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Apparent Complete Response of a Treatment Refractory and Recurrent Squamous Cell Carcinoma Lesion to Photochemical Internalization: A Clinical Case Study

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Abstract

Photochemical internalisation (PCI) depends on the delivery of sub-lethal photodynamic reaction to facilitate the work of a chemotherapeutic agent. We discuss our experience in managing a patient with extensive squamous cell carcinoma of the right face and scalp under the TPCS_{2a}-based bleomycin PCI treatment protocol. In this case, an 84-year-old Caucasian received 0.25mg/kg of TPCS_{2a} (Amphinex®). Surface illumination photochemical internalisation was carried out after 4 days, which was preceded by the chemotherapeutic agent infusion (Bleomycin). After one week from the illumination time, tissue necrosis was evident and tumour shrinkage was most noticeable at day 14 post-illumination. Follow-up at 6 weeks continued to show tissue healing and regeneration with no clinical evidence of recurrence. Multiple surgical biopsies were taken at 1 and 3 months post-illumination and found to be tumour free. PCI's depth of effect has been very significant with negligible damage to the collateral tissues. This technology has a role in interventional oncology especially when managing challenging cases.

Introduction

Photochemical internalisation (PCI) is a fairly new clinical technology that has been tested recently in first in-human phase one trial (1-3). The PCI reaction requires a photosensitive agent, which is administered systemically prior to the introduction of the chemotherapeutic agent and subsequent activation by light of a specific wavelength. PCI's main aim was to improve targeted intracellular delivery of active molecules (e.g. chemotherapeutics). This is usually facilitated via photosensitisers that usually colocalize with the active molecule in the same endocytic vesicles. By targeting these vesicles with a light of a specific wavelength an induction of reactive oxygen species is achieved causing rupture of the vesicles and release of the active molecules into the cytoplasm where they cause damage to the tumor cells (1,4).

The first human study utilising this technology indicated that PCI is safe and could be used in managing patients with advanced or recurrent malignancies. The phase I trial involved the use of TPCS_{2a} (disulfonated tetraphenyl chlorin, Amphinex®) as the photosensitiser, which was aimed to facilitate the effect of the chemotherapy agent (Bleomycin). Furthermore, PCI proved to be well tolerated due the low dose of both the photosensitizer and chemotherapeutic agents. A wide spectrum of cutaneous and subcutaneous carcinomas and sarcomas were successfully managed (3).

Reported adverse events using this new technology include peri-treatment pain, which has been positively linked to treatment response. Photosensitive skin reactions, when using high doses of the photosensitiser, were also reported. So far, most evidence suggests that his technology is highly tumor specific, with the ability to overcome variability in tumor depths, as well as control tumor margins and promote tissue regeneration (3).

Here, we discuss our experience in managing a patient with extensive squamous cell carcinoma of the right face using the TPCS-based bleomycin PCI treatment protocol.

Case report

An 84-year-old Caucasian male was diagnosed with extensive cutaneous squamous cell carcinoma of the right face. The patient underwent a number of major reconstructive surgeries and adjuvant radiotherapy. Unfortunately and despite these interventions, the patient presented with recurrent disease involving the right face and underneath the local flap in the right temporal area as well as the right temporo-parietal-occipital areas of the scalp (Figure 1A). The cutaneous disease was progressing at a very high rate, which was noted at the second clinic visit (Figure 1B) and this was only 3 weeks following the first clinic visit (Figure 1A). Here the disease was noted to involve more skin area of the right face, including the lateral canthal, supraorbital and infraorbital areas. At the time, the two cancerous areas of the right face had extended to involve the entire right face, as well as the right temporo-parietal-occipital areas of the scalp.

The patient's medical history included hypertension, ischaemic heart disease and subsequent coronary stent insertion in 2005. The patient reported an 8-year history of chronic lymphocytic leukemia but was in remission at time of presentation. His medication history included Aspirin, Ramipril, Bisoprolol and Simvastatin. This patient was part of the phase I TPCS_{2a} based Bleomycin PCI trial³. Specific data regarding the photosensitiser tolerability and photosensitive reactions were recorded and showed that the patient tolerated the photosensitiser and chemotherapeutic agent well and there were no recorded photosensitive reactions.

