 48, and 72 h after injection of liposomal doxorubicin without PEG, the doxorubicin concentrations were \( 49.3 \pm 21.0 \), \( 31.8 \pm 19.8 \), and \( 21.9 \pm 19.6 \) \( \mu g/g \) (mean ± SD; \( n = 5 \)), respectively, which were higher than those of liposomal doxorubicin with 6% PEG (63.0 ± 11.6, 20.2 ± 4.5, and 9.3 ± 1.9 \( \mu g/g \); Fig. 2). Twenty-four hours after injection of liposomal doxorubicin without PEG, the doxorubicin concentration in the tumor was higher than that of plasma, and this persisted up to 72 h. For the group with PEG liposomes, the drug concentration in the tumor was lower than that of plasma the entire time. The AUC of doxorubicin in tumor with liposomal doxorubicin without PEG was 1.44-fold higher than that of PEGylated group for the initial 72 h, and this result was reproducible in repeated experiments. The Te (AUC\(_{Tumor} \)/AUC\(_{Plasma} \)) of the group without PEG-modified lipid was 0.87, and this was much higher than that of the PEGylated group (0.31). Although PEGylation reduced RES uptake and increased the plasma AUC, the amount of drug entering the tumor was paradoxically diminished.

### Table 1

<table>
<thead>
<tr>
<th>Liposomal doxorubicin</th>
<th>0.0% PEG</th>
<th>1.2% PEG</th>
<th>3.0% PEG</th>
<th>6.0% PEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>( c_0^b ) (mg/l)</td>
<td>127.0</td>
<td>131.3</td>
<td>134.4</td>
<td>144.8</td>
</tr>
<tr>
<td>( t_{1/2}^b ) (h)</td>
<td>12.5</td>
<td>16.4</td>
<td>18.9</td>
<td>22.4</td>
</tr>
<tr>
<td>AUC (mg \cdot h/l)</td>
<td>1389</td>
<td>1996</td>
<td>2949</td>
<td>3061</td>
</tr>
<tr>
<td>AUMC (mg \cdot h^2/l)</td>
<td>22,699</td>
<td>39,594</td>
<td>63,762</td>
<td>71,758</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>16.3</td>
<td>19.8</td>
<td>21.6</td>
<td>23.4</td>
</tr>
<tr>
<td>( V_{ss} ) (l/kg)</td>
<td>0.071</td>
<td>0.060</td>
<td>0.044</td>
<td>0.046</td>
</tr>
</tbody>
</table>

\( a \) The pharmacokinetic study was performed 7 days after C-26 tumor implantation.

\( b \) \( c_0 \), initial concentration.
Comparison of in Vivo Subacute Toxicity. Weekly i.v. injections of a 10 mg/kg equivalent of doxorubicin were given to BALB/c mice to compare the subacute toxicity. There was no body weight difference between the empty liposome and saline control groups throughout the entire course (Fig. 3). The free drug group had lower body weight after the first injection ($P =$ 0.05; ANOVA, Dunn’s method). The liposomal doxorubicin groups, whether PEG conjugated or not, had lower body weights than the control, but the lower weights were not statistically significant. The PEGylated liposome group had a slightly lower body weight than the non-PEGylated group.

Histological examinations of organs obtained from mice treated with control or liposomal doxorubicin were also performed. The free drug group had marked atrophy of the testes, mild necrosis and degeneration of the myocardium, and severe necrosis in the glandular portion of the gastric mucosa. Both liposomal drugs showed milder organ changes, and again, there was no difference between the PEGylated and non-PEGylated groups. These results indicated that PEG might not further decrease the toxicity of liposomal doxorubicin.

