Reduction of the Cardiotoxicity of Doxorubicin in Rabbits and Dogs by Encapsulation in Long-Circulating, Pegylated Liposomes

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Accepted for publication January 11, 1999 This paper is available online at http://www.jpet.org

ABSTRACT
The relative cardiotoxicity of pegylated (STEALTH) liposomal doxorubicin (PL-DOX; Doxil) was compared to nonliposomal doxorubicin (Adriamycin) in rabbits and dogs treated i.v. for up to 22 weeks. No histological evidence of cardiotoxicity was seen in dogs treated with placebo liposomes or PL-DOX every 3 weeks for a total of 10 doses (cumulative doxorubicin dose = 10 mg/kg) either 1 or 5 weeks post-treatment. All dogs treated with the same cumulative dose of free doxorubicin showed marked cardiotoxicity (vacuolization and myofibrillar loss in the myocardium) at both time points. In rabbits, progressive cardiomyopathy was seen in both treatment groups, but was more frequent and severe with free doxorubicin (67% of doxorubicin-treated rabbits, cumulative dose = 12 to 14 mg/kg versus 16% of PL-DOX-treated animals, cumulative dose = 14 to 21 mg/kg). Five doxorubicin-treated rabbits died of congestive heart failure or with histologic evidence of cardiotoxicity (median severity score = 6). No PL-DOX-treated rabbits died of congestive heart failure, although two animals that died early showed microscopic evidence of mild cardiotoxicity (median severity score = 2.5). Cardiotoxicity increased during the post-treatment period in both treatment groups. Rabbits received up to 50% more PL-DOX with no increase in cardiotoxicity. Thus, results in two species demonstrate that the cardiotoxicity of doxorubicin is significantly decreased when administered as PL-DOX. Significantly more PL-DOX can be given without incurring an increased risk of cardiomyopathy. Recent clinical studies have confirmed that PL-DOX is also less cardiotoxic than the same dose of unencapsulated doxorubicin in humans.

Cardiotoxicity is a well described adverse effect of anthracycline chemotherapeutic agents (Olson and Mushlin, 1990). Doxorubicin (Adriamycin) is the most commonly used of the anthracyclines despite significant cardiotoxicity that has resulted in the establishment of maximal recommended total drug doses in the range of 500 mg/m² (Gottlieb et al., 1973). Doxorubicin-related cardiotoxicity has several features that set it apart from other types of heart failure (Shenasa et al., 1990), including widespread myocardial lesions characterized by vacuolization, edema, and myofibrillar and membrane disruption (Van Vleet and Ferrans, 1986). In mice, rats, rabbits, and dogs, doxorubicin induces clinical and pathologic evidence of chronic cardiomyopathy similar to that seen in humans (Iatropoulos, 1984; Doroshow et al., 1985), with lesions in rabbits reported to be the most similar histologically (Jaenke, 1974).

Because doxorubicin is so effective therapeutically, a variety of approaches have been evaluated to reduce its cardiotoxicity. Encapsulation in liposomes has been one of the more successful methods. The cardiotoxicity of doxorubicin encapsulated in conventional, nonpegylated liposomes is less in mice and dogs at equivalent cumulative doxorubicin doses (Forssen and Tokes, 1981; Herman et al., 1983; Kanter et al., 1993). Doxorubicin encapsulated in long circulating, pegylated liposomes (PL-DOX; Doxil) is also less cardiotoxic than free drug in rats (Working et al., 1994a), probably because cardiac uptake of doxorubicin is reduced in PL-DOX-treated animals (Engbers et al., 1995).

