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Electrochemotherapy in non-melanoma head and neck cancers: a retrospective analysis of the treated cases

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Abstract

Electrochemotherapy increases the permeability of tumours to drugs by electric voltages applied locally. Its value in tumours of the head and neck is unknown. We retrospectively reviewed a 2-centre database, and found 39 patients with squamous cell carcinoma (SCC) of the oral cavity or oropharynx (n=12) or non-melanoma skin tumours (n=27) who had been treated with bleomycin electrochemotherapy with needle electrodes. A further 3 patients were given cisplatin electrochemotherapy (n=2), or bleomycin electrochemotherapy by plate electrodes (n=1). Local toxicity was mild. The complete response rate was 38% and was associated with whether the tumour was primary or recurrent ($p<0.001$), its size ($p=0.02$), and the route by which the drug was given ($p=0.02$). We did not study enough patients with basal cell carcinomas to say whether the response was significantly better or not ($p=0.07$). Skin tumours and SCC of the oral cavity or oropharynx showed comparable complete responses (41% and 33%, $p=0.73$) and local control (1-year local progression-free survival, 51% compared with 59%, $p=0.89$), particularly if they were small ($p=0.001$), primary ($p=0.002$), chemonaive ($p=0.03$). Patients treated with cisplatin were unresponsive. Electrochemotherapy with bleomycin is an effective option for skin tumours of the head and neck and is a feasible alternative in highly selected (small, primary, and not previously treated by chemotherapy) SCC of the oral cavity and oropharynx.

Introduction

The management of skin tumours of the head and neck and squamous cell carcinomas (SCC) of the oral cavity and oropharynx may benefit from tissue-sparing, non-operative treatments. Electroporation, a minimally invasive drug delivery system, may be an appealing treatment for patients with head and neck cancer.[1] Recently electrochemotherapy has become a reliable alternative for patients with skin cancers, and an established palliative option for those with superficial metastases.[2] It combines an antneoplastic agent – bleomycin or cisplatin– with electroporation, achieved by means of locally-applied, high-voltage, electric pulses.[1] These voltages cause cells to become temporarily permeable to chemotherapy and so increase its cytotoxicity. Electrochemotherapy has been standard since 2006 (European Standard Operating Procedures of Electrochemotherapy,

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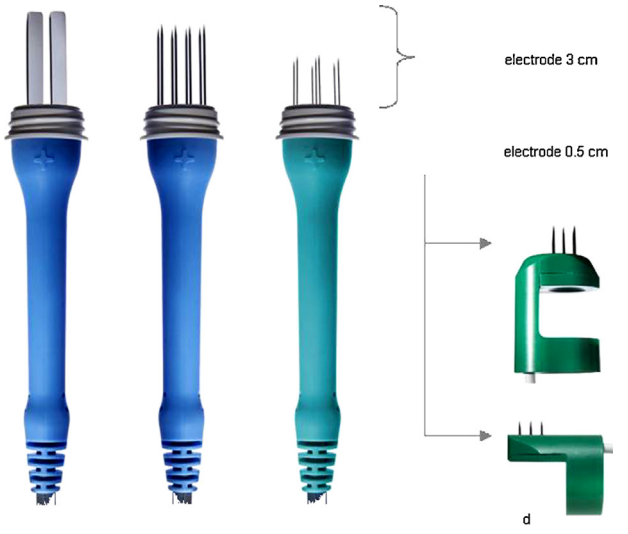

Fig. 1. Configurations of electrodes. Different types of needle electrodes were used together with the Cliniporator™ device: (a) the non-invasive plate electrode (2 parallel plates connected to a handle 13 cm long) was used by contact application for the electroporation of exophytic tumours; (b) the linear needle configuration (two parallel row arrays of needles connected to a handle 13 cm long) was used, by being placed into tumour tissue, for smaller infiltrating lesions; (c) the hexagonal needle configuration (an hexagonal array of needles connected to a handle 13 cm long) was used for larger infiltrating tumours; (d) the "finger" electrode configurations (two rows of 5 mm needles was used for targeting tumours of the oral cavity and oropharynx, through a transoral approach. These pulse applicators are provided with a thimble that can be held on a finger by the physician to increase the manoeuvrability of the electrodes. Two models of finger electrodes with different orientation of the needles with respect to the thimble are available: longitudinal configuration (upper electrode) and orthogonal configuration (lower electrode).

ESOPE).[2] A recent comprehensive review quoted overall and complete response rates of 59% and 84%, respectively, after a single cycle.[3] The clinical experience with cancers of the head and neck, however, relies on small series and heterogeneous protocols. Electrochemotherapy was pioneered at the Institute Gustave Roussy during the early nineties, and showed consistent antitumour activity.[1,4,5] The patients enrolled in these landmark trials presented with cancers that infiltrated the skin (permeation nodules) and the electrochemotherapy, although locally effective, was given with palliative intent.

During the following years it was tested on skin tumours, mucosal cancers and, sporadically, on lymph node metastases.[6–16] In recent years, technological advances and planned, image-guided treatment are paving the way to the electroporation of more challenging targets, such as brain, liver, and gastrointestinal tumours.[17] The present availability of custom-made pulse applicators (Fig. 1), has renewed interest in the treatment of mucosal cancers. Although the ease of the procedure[2] and the sustained antitumour activity[3] make it an attractive treatment, there is ongoing uncertainty about its feasibility (given some persisting limitations in current technology) and possible toxicity.

Here we have reviewed our clinical experience to evaluate the efficacy and safety of electrochemotherapy in patients with cancers of the head and neck.

Methods

Collection of data

Data were obtained from 2 institutions (Veneto Institute of Oncology, Padova and Institute of Oncology, Ljubljana) by merging 2 prospectively maintained databases. Treatment parameters were retrieved from the software of the pulse generator (Cliniporator™, Igea, Modena, Italy). Institutional ethics committees approved the retrospective analysis.

Indications for treatment

The use of electrochemotherapy was agreed by a multidisciplinary tumour board. The patients were those with tumours of the skin of the head and neck, recurrent, locally-advanced, or multiple non-melanoma skin tumours that were not amenable to conservative resection, chemotherapy, or radiation. The group with oral or oropharyngeal cancers included patients with recurrent or second primary tumours that were either unsuitable for conventional treatments or the patient had refused it. They had to be accessible through a transoral approach. When indicated, computed tomography (CT) or magnetic resonance imaging (MRI) was used to exclude bony infiltration. All patients were treated according to the Rules of Good Clinical Practice.

Treatment protocol

The procedure was done under mild sedation or general anaesthesia. When feasible, local anaesthesia consisted of tissue infiltration with 2% lignocaine with ropivacaine 2 mg/ml. Chemotherapy was followed by the application of electric voltages, according to the type of electrode (Table 1).

Drugs

Chemotherapy comprised bleomycin given intravenously or into the tumour, or cisplatin given into the tumour, as described by ESOPE.[2] Cisplatin was given into the tumour in a dose of 0.5-2 mg/cm^3 of the volume of the tumour; bleomycin was given intravenously in a dose of15 000 IU/m^2 body surface area, and into the tumour in a dose of 250-1000 IU/cm^3 of the volume of the tumour. The only deviation from the European protocol was when the 2 routes were combined, which was done for some patients to achieve adequate exposure of the tumour to chemotherapy. The injection into the tumour (a maximum of bleomycin 3 IU at each cycle of electrochemotherapy) was added to the intravenous infusion when tumours had previously been irradiated. Radiotherapy, by causing vascular damage, can lead to impairment of