Electrochemotherapy

Introduction
Electrochemotherapy has received considerable attention in the last 15 years as an emerging way of delivering therapies. Gene transfer and vaccines are current options along with standard chemotherapy. Its availability has been confined to outside the U.S. until now. Veterinary Oncology Services has the technology to provide this treatment.

Electrochemotherapy is a therapeutic approach providing delivery into cell interior of non-permeant drugs with intracellular targets. It is based on the local application of short and intense electric pulses that transiently permeabilize cell membrane, thus allowing transport of molecules otherwise not permitted by a cellular membrane [1,2]. Applications for treatment of cutaneous and subcutaneous tumors have reached clinical use (antitumor electrochemotherapy using bleomycin or cisplatin) [3-12]. Electrochemotherapy with bleomycin has been used to treat the patient for the first time in 1991 at the Institute Gustave Roussy in France [13], while electrochemotherapy with cisplatin has been used to treat the patient for the first time in 1995 at the Institute of Oncology, Ljubljana, Slovenia [14]. Since then more than 4000 patients were treated with electrochemotherapy all over the world (Australia, Austria, Belgium, Bulgaria, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Mexico, Nicaragua, Poland, Portugal, Slovenia, Spain, Sweden, UK, USA). Recently, new electrochemotherapy modalities have been developed for treatment of internal tumors using surgical procedures, endoscopic routes or percutaneous proaches to gain access to the treatment area [15, 16].

When a biological cell is exposed to an electric field of sufficient strength, an increase in the trans-membrane voltage is generated, which leads to structural rearrangements of the cell membrane structure [17-22]. These changes result in an increase of the cell membrane permeability, which allows nonpermeant molecules to enter the cell [13,23,24]. This phenomenon is called electroporation (or electropermeabilization) and is becoming widely used to improve anticancer drug delivery into cells, which is being referred to as electrochemotherapy. All biomedical applications of cell electroporation use monopolar DC short and intense pulses (even though in vitro, in bacteria, time-decayed pulses can be used). Amplitude of the pulses depends on the tissues and on the shape and position of the electrodes, but, in vivo, in the case of the tumors, the amplitude of the electric pulses has to be high enough to establish an electrical field of 400 V/cm in the area of tumor (8 pulses with duration of 100 microseconds) [25]. The length of pulses is usually one hundred microseconds. In early experiments, pulses were delivered with period of 1 second (i.e. at a repetition frequency of 1 Hz), nowadays however pulses are delivered in a much shorter time period, at a repetition frequency of 5000 Hz, resulting in a much less discomfort for the patient and in the shorter duration of treatment [26,27]. For treatment of deep seated tumors in relative vicinity of the heart, pulses are synchronized with absolute refractory period of the heart of each heartbeat to minimize the probability of interaction of pulses with the heart [28, http://www.clinicaltrials.gov/ct2/show/NCT01264952]
Description of the treatment

The electrochemotherapeutic treatment consists of delivering, either systemically or locally, non-permeant cytotoxic drugs (e.g. bleomycin) or low-permeant drugs (i.e. cisplatin) and applying electric pulses to the area to be treated when the concentration of the drug in the tumour is at its peak [12]. With the delivery of the electric pulses, cells are subjected to the electric field that causes the formation of nanoscale defects on the cell membrane which alter the permeability of the membrane. At this stage and for some time after pulses are delivered, molecules of the cytotoxic agents can freely diffuse into the cytoplasm and exert their cytotoxic effect. Multiple positioning of the electrodes, and subsequent pulse delivery, can be performed during a session to be able to treat the whole lesion, provided that drug concentration is sufficient [25]. Treatment can be repeated over the course of weeks or months to achieve regression of large lesions.
**Efficacy, clinical relevance**

In a number of clinical studies (phase II and phase III) investigators have concluded that electrochemotherapy of cutaneous or subcutaneous metastasis or tumors with bleomycin and cisplatin have an objective response rate of more than 80% [29]. Reduction of tumor size has been achieved with electrochemotherapy faster and more efficiently than in standard chemotherapy for both cutaneous and subcutaneous tumors. Patients with skin metastasis from melanoma, Kaposi sarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma or breast cancer have been successfully treated [4-7,9,10,30]. First clinical results of electrochemotherapy of internal tumors (e.g. liver metastases) are also promising and encouraging.

