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Lesion oxygenation associates with clinical outcomes in premalignant and early stage head and neck tumors treated on a phase 1 trial of photodynamic therapy

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ABSTRACT

Background: We report on a Phase 1 trial of photodynamic therapy (PDT) for superficial head and neck (H&N) lesions. Due to known oxygen dependencies of PDT, translational measurements of lesion hemoglobin oxygen saturation (S_tO_2) and blood volume (tHb) were studied for associations with patient outcomes.

Methods: PDT with aminolevulinc acid (ALA) and escalating light doses was evaluated for high-grade dysplasia, carcinoma-in-situ, and microinvasive carcinomas of the H&N. Among 29 evaluable patients, most (18) had lesions of the tongue or floor of mouth (FOM). Disease was intact in 18 patients and present at surgical margins in 11 patients. In 26 patients, lesion S_tO_2 and tHb was measured.

Results: Local control (LC) at 24 months was 57.5% among all patients. In patients with tongue/FOM lesions LC was 42.7%, and it was 50.1% for those with intact lesions. Lesion tHb was not associated with 3-month complete response (CR), but S_tO_2 was higher in patients with CR. In tongue/FOM lesions, baseline S_tO_2 [mean(SE)] was 54(4)% in patients (n = 12) with CR versus 23(8)% in patients (n = 6) with local recurrence/persistence (p = 0.01). Similarly, for intact disease, baseline S_tO_2 was 54(3)% in patients (n = 10) with CR versus 28(8)% in patients (n = 5) without CR (p = 0.03). In patients with intact disease, higher baseline S_tO_2 associated with 24-month local control (p = 0.02).

Conclusions: Measurement of the physiologic properties of target lesions may allow for identification of patients with the highest probability of benefiting from PDT. This provides opportunity for optimizing light delivery based on lesion characteristics and/or informing ongoing clinical decision-making in patients who would most benefit from PDT.

1. Introduction

Photodynamic therapy (PDT) involves delivery of a photosensitizer or photosensitizer precursor followed by illumination at a specific wavelength of light to an identified target. In applications to head and neck malignancies, PDT has been studied with photosensitizers/precursors that include Photofrin, aminolevulinc acid (ALA), and Foscan. As reviewed by several investigators, [1,2], PDT can be used for

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curative intent in the treatment of early stage primary or recurrent disease, such as that of the oral cavity, larynx, pharynx, and nasopharynx. It can also be used for palliation of later stage refractory disease. However, many benefits of PDT are particularly pertinent to the treatment of early stage oral malignancies, contributing to clinical success with several photosensitizers [3–5]. Lesions of the oral cavity are easily accessible to PDT light sources and the limited toxicity profile of PDT allows for repeated application [6]. This can be contrasted to functional limitations that can result from surgery, such as impairments in speech or difficulty in swallowing, or morbidities of external beam radiation therapy, such as changes in swallowing, taste, and salivation. When compared to resection of early stage lesions, PDT can achieve similar efficacy to this more invasive modality, making it relevant to consider the quality of life benefit that may accompany PDT [7].

We previously reported our experience of toxicities and early outcomes in this Phase 1 trial of patients with superficial head and neck lesions [8]. ALA-PDT was found to be tolerable among 29 evaluable patients who at that time had been followed for a minimum of 6 months. The primary toxicity was mucositis, occurring in 97% of patients, but in approximately half of the cases it did not exceed grade 1 in severity, and all cases resolved within 30 days after PDT. Transient elevations in liver enzymes, a known side effect of ALA [9], were noted in 59% of patients, with all but one being grade two or less.

Among patients treated with two-part (fractionated) illumination on this trial, we have also previously studied lesion physiology during and after PDT [10]. The present report is based, in part, on our previous observation that lesion oxygenation was low in two patients who had a poor clinical response to PDT. The significance of this observation lies in the known importance of tissue oxygen to the effectiveness of PDT with many photosensitizers. PDT cytotoxicity is reduced by a factor of two at an oxygen tension of 7.6 mmHg, corresponding to a blood oxyhemoglobin saturation of ~5% based on the oxyhemoglobin dissociation curve. Full photodynamic effect is achieved at normal tissue oxygenation of ~40 mmHg, corresponding to a blood oxyhemoglobin saturation of ~75% [11,12]. Thus, the presence of tissue hypoxia can impede PDT photochemistry and reduce treatment effect [13,14].

Although preclinical studies have documented correlations between tumor hypoxia and tumor control after PDT [15,16], few investigations have evaluated this association in clinical trials. Our results uniquely provide clinical evidence of better PDT response in patients with more highly oxygenated lesions. These data suggest the potential for personalizing administration of PDT based on clinical measurement of lesion physiologic properties.

