Use of metronomic chemotherapy for feline cutaneous squamous cell carcinoma

The cutaneous squamous cell carcinoma (cSCC) is a neoplasm with genesis in the cutaneous epithelium, also called spinocellular carcinoma, squamocellular carcinoma or epidermoid carcinoma. It corresponds to the most common malignant cutaneous neoplasia in cats, representing 9 - 25% of all cutaneous tumors of these animals. Surgical treatment, with complete excision and free margins of lesion, seems to lead to a better prognosis among the available therapeutic options. In situations with extensive lesions where surgical treatment is not possible, the use of parenteral chemotherapy, electrochemotherapy, intralesional chemotherapy, radiotherapy, cryosurgery and/or photodynamic therapy are suggested. However, there are situations where these different options of treatment become impossible, due to anatomical (related to the location, dimensions and prolongation of cSCC), technical, operational and/or financial problems, or an unsatisfactory therapeutic response, associated to the absence of tumor regression and recurrences. Failures to obtain cures related to the methodologies described have caused an increase in the number of researches looking for therapeutic alternatives. Cancer is a chronic disease and for this reason it should be treated as such. From this note, continuous protocols using low doses of cytotoxic agents administered at short and regular intervals were used as a possibility of therapy, called continuous low dose chemotherapy or metronomic chemotherapy.

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Objective

The present work aimed to report the use of antineoplastic drugs, metronomically, for the therapeutic control of cutaneous SCC in a specimen of the feline specie.

Methodology

A 10-year-old neutered domestic female cat was referred to a veterinary evaluation due to a proliferation in the face. The tutor reported a previous history of cutaneous SCC, duly diagnosed by histopathology. Three years ago the initial lesion related to SCC appeared in the rostral region and nasal plane. Cryosurgical therapy was performed and complete remission of the neoplastic process occurred. After this period, recurrence of the tegument neoplasm occurred (but in a different anatomical area). The patient was submitted to physical examination. Then, complete blood count (CBC), blood biochemistry (renal and hepatic), immunoenzymatic test for retroviruses, and skull and chest X-rays were requested. The topography and extension of neoformation did not allow the execution of surgical exeresis or cryosurgery sessions. Thus, it was decided to establish intralesional chemotherapy, with the use of carboplatin (1.5 mg of the drug for each cm$^3$ of the neoplasia). The applications were performed at intervals of seven days, totaling four sessions. For the accomplishment of each procedure, animals were properly submitted to anesthetic protocols. The manipulation and administration of antineoplastic followed all previously recognized safety standards. At the end of the four sessions, histopathological evaluation of cutaneous proliferation was performed again. It was decided to submit the animal to metronomic chemotherapy (oral), consisting of chlorambucil (4 mg.m$^{-2}$, every 24 hours) and piroxicam (0.3 mg.kg$^{-1}$, every 48 hours). All methods were recommended for the correct handling of chlorambucil. The patient was followed up monthly, consisting of clinical examination, hemogram and serum biochemistry (renal and hepatic). After a few months, the animal was euthanized and cutaneous material was collected for histopathological analysis.

Results

Clinically, vital parameters were normal. However, there is a cutaneous nodule (1.9 x 1.9 x 0.6 cm) in left maxilar region. The nodule had firm consistency, epidermodermal coverage, smooth form, sessile insertion base, ulcerated / necrotic surface and adhesion to deep planes (figure 1a). There were no apparent neoformations in other body areas. Complete blood count (CBC), blood biochemistry, viral screening, and imaging tests revealed no alterations. After the end of infiltrations of intralesional chemotherapy, there was no macroscopic regression of lesion. Histopathology revealed the persistence of a morphological pattern characteristic of SCC. The feline had an adequate tolerance to the other therapeutic alternative (metronomic chemotherapy), showing no adverse effects during clinical and laboratory follow-up. There was no neoplastic regression, but there was stabilization of neoformation dimensions, with no local dissemination. An adequate state of sanity was kept,
with quality of life and animal welfare. Although, four months after the beginning of the metronomic chemotherapy protocol, complete necrosis of the neoplasia was detected, resulting in friable fragile skin fragments with hemorrhagic crusts and surrounding tissue involvement (Figure 1b). At that moment the cat appeared cactic, apathetic, with anorexia and vomiting. In view of the overall appearance of the patient, euthanasia was justified (request and authorization of the tutor). In cutaneous histopathology, the diagnosis of SCC was maintained.

**Discussion**

Metronomic chemotherapy aims to reduce the side effects caused by conventional therapies and to stabilize the growth rate of progressive tumors, providing control of recurrent, unresectable or metastatic neoplasms. It is believed that this type of treatment acts on the endothelial cells of the neo-vessels formed in the neoplastic tissue, inhibiting the tumor angiogenesis. In this way, for the patient in question, the use of metronomic chemotherapy was legitimized, due to the absence of a satisfactory response from previous therapies. Although there was no deletion of the neoplastic tissue, the therapeutic protocol was essential in the temporary stabilization of the SCC and in improving survival of the cat described. Chlorambucil, an alkylating antineoplastic agent, has shown promising action in metronomic chemotherapy protocols. The involvement of cyclooxygenase-2 (COX-2) plays an important role in oncogenesis, since it acts on tumor development and angiogenesis.
Nonsteroidal anti-inflammatory drugs (NSAIDs), such as firocoxib, piroxicam and others, inhibit cyclooxygenase by enzymatic alteration or competition at the binding site\textsuperscript{7}. The isolated use of NSAIDs is not satisfactory in cutaneous SCC therapy in cats, but adjuvant use may be effective in reducing the progression of neoplasia and increasing survival in animals that did not have a favorable response in previous treatments\textsuperscript{7}. The bibliographies mentioned above encouraged the choice of chlorambucil and piroxicam for a metronomic use in the cat, to confer quality of life (for a limited time) and to minimize the evolution of oncological disease, evidently with acquired chemoresistance.

**Conclusion**

The metronomic chemotherapy emerges as a possibility of therapeutic option for cutaneous CCE in cats that are refractory to previous treatments.

**References**


