Photodynamic Therapy: A Means to Enhanced Drug Delivery to Tumors

John W. Snyder, 1 William R. Greco, 2 David A. Bellnier, 1 Lurine Vaughan, 1 and Barbara W. Henderson 1

1The Photodynamic Therapy Center and 2Department of Biostatistics, Roswell Park Cancer Institute, Buffalo, New York

Abstract

Using the photosensitizer 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a, we have determined that photodynamic therapy (PDT) can be used to facilitate the delivery of macromolecular agents. PDT regimens that use low fluences and fluence rates were the most successful. This effect was demonstrated for fluorescent microspheres with diameters ranging from 0.1 to 2 μm. Such treatment given immediately before administration of Doxil, a liposomally encapsulated formulation of doxorubicin with an average diameter of 0.1 μm, significantly enhanced its accumulation in transplanted murine Colo 26 tumors. The combination of PDT and Doxil led to a highly significant potentiation in tumor control without concomitant enhancement of systemic or local toxicity. Interestingly, concentration-effect modeling suggested that the enhanced cure rate was greater than what was predicted based on the increase in intratumor Doxil concentration. In summary, we have developed a novel PDT treatment that enhances the delivery and efficacy of macromolecule-based cancer therapies such as Doxil.

Introduction

PDT, 3 the activation of a tumor-localized photosensitizer by light, is generally applied as a single modality for the treatment of a variety of solid tumors, for which it has attained regulatory approval (reviewed in Ref. 1). Its dominant mechanism of action is the local generation of cytotoxic singlet oxygen, which causes the destruction of tumor cells and damage of the tumor microvasculature (reviewed in Ref. 2). PDT-mediated vascular effects can range from transient vascular spasm to total permanent vessel occlusion and can include enhanced vascular leakiness. In its conventional application, which aims for maximal local tumor control, shutdown of the tumor and surrounding normal tissue vasculature is known to be a significant factor contributing to tumor control, as well as a factor in dose-limiting local toxicity. Scientific interest thus far has focused on the vessel-occlusive effects of PDT, whereas the vessel-permeabilizing effects have not been further explored or exploited.

One of the major barriers to effective delivery of macromolecular therapeutic agents to tumors is the microvasculature, which impedes their egress from the vessels into the tumor interstitium, preventing them from reaching their intended target (reviewed in Ref. 3). Various approaches, including hyperthermia, irradiation, and administration of vasoactive factors, have been tried to enhance the permeability of tumor vessels to macromolecules. Here we test the hypothesis that PDT-induced vascular leakiness can be exploited for the purpose of improving the delivery of macromolecular therapeutic agents.

Materials and Methods

Animals and Tumor Models. Female BALB/c mice at least 6 weeks of age were purchased from Clarence Reeder (National Cancer Institute Frederick Cancer Research Facility, Frederick, MD) and housed in microisolator cages in a laminar flow unit under controlled ambient light. Mice received inoculations s.c. of 106 Colo 26 (murine colon carcinoma) cells from exponentially growing cultures in vitro. This tumor model is often used for pharmacokinetic and therapeutic studies defining the delivery of liposomal doxorubicin (4, 5).

Tumors were located on one or both shoulders, depending on the study, and were used for experimentation when they reached a diameter of 5–8 mm. All animal experiments were approved by the Roswell Park Cancer Institute Animal Care and Use Committee.

Photosensitizer. HPPH, prepared at Roswell Park Cancer Institute, was diluted in HBSS containing 2% ethanol and 0.1% Tween 80 and injected via a tail vein at a dose of 0.4 μmol/kg ~24 h before illumination, as described previously (6).

Fluorescent Tracer Molecules. FluoSpheres (carboxylate-modified fluorescent microspheres; 0.02–2.0 μm diameter; Molecular Probes, Eugene, OR) were administered at a dose of 100 ng/kg in a volume of 5 μl/g of mouse body weight. Thus, although the absolute number of FluoSpheres that were injected varied with diameter, the total FluoSphere volume remained constant. Fluorescein (JT Baker Chemical, Phillipsburg, NJ) was used to determine vascular perfusion as described (7).

