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Case report

Recurrent chondroblastic osteosarcoma of the right mandible subjected to photochemical internalization

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1. Introduction

Advanced or metastatic cancers in the head and neck are a challenge to manage, especially those who failed all available conventional modalities (*i.e.* surgery, radiotherapy and chemotherapy). These cancers have been linked to high morbidity and mortality, therefore it is crucial to continue to develop new and effective treatments that can help improve the quality of life and, potentially, prolong survival. [1]

Photodynamic therapy (PDT), the fourth modality in head and neck cancer management, has been used in treating these conditions with good and promising results. The principle of PDT is to selectively destruct cancer cells by light activation of a photosensitiser in the presence of oxygen. The therapeutic effect of PDT may be due to direct cell killing and/or vascular damage and immunologic responses [1].

Recently, a novel treatment (photochemical internalisation - PCI) for delivering therapeutic macromolecules from endocytic vesicles and lysosomes into the cytoplasm using a sub-lethal dose of photodynamic therapy has been developed for cancer treatment. This technology aims to minimise or avoid the side effects of most chemotherapeutics (by achieving the desirable effect with lower doses), eliminate chemotherapy resistance (a problem in oncology), reduce or avoid the skin photosensitivity (of photodynamic therapy) and enhance the efficacy and improve selectivity [2,3].

A recent first-in-man phase I clinical trial of $TPCS_{2a}$ (disulfonated tetraphenyl chlorin, Amphinex®)-based PCI of Bleomycin for treatment of patients with recurrent/advanced malignancies has concluded that the intervention was found to be safe with no major adverse events, and no significant skin photosensitivity problems. Furthermore, the intervention was found to be tolerable under the appropriate anaesthesia and the intra-/post-illumination pain can be controlled with local anaesthesia and analgesia. The therapeutic effect of PCI was not looked at as part of the trial, however some unique observations were noted within the trial [4].

In this case report, a unique and complex case of recurrent chondroblastic osteosarcoma of the mandible is subjected to $TPCS_{2a}$-based bleomycin PCI.

2. Case report

A 57-year-old Caucasian male was diagnosed with end-stage recurrent chondroblastic osteosarcoma in the right mandible. The patient underwent chemotherapy, radiotherapy and a number of major surgical reconstructions after his initial diagnosis (one loco-regional flap followed by two free flap surgeries). Unfortunately all interventions were not successful and associated with high morbidity. His medical history included myocardial infarct and a subsequently coronary stenting. His

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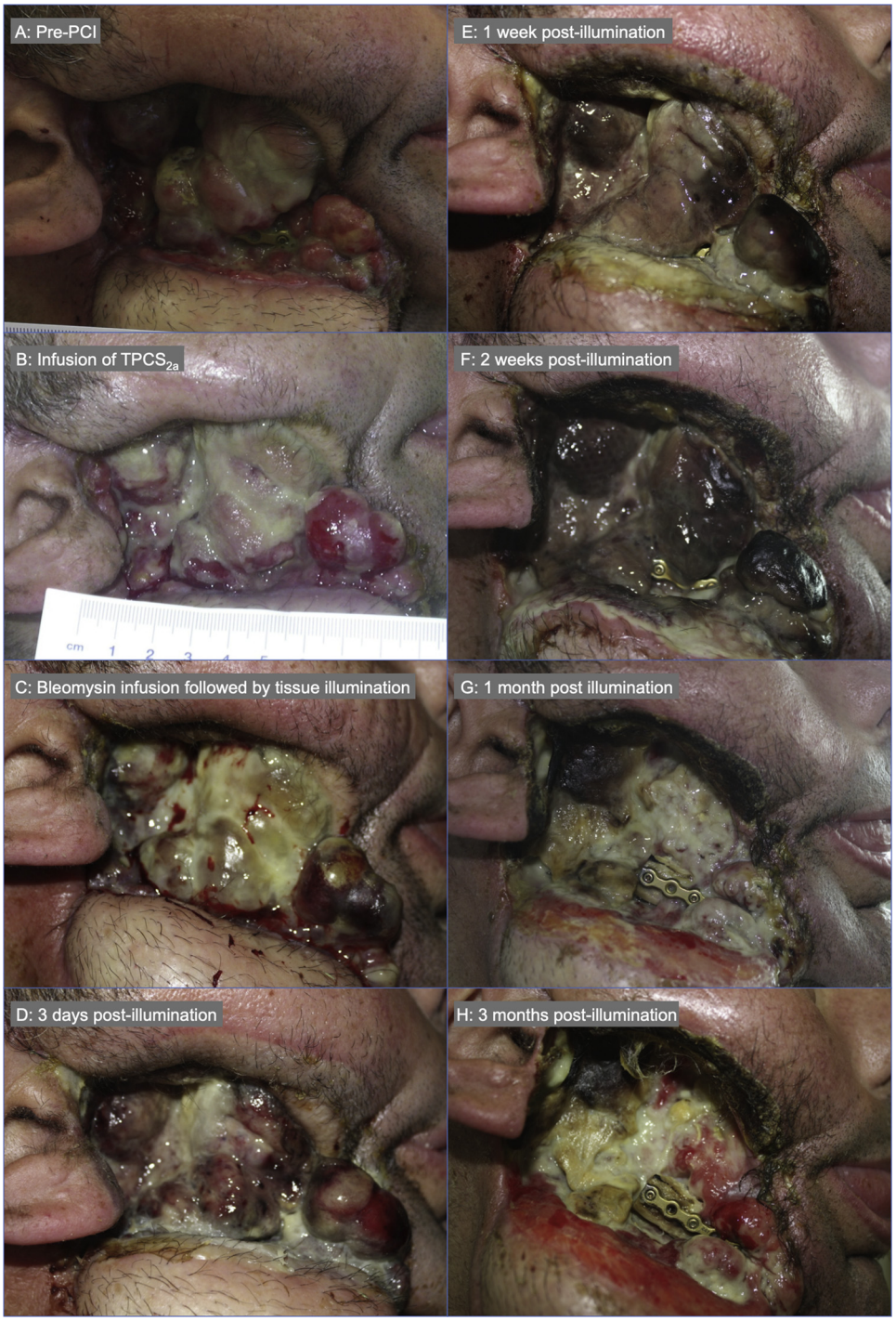

