THE USE OF A MISTLETOE EXTRACT FOR IMMUNOMODULATION AND CANCER THERAPY.

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SUMMARY

This paper outlines a holistic treatment for cancer using a whole mistletoe extract (Viscum album L), in combination with other complementary therapies.

From the holistic perspective, cancer is considered a disease of the whole organism. The integrity of the organism and its homoeostatic mechanism has been overwhelmed by a combination of external insults, deficiency states, disturbances of metabolism, and organ malfunction. The immune system is particularly affected and fails to distinguish between self and non-self and cannot differentiate between alien or defective cells and normal cells. The cancerous process is the chaotic and final stage in a progressive sequence of faulty cell development, with neoplasms resulting from reversion to an undifferentiated state, and with progressive liberation from the control mechanisms.

Whole extract of mistletoe counteracts the immunological deficit associated with cancer by enhancing immune function through cytokine-mediated immuno-modulation. Clinical responses to therapy include enhanced well being of patients, slowing down or cessation of tumour growth, regression of tumours, and prolonged survival times.

Helixor® mistletoe preparations are approved for adjunctive treatment of cancer in humans in Germany and in several other countries. The author presents data collected from his experience treating cats and dogs with Helixor® during the last nineteen years.

INTRODUCTION

Biologic therapies, such as mistletoe therapy, are growing in importance for the treatment of humans with cancer, and are used as an adjunct to standard modalities of surgery, radiology and chemotherapy. Paradoxically, conventional therapies are tumour-centred and immunosuppressive, whereas biologic therapies are organism-centred and immunostimulative. However rational and necessary conventional oncological approaches may be, they undeniably impose an additional burden on the already compromised immune system of the cancer patient, thereby exacerbating the existing immunologic deficit. Their benefit is particularly doubtful for patients with metastases or inoperable primary tumours. This paradox imposes a dilemma for the therapist. Conventional therapies such as chemotherapy and radiotherapy may negate the benefits of biologic therapies, however; studies show that biologic therapies can reduce the side effects of these conventional therapies and enhance wellbeing and extend survival time of human patients (1).

Biologic therapies are a rational option in addition to primary oncological therapy to help prevent relapse, metastasis and to support palliative care. The goal of treatment is immuno-modulation, regeneration of healthy tissue, improvement of the quality of life, better tolerance of aggressive conventional therapies, and prolongation of life.

The concept of holistic cancer treatment in humans embraces diet, lifestyle, psychological counselling and biologic therapies. Treatment with whole mistletoe extracts over the last thirty years has developed a reputation as a mainstay in the adjunctive biologic treatment of cancer. Whatever the perspective and approach to cancer treatment is, it is important to be mindful of the insidious nature of cancer and its overt clinical appearance usually months or years after initiation.

CURRENT KNOWLEDGE OF MISTLETOE THERAPY IN HUMAN MEDICINE

In 1921 Dr Rudolf Steiner, the founder of anthroposophy and anthroposophic medicine, was the first to give his indications for the use of preparations from the European white-berried mistletoe (Viscum album L) in the treatment of cancer. The efficacy of mistletoe therapy in human medicine is documented in numerous scientific publications and supported by decades of clinical use. A monograph on Viscum album produced by the former Commission C of the German Federal Health Authority (2) summarised its effects as follows:

- Improvement of the general condition and wellbeing in most patients independent of the effects of the cancer
- inhibition of cancer growth without adverse effects on normal tissues
- Prolongation of survival time.
- Elevation of body temperature
- Relief of tension and depression
- Mitigation of tumour associated pain

HISTORY OF MISTLETOE (Viscum album, family Loranthacae)

The European white-berried mistletoe is one of many plants whose extracts have been used in medicine. Historically, mistletoe-bearing oaks were holy to the early Germanic tribes. Their priests, the Druids, wearing white robes, would harvest the mistletoe with a golden sickle, catching it in a white cloth to prevent it touching the earth. Mistletoe was considered a remedy for all diseases and throughout the Middle Ages was used to treat epilepsy, sterility, high blood pressure and depression.

The extraordinary nature and behaviour of this plant are worthy of mention. The growth of mistletoe defies the expected pattern of plant growth, which, in some ways, is reflected in the unregulated growth of cancer. It is semi-parasitic, taking only water, mineral salts and traces of organic substances from its host. Mistletoe cannot grow on the earth nor can it flourish on every tree. It retains characteristics of both plant and animal, containing the amino acid arginine, which is rarely found in plants, and lacking glutamine and asparagine, which are found in all other plants. Unlike most plants, it shows no heliotropism or geotropism; that is, it does not grow towards the light nor is there a tendency for the roots to grow towards the centre of the earth. Furthermore, it follows its own seasonal rhythm out of line with other plants, flowering in winter and fruiting in summer.