Doxorubicin Liposomes. Doxil (doxorubicin HCl liposome injection; Alza, Mt. View, CA) was administered at single doses of 1.25, 2.5, 3.0, 5.0, 10.0, or 20.0 (for short-term experiments only) mg/kg (10 μl/g of mouse body weight) via a tail vein. Free doxorubicin (American Pharmaceutical Partners, Inc., Los Angeles, CA) was used in some experiments for comparison.

PDT Treatment. The delivery of light to tumors was carried out as described previously (6). Fluences ranging from 13 to 128 J/cm2 were delivered at fluence rates ranging from 3.5 to 112 mW/cm2.

Quantitation of Fluorescent Tracers in Tumor. Uptake of Fluospheres and fluorescein was determined after digesting tumor samples in 1 ml of Solvable (Packard BioScience Co., Meriden, CT) overnight at 49°C. Fluospheres were allowed to circulate for 24 h before harvest to allow clearance from the circulation (8). Fluorescence of the lysate was measured by a fluorometer (λex = 580 nm, Δλem = 593–700 nm; Fluoromax2; Jobin-Yvon Inc., Edison, NJ).

Quantitation of Doxorubicin. Doxorubicin was extracted from tumors, excised from mice that received injections of either Doxil or non-liposomal doxorubicin, as described in the report of Kong et al. (9). Doxorubicin fluorescence was measured by a fluorometer (λex = 479 nm, Δλem = 490–750 nm). The doxorubicin concentration was obtained by comparing the peak height in experimental samples to a standard curve. For purposes of clarity, doxorubicin extracted from mice that received injections of Doxil is referred to as Doxil.

Assessment of Tumor Response. Orthogonal diameters of tumors were measured once every 2 days with calipers. The tumor volume, \( V \), was calculated with the formula \( V = \frac{4}{3} l w^2 \), where \( l \) is the longest axis of the tumor and \( w \) is the axis perpendicular to \( l \). The tumors were monitored until they reached...
A volume &gt;400 mm³, at which time the mice were euthanized. Animals were considered cured if they remained tumor free for 90 days after PDT.

Assessment of Normal Skin Response. The skin response to PDT was assessed visually and rated based on the following scale: 0, no observable reaction; 1, minimally detectable erythema; 2, visible pale pink erythema, no vessels broken; 3, blanching, few broken vessels, no eschar formation; 4, definite erythema, thin yellow eschar formation; 5, severe reaction, eschar formation over &lt;50% of site; and 6, very severe, eschar formation over &gt;50% of site. This grading system is subjective, and the scale is ordinal.

Statistical Evaluation. All measured values are presented as means ± SE. The one-tailed Student’s t test was used for comparison between groups in all experiments except for tumor and skin response determinations, with Ps of 0.05 or less representing statistical significance. For tumor response data analysis, hours-to-event, i.e., to 400 mm³ tumor volume, was calculated for each animal by linearly interpolating between the times just before and after this volume was reached, using log (tumor volume) for the calculations; both tumor volume and hours-to-event calculations were performed using Excel (Microsoft, Redmond, WA; Ref. 6). Tumor responses between groups were compared using the method of Kaplan and Meier (10) and the log-rank test (Prism program, version 3.0; GraphPad Software, Inc., San Diego, CA). Differences in skin response between treatments were determined with the Mann-Whitney test, with the Minitab statistical package.

