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Palliation of haemorrhaging and ulcerated cutaneous tumours using electrochemotherapy

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ABSTRACT

By short, intense electric pulses it is possible to cause cell permeabilisation (electroporation) and this can be used to deliver chemotherapy to tumours (electrochemotherapy).

Preclinical studies have shown effects on vasculature of electroporation and electrochemotherapy, in particular in tumours. The effect on normal vasculature is a brief reflexory constriction; however in the fragile and abundant vasculature of tumours, a direct anti-vascular effect has been shown. This finding is mirrored in the clinical observation that bleeding, ulcerated lesions cease to bleed after application of electric pulses, and stay dry while the involution of tumours due to uptake of the cytotoxic agent takes place. Ulcerated, bleeding lesions are not uncommon in cancer patients, and cause discomfort due to bleeding and also stigmatisation when lesions are in visible areas. This report describes a case with ulcerated, bleeding lesions where the use of electrochemotherapy has led to efficient and immediate relief of symptoms.

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1. Introduction

Increasing emphasis is being put on palliation of terminally ill cancer patients. Bleeding skin metastases are one of the many grievances that may negatively affect quality of life. In the seriously ill patient, quick and effective palliation is highly important. In this regard, a once-only treatment giving a high probability of immediate relief is of very good use. Other treatment possibilities are surgery and radiotherapy. Surgery can be a good option for small lesions, but larger lesions require more extensive procedures. Radiotherapy is a well-known method to ameliorate bleeding from both internal and external tumours. However, generally 3–10 fractions are administered, and this means the patient needs to be treated daily over 1–2 weeks. Furthermore, the total treatment area is limited as toxicity is correlated to field size.

The use of electric pulses to enhance uptake of chemotherapy specifically within tumour lesions is gaining increasing momentum.^{1,2} The following report describes the

palliation of a patient with cutaneous metastases, and the particular effects of electroporation and electrochemotherapy on tumour vasculature are discussed.

2. Case report

A 58 year old male patient with disseminated malignant melanoma presented with several bleeding, ulcerated metastases on the head and scalp. Eight years after his primary melanoma was removed he had relapsed with metastases to lung, mediastinum and brain. The patient received stereotactic radiotherapy of brain metastasis, and of the mediastinum. Treatment trials with dendritic cells and thalidomide were unsuccessful. The patient was in good performance, and able to carry out usual activities. He developed several cutaneous metastases over a short period of time, and reported discomfort due to the metastases as they would often bleed, and were also a visible stigma of the cancer to himself and his surroundings. Surgery was a less attractive option as the lesions

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PANEL A:**PANEL B:**

Fig. 1 – Panel A. Treatment of haemorrhaging malignant melanoma tumor (left before treatment, middle during healing, right during follow-up). After one single treatment, the lesion went into complete remission which was still present at last visit 6 months after treatment. The lesion immediately ceased to bleed after treatment and a crust formed. After several weeks, the crust fell off revealing normal skin underneath. **Panel B.** (left before treatment, middle and right: during short and long-term follow-up). Under the lower lip, an exophytically growing tumor had developed. This had been treated during the first session, but progressed. It was felt that insufficient coverage of the tumour in the first treatment was the cause of this. In order to be sure to cover the tumor completely, plate electrodes were used to deliver one pulse sequence to the tumor, encompassing the exophytic part. Thereafter hexagonal needle electrodes were inserted to treat the tumour in the depth. After this, the tumour completely regressed. Another tumour on the left side of the chin was also treated and completely regressed. Needle marks were present after treatment, but faded with time.

were numerous and so large that transplants would have been required. Radiotherapy would have meant eight different electron fields to various sides of the scalp and face. Two of the metastases were placed such that mucosal reactions in the mouth would have been anticipated if radiotherapy were used.

The patient was treated according to the ESOPE protocol, approved by the local ethics committee and Danish Medicines Agency. Informed consent was given by the patient.

As there were eight metastases to be treated in total, and as the two largest metastases were adherent to periost, it was decided to treat the patient in general anaesthesia. Furthermore, as some of the metastases were very fragile, local injection of bleomycin was discarded in favour of systemic injection.

The patient was anaesthetised, and intubated because the patient would have to be repositioned during the procedure in order to treat all lesions. The patient was well oxygenated on an FiO_2 of max 30%, and bleomycin 15.000 IU/m^2 (Asta Medica, Sweden) was administered i.v. Eight minutes later, electrodes were placed in the tumours, one by one. Most of the metastases were covered through several applications of the electrodes. This was done in a pattern where tumour tissue in certain cases received more than one pulse application whereas normal tissue was generally spared from overlaps. Care was taken to treat both the tumour itself, and the peritumoural area. The patient was turned to treat lesions at the back of the head.

Fig. 1 shows the development of 2 of the 8 treated metastases. In the case of the bleeding metastases, that before treatment bled upon even light contact, these ceased to bleed and formed a crust within a few hours after treatment. The patient was treated over two sequences, and all but 1 of the

metastases were in complete remission after this ($7/8 = 87\%$ complete remission).

3. Discussion

One intriguing feature is the effect of the electroporation procedure itself and in particular the electrochemotherapy procedure on tumour vasculature. Thus, it has been shown that the electric pulses by themselves induce a transient hypoperfusion. From studies of electroporation of muscle tissue we know, that a brief constriction on the level of arterioles, mediated by the sympathetic nervous system occurs.³ However, in the case of tumour tissue severe hypoperfusion starts immediately after pulsation and lasts for 12 h (electroporation alone) or more than 5 days (electrochemotherapy).⁴ Several factors may contribute to this, thus a direct effect on tumour endothelial cells has been reported,⁵ and a possibility is also that permeabilisation induces collapse of the vascular structures in the tumour due to high interstitial pressures. After the electric pulse delivery, bleomycin quickly exerts a deadly effect on tumour cells: By causing several DNA strand breaks per molecule cell death is rapid and irreversible.¹ The direct access to the cell cytosol in the area encompassed by the electrodes gives rise to a several hundredfold increase in the cytotoxicity of bleomycin and thus an extremely efficient cell kill in the treated area – albeit systemic concentrations are those usually used for this drug. This means that ECT can be given as a once only treatment, and it also means that the effect on tumour vasculature transits into tumour involution, as the effect of the delivered bleomycin sets in with efficient cell kill within the time of the tumour vasculature shut down.

In the case presented here, the patient was palliated for his symptomatic skin metastases in a phase where he was

fully ambulant and able to carry out activities of daily living. This case presented here is in line with previous observations.^{6,7}

In conclusion, palliation of haemorrhaging and ulcerated skin lesions is one of the key indications for electrochemotherapy as this provides fast and efficient relief for patients who need symptomatic treatment with as little hospitalisation as possible.

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