**Safety**

Electrochemotherapy employs lower dosages of chemotherapeutic drugs than standard chemotherapy protocols. In the clinical use of electrochemotherapy limited side effects related to bleomycin or cisplatin use are recorded. Provided that appropriate anesthesia is used for alleviation of the symptoms associated with application of electric pulses, the control of the pain level during the electrochemotherapy is good and acceptable for the patients. Beside pain which is limited to the treated tumor and surrounding tissue, muscle contraction during electric pulse delivery is the only discomfort for human patients associated with electrochemotherapy [4]. There is also induction of a vascular lock by the type of pulses used in electrochemotherapy: for a few minutes blood flow is interrupted in the treated volume in the normal tissues [31,32]. Its duration is too short to induce deleterious effects due to ischemia. In tumors however, vascular lock is of a longer duration and can contribute to the effectiveness of the electrochemotherapy. A good indicator that electrochemotherapy is not a stressful or painful procedure is that the majority of the people interviewed during a clinical study aimed at defining the European Standard Operating Procedure of Electrochemotherapy (ESOPE) would be willing to accept the treatment another time if it would be necessary [4].

**Endoscopic Applications**
Veterinary Use

Electrochemotherapy is also used in veterinary oncology in dogs, cats, exotics and horses. There are centers in Brazil, France, Italy, Ireland, Slovenia and UK where this treatment is available. It is used for a wide variety of tumors [33].

- Fibrosarcoma in the mouth, eyelid, foot pad, skin or distal limb, Feline vaccine-associated fibrosarcoma before and after surgery
- Melanoma in the mouth, eyelid or foot pad.
- Squamous cell carcinoma in mouth, eyelid, ear, nasal planum or foot pad.
- Incompletely resected soft tissue sarcomas where aggressive surgical treatment would necessitate amputation
- Feline vaccine-associated fibrosarcoma before and after surgery
- Localized cutaneous lymphoma in dogs or cats
- Local control of mast cell tumors
- Perianal & rectal tumors
- prostate
- pancreas
- Hepatocellular carcinomas/adenomas after resection
- Operation site margins where there is significant risk of remaining tumor tissue
- Sarcoids and squamous cell carcinomas in horses
- Superficial tumors on exotics (small mammals, birds & zoo animals)

Advantages

The process does require heavy sedation but is overall well tolerated and many tumors can be treated in 1-3 treatment sessions. Some tumors may require additional future treatments to maintain remission. 1) easy to perform on an outpatient basis 2) low cost and 3) requires only one or two sessions of heavy sedation to short anesthesia versus standard full course radiation therapy.

References


What is Electrochemotherapy?

Electrochemotherapy is a localized treatment that requires giving a very low dosage of a chemotherapy drug. Injection of the drug is combined with local application of electric pulses that increases the drug's effect.

When is Electrochemotherapy used?

Electrochemotherapy is a safe, simple, and effective procedure to treat tumors including Melanoma, Mast Cell Tumors, Prostate Tumors, Brain Tumors, Soft Tissue Sarcomas, Fibrosarcomas, Perianal Tumors and Anal Sac Carcinomas. It is particularly useful for lesions that cannot be removed with surgery, or have proven resistant to chemotherapy or radiotherapy.

How is Electrochemotherapy given?

While your pet is under a brief anesthesia we will administer the chemotherapy drug, bleomycin or Cisplatin, directly into the tumor. Following this chemotherapy administration, the applicator, which consists of a number of small needles on a round disc, will be inserted in the same lesion. When it is
turned on, a small electrical current is released throughout the immediate area. This current will open up the cells and allow the chemotherapy drug to enter them, thus causing destruction of the lesion.

What can be expected after Electrochemotherapy?

- Following the procedure the lesions may be covered with a bandage to aid in comfort. An e-collar may be needed to prevent your pet from licking or chewing.
- Lesions may turn black, scab, and may look worse before seeing improvement. This is a normal and expected reaction.
- Your pet may experience a feeling of warmth around the site of Electrochemotherapy for up to two weeks after the procedure.
- When the lesions have healed, the skin may be left with darker or lighter pigmentation.

Are there any possible side effects of Electrochemotherapy?