PL-DOX has altered plasma pharmacokinetics and tissue distribution compared with nonliposomal doxorubicin, with a longer plasma half-life and higher area under the curve (AUC; Working et al., 1994b; Northfelt et al., 1996). Immediately after injection, most of a PL-DOX dose remains in the blood and slowly distributes to tissues over time, with increased tumor levels compared with treatment with nonliposomal doxorubicin (Vaage et al., 1992, 1994; Northfelt et al., 1996). Essentially all of the encapsulated doxorubicin remains associated with the liposomes during circulation, with little free drug bioavailable (Working and Dayan, 1996). Once extravasated from the circulation, PL-DOX liposomes release their contents, and doxorubicin becomes available for cellular uptake or is subsequently metabolized and cleared. The slow release of doxorubicin from PL-DOX liposomes is believed to contribute to the observed reductions in doxorub-

ABBREVIATIONS: PL-DOX, pegylated liposomal doxorubicin (Doxil); CHF, congestive heart failure; AUC, area under the curve.
alcohol and infiltrated with methylacrylate resin for a mini-
buffered formaldehyde. Fixed heart sections were dehydrated with
section was processed individually and fixed for at least 7 days in 4%
ventricle near the auricles, the left ventricular papillary muscle, and
grossly sectioned before further fixation. Separate 1-
were immersed in 4% buffered paraformaldehyde at autopsy and
possible microscopic evaluation.

In each study, doses were adjusted based on the
individual body weight measured on each day of treatment. Doses
are reported as doxorubicin equivalents, i.e., a dose of 1 mg/kg
PL-DOX and free doxorubicin each represent a 1 mg/kg dose of
doxorubicin. Both studies incorporated control animals that received
sterile 0.9% NaCl and, in the dog study only, an additional control
group was treated with placebo liposomes that contained no doxor-
PL-DOX liposomes composed of hydrogenated
soy phosphatidylcholine, methoxy polyethylene glycol-di-stearylphos-
phatidylethanolamine, and cholesterol in an approximately 56:38:5
molar ratio and containing doxorubicin were prepared as described
previously (Vaage et al., 1992). Placebo liposomes were identical in
lipid content and concentration to PL-DOX, but did not contain
encapsulated doxorubicin. Doxorubicin (Adriamycin RDF; Adria S.P.
Inc., Dublin, OH) was reconstituted with sterile 0.9% NaCl. When
necessary, dilutions of test material were performed with sterile
0.9% NaCl.

Study Design. In each study, doses were adjusted based on the
body weight measured on each day of treatment. Doses
are reported as doxorubicin equivalents, i.e., a dose of 1 mg/kg
PL-DOX and free doxorubicin each represent a 1 mg/kg dose of
doxorubicin. Both studies incorporated control animals that received
sterile 0.9% NaCl and, in the dog study only, an additional control
group was treated with placebo liposomes that contained no doxor-
PL-DOX doses and dosing intervals were based on pharmacoki-
metics in rabbits and tolerability in dogs; however, the cardioto-
icity of doxorubicin is related to cumulative dose, not dosing interval,
so the rabbit and dog studies are directly comparable. Doxorubicin
dose levels were based on data in the literature when available. All
animals had access to food and water ad libitum and were housed
under conditions that conformed to USDA requirements. Clinical
observations of toxicity were performed once or twice daily in all
studies. Body weights were determined before each dose during
treatment and weekly during recovery.

Dog study. Male and female beagles (7–12 kg; n = 6/sex/treatment
group) were randomly assigned to treatment groups that received i.v.
injections of 0.25, 0.75, or 1 mg/kg PL-DOX or 1 mg/kg doxorubicin
once every 3 weeks for a total of 10 treatments. Additional groups of
animals were treated with saline or placebo liposomes on the same
schedule. Animals were necropsied 1 and 5 weeks after treatment
completion. Rabbit study. Male New Zealand White rabbits (2.3–3.1 kg; n
= 15–25 per treatment group) were randomly assigned to treatment
groups that received a 1 mg/kg i.v. bolus dose of PL-DOX or nonli-
posomal doxorubicin every 5 days for a total of 14 treatments. A
control group of 15 rabbits received saline on the same treatment
schedule. Surviving animals were euthanized 1, 5, or 13 weeks after
the final dose. Additional groups of rabbits (n = 10 per group) treated
with PL-DOX or saline for 21 doses were scheduled to be euthanized
13 weeks after the 21st dose. All rabbits that died or were euthanized
early or were euthanized as scheduled were necropsied and exam-
inied grossly for lesions. An extensive set of tissues was collected for
possible microscopic evaluation.

