

Electrochemotherapy in Non-satisfactory Responding Tumors in Vet Patients: Combined Administration of Bleomycin, Systemic and Local

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Abstract— Electrochemotherapy (ECT), a medical treatment widely used in human tumor treatment, consists in the administration of bleomycin either systemically or locally followed by the application of an electric field. This procedure increases the toxicity of the bleomycin by 1000 fold in the treated area with an objective response rate of around 80%. Despite its success related to efficiency, low cost and minimum side effects, there is still a 20% of cases in which the ECT treatment is not responding. This could be ascribed to the fact that bleomycin, administered in the preferred way, that is, systemically for large tumors, is not properly reaching the whole tumor mass. The main cause is poor tumor vascularization, in which case local administration could cover areas unreachable with systemic administration. To address this problem here we propose the combined administration of bleomycin, systemic and locally, using companion animals as models for ECT tumor treating. Accordingly, we selected 7 canine and 2 feline patients with a single tumor with poor or no response to ECT, and then we repeat the treatment with ECT but now with a combined administration of bleomycin, systemic and local. The results show, according to an evaluation using the WHO criteria of tumor response, that from the 9 cases, 5 achieved a Complete Response, 3 a Partial Response, and 1 a Stable Disease after 30 days from the combined treatment date. In conclusion, the combined administration of bleomycin, systemic and local, in ECT could provide a good response in tumors that previously showed an unsatisfactory response. It is expected that these results could hopefully increase ECT efficiency.

Keywords— electrochemotherapy, combined, local systemic, bleomycin.

I. INTRODUCTION

Electrochemotherapy (ECT) is a treatment modality that has been rapidly growing in human and veterinary medicine in the last years. In ECT the response is achieved by administering bleomycin followed by the application of an electric field in the tumor. This technique can increase the toxicity of the drug inside the tumor by 1000 fold. This treatment modality has an objective response of around 80% [1, 2, 3].

Despite its success related to low cost and minimum side effects ECT has still plenty of room for its improvement. Even with a high response rate of 80%, there is a 20% in which attention must be focused in order to improve the

outcome of the treatment. We believe that the principal cause of the absence of response in the remaining 20% of the cases treated with ECT could be ascribed to the fact that bleomycin is not properly reaching the whole tumor.

The systemic administration of bleomycin consists in injecting the drug into a vein, thus allowing the drug to reach the tumor through the circulation and diffuse from the vessels inside the tumor. Of course the distance from the smallest vessel to the target (tumoral tissue) is limited. Tumors usually have an inhomogeneous blood flow due the characteristics of tumor vessels which could compromise the distribution of the drug. On the other hand, local administration of bleomycin consists in directly injecting the drug into the tumor tissue, thus allowing it to diffuse from the injecting point to the target. Multiple injections into the tumor can provide an adequate coverage in selected tumors. The problem here is that it is very difficult to homogeneously cover large tumors; the same is happening when there are many tumors.

Many factors linked to tumor and tumor micro environment have an influence over the response to the ECT treatment with systemic bleomycin, i.e. the size and vasculature of the tumor, among others. It is well known that tumor vasculature has many abnormalities due to its anarchic growth, and many areas of a tumor are usually very poorly irrigated [4]. This characteristic of the tumor vessels could lead to an insufficient distribution of the bleomycin when administered systemically. However, with local administration, the drug can reach tumor areas even if vasculature is poor. To address this problem here we propose the combined administration of bleomycin, systemic and locally, using companion animals as models for ECT tumor treating.

The application of ECT treatment in companion animals followed the same pattern of success as in humans, many studies demonstrated its high efficiency, with a response rate very similar to the one achieved in human patients [5, 6].

The use of companion animals with spontaneous tumors as models for tumor treatment therapy became a generalized practice due to its many advantages. The most important being that these tumors behave more likely as human ones, and thus are better preclinical models for testing new

therapies. As these animals were exposed to environmental carcinogens, they developed the tumors in the context of an intact immune system that has the same tumor-host interactions [7, 8].