Therapeutic Effect in a C-26 Implant Tumor Model. The therapeutic effect of drugs was compared in a C-26 tumor-implant model. Treatments were started 4 days after tumor implantation and were repeated weekly. The survival of the mice was monitored daily. The result was reproducible in three repeated experiments. The pooled data are displayed in Fig. 4 ($n =$ 30 for each group). The tumors became larger, and the mice in the control group became weaker and died between 20 and 45 days. There was no improvement in survival with free doxorubicin treatment in comparison with the saline control group. The survival of both liposomal drug groups was prolonged ($P <$ 0.0001 by Breslow test and Mantel-Cox test). In comparison with the control, the increase in median survival was 67.6% for the group without PEG and 58.5% for the PEGylated liposome group (Fig. 4). The difference between these two liposomal drug groups was not significant. From the

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**Table 2** AUC* of organs in C-26 tumor-bearing BALB/c mice after 10 mg/kg liposomal doxorubicin injection

<table>
<thead>
<tr>
<th></th>
<th>Plasma</th>
<th>Tumor</th>
<th>Heart</th>
<th>Liver</th>
<th>Spleen</th>
<th>Lung</th>
<th>Kidney</th>
<th>Subcutis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPLD**</td>
<td>24 h</td>
<td>1889</td>
<td>637</td>
<td>318</td>
<td>900</td>
<td>376</td>
<td>127</td>
<td>485</td>
</tr>
<tr>
<td></td>
<td>72 h</td>
<td>2586</td>
<td>2255</td>
<td>969</td>
<td>2781</td>
<td>2387</td>
<td>572</td>
<td>1552</td>
</tr>
<tr>
<td>PLD</td>
<td>24 h</td>
<td>3206</td>
<td>541</td>
<td>306</td>
<td>685</td>
<td>259</td>
<td>132</td>
<td>782</td>
</tr>
<tr>
<td></td>
<td>72 h</td>
<td>5136</td>
<td>1570</td>
<td>898</td>
<td>1861</td>
<td>916</td>
<td>431</td>
<td>2138</td>
</tr>
<tr>
<td>NPLD/PLD</td>
<td>24 h</td>
<td>0.59</td>
<td>1.18</td>
<td>1.04</td>
<td>1.31</td>
<td>1.45</td>
<td>0.96</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>72 h</td>
<td>0.50</td>
<td>1.44</td>
<td>1.08</td>
<td>1.49</td>
<td>2.61</td>
<td>1.33</td>
<td>0.73</td>
</tr>
</tbody>
</table>

* AUC ($h \cdot mg/g$) calculations over 0–72 h ($n =$ 3–5) by the trapezoid method. Plasma AUC is given as $h \cdot mg/ml$ ($n =$ 5).
** NPL, non-PEGylated liposomal doxorubicin; PLD, liposomal doxorubicin with 6% PEG-modified lipid.
experiment, it was evident that PEGylation did not improve the therapeutic effect of liposomal doxorubicin in the C-26 tumor model.

**DISCUSSION**

PEG altered the pharmacokinetic property of the DSPC/cholesterol liposomal doxorubicin by decreasing the $V_{ss}$ and clearance, and thereby increasing plasma AUC. These results are consistent with the notion that sterically stabilized liposome may reduce the RES uptake and enhance the longevity of liposomal doxorubicin in circulation, but above 3%, the gain in pharmacokinetic advantage was only slight. Compared with conventional liposomes, sterically stabilized liposomes have a 100-fold increase in AUC (3). However, for the DSPC system used in this study, the AUC of liposomal doxorubicin with 6% PEG-modified lipid was only approximately twice that of liposomal doxorubicin without PEG, regardless of dosage or tumor-bearing status. Daunorubicin liposomes composed of DSPC/cholesterol without PEG also had a similar AUC (20). The higher transition temperature and homogeneity in fatty acid of DSPC confers the higher stability to this DSPC/cholesterol liposomal system.

The movement of drugs from the plasma compartment to the tumor site can be assessed with the $T_e$ parameter, relating the AUC in the circulation to the tumor AUC. Parr et al. (11), using a murine Lewis lung carcinoma model, showed that DSPC/cholesterol liposomes had a 2-fold $T_e$ of PEGylated liposome when given at the maximal tolerated dose of 55 mg/kg. In our study, at a commonly used therapeutic dose of 10 mg/kg, the $T_e$ of liposomal doxorubicin without PEG was 0.87. This was more than twice that of liposomal doxorubicin with 6% PEG (0.31). Sterically stabilized egg phosphatidylcholine/cholesterol liposome has been shown to have a 2-fold higher vascular permeability in tumors when compared with conventional liposome, but this has been proven only with fluorescent dye, tetramethylrhodamine thiochromamyl-dihexadecanoyl phosphatidyl-ethanolamine, but not with doxorubicin (21). Nevertheless, the lipid component is different (DSPC versus egg phosphatidylcholine), and the presence of doxorubicin has been shown to stabilize the liposomes and may alter the pharmacokinetic properties (22–24).