Microscopic Evaluation of Hearts. In both studies, hearts
were immersed in 4% buffered paraformaldehyde at autopsy and
grossly sectioned before further fixation. Separate 1-×0.5-×0.5-cm
heart sections that included as much of the full longitudinal face as
possible were collected from the septum (near the auricles), each
ventricle near the auricles, the left ventricular papillary muscle, and
the apex (at the junction of the right ventricle and septum). Each
section was processed individually and fixed for at least 7 days in 4%
buffered formaldehyde. Fixed heart sections were dehydrated with
ethyl alcohol and infiltrated with methacrylate resin for a mini-

<table>
<thead>
<tr>
<th>Histologic Evaluation of Cardiotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 = Very slight degree of change (scattered, single myocardial fibers affected)</td>
</tr>
<tr>
<td>Grade 2 = Slight degree of change (scattered small groups of altered myocardial fibers throughout the myocardium)</td>
</tr>
<tr>
<td>Grade 3 = Moderate degree of change (disseminated myocardial fiber change with occasional focal unaffected areas)</td>
</tr>
<tr>
<td>Grade 4 = Marked degree of change (confluent groups of affected fibers—most myocardial fibers affected)</td>
</tr>
</tbody>
</table>

Nine early deaths occurred in the PL-DOX treatment
group; six were considered secondary to the effects of treatment-related dermal lesions (described below), and three were considered to be due to cardiotoxicity. Of these, two occurred after a cumulative dose of 14 mg/kg, and one occurred after a cumulative dose of 21 mg/kg. The median cardiotoxicity score in the three affected animals was 2 (range, 1–5; Table 3). In contrast, five early deaths were seen in the doxorubicin treatment group; three before receiving the 14th dose after a cumulative doxorubicin dose of 12 or 13 mg/kg (one and two animals, respectively) and two after the final dose. Cause of death was congestive heart failure (CHF) in four of five animals, with significant evidence of cardiotoxicity and CHF in the fifth rabbit, which died secondarily to hair ingestion. The median cardiotoxicity score of the early death doxorubicin animals was 6 (range, 3–11; Table 4).

Surviving PL-DOX-treated rabbits tolerated a cumulative dose of 14 mg/kg with no evidence of cardiotoxicity at scheduled necropsies 1 or 5 weeks post-treatment (0/4 and 0/5, respectively; Table 3). One of two doxorubicin-treated rabbits surviving to the first necropsy exhibited signs of cardiotoxicity (score = 1), as did 1/3 surviving to the 5-week necropsy (score = 1). At 13 weeks after the final treatment, 1/4 of PL-DOX-treated rabbits had evidence of cardiotoxicity, compared with 3/5 of the rabbits that were treated with the same

### TABLE 2

<table>
<thead>
<tr>
<th>Site</th>
<th>PL-DOX&lt;sup&gt;a&lt;/sup&gt; 0.25 mg/kg</th>
<th>PL-DOX&lt;sup&gt;a&lt;/sup&gt; 0.75 mg/kg</th>
<th>PL-DOX&lt;sup&gt;a&lt;/sup&gt; 1.0 mg/kg</th>
<th>DOX&lt;sup&gt;a&lt;/sup&gt; 1.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Week Post Right Ventricle</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>2/8</td>
</tr>
<tr>
<td>Left Ventricle</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>5/8</td>
</tr>
<tr>
<td>Papillary Muscle</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>5/8</td>
</tr>
<tr>
<td>Septum</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>4/8</td>
</tr>
<tr>
<td>Apex</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>6/8</td>
</tr>
<tr>
<td>Total Affected</td>
<td>0/8</td>
<td>0/8</td>
<td>0/8</td>
<td>8/8</td>
</tr>
<tr>
<td>Cardiotoxicity Score</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Median (Range)</td>
<td></td>
<td></td>
<td></td>
<td>(1–8)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pegylated liposomal doxorubicin.

