Oncothermia research at preclinical level

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Background
Oncothermia method (OTM) has been applied in human oncology since 1989 [1]. Its clinical results excellently show the advantages of the method [2], however the details of its mechanism are being intensively investigated even now. Oncothermia research group conducts investigations at all levels of scientific research, from in vitro studies to human clinical trials [3]. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven in vivo [4], but the complex electromagnetic parameters playing crucial role in achieving these antitumor effects have not yet exactly been determined. On the other hand in the veterinary oncology practice there is a huge need for an effective treatment to cure malignant diseases due to the increasing incidence of cancer in pet animals [5], and the lack of a really effective and relatively cheap method to cure. For these reasons, Oncotherm created a specialized research device for preclinical investigations/veterinary clinical use, the VetEHY510 system, presented in Figure 1.

![Figure 1. The VetEHY-510 system prototype and its main parts: A: Main unit, B: Metal treating table as a grounded counter-electrode, C: Active treatment electrode, D: Electrode holder arm, E: Patient box, F: Controlling computer, G: Table heater and electrode cooling water thermostat and pump unit.](image)

The VetEHY510 system was created to serve dual purposes:
1. To give a powerful, effective and easy to use device for veterinary oncologists to fight against pet cancer and to provide information about the treatment efficacy of oncothermia method for comparative clinical oncology.
2. To collect information and a wide range of measured electromagnetic parameters, which can help to optimize the treatment protocols and clarify the real role of electromagnetic treatment parameters which govern the best clinical outcome.

Material and methods
Using VetEHY device in Tottori University, Veterinary Medical Center we treated companion animals (dogs and cats) having different kind of tumors (liver tumor, soft tissue sarcomas, lung tumor, lymphomas, melanoma, etc.) under supervision of professional vet oncology specialists and kept the animal ethical regulations. The use of the dedicated veterinary device is shown in Figure 2.
Figure 2. The VetEHY510 system in use, treating different companion animal cancer patients: A: Treatment of a dog having pulmonary metastasis, B: Treatment of a dog having brain tumor (glioblastoma) using a special forceps electrode system, C: Treatment of a dog having liver tumor, D: Treatment of a dog having a large lesion in the lung originated from a malignant lymphoma.

These spontaneously occurring tumors are the best “models” of human malignant diseases. Getting treatment information and experiences on the behavior of these tumors from these pet patients are extremely valuable, transformed directly to human practice to improve the clinical results. (Figure 3.)

Figure 3. A representative example of the similarity of the clinical manifestation between humans and companion animals. A: X-ray image of the pulmonary metastases from recurrent melanoma in a human patient (image courtesy of Dr. D. G. Borgeson), B: X-ray image of the pulmonary metastases from melanoma in a Labrador dog (patient from our veterinary hospital).

Scientist in oncology are just starting to realize the importance of the involvement of veterinarians in a real preclinical research work. The newest edition of Withrow and Mac Ewen’s Small Animal Clinical Oncology [5] briefly summarizes the aspects of companion animal cancer that enable attractive comparative models in a real preclinical investigation. To emphasize the real value the information which can be collected during the experimental treatment of companion animals, we would like to cite some points form the afore-mentioned book:

1. Companion dogs and cats are immunologically intact animals (like humans) as opposed to many experimental models of rodents and other animals.
2. Cancers seen in practice are spontaneously developing as opposed to experimentally induced and they recapitulate the natural human and veterinary condition better.
3. Companion species have a higher incidence of some cancers (e.g., osteosarcoma, non-Hodgkin’s lymphoma) than humans.
4. Most animal cancers progress by more rapid rate than their human counterpart. This permits more rapid and less costly outcome determinations such as time to metastasis, local recurrence, and time of survival.
5. As fewer established “gold standard” treatments exist in veterinary medicine compared to human medicine, it is ethically acceptable to attempt new forms of therapy (especially single-agent trials) on an...
untreated cancer rather than to wait to initiate new treatments until all “known” treatments have failed, as it is common in the human condition.

6. Companion species’ cancers are more skin to human cancers than are rodent tumors in terms of patient size and cell kinetics. Dogs and cats also share similar characteristics of physiology and metabolism for most organ systems such as surgery, radiation, and chemotherapy to be made between animals and humans.

7. Dogs and cats have intact immune systems as opposed to many rodent model systems, which allows immunologic assays and treatment approaches to be explored.

8. Companion animal trials are generally more economical to perform than human trials.

9. Companion animals live long enough to determine the potential late effects of treatment.

10. Dogs and cats are large enough for high-resolution imaging studies and multiple sampling opportunities, as well as for surgical intervention.

II. The VetEHY510 device contains many new technical solutions, which can ground the further development of the human clinical device. The main unit contains an E-class type resonant RF source operating at 13.56 MHz, and the high precision dual-directional coupler for precise forwarding and reflected RF power measurement. The main unit also contains a 6 bands wide range, real time automatic tuner system with autocalibration function for proper impedance matching for any kind of load impedance, according to the high variability of the companion animal’s body size and anatomical shape. This tuner system has an ultra-fast real time interfering dynamic element, so the continuous changes of the load impedance (for example according to the breathing movement of the animal) can be balanced every second, to keep the SWR (standing wave ratio) value in optimal range during the treatment (Figure 4.)

