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Photodynamic therapy in the management of basal cell carcinoma: Retrospective evaluation of outcome

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ABSTRACT

Introduction: Photodynamic therapy (PDT) is a relatively new method of treating various kinds of pathologies. In this retrospective study, a total of 148 patients with basal cell carcinoma (BCC) were treated with surface illumination methyl aminolevulinate – photodynamic therapy (MAL-PDT) or *meta*-tetrahydroxyphenylchlorin (mTHPC-PDT). Comparisons with the clinical features, rate of recurrence and overall outcome were made.

Materials and methods: Surface illumination PDT was offered under local or general anaesthesia. For thin BCCs, the 16% strength cream (MAL) was applied topically 3 h prior to tissue illumination. A single-channel 628 nm diode laser was used for illumination and light was delivered at 100J/cm^2 per site. For thick BCCs, 0.05 mg/kg mTHPC was administered intravenously prior to tissue illumination. A single-channel 652 nm diode laser was used for illumination and light was delivered at 20J/cm^2 per site. Lesion response evaluation was carried out according to RECIST.

Results: The MAL-PDT sub-group included 86 patients with 127 thin BCCs; 80 patients had complete response (CR) after one round of treatment. The mTHPC-PDT sub-group included 62 patients with 116 thick BCCs; 60 patients had complete response after one round of treatment. Statistically significant factors associated with complete response to MAL-PDT included superficial BCC histotype ($P < 0.001$), ≤0.5 mm tumour thickness ($P < 0.001$) and lack of ulceration ($P < 0.001$). While for the mTHPC-PDT sub-group, both superficial and nodular types responded significantly better than invasive type ($P < 0.001$); the lack of ulceration was insignificant factor in achieving complete response.

Conclusion: PDT achieved high efficacy in the treatment of basal cell carcinomas with greatly reduced morbidity and disfigurement. The technique is simple, can commonly be carried out in outpatient clinics, and is highly acceptable to patients.

1. Introduction

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) represent the majority of non-melanotic skin cancer (NMSC) [1]. They continue to be a major concern in the developed world with more than 100,000 new cases per year. BCCs are mostly slow growing localized tumours with minimal invasion capacity, unlike SCCs, which are fast growing invading tumours that usually metastasize to the loco-regional lymph nodes [2]. 80% of NMSC cases occur in people aged 55 years and over. They are mainly caused by cumulative exposure to ultraviolet B radiation and as such mainly found in the head and neck region [3].

The skin type is another well-established risk factor. People with fair skin have 20 times higher risk of developing skin cancer than dark skinned ones due to the melanin protective effect. Other risk factors include chemical exposure, radiation treatment and other immune system depleting interventions. A diagnosis maybe confirmed through histopathology, which remains the gold standard [4]. Punch biopsy is usually required to determine the sub-type of BCC.

Approximately 30–40% of patients with BCC will develop one or multiple lesions within 10 years from their first diagnosis [5]. In addition to the classic rodent ulcer characteristics with indurated edge and central ulceration, other BCC sub-types include nodular, cystic, superficial, morphoeic and pigmented [6]. 10–40% of BCCs seems to have a mixed pattern of two or more sub-types. Unlike BCCs, squamous-cell carcinomas can have precursor lesions, such as actinic keratosis and SCC in situ (Bowen's disease) [7].

The relative 5-year survival rate for patients with BCC is more than 99%. Less than one-tenth of a percent of BCCs spread to locoregional

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lymph nodes. Patients whom BCCs have invaded locoregional or distant organs have a 5-year survival rate of about 10% [8,9]. According to Telfer et al. the factors influencing prognosis of basal cell carcinoma include: tumour site and size, definition of clinical margins, histological subtypes, histological features of aggression and failure of previous treatment as well as immunosuppression. Surgery is the current gold standard treatment with the aim to eradicate the tumour in a manner likely to result in a good cosmetic outcome. The most commonly used techniques include excision with predetermined margins and Mohs micrographic surgery. Other non-surgical techniques include: cryosurgery, carbon dioxide laser and photodynamic therapy have been described in the treatment of low-risk basal cell carcinomas. While radiotherapy can be used as a primary or adjuvant intervention in managing high risk BCCs [10].

Photodynamic therapy (PDT) is a relatively new modality of treating various kinds of tissue pathologies [11]. The treatment can be carried out under local or general anaesthesia, and the delivery technique can include surface illumination or interstitial application. The photosensitizer is administered either topically or intravenously; few to several hours prior to light delivery [12,13]. The selective uptake and retention of a locally or systemically administered photosensitizer in tumour tissue is an important factor in the photodynamic process [14]. The photosensitizer is activated by non-thermal light of appropriate wavelength, which results in the production of oxygen-free radicals and the formation of intracellular singlet oxygen, which causes tumour cell death by intracellular oxygenation and vascular shutdown [15,16].

PDT is considered an effective treatment option in BCCs. However, a number of comparative studies have confirmed that surgery still the most effective treatment [17,18]. PDT is indeed an effective treatment both for superficial BCC and nodular BCC, however it is considered to be of less efficacy than surgery with nodular BCC [19]. It is worth mentioning that morphoeic BCC is not suitable for PDT intervention, with surgery being the treatment of choice. Furthermore, tumour depth seems to have a detrimental role on the outcome for patient treated with PDT. Morton et al. showed that thickness significantly affected PDT response, with no response in four BCCs more than 2 mm thick [20].