### TABLE 3

<table>
<thead>
<tr>
<th>Necropsy&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Saline</th>
<th>PL-DOX 1.0 mg/kg</th>
<th>DOX 1.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 mg/kg Cumulative Dose</td>
<td>1/Week</td>
<td>0/5</td>
<td>0/4</td>
</tr>
<tr>
<td>13-Week</td>
<td>0/5</td>
<td>0/5</td>
<td>1/3</td>
</tr>
<tr>
<td>Early Deaths</td>
<td>0/5</td>
<td>2/5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5/5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total Affected (%)</td>
<td>0/15 (0)</td>
<td>3/15 (20)</td>
<td>10/15 (67)</td>
</tr>
</tbody>
</table>

<sup>b</sup> Weeks after last dose.

<sup>c</sup> Cumulative delivered dosage of 14 mg/kg. Deaths occurred on days 87 and 143.

<sup>d</sup> Cumulative delivered dosage of 21 mg/kg. Death occurred on day 216.

### TABLE 4

<table>
<thead>
<tr>
<th>Test Material</th>
<th>Weeks Postdose</th>
<th>N&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cardiotoxicity Score, Median (Range)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin (14 mg/kg)</td>
<td>1</td>
<td>1</td>
<td>1 (1–4)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>1</td>
<td>1 (1–4)</td>
</tr>
<tr>
<td>PL-DOX (14 mg/kg)</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>PL-DOX (21 mg/kg)</td>
<td>13</td>
<td>2</td>
<td>2.5 (1–5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number of animals affected.

<sup>b</sup> U = Unscheduled death.
Cumulative dose of free doxorubicin. The cardiotoxicity score of the one affected animal in the PL-DOX group was 4, compared to scores of 1, 1, and 4 in the three rabbits in the nonliposomal doxorubicin treatment group.

Cardiomyopathy did not increase in either incidence or severity in animals that received up to 21 doses of PL-DOX (cumulative dose = 21 mg/kg), in which only 1/10 animals was affected. This rabbit, which received a cumulative dose of 21 mg/kg PL-DOX but died before scheduled necropsy, exhibited histopathologic evidence of cardiotoxicity (score = 2), but no evidence of CHF. The three rabbits that survived to scheduled necropsy, as well as the other six early death rabbits in this group, had no signs of cardiotoxicity.

**Other Drug-Related Toxicity.** The most notable noncardiologic drug-related toxicity in PL-DOX-treated rabbits and dogs was dermal lesions, including redness, eschar, ulcers, and alopecia of the legs, head, and paws (data not shown). The lesions resolved readily upon cessation of dosing, but were a treatment-limiting factor in the rabbit study, in which dosing was halted for two separate 26-day intervals (between doses 7 and 8 and doses 17 and 18) to allow PL-DOX-treated animals to recover. Treatment was similarly halted in the doxorubicin treatment group. The effects of the dermal lesions were generalized weight loss and decreased food consumption, leading to early death in at least 6 of the 25 PL-DOX-treated rabbits. Dermal lesions were generally less severe in dogs due to the longer dose interval utilized in this study, but were otherwise similar. No similar lesions were seen in animals that received free doxorubicin, saline, or empty placebo liposomes. Apart from the dermal toxicity, toxicities in PL-DOX-treated dogs and rabbits were generally similar to those seen in the doxorubicin treatment groups; these included gastrointestinal and bone marrow toxicity, but were typically less severe in animals that received PL-DOX.