Other features express its primitive nature. The plant grows by dichotomous branching, does not form bark, the leaves have no upper or lower surface, and do not wither and fall during the first four years. Chlorophyll is present throughout the plant, even in the areas not exposed to light. Unlike other plants it germinates in the light and, without displaying a latent period before germination, may begin germinating while still in the berry. It has been described as a survivor of an earlier

period (Old Moon Period) in the evolution of the earth when plants, at a stage between our present plants and animals, could live.

Rudolf Steiner, founder of spiritual science in the 1920s, recognised the unusual qualities of this plant. He called it “insane aristocracy”. He described three formative forces; etheric, astral and ego, which shape the cellular structure of the physical body. These forces compel the specialisation of cells to constitute the organs of the body, and regulate their functions. A weakening or disruption of these forces allows cells to escape control and develop “autonomous cellular propagation” (3). In 1917 Steiner gave an indication for the use of mistletoe in cancer treatment. “The emancipation of the mistletoe from the spatial and chronological order governing its environment can be seen as reflecting the characteristics of tumour cells which rebel against the order governing the function of the organism by liberating themselves from its regulatory processes”.

Helixor® is a non-fermented, whole liquid extract produced from blending four seasonal harvests of mistletoe. It is unprocessed, and undergoes micro-filtration to achieve sterility. The four seasonal extracts are blended in an egg-shaped vessel where a vortex has been created by an impeller. The special whirling process enhances the potency of the extract and is reminiscent of the stirring method used in the preparation of the biodynamic preparations 500 and 501 used in biodynamic farming. There are three kinds of Helixor® corresponding to the three different botanic subspecies of Viscum Album L:

Helixor® M from the apple tree,
Helixor® A from the fir tree,
Helixor® P from the pine tree.

The three preparations show some differences in their therapeutic effects as well as their biochemical profiles. Helixor® M induces the greatest reaction (fever and local swelling) and causes the greatest tumour inhibition and inflammatory stimulant effects. Helixor® A shows the least reaction and is the best tolerated and has the most potent immunoprotective and roborant effect. Helixor® P comes somewhere in between these two, and is the one preferred by the author. Helixor® is provided in glass ampoules of varying concentrations from HELIXOR Heilmittel GmbH & Co. KG, Germany. There are several other commercial preparations of mistletoe available.

BIOLOGIC THERAPY

Biologic therapy is now regarded by oncologists as the fourth modality after surgery, radiation and chemotherapy. It refers to those cancer treatments that produce anti-tumour effects by stimulating host defences. Activation of the host’s reponses occurs through modulation, augmentation and restoration of immune function as well as direct anti-tumour activity. There is also a protective effect on normal cells against the adverse effects of other cancer therapies.

Biologic therapies trigger the immune cascade. This immune cascade is instigated through phagocytes, natural killer cells, and T and B lymphocytes. In addition to these cells, a number of lymphokines play an important part in immune activity. Cytokines such as tumour necrosis factor (TNF α), colony-stimulating factors (G-CSF and GM-CSF), and interleukin-2 (IL2) have all been studied in veterinary oncology (4).

Helixor® has been shown to have an immuno-modulating, anti-mutagenic and immuno-protective action. Specifically it increases the number and activity of natural killer cells and neutrophils; it induces cytokine release (TNFα, IL1, 2 and 6) (5,6,7); it increases γ interferon (8); it is cytotoxic (in vitro); it has a DNA stabilising effect; it stimulates T cells and the production of GM-CSF (9); it enhances new collagen formation and inhibits collagenase activity of cancer cells; it increases fibroblastic activity which restores matrix (10); and it protects peripheral blood lymphocytes against chemotherapy-induced mutagenicity and immunosuppression (11).These effects explain many of Helixor’s clinically established effects of fever, leucocytosis, release of CRP and other acute phase proteins, and stimulation of medullary haematopoeisis. These tumour growth inhibiting effects result in a slowing down or cessation of tumour growth.

A number of biologically active substances in Viscum album have been described (12,13). The predominant constituents are carbohydrates (oligosaccharides and polysaccharides), proteins (lectins), amino acids (especially arginine), and flavenoids. Some constituents have specific effects; however, the whole extract has been shown to be the most effective formulation for cancer therapy.