Clinical response parameters were not examined under the protocol of the phase I trial. However, our group have looked into this parameter in detail for the complex cases that were treated. This was mainly carried out due to clinical interest and that this could help guide designing future trials. This was discussed with the patient in full and he signed an informed consent. The South West Research Ethics Committee, UK, granted ethical approval to conduct this work.

A clinical decision was made to treat the majority of the superficial disease, as in figure 1B, under the PCI protocol (TPCS_{2a} [Amphinex®]-based Bleomycin). The deeper tumour areas (i.e. disease under the temporal flap area) were left to be treated at a later stage. At the time we only had developed a clinical protocol to deal with superficial disease with photochemical internalisation

(PCI), hence deep-seated disease was left to be treated with interstitial photodynamic therapy using mTHPC (meta-tetrahydroxyphenylchlorin) as the photosensitiser.

The patient received 0.25 mg/kg of Amphinex[®] (Figure 1C) by slow intravenous injection (1–6 min) into the median cubital vein, with the patient monitored constantly during this process. Dexamethasone (1 mg intravenously) and chlorphenamine (10 mg intravenously) were given soon afterwards to reduce any potential allergic reaction. The patient was kept in a dimly lit side room to avoid photosensitivity reactions in the skin or the eyes, and monitored closely for adverse events. No clinical changes were expected to tissue at this stage. Lesions were measured mainly to assess for any possible partial response or no response to treatment.

Four days later, surface illumination based photochemical internalization (PCI) (652 nm diode laser, 60 J/cm² delivered at irradiance 100 mW/cm²) was carried out 3 hours after the slow intravenous infusion of Bleomycin (dose of 15000 U/m² over 15 mins). Each illumination process covered a circle of up to 5 cm in diameter and lasted 600 s at an irradiance of 100 mW/cm, to achieve a fixed light dose of 60 J/cm. A margin of 10 mm beyond the macroscopic tumour margin was treated to eliminate any infiltration of cancer cells into the tumour microenvironment.

During and after the illumination period, we noted immediate changes to the pathological tissue colour (erythema), (Figure 1D). Pre-emptive analgesia was given [Co-Codamol 30/500 mg 2 tablets] prior to illumination but unfortunately pain was an immediate adverse event, which responded to further opiates and local infiltration of 10–20 mL of 0.5% bupivacaine (with no vasoconstrictor). Pain was completely eliminated within less than 12 hours post-illumination. This phase was also associated with transudate/exudates (yellow in colour) leakage from the treated areas as well as local tissue inflammation leading to periorbital swelling.

Following this, blanching of tissues from day “two” to day “five” post-illumination were noted which was related to the Bleomycin release (Figure 1E). At “one” week post-illumination, further tissue changes were noted including darkening and hardening of the treated skin tissue which indicated early stages of necrosis (Figure 1F). At two weeks post-illumination, maximal discharge

from the necrotic tissues was noted and was associated with further darkening and hardening of treated tissue indicating tissue death and tumour reduction. Severe malodour was associated with it (Figure 1G). Flamazine and hydrogel were used to dissolve the necrotic tissue aiming to avoid any potential need for surgical debridement.

Further follow-up at 6 weeks (Figure 1H) continued to show tissue healing and regeneration with no clinical evidence of recurrence. Three surgical biopsies were taken after 1 month post-illumination, which revealed inflammatory cells and no malignancy (Figure 2a). The biopsies were randomly taken from the anterior scalp, posterior scalp and face. Three further biopsies were taken after 3 months post-illumination and showed granulation tissue with mixed acute and chronic inflammatory cells, and no malignancy (Figure 2b).

The patient required treatment for deeper tumour areas, mainly in the right temporal and supra-orbital regions, which was carried out with interstitial photodynamic therapy (drug and dose was 0.15 mg/kg mTHPC, drug light interval was 96 hours, light illumination was with 652 nm diode laser and total energy delivered per port was 20 joules per linear cm of fibre). Skin grafting of the face was carried out at the same time (Figure 1I, blue arrows highlighting the interstitial fibers). No recurrence was identified at the last clinic review (18 months).