Fig. 1. $TPCS_{2a}$-based bleomycin PCI in a 57-year-old Caucasian male with end-stage recurrent chondroblastic osteosarcoma in the right mandible.

drug history included Aspirin, Atrovastatin, Amitriptyline and Oramorph.

The patient took part in the first-in-man phase I $TPCS_{2a}$ based bleomycin PCI that looked at the photosensitiser's safety as well as the pharmacokinetics. The patient tolerated the photosensitiser and no adverse events were reported. Clinical therapeutic effect of PCI was not a parameter that fell within the scope of the phase I trial, but detailed clinical documentation of the response took place to ensure clinical safety as well as clinical interest and future learning. The patient signed fully informed consent for treatment and ethical approval was provided by the South West Research Ethics Committee, UK.

Clinical examination, at presentation, revealed extensive sarcoma affecting the right mid and lower face, extending from the tragus posteriorly to the corner of the mouth anteriorly, and from the zygomatic arch superiorly to the remaining bulk of the pectoralis major flap inferiorly. Furthermore, the tumour has eroded through the cheek resulting in a large oro-cutaneous fistula. Radiological evaluation confirmed further recurrence in the posterolateral tongue, tongue base and inside the bulk of the pectoralis major flap. It was decided to initially treat the main bulk of the tumour as in Fig. 1A with surface illumination $TPCS_{2a}$-based bleomycin PCI, and deal with the smaller deeper areas with interstitial mTHPC (meta-tetrahydroxyphenyl chlorin)-PDT at a later stage. This is mainly due to the lack of interstitial protocol for PCI to deal with deep-seated lesions.

The patient received 0.25 mg/kg $TPCS_{2a}$ (Amphinex®) through intravenous infusion. At the time of infusion and as illustrated in Fig. 1B, the tumour have grown in size by 8–10 mm, on clinical examination, and have covered the reconstructive titanium plate which could be seen in the previous Fig. 1A. The duration of this growth took place over a period of less than 2 weeks, highlighting the aggressive nature of the sarcoma.

Four days later, surface illumination based photochemical internalization (PCI) (652 nm diode laser, 60 J/cm^2 delivered at irradiance 100 mW/cm^2) was implemented 3 h after the slow infusion of Bleomycin (dose of 15,000 U/m^2 giving a total dose of 18,000 U over 15 min.). This phase was associated with immediate changes in tissue colour (blanching), (Fig. 1C), which is related to the bleomycin release following the tissue illumination. Furthermore there was a report of intra-illumination and post-illumination pain (9.9/10 on the severity scale) for 2 h, which then rapidly abated to 2.2/10 after 4 h.