**Discussion**

These studies demonstrate that PL-DOX is less cardiotoxic than unencapsulated doxorubicin at the same and higher cumulative doses. The progressive myocardial changes caused by PL-DOX, which were characterized by vacuolar degeneration and myofibrillar disruption of the myocardium, are consistent with doxorubicin-induced cardiac changes described in animals by other investigators (Jaenke, 1976). Cardiac lesions in rabbits are similar to those in humans, where vacuolation, edema, mitochondrial degeneration, and myofibrillar disruption with noninflammatory myocyte lysis occur (Jaenke, 1976). In our studies, cardiac lesions in the dog were also histologically similar to those seen in humans. Rabbits exhibit the same delayed progressive cardiomyopathy that may occur in human patients (Jaenke, 1976), and we report here similar findings in dogs. Similarly decreased cardiotoxicity has been reported for doxorubicin encapsulated in nonpegylated liposomes in earlier studies (Forssen and Tokes, 1981; Herman et al., 1983; Kanter et al., 1993).

The cardiotoxicity of doxorubicin is related to dose intensity and, to a certain extent, to peak plasma and tissue concentrations. Studies in animals and in human clinical trials have demonstrated that the use of frequent, divided doses or long-term continuous infusion decreases the risk of anthracycline toxicity (Chlebowski et al., 1980; Legha et al., 1982), and the tissue distribution of doxorubicin is known to be schedule-dependent (Pacciarini et al., 1978). Frequent, divided doses result in lower doxorubicin levels in the myocardium than does a single bolus injection of the same cumulative dose, although equivalent drug levels are seen in tumors. Similarly, encapsulation of doxorubicin in either conventional or pegylated liposomes also decreases the concentration of doxorubicin in the heart (Gabizon et al., 1982; Engbers et al., 1995). Heart concentrations of doxorubicin were not assessed in the current study.

Cardiotoxicity is reduced when doxorubicin is administered as fractionated lower doses or as long-term infusions, but antineoplastic activity is unchanged (Weiss et al., 1976; Legha et al., 1982). Peak plasma levels are reduced up to 99% from those seen with bolus injections, but cumulative AUCs for equal doses are comparable for each dosing regimen (Speth et al., 1988). These findings suggest that doxorubicin-mediated cardiotoxicity is most directly related to peak plasma and/or tissue concentration of drug, but that antitumor activity is more closely related to plasma AUC.

A single dose of PL-DOX provides plasma drug exposure kinetics similar to those of a long-term infusion of nonliposomal doxorubicin, perhaps explaining its reduced cardiotoxicity. After i.v. administration of PL-DOX, the peak plasma concentration of free doxorubicin is lower, but the overall (liposomal and nonliposomal drug) plasma concentration is significantly higher than after an equal dose of nonliposomal doxorubicin (Gabizon et al., 1993; Working and Dayan, 1996). Most (>93%) of the doxorubicin measured in plasma after administration of PL-DOX is encapsulated in liposomes, and immediately after i.v. injection, doxorubicin is primarily confined to the intravascular compartment, with an apparent volume of distribution that approximates blood volume. In contrast, after administration of nonliposomal doxorubicin, the drug rapidly distributes to tissues, with a volume of distribution that is many times larger than blood volume. Relatively little drug is released from PL-DOX liposomes in the blood, and most of the doxorubicin becomes available after the liposomes extravasate and enter the tissue compartment (Gabizon et al., 1993). The reduced cardiotoxicity of PL-DOX, therefore, is most likely related to the decreased peak levels of free doxorubicin in the plasma.

Peak concentrations of doxorubicin in the heart are nearly 2-fold lower in tumor-bearing mice that receive PL-DOX than in those treated with the same dose of nonliposomal doxorubicin, but peak tumor levels of doxorubicin are over 3-fold higher in the same animals (Engbers et al., 1995). Cardiotoxicity is not increased, but antitumor activity in a number of murine and human xenograft tumor models is (Papahadjopoulos et al., 1991; Gabizon et al., 1994). Alterations in the tissue distribution of PL-DOX and associated reductions in peak plasma and tissue doxorubicin concentrations thus correlate with reductions in cardiotoxicity. In the rabbit study reported here, increasing the cumulative PL-DOX dose by 50% (from 14–21 mg/kg) did not result in an increase in the incidence or severity of drug-related cardiac lesions, probably because high peak plasma and cardiac concentrations of doxorubicin were avoided.