The relationship between the intratumor concentration of doxorubicin and the proportion of cures was modeled with a variant of the Hill concentration-effect equation (11) for the structural component of the model (Eq. A) and the binomial distribution for the data variation component of the model (12). The composite model was fit to data with maximum likelihood estimation via iteratively reweighted nonlinear least squares regression (13) with the NLIN procedure in SAS (SAS Institute, Inc.).

$$P = PDT \cdot back_{PDT} + (1 - (PDT \cdot back_{PDT})) \left( \frac{dox}{\exp(\beta \cdot PDT \cdot ED_{dox})} \right)^n \left( 1 + \frac{dox}{\exp(\beta \cdot PDT \cdot ED_{dox})} \right)^n$$

(A)

In Eq. A, P is the proportion of cures; dox is the extracted intratumor concentration of doxorubicin; PDT is a binary indicator variable, which is equal to 1 when PDT is applied and equal to 0 when doxorubicin is given without PDT; ED_{dox} is the concentration of extracted intratumor doxorubicin that results in an increase of 50% in the proportion of cures between the background cure rate and 100% cures; β is the parameter that quantifies the shift in the ED_{dox} caused by PDT; m is the Hill slope parameter; and back_{PDT} is the background cure rate for PDT treatment alone.

Results

HPPH-PDT Enhances Vascular Permeability. Transiently enhanced vascular leakiness, followed by vascular shutdown, has been observed for therapeutic doses of PDT with a number of photosensitizers (14). We used fluorescent microspheres to determine whether the photosensitizer HPPH also elicits vascular leakiness when activated by light. Our intent was to employ PDT doses that enhance vascular permeability without causing acute vascular shutdown because the latter would counteract subsequent drug delivery to the tumor. We first chose microspheres of intermediate diameter (0.2 μm) to map the PDT dose response surface for microsphere uptake, which has been shown previously to be a function of vascular permeability as well as particle size (3). FluoSpheres were injected immediately after completion of light treatment. Fig. 1A demonstrates that HPPH-PDT is highly effective in enhancing the accumulation of fluorescent microspheres in tumors in a fluence and fluence rate-dependent manner. The highest fluorescence values were obtained within the range of 48–88 J/cm² and 14–28 mW/cm². The lowest fluence rate tested (3.5 mW/cm²) was also effective in enhancing microsphere uptake within the fluences given. These fluences, however, were limited by the time required to deliver the HPPH-activating light; therefore comparison with other fluence rates at higher fluences was not possible. FluoSphere fluorescence values fell off sharply toward higher fluence rates, even when higher total fluences were given.

To delineate the pore size for PDT-induced vascular permeability, we administered fluorescent microspheres ranging in diameter from 0.02 to 2.0 μm to tumor bearing mice immediately after light exposure (48 J/cm², 28 mW/cm²) of the tumor, and assessed tumor fluorescence 24 h later. Fig. 1B shows that HPPH-PDT induced a significant (P &lt; 0.05) increase in uptake for all sizes of FluoSpheres compared with untreated control tumors, except the smallest (0.02 μm). Maximum uptake was achieved with sizes ranging from 0.1 to 0.5 μm, with a clear decline above that size. Fluorescence was barely detectable in tumor samples, treated or untreated, taken from mice that were injected with the smallest FluoSpheres (0.02 μm in diameter), indicating a lack of retention and/or rapid clearance of these particles. Contralateral control tumors exhibited minimal but detectable fluorescence of larger microspheres. This is consistent with the inherent hyperpermeability of tumors to macromolecules (3).

PDT Facilitates the Tumor Uptake of Doxil. To determine whether the HPPH-PDT enhancement of tumor uptake would also occur with liposomal drug carriers, Doxil was administered immediately after completion of light treatment to the mice and tumor uptake was assessed. First, we used fluorescence microscopy to visualize relative doxorubicin levels and distribution in tumors. PDT with 48 J/cm² at 14 mW/cm² (determined in preliminary experiments to provide maximum Doxil uptake; data not shown), and Doxil doses of 20 mg/kg were used for these short-term experiments. Fig. 2A demonstrates enhanced Doxil fluorescence intensity and increased fluorescence distribution in the PDT-treated tumor compared with its contralateral unilluminated control. Fig. 2B shows the amounts of doxorubicin extracted from tumors 3 and 24 h after administration, where Doxil was injected immediately after completion of PDT.
2C shows the changes in tumor uptake of fluorescein and Doxil as a function of time interval between completion of PDT treatment and injection of the agent. Fluorescein was used as a marker for vascular perfusion and was measured within 5 min of injection, monitoring the accessibility of the tumor tissue to systemically delivered agents (7). To visually compare the changes in fluorescein and Doxil uptake, the maximum uptakes, found with injection immediately after light treatment, were normalized to 1.0 (pretreatment values were ~0.4). It is apparent that the access to the tumor of both the perfusion marker fluorescein and Doxil was decreased with time after PDT, only partially recovering by 24 h.

