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Case Report

Fullerene - Photodynamic Therapy Effect on Oral Squamous Cell Carcinoma of the Tongue: A Case Study

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Abstract

Photodynamic therapy produces localized Type 1 and Type 2 photochemical damage in targeted cancer cells. It has been established as a safe and non-invasive modality in the treatment of squamous cell carcinoma, as well as other tumors. Fullerenes have demonstrated tremendous potential as photosensitizers due to their excellent biocompatibility and unique characteristics. Here we present the case of an oral squamous cell carcinoma (OSCC) on the tongue of a 50-year-old female who underwent a limited course of photodynamic therapy (PDT) using a pristine nanocarbon onion-like fullerene (NOLF) before undergoing surgical excision. The fullerene- PDT treatment using violet and blue light resulted in a significant reduction in the size and appearance of the lesion. Additionally, the use of pristine (NOLF) as a photosensitizer has never been reported in the literature to our knowledge.

Keywords: *Fullerenes; Nanocarbon Onion-Like Fullerenes; Oral Squamous Cell Carcinoma; Photodynamic Therapy; Type 1 Photochemistry; Type 2 Photochemistry*

Abbreviations

NOLF: Nanocarbon Onion-like Fullerene; PDT: Photodynamic Therapy; OSCC: Oral Squamous Cell Carcinoma; HPV: Human Papillomavirus: PET Scan: Positive Emission Tomography

Introduction

Oral Squamous cell carcinoma (OSCC) is a common malignancy of the head and neck. OSCC is associated with tobacco and alcohol use, poor dental hygiene, nitrosamine, periodontal disease, candidiasis and human papillomavirus (HPV) infection [1]. These contributors induce loss of normal cell cycle restraint, dysmaturation of stem cells, and dysplastic tissue formation, which is followed by loss of replicative senescence and unlimited proliferation in the pre-malignant state, eventually leading to OSCC if left unchecked [2]. Due to a high rate of mortality (50%) despite treatment, the mutilating nature of conventional therapy, and numerous complications, alternative therapies are being sought [1]. PDT is a promising alternative to conventional therapy as it is minimally invasive and potentially highly effective. Cerrati reported that a meta-analysis of 24 studies found no statistical difference between the response, locoregional control, and reoccurrence between PDT and surgery in the early stages of OSCC [3]. Similarly, the use of PDT in the early stages of head and neck squamous cell malignancies does not interfere with future surgery or radiation treatment [4].

The interest in fullerene materials for use in medicine is driven by their unique characteristics and excellent biocompatibility *in vivo* [8,9]. Fullerene materials, both functionalized and pristine, have emerged as having excellent potential as photosensitizers [6,10-14].

Case Report

The patient was a 50-year-old Caucasian female who works as an office manager for a medical practice. She has a multi-year history of a sore tongue and repeated ulcerations or abrasions to the left side of her tongue. She reported that her dentist attributed it to frequent trauma from her teeth, and had several filings of the teeth on that side of the mouth. The dentist also filed her teeth in an attempt to reduce frequent trauma to her tongue. One year earlier, her dentist had referred her to an oral surgeon who recommended a biopsy of the area. However, the patient did not follow through with this recommendation. The patient's history is negative for both alcohol and tobacco use, but she reported that she was heavily exposed to secondhand cigarette smoke as a child. Familial history was positive for a mother who died of lung cancer despite being a non-smoker, but who was also exposed to heavy second-hand smoke. Her past Medical History was remarkable only for obesity.

Her initial examination revealed an inflammation surrounding a white plaque covered lesion, approximately 5 cm x 1.5 cm along the posterior ¾ of the left side of her tongue, and excluding the biopsy site, remained mostly unchanged before PDT (Figure 1). No cervical lymphadenopathy was appreciated, and she was subsequently referred for a biopsy. The biopsy removed a 2 cm x 0.6 cm x 0.6 cm brown elliptical specimen that revealed multiple areas of squamous cell carcinoma with muscular invasion and suspicion for lymphovascular invasion. The tumor extended to margins and was moderately differentiated.

The patient then underwent a PET scan that showed uptake in the area of the tongue with no suspicion of metastatic disease. Initial blood work indicated that this was a highly aggressive tumor with multiple markers which suggested a high metastatic potential, therefore surgical excision was recommended.

The patient initially inquired about trying NOLF as an adjunct to her traditional cancer therapy due to familiarity with fullerene research. She was given additional information regarding NOLF and PDT and completed an informed consent regarding NOLF and fullerene-PDT.

To prepare the OSCC lesion for photodynamic therapy using this pristine NOLF in the absence of a tumor-targeting ligand, the lesion site was exposed to pristine NOLF photosensitizer in the following manner to maximize both topical and internal tumor cell uptake. Approximately 200mg of a novel, pristine NOLF material in powder form was obtained from Graphitic Nano Onions, (LLC) and mixed with 10 ml of food-grade virgin coconut oil to form a suspension at a concentration approximating 20mg/ml. This was was then topically applied to the lesion daily and 10 minutes before each PDT session. Additionally, two capsules containing 10mg of NOFL material in a base of approximately 200mg of beta glucan was obtained by Super Fullene Labs LLC, which was taken orally three times daily.