Discussion

The PCI technology, still in the clinical research phase has been used so far in managing advanced and recurrent tumours with high levels of success in eliminating tumours with minimal morbidity and adverse events. Future application of this technology in managing primary disease is yet to come although a phase II clinical trial on inoperable cholangiocarcinoma has recently been initiated (clinicaltrials.gov identifier NCT04099888) (3).

The present case describes an advanced, recurrent and extensive squamous cell carcinoma of the face, which had previously failed to respond to conventional interventions. PCI can be an option

specifically when dealing with end-stage disease when the patient has exhausted all conventional treatment options. However, a potential application may also include managing primary disease, which should be considered in future trials.

The clinical therapeutic response in this complex extensive SCC of the face was so unanticipated and remarkable we felt bound to report it and also to describe the changes in the treated tissue for guiding future trials and interventions. Managing of such an aggressive and widespread form of disease is a real challenge to any clinician. All the treated areas of the face and scalp had responded positively to the intervention after only 3 days from the illumination. The PCI anti-tumour activity was highly effective and this was proven by randomly surgical biopsies acquired at two different times (as highlighted above).

We have previously highlighted the tumour-specificity of the technology and its correlation with clear margins (3,5). A preclinical study in mice by Norum et al. had shown that photodynamic therapy (PDT) is less efficient in the tumor periphery than in the tumor center, when compared to photochemical internalization (PCI). The researchers suggested that when endocytosed bleomycin is released via the PCI process, a larger zone of necrosis and nearly complete inhibition of tumour regrowth in the peripheral zone was observed (6). As there are many approaches to light-activated therapy and to photodynamic therapy, it is early to suggest that one intervention is superior to other.

In this patient, the PCI effect on the tumour margins was impressive. The depth of the tumour in this case was 4-10 mm and the complete response of the tumour tissue with minimal collateral tissue damage suggesting increased selectivity when compared to PDT. These data are supported by the clinical observation of tissue necrosis and regeneration. The excellent response reported here with PCI is reinforced by a case recently published by our group involving a recurrent chondroblastic osteosarcoma of the right mandible. The treated margins, in the previously published case, were tumour free for at least 6 months post-illumination (5).

Competing interests

Anders Høgset is affiliated with PCI Biotech AS, Oslo, Norway, which funded the initial, phase I clinical trial of TPCS_{2a}-based PCI of Bleomycin.

References

1. Berg K, Selbo PK, Prasmickaite L, Tjelle TE, Sandvig K, Moan J, Gaudernack G, Fodstad O, Kjølsvrud S, Anholt H, Rodal GH, Rodal SK, Høgset A. Photochemical internalization: a novel technology for delivery of macromolecules into cytosol. *Cancer Res.* 1999 Mar 15;59(6):1180-3.
2. Jerjes W, Upile T, Akram S, Hopper C. The surgical palliation of advanced head and neck cancer using photodynamic therapy. *Clin Oncol (R Coll Radiol).* 2010 Nov;22(9):785-91.
3. Sultan AA, Jerjes W, Berg K, Høgset A, Mosse CA, Hamoudi R, Hamdoon Z, Simeon C, Carnell D, Forster M, Hopper C. Disulfonated tetraphenyl chlorin (TPCS_{2a})-induced photochemical internalisation of bleomycin in patients with solid malignancies: a phase 1, dose-escalation, first-in-man trial. *Lancet Oncol.* 2016 Sep;17(9):1217-29.
4. Selbo PK, Sivam G, Fodstad O, Sandvig K, Berg K. In vivo documentation of photochemical internalization, a novel approach to site specific cancer therapy. *Int J Cancer.* 2001 Jun 1;92(5):761-6.
5. Jerjes W, Hamdoon Z, Berg K, Høgset A, Hopper C. Recurrent chondroblastic osteosarcoma of the right mandible subjected to photochemical internalization. *Photodiagnosis Photodyn Ther.* 2019 Sep;27:288-290.
6. Norum OJ, Gaustad JV, Angell-Petersen E, Rofstad EK, Peng Q, Giercksky KE, Berg K: Photochemical internalization of bleomycin is superior to photodynamic therapy due to the therapeutic effect in the tumor periphery. *Photochem Photobiol* 2009, 85(3):740-749.