**HPPH-PDT Followed by Doxil Significantly Enhances Tumor Control.** To test the therapeutic efficacy of the combination of PDT and Doxil, PDT conditions that led to optimal Doxil uptake in the tumor (48 J/cm², 14 mW/cm²) were combined with single Doxil doses ranging from 1.25 to 10 mg/kg, administered immediately after completion of light treatment. The data are shown in

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**Fig. 2. Uptake and distribution of Doxil after PDT.**

*Panel A:* Fluorescence micrographs of Doxil distribution in PDT-treated and untreated contralateral Colo 26 tumors. Tumors were harvested 3 h after injection of Doxil (20 mg/kg). *Panel B:* Dose-response curves for the cumulative uptake of Doxil after injection of different doses of Doxil. Each column represents data from five animals. *Panel C:* The effects of time interval between PDT (48 J/cm², 14 mW/cm²) and injection on the uptake of Doxil (○, 4 mg/kg; 5 min after injection; n = 5) or fluorescein (○, 20 mg/kg; 3 h after injection; n = 5) in Colo 26 tumors. The maximum uptakes, found with injection immediately after light treatment, were normalized to 1.0. Values represent the means; bars, SE.

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**Fig. 3. Efficacy and selectivity of PDT + Doxil combination therapy.** A, a Kaplan-Meier plot of the Colo 26 tumor response to the PDT + Doxil combination therapy and monotherapies. ●, PDT + 5.0 mg/kg Doxil; ▼, PDT + 3.0 mg/kg Doxil; ▲, PDT + 2.5 mg/kg Doxil; ○, PDT alone; □, 5.0 mg/kg Doxil; △, 3.0 mg/kg Doxil; ○, 2.5 mg/kg Doxil; ▽, 1.25 mg/kg Doxil; ◦, untreated. The number of animals in each group is given in Table 1. B, relationship of the proportion of cures to the sum of the intracellular doxorubicin concentration extracted at 3 and 10 h. The data (○) and fitted curves (---) are labeled. The dotted curve (--) is a simulation of the fitted concentration-effect model for the combination treatment and control, both with the background parameter fixed at zero. This curve serves to illustrate that even when taking into account the increased intratumor concentration of doxorubicin, and the cure rate of PDT alone, there is still an apparent shift to the left of the concentration-effect curve, suggesting an increased potency of the combination treatment over Doxil alone.

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The importance of time interval between completion of PDT and administration of Doxil is demonstrated in Fig. 2C. It had been expected that the mild PDT conditions used might not affect tumor vascular perfusion and would not impede drug delivery because of vascular shutdown. This expectation was only partially fulfilled.

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**Drug Delivery Through Photodynamic Therapy**

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...adapted from the original text...
The combination of PDT and 2.5 mg/kg Doxil resulted in a median time in days for tumors to reach 400 mm$^3$, and the percentage of animals cured/group. Individual treatment results were compared with control, PDT-alone, and Doxil-alone groups using the log-rank test. Two-tailed $P$s are reported, and survival curves are considered significantly different if $P < 0.05$.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of mice</th>
<th>Median time to regrowth (days)</th>
<th>% cures</th>
<th>$P$ vs. Control</th>
<th>$P$ vs. PDT alone</th>
<th>$P$ vs. Doxil alone</th>
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<tr>
<td>Control</td>
<td>7</td>
<td>8.00</td>
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<td>PDT alone</td>
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<td>0</td>
<td>0.1390</td>
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<tr>
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<tr>
<td>10 mg/kg</td>
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Table 1 Comprehensive summary data for Colo 26 tumor response to PDT and Doxil

