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Electrochemotherapy for the treatment of squamous cell carcinoma in cats: A preliminary report

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Abstract

Squamous cell carcinomas (SCC) of the skin are commonly described in cats. Reported treatments include surgery, radiation therapy and photodynamic therapy. This preliminary study reports on the management of these lesions combining the local administration of bleomycin (plus hyaluronidase for a more uniform distribution) with permeabilizing biphasic electric pulses. Nine cats with SCC graded T_2–T_4 were treated over a 5 year period, and each cat received two sessions of electrochemotherapy (ECT) 1 week apart. The side effects of this treatment were minimal and limited to mild erythema of the nose. Seven of the cats (77.7%) had a complete response lasting up to 3 years. ECT seems to be a safe and effective option for the treatment of feline sun-induced squamous cell carcinomas and warrants further investigation.

Keywords: Bleomycin; Carcinoma; Electrochemotherapy; Feline; Hyaluronidase

Introduction

Cutaneous squamous cell carcinomas (SCC) are frequently described in cats and are generally considered to be secondary to ultraviolet (UV) light exposure since they are mostly localised in the nose, eyelids and ears of animals with un-pigmented or lightly pigmented skin (Vail and Whithrow, 2001). The lesions probably originate from actinic damage secondary to photo-carcinogenesis, then progress to in situ carcinomas and overt carcinomas (Dorn et al., 1971). SCC rarely metastasise (Lana et al., 1997), but have a tendency to progress toward cancerous ulcerations leading to painful and non-healing injuries.

Despite the resulting disfigurement, cats with advanced SCC may live for extended periods, and anticancer treatments should therefore be aimed at symptom alleviation and tumour control with reasonable cosmetic results. Several therapeutic approaches have been reported in the literature, including surgery (Withrow and Straw, 1990; Lana et al., 1997), cryotherapy (Clarke, 1991), radiation therapy (Thèon et al., 1995; Fidel et al., 2001; Melzer et al., 2006), plesiotherapy (Goodfellow et al., 2006), photodynamic therapy (Peaston et al., 1993; Frimberger et al., 1998) and intra-lesional chemotherapy (Thèon et al., 1996). Each of these has been employed, with different degrees of efficacy, especially for early lesions classified by the World Health Organization (Owen, 1980) as T_{is}, T_1, and T_2 (Table 1).

Electrochemotherapy (ECT) involves the administration of a chemotherapeutic agent alongside the delivery of appropriate waveforms that induce an increased uptake of the drug by cancer cells (Spugnini and Porrello, 2003). Following reports from human patients (Daskalov et al.,

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Table 1
World Health Organization TNM classification system for feline tumours of epidermal origin (Owen, 1980)

Stage	Feature
T	
T_0	No evidence of tumour
T_{is}	Tumour in situ
T_1	Tumour < 2 cm diameter
T_2	Tumour 2–5 cm diameter or minimally invasive
T_3	Tumour > 5 cm diameter or with invasion of subcutis
T_4	Tumour invading other structures such as fascia, muscle or bone
N	
N_0	Absence of lymph node metastasis
N_1	Presence of lymph node metastasis
M	
M_0	Absence of distant metastasis
M_1	Presence of distant metastasis

1999), several trials have been undertaken in cats and dogs with spontaneously occurring neoplasms using trains of electropermeabilizing biphasic pulses. Preliminary studies aimed at identifying responsive neoplasms (Spugnini and Porrello, 2003) and developing proper electrodes (Spugnini et al., 2005). We have used ECT to treat several cohorts, including dogs with melanomas (Spugnini et al., 2006a), cats with soft tissue sarcomas (Spugnini et al., 2007), and dogs with mast cell tumours (Spugnini et al., 2006b). Based on promising results we decided to test ECT in the treatment of cats with cutaneous SCC in view of the high prevalence of these neoplasms among the Italian cat population and to consider the study's putative value as a preclinical model for humans.

Material and methods

Patient selection

Privately owned cats with histopathologically confirmed SCC of the nasal planum and skin (pinna and skin adjacent to the ocular canthii) were selected for the study. Previous informed consent was obtained from the owners according to Italian law (116/92). In order to be enrolled, the animals were required to have normal renal function (normal serum blood urea nitrogen, creatinine and urine specific gravity), and to be free of underlying life threatening diseases or other medical complications (e.g., diabetes mellitus).