![Figure 4. Newly developed technical solutions in the VetEHY510 system](image)

The main unit contains a dynamic real time tuner system which can keep the SWR in optimal range during the treatment in real time

There is a very special part of the VetEHY510 system, the so-called patient box (Figure 5.) This device is a small box on the top of the treating table in a close proximity of the patient and makes the RF contact between the main unit and the treating electrode system. This unit is full with highly specialized measurement electronics and is able to measure the extended amount of electromagnetic and thermal parameters during the treatment. These are the electrode voltage, load current and their phase together with the impedance matching parameters and the temperature. This unit also contains a precise, four-channel temperature measurement system which is completely insensitive to the strong electromagnetic field according to its unique electronic solution, since this system is able to measure temperature under the treating electrode.

![Figure 5. The patient box and its display during treatment](image)

The treating electrode system is also a new development. The shape-adapting electrode-holder bolus together with the flexible electrode material can be seen in Figure 6.
Results

1. Shrinkage of tumor size, decrease of the tumor-associated pain and improvement of the quality of life of the animals were observed after oncothermia monotherapy treatments. More emphasized beneficial effects were observed, when oncothermia was used in combination with low dose chemotherapy. Veterinary oncothermia clinical investigations are still in progress. To illustrate the clinical success in a relatively severe cases some case reports are presented.

Case 1.: Case No.: 12082,8 years old mini dax. Symptoms: severe ataxia, the dog was not able to move and keep his balance. Diagnosis: supposed meningioma in the cervical region (C3) as revealed by MRI investigations. Treatment: oncothermia treatment as a monotherapy (1 session- 6 times in 2 weeks, after oncothermia treatment 1-2 times/month) using the special forceps electrode (Figure 7.)

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Figure 6. The treating electrode system
A: adjusting the electrode holder, B: the shape-adapting electrode-holder bolus and the flexible textile electrode in contact with the body, C: microscopic image of the fiber structure of the electroconductive textile material. The fibers are coated with palladium-copper-silver alloy.

Figure 7. Summary of case No. 1.
A: at the time of the hospitalization the dog was suffering from severe ataxia and hemiparesis before the treatment, B: the dog during the oncothermia treatment, using a special forceps electrode, C: after several treatments the dog can walk and run again without any problem, D: before the treatment the MRI image showed a lesion in the cervical region (c3) which compressed the spinal cord causing the severe symptoms, E: after the first treatment session the size of the lesion was decreased as shown in this MRI image, and the spinal cord was released from the pressure.
Case 2.: Case No.: 11461, a 8 years old castrated male Cocker spaniel. Diagnosis: melanoma was found on the toe of the right hind leg, which was surgically removed. Then severe lung metastases were developed. Treatment: low dose Carboplatine (2 times, 100 mg/m2, what is 1/3 of the prescribed dose) + Oncothermia treatment (10 times in 2-3 days interval)

Figure 8. Summary of case No. 2.
A: X-ray image of the primary melanoma on the toe of the right hind leg, B: the dog during oncothermia treatment, C: the dog is still alive and has a good condition, without symptoms, D: CT image series in different slices of the lung before the treatment. Several large lesion can be visible in the lung, marked with red arrow, E: CT image series of the same slices of the lung after the treatment. The size of the lesions are dramatically decreased and in some cases completely disappeared

Case 3.: Case No.: 9417, 9 years old, castrated male golden retriever. Diagnosis. Lymphoma in the thoracal cavity. Treatment: low dose COP (Cyclophosphamide-Oncovin-Prednisolon coctail, 2 times, 1/3 rd of the prescribed dose) + Oncothermia (15 times at the first session then 1-2 times / month)
A: In this X-ray image series the changes of the status of the lesion in the thoracic cavity can be tracked. B: CT image series in different slices of the lung before the treatment. The large tumor mass can be visible in the mediastinum, compressing the large part of the lung making serious difficulties in breathing. C: CT image series of the same slices of the lung 11 months after the treatment started. The size of the lesion significantly decreased, the lung was partially released from the compression.

This case was a typical example of a rapidly progressing deadly disease becoming a manageable chronic disease.

II. During these treatments we measured and collected many valuable electromagnetic parameters which can help to understand what is really happening during oncothermia treatment in electromagnetic sense.

Figure 10.: Graph series of the most important measured electromagnetic and thermal parameters during a standard 30 min treatment. A: Treatment power (forwarding and reflected) measured in the main unit RF generator and dissipated power measured in the patient box. B: Skin surface temperatures under the treating electrode. C: Electrode voltage and load current measured in the patient box. D: The phase of the electrode voltage and load current. E: Treatment power measured by the power meter in the patient box. F: Tuner parameters.

Our opinion is that the accurate analysis of these precisely measured treatment-related electromagnetic parameters can help to reveal the most critical electromagnetic parameter to achieve the best biological response. Using the results of these measurements we can optimize the technical solutions of further developments of the oncothermia devices for the human oncological applications and for the veterinary practice, too.
Conclusion
Oncothermia method and the VetEHY510 system is a new hope to effectively cure companion animal cancer patients, fulfilling the huge demand from veterinary market. The newly developed VetEHY510 device is a powerful research tool for comparative clinical oncology and to understand the role of critical electromagnetic parameters to improve the oncothermia method in human clinical practice too.

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