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Toxicities and early outcomes in a phase 1 trial of photodynamic therapy for premalignant and early stage head and neck tumors

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SUMMARY

Objectives: Management of early superficial lesions in the head and neck remains complex. We performed a phase 1 trial for high-grade premalignant and early superficial lesions of the head and neck using photodynamic therapy (PDT) with Levulan (ALA).

Materials and methods: Thirty-five subjects with high grade dysplasia, carcinoma in situ, or microinvasive ($\leqslant$1.5 mm depth) squamous cell carcinoma were enrolled. Cohorts of 3–6 patients were given escalating intraoperative light doses of 50–200 J/cm^2 4–6 h after oral administration of 60 mg/kg ALA. Light at 629–635 nm was delivered in a continuous (unfractionated) or fractionated (two-part) schema.

Results: PDT was delivered to 30/35 subjects, with 29 evaluable. There was one death possibly due to the treatment. The regimen was otherwise tolerable, with a 52% rate of grade 3 mucositis which healed within several weeks. Other toxicities were generally grade 1 or 2, including odynophagia (one grade 4), voice alteration (one grade 3), and photosensitivity reactions. One patient developed grade 5 sepsis. With a median follow-up of 42 months, 10 patients (34%) developed local recurrence; 4 of these received 50 J/cm^2 and two each received 100, 150, and 200 J/cm^2. Ten (34%) patients developed recurrence adjacent to the treated field. There was a 69% complete response rate at 3 months.

Conclusions: ALA-PDT is well tolerated. Maximum Tolerated Dose appears to be higher than the highest dose used in this study. Longer followup is required to analyze effect of light dose on local recurrence. High marginal recurrence rates suggest use of larger treatment fields.

Introduction

Photodynamic therapy (PDT) uses a photosensitizing agent and light to kill cells, involving delivery of a photosensitizer or photosensitizer precursor followed by illumination at a specific wavelength of light. The appeal of PDT in oncology has been that photosensitizers such as Photofrin are retained in tumor tissues for longer periods compared to normal tissue. The selectivity of photosensitizer for diseased tissue, as well as the ability to target the light directly to diseased areas, has prompted interest in studying PDT as an organ-preserving treatment for premalignant and malignant conditions. Clinical reports of PDT in the treatment of malignancies include head and neck cancers [1], lung cancer [2,3], mesothelioma [4], esophageal [5], brain [6], breast [7,8], bladder [9,10], and prostate cancers [11].

Early superficial lesions in the oral cavity, larynx and pharynx are ideal PDT targets because head and neck anatomy often offers direct access for the laser. Depth of penetration of the laser light

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ranges from a few millimeters up to 20 mm depending on wavelength [12]. In a report of his experience and literature review, Biel showed an 89% complete response rate in patients with carcinoma in situ or early stage head and neck cancers treated with PDT and Photofrin as photosensitizer [13]. Preclinical reports of Photofrin for head and neck cancer have indicated possible benefit to two-part fractionated light delivery for tumor control [14]. PDT offers an attractive function-preserving alternative for patients in circumstances in which surgical resection can be cosmetically and functionally debilitating.

Using Photofrin as photosensitizer in PDT is associated with an extended period of skin sensitivity to light, lasting up to 6–8 weeks after drug administration, which is a deterrent for ambulatory patients with early stage disease. One Photofrin alternative is 5-aminolevulinic acid or ALA (Levulan®, DUSA Pharmaceuticals, Inc.), a natural precursor in the heme biosynthetic pathway. ALA can be administered orally or topically, leading to the endogenous production and accumulation of protoporphyrin IX (PpIX). PpIX is activated at the same light wavelength as Photofrin (630 nm). Compared to the 6–8 week photosensitivity with Photofrin, ALA-induced PpIX skin photosensitivity persists for 24–48 h after administration. ALA-mediated PDT has been used in animal studies for esophageal [15], brain [16,17], and prostate cancer [18]. Orally administered ALA has been evaluated clinically for high grade dysplasias and superficial cancers of the esophagus. A series of 5 patients of high-grade dysplasia with Barrett's esophagus were treated, without toxicities or recurrences [19]. A series of 66 patients treated for high-grade intraepithelial neoplasia (31) or early adenocarcinoma (35) demonstrated no major complications [20]. With median 37 month follow-up, disease free survival was 89% for high-grade intraepithelial neoplasia and 68% for mucosal cancer. Oral ALA has been reported for a total 14 patients with high-grade dysplasia or microinvasive cancer of the head and neck. The above studies identify a dose of 60 mg/kg of oral ALA as safe in PDT for superficial epithelial lesions.