Increases in the severity of doxorubicin-induced cardiotoxicity after treatment ceased were seen in both PL-DOX- and doxorubicin-treated animals, but there was no evidence that the latency of lesion development was greater in animals.
treated with the liposomal drug. Latency in the development of anthracycline-induced cardiomyopathy is also reported in patients, in whom drug-related cardiotoxicity may become evident months to years after the final treatment (Steinherz et al., 1991).

A secondary PL-DOX-associated toxicity was the development of reversible dermal lesions with repeated treatment. Similar cutaneous lesions of the extremities, known as hand-and-foot syndrome or palmar-plantar erythrodysesthaea, are also seen in humans who receive continuous infusions of nonliposomal doxorubicin (Lokich and Moore, 1984; Vogelzang and Ratain, 1985). In hamsters, degenerative changes in the skin, generally appearing after the second week of treatment, are evident after repeated i.p. injections of doxorubicin HCl (Dantchev et al., 1979). The lesions are apparently a toxic response of the dermis to long-term exposure to low levels of certain cytotoxic drugs, including doxorubicin and 5-fluouracil (Smith et al., 1995). Studies in dogs have demonstrated that the incidence and severity of the dermal lesions induced by PL-DOX can be decreased by the utilization of lower doses and/or longer dosing intervals (Amantea et al., 1998). These dosing strategies should minimize adverse skin effects in PL-DOX-treated patients, and tolerable dose levels of PL-DOX have been reported to have a significant antitumor response (Muggia et al., 1997; Ranson et al., 1997). In addition, a recent study in dogs with nonHodgkin’s lymphoma showed that concomitant administration of oral pyridoxine (50 mg, twice daily) with PL-DOX reduced by more than 4-fold the likelihood of developing severe palmar-plantar erythrodysesthaea (Vail et al., 1998). Although tumor response rates were not different between pyridoxine-PL-DOX treatment and dogs receiving PL-DOX only, a trend of longer duration of response and survival was seen with the combination treatment, probably because higher cumulative doses of PL-DOX could be administered with concurrent pyridoxine treatment. These findings suggest that effective palliative measures may permit the use of higher doses with consequent improved therapeutic responses.

One concern with agents or processes that reduce the toxicity of chemotherapeutic agents is whether they might also reduce the therapeutic activity of the drug. Formulations of doxorubicin in conventional, nonpegylated liposomes are reported to be approximately equivalent therapeutically to free doxorubicin in mouse tumor models (Mayer et al., 1989), whereas the antitumor activity of PL-DOX in syngeneic human and murine xenograft tumor models is as much as 4-fold greater than that of free doxorubicin on a weight basis (Vaage et al., 1994; Working et al., 1994b). Moreover, studies in murine tumor models comparing the activity of PL-DOX to doxorubicin encapsulated in conventional liposomes show that PL-DOX is more effective (Vaage et al., 1992). Two recently reported independent clinical trials in breast cancer patients have shown that essentially the same clinical response can be achieved using approximately one-half the dose intensity of PL-DOX as doxorubicin encapsulated in conventional liposomes (TLC D-99; Ranson et al., 1997; Harris et al., 1998), further suggesting that therapeutic activity of doxorubicin is increased by encapsulation in pegylated liposomes but not conventional liposomes (however, neither study directly compared the two types of liposomal formulations). Regardless of the relative activities of doxorubicin in pegylated and nonpegylated liposomes, liposome encapsulation apparently does not reduce therapeutic activity compared to free doxorubicin.

In summary, the studies reported here demonstrate that PL-DOX is less cardiotoxic than nonliposomal doxorubicin at the same and even higher cumulative doses in animals. Recent studies with both PL-DOX and doxorubicin encapsulated in conventional, nonpegylated liposomes have also demonstrated reduced cardiotoxicity in human patients (Batist et al., 1998; Berry et al., 1998), consistent with findings in animals. The development of a less cardiotoxic anthracycline therapy offers potential benefit to patients who require long-term antineoplastic chemotherapy.

References


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