Based on the expected absorption spectrum of large onion-like fullerenes, a three-watt 365 nm (violet) LED with a maximum output of 115 mw.cm^2 and a 3M Dental Curing Light 2500 with high- intensity 75 Watt tungsten/halogen lamp 420 nm - 500 nm (peak 460 nm - 470 nm) with an output of 650 mW/cm^2 was selected to encompass the expected absorption range of the NOLF sensitizer. Seven photodynamic therapy treatments were administered over sixteen days using simultaneously applied light sources before surgery. The initial three treatments delivered PDT for 180 seconds and the remaining four treatments for 360 seconds. The combined light source output was approximately 750 mW/cm^2. Total tumor exposure was approximately 68 J/cm^2 and 135 J/cm^2 at 180 and 360 seconds, respectively.

Results

The appearance and size of the lesion site and white plaque before PDT (Figure 1) was significantly smaller post-PDT (Figure 2). The greatest dimension of the tumor at the time of surgery was 1.8 cm x 1.3 cm, extending to the margins with a depth of 5 mm and was mod-

erately differentiated. Following surgical removal of the tumor and modified neck dissection, the final pathology demonstrated minimal residual tumor cells and clear margins, which only required an unexpected single resection. There was a 5 mm depth of invasion, and perineural invasion was present. The nearest peripheral margin was 2 mm and a deep margin of 7 mm. Biopsies throughout the tongue and lymph nodes were taken, revealing 1 of 8 positive lymph nodes; however, random biopsies were negative for tumor.

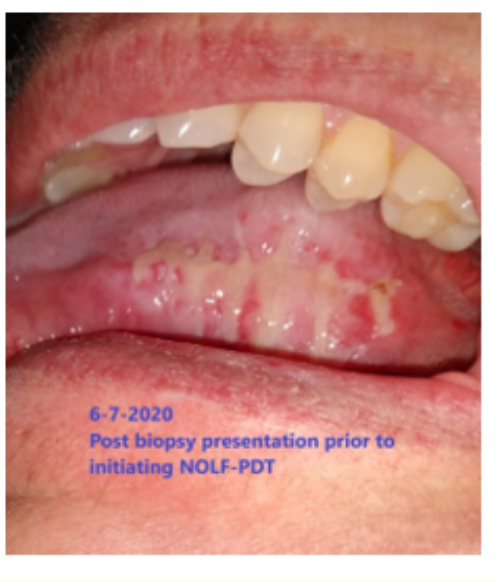

Figure 1

Figure 2

Following surgery, she was started on external beam radiation therapy. The oncologist did not recommend adjuvant chemotherapy despite the blood test results showing malignant cells in her systemic circulation, and her positive lymph node status, and preferred only to treat if a metastasis appears on follow-up PET scans.

Discussion

The use of PDT is an established and safe modality that has both experimental and regulatory approval for the treatment of several cancers and has mainstream acceptance in the treatment of actinic keratosis and basal cell carcinoma. PDT involves the use of a drug or dye that can absorb light and be stimulated to its triplet state, which then reacts with ground state oxygen to produce singlet oxygen, or in the presence of reducing agents, the superoxide anion and other reactive oxygen species (ROS). Singlet oxygen and other ROS can then react with biological molecules in cells to cause oxidative damage, apoptosis, and cell death [5-7]. Efficient photochemical agents require high levels of light absorption at the treatment wavelength, high photochemical efficiency, photostability, minimal toxicity when not exposed to light and excellent biocompatibility [4].

PDT has been used to treat cancer in the clinic for more than 40 years, and research into more effective photosensitizing agents that are highly biocompatible continues [4]. The photophysical, photochemical, and absorption characteristics of fullerene materials are well known [15,16]. The degenerative electron orbital characteristics of fullerene material can be excited using a wide range of wavelengths in the UV through NIR light [14]. The photochemistry effect results in useful Type 1 and Type 2 photochemical ROS mediated killing of cancer cells [1,5-7,11]. Additionally, fullerene materials have diverse effects on biological systems. These include DNA, mitochondrial, immune, potential to induce stem cell differentiation, and neurohumoral defense mechanisms that suggest their promising use as antitumor agents; however, much is yet unknown [12,17].

Conclusion

Mainstream adoption of fullerene-PDT for the treatment of various cancers requires confirmation in successful prospective randomized clinical trials. Although this case study is limited in scope, it demonstrates the potential use of pristine NOLF material as a photosensitizer, as well as NOLF's potential use to treat localized OSCC non-invasively. Additionally, the use of NOLF, and other fullerene materials, may have PDT potential for use in combination with other modalities, including chemotherapy and immunotherapy.

Author Disclosure Statement

Daniel Bourassa is a managing member and biomedical consultant for Carbone Quantique Biomedical, LLC, which contracts with the nanocarbon fullerene industry, including Graphitic Nano Onions, LLC of Daleville, IN, who provided the Grafex ™ powder for PDT, and Super Fullerene Labs, LLC of Houston, TX, who provided the oral NOLF (Grafex ™) capsules used in this case study. No direct financial support or other involvement has been provided by the CTIC or SuperC60 Fullerene, LLC. The other author has no commercial or financial relationship to declare.

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