The response of the Colo 26 tumor to PDT alone (48 J/cm$^2$, 14 mW/cm$^2$, 0.4 μmol/kg HPPH), free doxorubicin alone (2.5 mg/kg), PDT alone (1.25, 2.5, 3, and 10 mg/kg), PDT + free doxorubicin, and PDT + Doxil was assessed to determine the efficacy of the PDT + Doxil combination therapy. Reported is the number of mice/treatment group, the median time in days for tumors to reach 400 mm$^3$, and the percentage of animals cured/group. Individual treatment results were compared with control, PDT-alone, and Doxil-alone groups using the log-rank test. Two-tailed $P$s are reported, and survival curves are considered significantly different if $P < 0.05$.

![Image](cancerscience.jacsociety.org)
Discussion

Although a number of studies combining PDT with chemotherapy have been published, we present here a highly effective, novel approach that exploits the vascular permeabilizing effects of low fluence rate/low fluence PDT for delivery of macromolecular drug carriers, in particular liposomally encapsulated doxorubicin (Doxil). Earlier studies using free doxorubicin delivered before conventional PDT showed additive or marginally potentiating effects (16–19). Administration of free doxorubicin after PDT was ineffective (16), consistent with our findings that showed absence of enhanced intratumoral accumulation of free doxorubicin after PDT and a lack of potentiating of antitumor effects.

The work presented here differs in approach from these earlier studies in that it is based on the hypothesis that vascular leakiness (14) induced by PDT can permit the enhanced egress from the vascularule of macromolecular therapeutic agents. The transport of macromolecules across the vascular barrier occurs through endothelial gaps and is limited by the size of these gaps (3, 8, 20), which varies as a function of, among other factors, the tumor (tissue) type and micro-environment (8). As demonstrated here, PDT regimens can be identified that significantly enhance the tumor accumulation of fluorescent microspheres ranging in size from 0.1 to 2.0 μm, as well as Stealth liposomes (0.1 μm) carrying doxorubicin. We presume that the mechanism of this effect is through the formation and/or enlargement of endothelial gaps, because Fingar (21) observed the very rapid formation of large endothelial gaps in response to PDT. It is important to note that these regimens require low fluence rate light delivery, because uptake of microspheres declines sharply at high fluence rates, regardless of fluence. At least two explanations can be offered for this decline: high fluence rate PDT can deplete oxygen critically needed for photodynamic damage even in the vascular/perivascular regions, leaving portions of the tumor untreated; given adequate oxygen supply, high fluence rate PDT favors vascular constriction and occlusion (22, 23). The low fluence rate PDT regimen that proved optimal for enhancement of vascular permeability to Doxil did not result in vascular collapse or induction of hypoxia in the tumor during PDT treatment. However, even these mild PDT conditions were sufficient to cause significant reductions in tumor perfusion after treatment.

The precise mechanisms for gap formation by PDT are unknown, but they likely include direct PDT effects on the endothelial cytoskeleton that lead to cell rounding and contraction, probably mediated by PDT-induced microtubule depolarization (24). The suggestion that vascular changes are the result of direct PDT action upon the endothelium is supported by the fact that we were unsuccessful in influencing PDT-induced vascular leakiness by the inhibition/neutralization of factors known to affect vascular permeability and to be released and/or up-regulated by PDT (2), including prostaglandins, nitric oxide, histamine, bradykinin, tumor necrosis factor-α, and serotonin and the inflammatory chemokine MIP-2 (data not shown). Similarly, a major involvement of VEGF, also referred to as vascular permeability factor, is unlikely. VEGF, a regulator of vascular permeability (3), is barely detectable by Western blotting in untreated Colo 26 tumors, is minimally expressed at 4 h after PDT under low fluence rate conditions, and is undetectable thereafter out to 48 h of observation (data not shown). The fact that vascular permeability is increased even after very short PDT treatments, time periods insufficient for up-regulation of VEGF, speaks against VEGF-mediated mechanisms.

