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*Letter to the Editor***Synergistic Photodynamic and Photothermal Treatment of Port-Wine Stain?****Sol Kimel, PhD, Lars O. Svaasand, PhD, Kristen M. Kelly, MD, and J. Stuart Nelson, MD, PhD****Beckman Laser Institute, University of California-Irvine, Irvine, California*

The objective of port-wine stain (PWS) laser treatment is to maximize thermal damage to targeted blood vessels while preventing injury to the normal epidermis. Pulsed dye laser (PDL) treatment produces reasonably good results in a limited population of PWS patients due to its ability to destroy selectively dermal blood vessels. Yellow light emitted by the PDL is preferentially absorbed by hemoglobin in dilated PWS blood vessels where, after being converted to heat, causes thermal damage and thrombosis [1,2]. Although laser manufacturers have introduced controls which permit the operator to vary treatment parameters such as wavelength, pulse duration, light dosage, and skin cooling [3,4], the degree of PWS blanching following PDL therapy remains variable and unpredictable. If the ultimate standard required is complete blanching of the lesion, the average success rate is below 25%, even after undergoing multiple PDL treatments [5,6]. Because of the failure of PDL therapy to remove the PWS completely in the majority of patients, any new approach that shows therapeutic promise deserves careful examination.

In Photodynamic therapy (PDT), a photosensitizing drug is administered to the patient as the first step in treatment. In the second step, the tissue-localized drug is exposed to light at a wavelength appropriate for absorption by the photosensitizer. Excited molecules subsequently react with a substrate, such as oxygen, to generate short-lived highly reactive species, including singlet oxygen, which causes irreversible oxidative damage to biologically important intracellular structures. On the molecular level, phototoxic reactions take place within the cell on a time scale of nanoseconds, while associated macroscopic events occur within minutes. PDT is now a modality of great interest for imaging and eradication of a variety of benign, premalignant, and malignant conditions [7]. However, application of PDT for treatment of PWS has not been fully developed [8].

Why is PDT a potentially promising approach to the clinical management of patients with PWS? Histopathology shows local hemorrhage and red blood cell extravasation are common findings after PDT, both in animals [9,10] and humans [7]. This suggests that effects of PDT are not exclusively the result of direct tumor cell kill but can be secondary to vascular effects such as constriction, thrombosis, endothelial cell damage, and loss of vessel wall

integrity with increased permeability, which disrupts the microvasculature. Taken together, these studies suggest that the vascular compartment represents an important target for PDT of tumors and, possibly, for hypervascular skin lesion such as PWS (Fig. 1) and hemangiomas.

Persistent generalized skin photosensitivity is the most significant disadvantage of PDT when using photosensitizers systemically. Several second-generation photosensitizers with rapid metabolic clearance, thus reducing the duration of skin photosensitivity, are currently under development. Ideally, for treatment of PWS, the photosensitizer should remain confined to the vascular compartment. Benzoporphyrin derivative monoacid (BPD) is a photosensitizing drug that meets these requirements [11–14]. Moreover, BPD is intriguing because of its strong absorbance at 576 nm (molar extinction coefficient $\epsilon = 15,000 \text{ M}^{-1}\text{cm}^{-1}$), and at 690 nm ($\epsilon = 30,000 \text{ M}^{-1}\text{cm}^{-1}$) [12]. Successive treatments, using yellow and red light in that order, can achieve progressively deeper PDT treatments which might be useful, especially in the presence of thick PWS or hemangiomas.

Prior to clinical use for PWS, the complex nature of the response of human skin to photoactivated BPD must be elucidated with studies devoted to structural changes produced in skin [11–14]. After PDT, the structural integrity of collagen and other supporting structures is generally superior to that after photothermal treatment [15]. Despite full thickness necrosis produced by both treatment modalities, healing proceeds only after PDT. This might explain the excellent cosmetic results produced after PDT of human skin lesions [7,16–18].

Unlike PDL, which delivers short pulses at high irradiance, in PDT a laser or filtered non-coherent source merely has to provide photons at the desired wavelength in order to drive photodynamic reactions without heat generation. Milliwatt light exposure used with PDT will avoid

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Fig. 1. Blanching of an adult PWS site with a light dose of 75 J/cm^2 ($\lambda = 630 \text{ nm}$ at 100 mW/cm^2) delivered 30 min after intravenous administration of Photofrin[®] (1 mg/kg).

the epidermal thermal injury produced by high peak power PDL. Furthermore, because PDT uses continuous low irradiance over long exposures (several minutes), the dose effect, also at deeper skin layers, accumulates as exposure time is increased. This property contrasts sharply with conventional photothermal therapy which must achieve a sufficient “temperature jump” with a single PDL exposure (~ 1 millisecond). Multiple pulses do not increase the depth of treatment or improve PWS blanching response but subject the epidermis to a higher risk of thermal injury [2].

An exciting use of PDT is its potential combination with PDL. Might there be a synergistic effect by combining

PDT-induced photochemical and PDL-induced photothermal injuries leading to enhanced therapeutic efficacy of PWS treatment?

Unlike photothermolysis, which spares microvessels ($5\text{--}20 \mu\text{m}$ diameter) from PDL-induced photocoagulation [19], PDT destroys all vessels containing photosensitizer. A sub-therapeutic PDT exposure, using yellow light ($\lambda = 576 \text{ nm}$) absorbed by BPD, could conceivably be used to make PWS blood vessels more vulnerable to subsequent photothermal damage. Transient changes including thrombus formation at the vessel wall have indeed been observed by us *in vivo* after sub-threshold BPD–PDT [20]. Such thrombi are not likely to be dislodged subsequently by low venous blood pressure. PDL irradiation could then heat selectively the pre-treated vessels compromised by PDT. Moreover, use of yellow light for both PDT and PDL would confine therapeutic effects to the upper $500 \mu\text{m}$ of the dermis, containing ectatic PWS venules, while reducing the risk of possible skin infarction which could result from destruction of the lower vascular plexus (Fig. 2) [21]. Optical Doppler tomography (ODT) can image blood flow in human skin with high ($10 \mu\text{m}$) spatial resolution [22] and could be used to monitor the response to sub-threshold PDT and PDL irradiation *in-situ* and in real time [22,23]. This may enable optimization of PWS light exposure and determination of the treatment end point on an individual patient basis.

In conclusion, the potential advantages of combined PDT + PDL over conventional PDL of PWS are very convincing. Prospective, comparative, and controlled clinical studies against accepted treatment regimens on a multi-center basis are required so that the role of combined PDT + PDL treatment in the clinical management of PWS patients can be fully defined.

Fig. 2. Intradermal fluence in skin types II–III for incident radiant exposure of 1 J/cm^2 (indicated by the horizontal line). The ratio between fluence in the lower vascular plexus (at 1 mm depth) and the papillary dermis (at 0.1 mm depth) is 0.04 at 576 nm (**panel A**) and 0.50 at 690 nm (**panel B**).

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