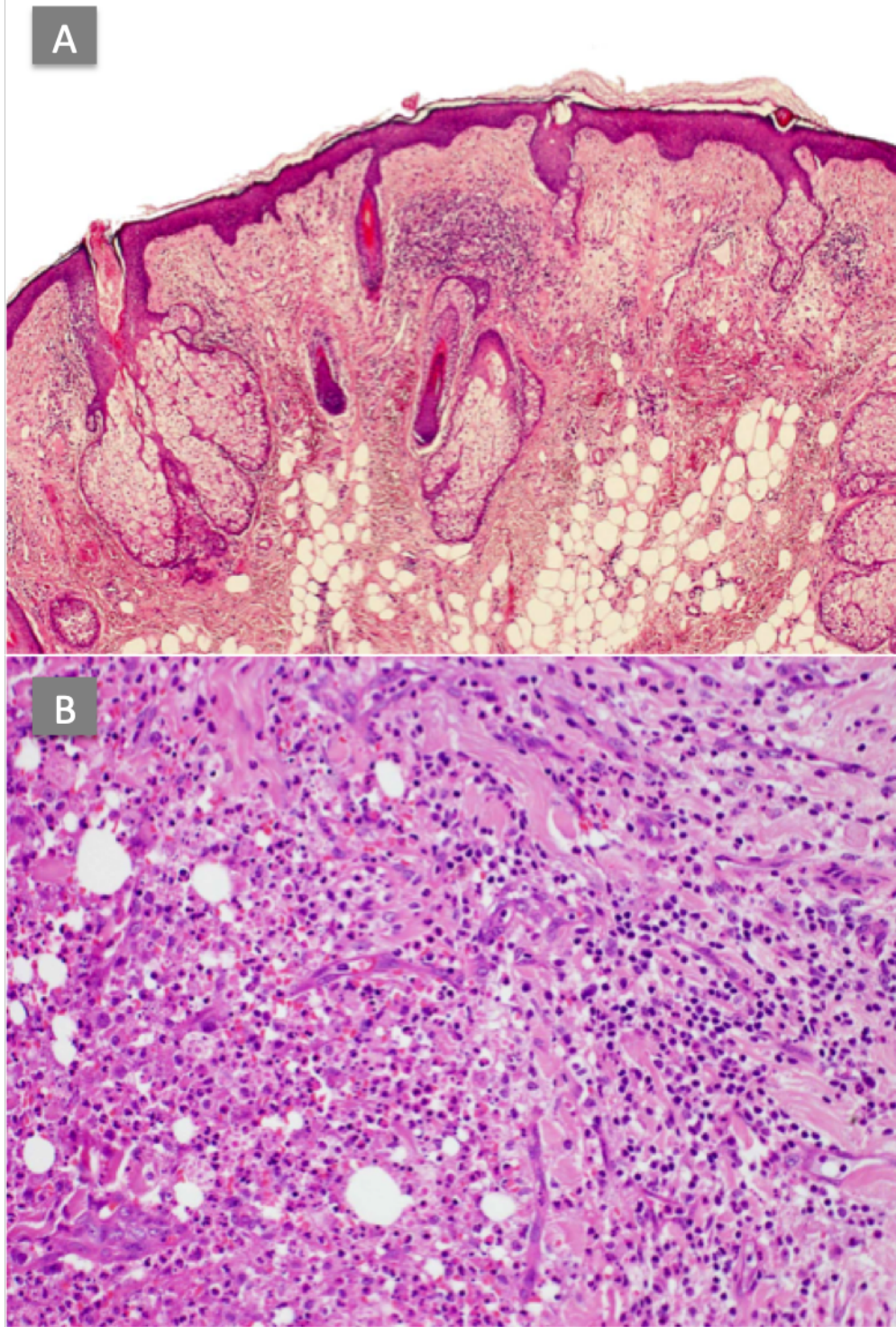
Figures

Figure 1. TPCS_{2a}-based bleomycin PCI in an 84-year-old Caucasian male with extensive cutaneous SCC of R face and scalp.

Figure 2. Histopathology images acquired at 1 month (low power) and 3 months (high power) post-illumination. Both show skin inflammation and no malignancy. Granulation tissue is noted in the 3-month post illumination H&E slide.



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