2. Materials and methods

2.1. Clinical trial

Patients were enrolled if they had high-grade dysplasia, carcinoma-in-situ, or early microinvasive (≤1.5 mm depth of invasion) squamous cell carcinoma of the head and neck. Patients with intact disease or who underwent resection and had residual disease present at the resection margin were eligible, as long as the PDT procedure was within 4 months of pathologic diagnosis. All subjects were treated in accordance with protocols approved by the Institutional Review Board at the Hospital of the University of Pennsylvania.

As previously described [8], 29 evaluable patients were enrolled and treated on this trial between November 2009 and October 2014. One patient was not evaluable due to grade 5 toxicity secondary to pneumonia, sepsis and respiratory failure under circumstances of immunosuppression not allowing for a post-treatment follow-up interval to evaluate for response assessment. On autopsy, cause of death in relation to ALA and PDT could not be conclusively determined.

ALA was administered as an oral dose of 60 mg/kg. Vital signs were assessed immediately before and after ALA administration, every 15 min for the first two hours, and then hourly until the procedure. Illumination was delivered ~4–6 h after ALA administration, with activating light (629–635 nm) generated using a Ceralas Series GaAlAs diode laser (Biolitec Inc, Jena, Germany). Light delivery used either a microlens (MedLight SA, Ecublens, Switzerland) or a balloon-diffusing fiber (MedLight SA, Ecublens,Switzerland). Most patients presented with lesions accessible to microlens delivery, which provided a collimated laser beam covering a superficial circular area. For 9 patients, a microlens could not adequately cover a concave lesion. In these cases, a cylindrical diffusing fiber (active length of 2, 3, 4, or 5 cm) was placed within a balloon catheter. The balloon was inflated by saline to keep it in contact with the treated area. A fluence rate of 100 mW/cm^2 was delivered to the lesion surface, measured by a calibrated isotropic detector that was placed on the target surface. Escalating doses of total fluence at levels of 50, 100, 150 and 200 J/cm^2 were delivered to cohorts of 3–6 patients each. At each light dose, separate cohorts of patients were treated with continuous (unfractionated) illumination or fractionated light (two-part illumination). Fractionated illumination incorporated a 90–180 s break in illumination when 20% of the fluence had been delivered. After this short dark interval, illumination resumed to the full treatment fluence. With the exception of one patient with an easily assessable lesion on the lower lip mucosa, PDT was delivered to patients under general anesthesia.

Light precautions were initiated at the time of ALA administration and included the optical filtering of operating room lights. As needed, normal tissue was shielded using blue surgical towels or by painting with a solution of methylene blue during the intraoperative period, and drapes or clothes were used to protect the patient's skin. Patients were instructed to avoid sunlight for 3 days following ALA administration.

Patients were followed for response at week 1, weeks 2–3, day 30, day 90, every 3 months until 24 months after PDT administration, and then annually. A complete response (CR) was defined as complete ablation or absence of the index lesion in the area treated with light. In the absence of a CR, evaluation was performed for the presence of local recurrence. Patients were taken off protocol if they experienced a recurrence but followed off-protocol for further in- and out-of-field progression.

2.2. Fluorescence/reflectance spectroscopy system

Prior to delivery of the PDT light, the oxygenation, blood volume, and photosensitizer fluorescence of the target was measured using an integrated contact fluorescence and reflectance spectroscopy (CFRS) system. Immediately after completion of PDT light delivery, repeat measurements in the same areas were taken. Measurements were performed using a custom-built fiber-based optical probe that was placed in contact with the tissue surface. This probe consists of two source optical fibers and a series of detection fibers spaced between 0.14 and 0.88 cm away from the first source fiber, but for the present study the signal from only the closest four fibers (source-detector distances ≤0.34 cm) was evaluated because of the size and curvature of the lesions. This probe allowed collection of diffuse reflectance using a white light source (Avalight; Avantes, Broomfield, CO) coupled to the first source fiber for assessment of tissue physiologic properties by diffuse reflectance spectroscopy (DRS), while fluorescence spectra to assess relative photosensitizer levels were measured using a 403 nm excitation laser (Power Technologies, Inc., Little Rock, AK) coupled to the second source fiber. Both measurements use the same set of detection fibers, which are imaged by an integrated imaging spectrometer/multichannel CCD system (Inspectrum; Roper Scientific, Trenton, NJ). Data acquisition was sequential, such that repeated diffuse reflectance, background and fluorescence spectra were acquired at each of multiple sample locations.

2.3. Spectroscopy data analysis

Data were analyzed using an iterative fitting algorithm (fminsearch)