- The lesions of interest are often sensitive areas for the pet already and a mild pain medication may be necessary for a few days after the procedure.
- In rare circumstances the lesion could become infected and require antibiotic treatment.
- As with any drug, there is always a rare chance for an allergic reaction.

Endoscopic Treatment of Inoperable Cancer
With a Endoscopic Electroporation System (EES)

A new approach to treating solid tumors (both operable and inoperable)

Work at the Cork Cancer Research Centre in Ireland has led to the development of a novel new energy based therapy for treating inoperable human cancers including those unresponsive to conventional chemo and radiotherapy. Since 2004 over 400 energy focused cancer treatments have been provided to patients with unresponsive skin based cancers at the Mercy University Hospital, Cork. Over 85% of the tumors treated have been reduced in size by more than 50% after one treatment.
The treatment involves the application of a brief electrical pulse with chemotherapy, electrochemotherapy (under local anesthetic) directly to the tumor tissue. This causes the tumor cells to become temporarily porous and results in a significant increase in the tumor cells absorption of the chemotherapeutic drug. This treatment is extremely suitable for animals particularly in cases where the cancer is considered inoperable. This technology is available here through VOS. Esophageal, gastric, colonic tumors are treatable with this technology.

**Frequently Asked Questions about Electrochemotherapy (F.A.Q):**

1) **Will this therapy cure the cancer?**

   The therapy is effective at the location where the electrodes are placed on the animal i.e. the visible tumor mass; provided contact can be made endoscopically the tumor mass can be reduced if not eliminated with minimal side effects.

2) **How long does the treatment take?**

   The procedure used can be completed in under 30mins and involves placing the animal under anesthetic (isoflurane), injection of a low dose of chemotherapy (the total is 5% of what would be used conventionally) and application of electrodes directly to the tumor. The pulses used take less than \( \frac{1}{10} \)th of a second to deliver. The pet is treated and able to go home the same day.

3) **What chemotherapy drug is used? Is the chemotherapy toxic?**

   The drug used in combination with the electric pulses is Bleomycin. Bleomycin is very poorly absorbed by cells as a standard administration and is considered a poor drug for the treatment of cancer. However, by making the tumor cells porous (because they receive an electrical pulse), the drug can enter locally (but not to other cells in the body), and this results in the tumor cells dying. It also means that the toxicity is limited to the site of where the electrodes are placed which means **side effects are truly unlikely.**

4) **Will my pet lose its hair from the chemo?**

   **No.** A very low concentration of drug is used and is only toxic at the location the electrodes are placed i.e. on the tumor tissue.

5) **Does anesthetic need to be used? Will my pet feel pain or discomfort?**

   Human patients who receive local anesthetic feel the electric pulse and have described it as a dull thud. The anticipation is apparently worse than the discomfort of the pulse which it is important to point out subsides virtually immediately (the pulse lasts \( \frac{1}{10} \)th of a second). In animals the easiest solution is general anesthetic (isoflurane) normally for between 15-30mins in total. In this case no discomfort is felt by the pet.

6) **Is it an invasive treatment, does it involve surgery and stitches afterwards?**
No surgery is involved and therefore the therapy does not involve stitches.

For extremely large tumors that are operable a possible combination treatment is to deliver the treatment to the healthy tissue margins afterwards to minimize the risk of residual cancer cells escaping.

7) What side effects does the treatment have?

No side effects have been reported from the drug or the electric pulses in humans. Some inflammation may occur in larger tumors but this can easily be managed with medication or with many cases subsides without additional therapy needed.

8) What should happen after treatment? How long will it take to see a response?

The tumor is not surgically removed; it shrinks and regresses in size over a period of a few weeks after treatment. The speed at which this happens can vary depending on the type and size of the tumor. Normally a reduction in size can be seen within 2 weeks and regression can continue for up to 2 months. Aggressive cancers can be retreated after 4-6 weeks to improve the speed of regression.

9) Which patients are best for treatment?

Any animal with a solid tumor can be treated. Dogs, Cats, and Horses have all been treated successfully.

10) Which cancers are best for treatment?

Any solid tumor can be treated. Those located on the skin are the most straightforward to identify, diagnose and treat. Internal cancers can be treated during open surgery or via this specially designed endoscopic equipment developed at the Cork cancer research centre. Particularly suited are those cancers considered inoperable or that involve invasive surgery e.g. to the head, legs or internal organs.