Three days post-illumination, we noted further clinical changes (indicative of tissue necrosis), which could be attributed to the chemotherapy effect (Fig. 1D). Pathological analysis of small surgical biopsies taken from a number of areas reported osteosarcoma showing extensive necrosis; only scant viable tumour cells were present. At 7 days post-illumination, further tissue changes were noted with further tissue shrinkage and necrosis (Fig. 1E).

The maximal discharge from the necrotic tissues was noticed 14 days post-illumination and for the first time a fraction of the titanium plate could be identified (Fig. 1F). The marked tissue death in several areas was associated with severe mal-odour. Further follow-ups at 1 month (Fig. 1G) and at about 3 months (Fig. 1H) continued to show clinical tumour shrinkage and death. Surgical biopsies were taken from multiple sites at about 3 months post-illumination and confirmed that the treatment area remained sarcoma free. No recurrence was identified, in the treatment area, at the last review clinic review.

Later on, the patient required endoluminal carotid stenting and treatment for deeper tumour areas, mainly in the tongue base, as previously highlighted. The patient was being considered for the palliative option of mTHPC (Foscan®)-PDT but unfortunately he succumbed to cardiorespiratory failure 6 months from the start of the $TPCS_{2a}$-based Bleomycin PCI intervention.

3. Discussion

The clinical response in this complex case was so unexpected and impressive we were compelled to present it and also to accurately present the clinical changes to the treated tissue for future reference. There is clear scientific evidence that PCI is a clinically relevant technique that has a huge potential in the treatment of tumours that are resistant to chemotherapy.

All the illuminated areas have also responded favourably to the treatment after only 3 days from the illumination. The PCI anti-tumour activity was superior to photodynamic therapy and this was proven by close and regular clinical assessment as well as histopathology. The effect on the tumour margins has been impressive with biopsies (at about 3 months) confirming the area to be sarcoma-free. There appears to be a good depth of effect, in this case 25 mm, with minimal collateral tissue damage suggesting increased selectivity when compared to PDT. This information is augmented by the clinical observation of tissue changes, necrosis and regeneration.

The transient peri-illumination pain is likely to be related to the high levels of tumour cell death. The pain was localized to the site of the cancer. The pain appeared to be correlated with completeness of tumour cell killing (clinical response). We hypothise that the induction of acute necrosis with the release of intracellular degradation products may have stimulated small pain fibres either directly or through histamine release.

The present case represents one of the most difficult tumours to treat namely chondroblastic-osteosarcoma of the jaw, which had previously failed to respond to all the three conventional therapeutic modalities. Many of the factors discussed here needs further revalidation with further clinical trials before PCI could be offered as a routine intervention. This option may offer some therapeutic space to manoeuvre especially in situations of end-stage recurrence where conventional modalities are not deemed feasible.

Declaration of Competing Interest

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] W. Jerjes, T. Upile, S. Akram, C. Hopper, The surgical palliation of advanced head and neck cancer using photodynamic therapy, Clin. Oncol. R. Coll. Radiol. (R Coll Radiol) 22 (November 9) (2010) 785–791.
[2] K. Berg, P.K. Selbo, L. Prasmickaite, T.E. Tjelle, K. Sandvig, J. Moan, G. Gaudernack, O. Fodstad, S. Kjølsrud, H. Anholt, G.H. Rodal, S.K. Rodal, A. Høgset, Photochemical internalization: a novel technology for delivery of macromolecules into cytosol, Cancer Res. 59 (March 6) (1999) 1180–1183.
[3] P.K. Selbo, G. Sivam, O. Fodstad, K. Sandvig, K. Berg, In vivo documentation of photochemical internalization, a novel approach to site specific cancer therapy, Int. J. Cancer 92 (June 5) (2001) 761–766.
[4] A.A. Sultan, W. Jerjes, K. Berg, A. Høgset, C.A. Mosse, R. Hamoudi, Z. Hamdoon, C. Simeon, D. Carnell, M. Forster, C. Hopper, Disulfonated tetraphenyl chlorin (TPCS2a)-induced photochemical internalisation of bleomycin in patients with solid malignancies: a phase 1, dose-escalation, first-in-man trial, Lancet Oncol. 17 (September 9) (2016) 1217–1229.