Both the half-life in the blood and the ability to traverse the endothelium determine the delivery of liposomal drug to the tumor tissue. If molecules have similar plasma AUCs, the rate of traversing the endothelium is critical in tumor delivery. In the system we used, the plasma AUC of non-PEGylated liposomal doxorubicin was half of that of liposomal doxorubicin with 6% PEG-DSPE, but the tumor AUC was 1.44-fold. The difference in $T_e$ might be explained by the reduced interaction of liposomes with cells and the steric hindrance conferred by PEGylation.

Evidence for endothelial uptake of liposomes and transcytosis across endothelial cells has been documented (25). Given the effects of PEG on inhibiting liposome-cell interactions, this polymer may reduce endothelial cell interactions, and this in turn would reduce the rate of extravasation. The mean diameter of PEGylated liposomal doxorubicin was only slightly larger (75 nm versus 70 nm), but an electron density study disclosed that a PEG molecule extends from the lipid surface by ~40 nm (26), depending on the percentage and molecular weight of PEG used. The gaps in the endothelial layers can range in size from 30 nm for fenestrated capillary to >500 nm in liver and diseased sites (27, 28). Video microscopy investigations have also indicated that the majority of liposome extravasation occurs directly through the openings present in tumor neovasculature (21, 29). It was also noted that the relationship between tumor liposome uptake and plasma liposome AUC is linear for both conventional and sterically stabilized liposomes (11). This suggests that
mass action does appear to drive the accumulation of specific types of nontargeted small liposomes into tumors and that the steric hindrance conferred by PEGylation may be disadvantageous.

Both PEGylated and non-PEGylated liposomal doxorubicin had milder side effects than free drug in terms of body weight loss and histological changes. The difference between two liposomal doxorubicin groups was not of statistical significance, possibly because of the small sample size. However, there was a trend toward the non-PEGylated liposomal doxorubicin group having less body weight loss than the PEGylated liposomal doxorubicin group. This may be of clinical importance considering the palliative nature of treatment of metastatic cancers. Clinical trials also have found that use of PEGylated liposomal doxorubicin results in high incidences of stomatitis (30) that might lead to reduced food intake. In the DSPC liposomal system, PEGylation of liposomal doxorubicin may not be able to reduce the side effects of liposomal doxorubicin.

The study of therapeutic effect demonstrated that PEGylated doxorubicin has better efficacy than free drug, but there was no improvement with PEGylation. In terms of both tumor shrinkage (data not shown) and survival, the non-PEGylated group was slightly better than the PEGylated group. This observation was compatible with the data indicating that non-PEGylated liposomal doxorubicin had a tumor AUC not less than that of liposomal doxorubicin with 6% PEG-modified lipid.

We demonstrated that PEGylation increased the plasma AUC of this DSPC/cholesterol liposomal doxorubicin system by only 2-fold. The lower drug clearance was obtained at the expense of lower tumor-targeting efficiency. There was no difference in toxicity and therapeutic effect for liposomal doxorubicin with or without PEGylation. Apparently, the necessity of PEGylation in this liposomal drug system needs scrutiny, as the gain in plasma AUC was not reflected in therapeutic effect. In addition, higher plasma AUCs may increase the incidence and severity of stomatitis.

The superiority in therapeutic effect of liposomal doxorubicin to free drug was not well explained merely by the higher plasma AUC achieved. Considering the very high IC50 of liposomal doxorubicin in vitro (>10 μg/ml; data not shown), the amount of liposomal doxorubicin entering the tumor was not high enough for tumor killing if doxorubicin could not be released efficiently. The biology of tumor cells and interaction with the microenvironment may determine the fate and effect of liposomal drug, and this may account for the wide variation in therapeutic effect of liposomal drugs in different tumor models. Clearly, from the results of this study, to enhance the therapeutic effect of liposomal drugs, increasing the plasma AUC by PEGylation is not satisfactory. Approaches such as local hyperthermia (31) and immunoliposomes (18, 32) to try to increase local or intracellular free drug concentrations are worthy of further investigation.

REFERENCES


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