Due to the favorable absorption and clearance profiles of PpIX, we conducted a phase 1 trial of orally administered ALA with escalating doses of PDT light for head and neck lesions. The trial included patients with severe dysplasia, carcinoma in situ, or microinvasive carcinoma of the head and neck, dividing treatment into fractionated and non-fractionated cohorts. The primary purpose was assessing the safety and maximum tolerated PDT light dose with orally administered ALA. Due to limited data on efficacy of ALA-mediated PDT in this population, the secondary purpose was preliminarily assessing efficacy of ALA-PDT in this population.

Methods

Patients were eligible if they had high-grade dysplasia, carcinoma in situ, or invasive squamous cell carcinoma of the head and neck with depth of invasion $\leqslant$1.5 mm on surgical biopsy or resection specimen as read by a dedicated pathologist. Patients with intact disease or 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 University of Pennsylvania. Pretreatment evaluation included a complete history and physical examination, informed consent, fiber-optic nasopharyngolaryngoscopy with digital photographs, routine laboratory examination, and tissue diagnosis by the Department of Pathology.

ALA was administered as an oral dose of 60 mg/kg dissolved in 50 ml water 4–6 h prior to light delivery. After oral administration of ALA, subjects remained in clinic with light precautions. Vital signs were assessed before, immediately after ALA administration, every 15 min for the first two hours, and then hourly until the procedure.

Activating light generated using a Ceralas Series GaAlAs diode laser (Biolitec Inc., Vienna) was applied 4–6 h after ALA administration. Study subjects were treated with a total fluence of 50, 100, 150 and 200 J/cm^2 using red light (629–635 nm). Light was delivered using either a microlens (MedLight SA, Ecublens, Switzerland) or with a balloon diffusing fiber (MedLight SA, Ecublens, Switzerland) depending on tumor location and shape. The microlens provided a collimated circular laser beam covering a superficial circular area in accessible areas, and was used for most patients. For 9 patients, a microlens could not adequately cover a cylindrically-shaped lesion. In these cases, a cylindrical diffusing fiber with a chosen active length (2, 3, 4, 5 cm) was placed within a balloon catheter. The balloon was inflated by saline to keep it in contact with the treated area. The light doses were measured using an isotropic detector located in-situ at the treated surface for all patients. As a result, the light dose was always correctly quantified regardless of applicator geometry. A fluence rate of 100 mW/cm^2 was delivered to the target, measured by a calibrated isotropic detector positioned on the tissue surface. At each light dose, separate patient cohorts were treated with continuous (unfractionated) or fractionated (two-part) illumination. Fractionation involved delivery of 20% of fluence, a 90–180 s break, then resumption to full fluence.

Almost all treatments were performed under general anesthesia. One patient with lower lip pathology was treated as an outpatient under local anesthesia to the submental nerve. All subjects were hospitalized overnight for observation. Biopsy specimens of diseased tissue were collected before PDT in order to establish eligibility, as well as after PDT in order to assess response (1 month in patients without a clinical response and at 3 months in all patients).

Post-treatment, all patients were instructed to avoid sunlight for 3 days. Toxicity endpoints were graded using the Cooperative Group Common Toxicity Criteria (CTCAE v.3.0). Patients were followed week 1, week 2–3, day 30, day 90, every 3 months for 24 months, and then annually. Dose-limiting toxicity (DLT) was defined by a grade 3 toxicity by 30 days after administration of PDT. Patients were taken off protocol if they underwent a recurrence, but followed off-protocol for further progression.

For purposes of statistical analysis of treatment response, patients were divided into groups receiving low (50 and 100 J/cm^2) and high PDT light dose (150 and 200 J/cm^2). Complete response at 3 months was evaluated with a planned biopsy at that timepoint. Kaplan Meier analysis with log-rank analysis of local recurrence-free survival was used to compare the low and high PDT light dose groups. For assessment of toxicity between the low and high dose groups, two-sided Fisher exact test was used to assess for statistical significance between the two groups.

Results

From November 2009 to October 2014, 35 subjects were enrolled. Two of the subjects were the same patient undergoing separate treatment for a second primary (1 subject) or recurrent disease (1 subject). One patient who tolerated initial treatment at 50 J/cm^2 without complication was treated for a second time 10 months later for a local recurrence at a higher dose (150 J/cm^2, fractionated). This patient who had history of liver transplant on immunosuppression underwent treatment and developed expected edema at the treatment site which quickly resolved but then developed pulmonary edema and sepsis of either pulmonary or urinary origin, and significant hypoxemia from a tension pneumothorax. It was determined that the pneumonia, sepsis and respiratory failure could possibly be related to study treatment with the patient's immunosuppression as a possible contributing factor.