Low fluence/low fluence rate PDT pretreatment of Colo 26 tumors resulted in an ≈2.5-fold higher uptake of liposomally delivered doxorubicin for all drug doses >2.5 mg/kg, when assessed at 3 h after drug administration. This compares favorably with the uptake enhancement (1.5-fold) of that agent after local hyperthermia in the same tumor model (5). Enhancement ratios for Doxil were lower than those for fluorescent microspheres, probably because of, in part, different clearance kinetics of the delivery systems (4, 8). As expected from the local nature of the PDT treatment, it did not affect drug accumulation in normal tissue distant from the tumor, such as the heart, a dose-limiting organ for doxorubicin therapy in mice.

For tumor response studies, we chose to keep the HPPH-PDT dose regimen fixed at 48 J/cm² and 14 mW/cm², because it was optimal for Doxil uptake. This regimen was effective by itself, achieving long-term tumor control in ~18% of animals in this tumor system, which is relatively PDT resistant at higher fluence rate PDT (no long-term tumor control with 135 J/cm² at 75 mW/cm²; data not shown). These results confirm earlier observations with other photosensitizers and tumor systems, which showed that PDT efficiency increased dramatically with the lowering of irradiance because of the avoidance of photochemical oxygen depletion and therefore maintenance of tumor oxygenation during light delivery (22, 25). Doxil alone achieved significant growth delays only at 5 and 10 mg/kg. When combined with neoadjuvant “permeabilizing” PDT, highly effective antitumor effects were observed. It is clear from the analysis of data shown in Fig. 3B that PDT enhances the cure rate of Doxil alone more than can be accounted for by the increased intratumor doxorubicin concentration or the background cure rate of PDT alone, or the combination of the two phenomena. Studies have been initiated to determine whether permeabilizing PDT affects the Doxil response of tumors expressing the multidrug resistance phenotype, which exhibit an outward transport system for numerous chemotherapeutic agents including anthracyclines. It has been established that the multidrug resistance phenotype does not diminish the cellular uptake of photosensitizer (26).

Combination therapies are only useful if they do not potentiate equally the effects on tumor and normal tissue but rather offer enhanced treatment selectivity. Concerns about PDT toxicities in mice and humans focus on damage to tumor-surrounding normal tissue, i.e., in the mouse model normal skin. The toxicity profiles for Doxil differ significantly for mice and humans (15). In humans, mucocutaneous toxicity is dose limiting, whereas mice suffer dose-limiting cardiac toxicity and rarely show skin toxicity. Doxil is also associated with mild myelosuppression. In the present study, Doxil doses were kept below levels that would cause systemic toxicity (up to 10 mg/kg). This was reasonable because escalation to 10 mg/kg achieved no further therapeutic benefit in the combination therapy. To address the question of therapeutic index, the toxicities of the combination treatment and equimolar/ equitumoridical doses of the PDT monotherapy were compared, the combination showing significantly reduced normal tissue phototoxicity. Although this outcome is promising for the clinical application of this combination therapy, the data have to be interpreted with caution because the mouse model does not adequately represent the potential for Doxil-mediated skin toxicity in humans.

In conclusion, we have presented preclinical evidence for the possible improvement of the treatment of solid tumors through the combination of low fluence rate/low fluence PDT and Doxil. These findings may also apply to other macromolecular therapeutic agents. They are of immediate clinical relevance because HPPH-PDT is currently undergoing Phase I/II clinical trials. A wide range of, especially large, carcinomas and sarcomas that are amenable to PDT through the interstitial placement of optical light delivery fibers should benefit from this combination treatment (1).

References
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