The staging process included a thorough anamnesis, physical examination, complete blood cell count and serum biochemistry profile, and were screened for feline leukemia virus and feline immunodeficiency virus. Regional lymph node aspiration and cytological examination were performed if lymph nodes were palpable. We also took thoracic radiographs (three projections: two laterals and one ventro-dorsal), and a biopsy of the tumour. In order to confirm the diagnosis, histological examination of the biopsies was performed by one of the authors (AB) following standard staining protocols using haematoxylin/eosin and haematoxylin/Van Gieson's. All cats had an ultrasonographic evaluation of the abdomen at the time of enrollment to rule out underlying disease.

Treatment

Under sedation with medetomidine and ketamine (according to the manufacturer's instructions), the cats were given two sessions of ECT, 1 week apart. The tumour bed and the margins were infiltrated 0.5 cm in all directions with a combination of hyaluronidase and lidocaine (Lido-Hyal B, Laboratori farmaceutici Giovanni Ogna & figli S.p.A.), as previously described (Spugnini et al., 2007). After 5 minutes, bleomycin (Bleomicina Solfato, Aventis Pharma) was injected at a concentration of 1.5 mg/mL such that the total dose ranged from 1–2 mL based on the size of the lesion (approximately 1–1.5 mg/cm^3).

Five minutes after the double infiltration, trains of eight biphasic electric pulses lasting 50 + 50 μs each, with 1 ms interpulse intervals, were delivered by means of modified calliper electrodes or through paired needle electrodes for difficult sites, as in the case of the patient with SCC close to the eye canthus.

Response to treatment and local toxicity were assessed after the first treatment and 1 week after the second application of ECT. The animals had monthly re-checks for the first 6 months and every third month thereafter. At the 6 month re-check, and every 3 months until the completion of the first year of follow up, thoracic radiographs were taken to check for any pulmonary spread and regional lymph nodes were palpated for signs of metastasis. Response criteria are summarised in Table 2. Toxicity was defined as any disease processes (erythema, chronic inflammation of the soft tissues etc.) that occurred secondary to changes of the electroporated tissues within the treatment field.

Pulse generator

The chemopulse was built up using a toroidal core transformer generating a roughly rectangular pulse split in two halves that are sequentially driven to obtain a biphasic pulse. The pulses are not singularly produced but are created in bursts of eight, thus reducing the treatment time and the overall patient morbidity. The equipment allows a broad range of voltages (from 450 to 2450 V) at sequential increases of 200 V and the number (1–16) and duration (50–100 μs) of the pulses can be regulated. The standard setting is eight pulses of 50 + 50 μs at 1300 V/cm. The pulse repetition frequency was 1 Hz while the frequency of burst repetition was 1 kHz, resulting in a total burst duration of 7.1 ms (Daskalov et al., 1999).

Electrodes

These were either (1) modified monolateral compass electrode steel, bachelite, plastic with perforated metal plates (dimensions 22 mm long × 10 mm high × 1 mm wide; (Spugnini et al., 2005), or (2) of a vaccine type twin needle array electrode made of steel and plastic and of needle length 20 mm and array diameter 20 mm (Spugnini et al., 2005).

Results

Nine cats were enrolled over a 5 year period. Individual data on the animals in the study are summarised in Table 3. The median age of the cats was 11.8 years (range 3–19). There were five female spayed and four male castrated cats. Seven cats had tumours of the nasal planum, one had a tumour of the pinna and one of the eye canthus. At presen-

Table 2
Tumour response criteria

Complete remission (CR) – the disappearance of all evidence of cancer in all sites for a defined period of time
Partial remission (PR) – the decrease in size of all tumours by 50% or greater as measured by the sum of the product of two diameters of each tumour for a defined period of time
Stable disease (SD) – the decrease of <50% or an increase of <25% in the sum of the product of two diameters for a defined period of time
Progressive disease (PD) – the increase of 25% or more in the sum of the product of two diameters for a defined period of time