Methyl aminolevulinate (MAL), a photosensitiser, is an ester of 5-aminolevulinic acid (5-ALA), a naturally occurring precursor in the heme biosynthetic pathway. It is converted to the endogenous photosensitiser protoporphyrin IX, which can be activated by red, green and even blue light. 5-ALA can be delivered in topical (MAL), oral or intravenous formulations and can be triggered by many light sources. Its uses are constrained by its depth of effect (< 0.2 cm) to thin cutaneous lesions. With the formation of protoporphyrin IX, a maximum absorption can be reached at 635 nm. On the other hand, *meso*-tetrahydroxyphenyl chlorin (mTHPC) is a more potent photosensitiser for cancer management with longer period of photosensitivity, when compared to 5-ALA with maximum absorption is at 652 nm and increased depth of effect of up to 10 mm which makes it suitable for thicker cutaneous lesions [14–16].

Notable adverse events in the immediate post-PDT phase include pain and swelling [11]. The pain usually requires short-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and opiates [12]. The reporting of pain is mirrored by a temporary rise in white blood cell levels, which follows the induction of tissue necrosis and the generation of acute and chronic inflammatory responses [13]. The major side effect of PDT is residual local/systemic photosensitization, which depends on the photosensitizer, its dose and the mode of administration [14]. The use of topical photosensitizer is the best way to avoid residual systemic photosensitivity and the need for the patient to stay out of bright light and sunlight for several days or weeks after receiving PDT [15]. However, the major disadvantage of a topically applied photosensitizer is the small treatment depth of only 1–2 mm that can be obtained. Therefore, only very superficial tumours of less than 1 mm can be treated successfully [16].

In this retrospective study, a total of 148 patients with basal cell carcinoma (BCC) were treated with surface illumination MAL-PDT or mTHPC-PDT for shallow and deep BCCs, respectively. Comparisons with the clinical features, rate of recurrence and overall outcome were made.

2. Materials and methods

Following a number of prospective ethically approved multicenter trials; the European Medicines Advisory Committee approved PDT. 5-ALA as a treatment for skin cancer was approved as well as mTHPC for advanced/recurrent head and neck cancer. The application of photodynamic therapy at the Head and Neck Unit, University College London Hospitals (UCLH) is commonly practiced. Most referrals for this tertiary care unit include patients with advanced or recurrent disease who failed previous conventional interventions as well as patients with skin pathologies.

Every treated patient signed an informed consent prior to the intervention and was regularly updated on the treatment progress and outcome. The patients' data were entered into proformas, which were validated and checked by interval sampling. The fields included a range of clinical, operative and histopathological variables. Data collected also included dates of recurrence and of last clinic review. These treatments were carried out at the UCLH Head and Neck Unit between 1996 and 2006. These patients were followed-up for a mean of 7.8 years.

The medical records of 148 consecutive patients who presented with suspicious skin lesions and diagnosed with basal cell carcinoma were examined. The minimum clinical data included age, gender and race, smoking status, risk factors and any relevant medical history (i.e. previous AK, BCC and skin SCC as well as immunodeficiency). Smoking status was classified into 5 categories each: life long smoker < 20cig/year, life long smoker > 20cig/year, ex-smoker < 20cig/year, ex-smoker > 20cig/year and non-smoker.

The diagnosis of these lesions was made through close skin examination; followed by incisional biopsy or shave biopsy about 4 week before treatment for diagnostic confirmation and histologic classification. Every lesion size and location was accurately documented. The lesions were pathologically classified into superficial, nodular and infiltrative. Data on ulceration were also included. Tumour thickness in each biopsy was measured as per the Breslow's technique commonly used for melanomas. Patients were excluded if they received previous treatment of BCC in the last 30 days, were non-compliant with treatment or had photosensitive disease. No pigmented or morpheaform BCCs were treated nor lesions with deep infiltration confirmed histologically.

These patients, with 243 BCC lesions, were treated with surface illumination MAL-PDT or mTHPC-PDT depending on the thickness of lesion. For thin BCCs (< 1 mm in thickness), the 16% strength cream (MAL) was applied topically and covered with occlusive dressing 3 h prior to tissue illumination. EMLA cream (2.5% lignocaine and 2.5% prilocaine) was offered to every patient. A single-channel 628 nm diode laser (by biolitec AG, Vienna, Austria) was used for illumination and light was delivered at 100 J/cm^2 per site. Patients were advised to avoid direct sun light exposure for few days to avoid local tissue photosensitive reactions. For thick BCCs (≥ 1 mm in thickness), a 0.05 mg/kg mTHPC was administered intravenously into the midcubital vein 48 h prior to tissue illumination. Early introduction of the photosensitizer would allow the agent to accumulate in the pathological area, which would increase the efficacy. On the day of treatment, shielding of the macroscopically healthy surrounding tissue was employed. A safety margin of 2–3 mm around the suspicious lesion was included and illuminated as part of the treatment. Here adjacent tissues were infiltrated with an anaesthetic agent (marcaine: bupivacaine without epinephrine) and in very few cases (large and multiple