Accordingly, in this work we used companion animals with spontaneous tumors. We chose previously treated patients with unsatisfactory ECT response, we repeated the treatment with ECT but now with a combined administration of systemic and local bleomycin and we evaluated the response.

II. PATIENTS AND METHODS

We selected 7 canine and 2 feline patients meeting the inclusion criteria for the application of a combined treatment of ECT with systemic and local administration of bleomycin:

1. Single tumor previously treated with ECT with poor response. In this cases we expected a complete response and we obtained a partial response.
2. Schwannomas that according to our previous experience, have no objective response with the ECT treatment.
3. Tumors that because of its size, an objective response was not expected.

The treatment consisted of:

General Anesthesia: Premedication with 0.5 mg/kg of xylazine, 2 mg/kg of tramadol. Induction with 3 mg/kg of propofol. Maintenance with 2-3% of isoflurane and 2 mcg/kg of fentanilo. Meloxicam (0.2 mg/kg) was administered as analgesic after the treatment. This scheme of anesthesia provided an adequate comfort during the treatment. Prophylactic antibiotics were administered.

Device and electrodes: The pulses were administered using a six needle electrode, consisting of three rows of two needles 2 cm long and 1 mm diameter. Each row separated by 4 mm and each column separated by 8 mm. The pulse generator used was a BTX ECM 830 (Harvard Apparatus, Holliston, MA, USA).

Combined administration procedure:

ECT with systemic bleomycin: An intravenous bolus of bleomycin (Blocamicina®) at a dose of 15 U/m² BSA in 30-45 seconds was administered. **Local bleomycin administration:** Eight minutes after the administration of intravenous bleomycin (for allowing drug distribution), local administration of bleomycin at a dose of 0.25 U/cm³ of tumor [9] was performed.

Total dose of bleomycin with the combined treatment was slightly higher than with the systemic alone administration and showed no toxicity or side effects.

Electric field pulses: Immediately after local bleomycin administration, a train of 8 electric pulses (1000 V/cm, 100 microseconds, 10 Hz) were applied, covering the whole tumor [9].

The response to the standard and combined treatment also was performed with the WHO criteria for tumor response [10]. This was evaluated 30 days after the treatment.

Owner's consent was obtained to use the dog's image in scientific work and for the treatment of the other patients. In any case, all recommendations by the Consejo Profesional de Medicos Veterinarios de Buenos Aires were followed. The local normative law in Argentina, law No. 14072 regulating the practice in veterinary medicine, was followed too.

III. RESULTS

Table I present the results: from the 9 cases treated with the combined approach: 5 achieved a Complete Response, 3 a Partial Response and 1 remained with Stable Disease. Table I shows that the combined administration of bleomycin in tumors, systemic and local can provide a better response to the treatment for selected cases.

Table 1. List of the patients selected. FT: First Treatment with systemic bleomycin ECT response, ER: expected response, CTR: combined treatment response, SCC: squamous cell carcinoma, SDC: Solid differentiated carcinoma, CR: complete response, PR: partial response, SD: Stable disease and PD: Progressive Disease. In the patients marked with an * a very poor response was expected (SD) because of the large size of the tumors.

Patient	FT	ER	CTR
1.Labrador Retriever, Mastocitoma (dog)	PR	CR	CR
2.Cross-breed, Fibrosarcoma (cat)	PR	CR	CR
3.Cross-breed, Schwannoma (cat)	-	SD	CR
4.Cross-breed, SCC (dog)	-	SD*	PR
5.Labrador Retriever, SCC (dog)	PR	CR	CR
6.Yorkshire terrier, SDC (dog)	SD	SD*	SD
7.Cross-breed, Schwannoma (dog)	SD	SD	PR
8. Rottweiler, Fibrosarcoma (dog)	SD	CR	CR
9. Labrador Retriever, SCC (dog)	SD	CR	PR