A combination of mistletoe therapy with radiotherapy or chemotherapy is beneficial. It has been shown that the side effects of nausea, vomiting, bone marrow suppression, and immunosuppression can be reduced by concurrent mistletoe therapy. Moreover, there is less need to interrupt antineoplastic therapy because of bone marrow depression. Studies also show an improvement of quality of life and survival times for human patients treated with a combination of chemotherapy and helixor compared to chemotherapy alone (1). An increasing number of clinical trials on mistletoe therapy are available to support the efficacy of this cancer treatment. Kienes`s critical analysis showed that four out of six studies confirmed statistically significant results when groups of patients were compared with their respective control groups (14).

INDICATIONS FOR HELIXOR (in humans)

Helixor® is indicated in humans for the following situations :

- As an adjunctive and palliative therapy for inoperable solid tumours (carcinoma, sarcoma, melanoma) and systemic malignancies (lymphoma, leukaemia).
- As a preoperative or postoperative therapy to help prevent relapse and metastases.
- Precancerous conditions (cervical intraepithelial myoplasias,chronic hepatitis B and C, ulcerative colitis, intestinal polyps)
- Treatment induced myelosuppression (aplastic anaemia)

Contraindications for use are allergic reactions to Helixor® are persistent high fever, severe inflammatory disease, pregnancy, and severe hyperthyroidism. Pronounced allergic reactions are very rare.

MISTLETOE THERAPY IN CATS AND DOGS

The author has used Helixor® extracts since 1984 for treating cancer in cats and dogs. He has modified the human protocols to suit veterinary medicine and provide ease of use for clients who are responsible for implementing the treatment. Clients give the injections and record daily temperatures at home.

CASE SELECTION

Effective treatment requires a dedicated commitment from veterinarian and client. Careful observation, high motivation, compliance, and willing co-operation from the client are essential to the effectiveness of therapy. Patients should be selected carefully using the following criteria:

- The general health of the patient and the presence of concurrent debilitating disease and/or paraneoplastic complications.
- The duration of the cancer prior to presentation.
- Tumour type. Hard tumours appear less responsive and fast growing anaplastic tumours are often very responsive to treatment.
- Previous treatments such as surgery, radiation, and immunosuppressive drug therapy. The ability of the animal to respond may be compromised by age, immune competence and general debility.
- The site and the size of the tumour. Large tumours may be less responsive and the site of the tumour may cause physical obstruction or interfere with organ function and mobility.

A realistic appraisal should be given at the outset along with any ethical requirement to inform the client of the unorthodox nature of the treatment. The veterinarian should provide caring support, an honest assessment of treatment, and be accessible to the client at all times especially during the first three weeks of treatment. Because it is difficult to predict the progression of this disease and the individual's response to treatment, it is important to maintain close communication with the client and provide frequent assessment of the patient to ensure that the quality of life of the patient is protected.

TREATMENT PROTOCOL

Treatment commences with daily subcutaneous injections starting with 1.25mg and increasing in 1.25-2.5mg increments until a reaction occurs. The author uses either 50 unit (0.5cc) or 100 unit (1cc) insulin syringes to aspirate the contents of a 100mg ampoule (2cc) of Helixor® P. Alternatively, the contents of an ampoule can be transferred to a 3cc vaccutainer without additive (yellow top) or an empty vaccine diluent vial, which must then be stored in the fridge. The daily dose can be aspirated from the vial. The appearance of flocculent material is indicative of fungal contamination and the contents should be discarded.

Injections are given subcutaneously on both sides of the body between the neck and costal arch. Injection sites are rotated to avoid giving injections in the same place twice. These sites are chosen for ease of administration; however, it is often preferable to inject as close as possible to the tumour and may, in some cases, be more beneficial to inject into the tumour. Marking the site of injection by marking the fur with a felt-tipped pen helps identify where injections have been given.

The reaction manifests as a fever and/or a localised swelling at the site of injection, and the animal may also show malaise and inappetence. At the onset of these symptoms, assuming that they are related to the therapy and are not paraneoplastic in origin, the dose is kept the same as the previous one until these signs abate. If the fever is marked (>39.5°C) or lethargy persists, no further injections are given until the fever abates and demeanour improves. By constantly measuring rectal temperature in the morning and evening and recording it graphically, a pattern of response can be observed. The fever response can be detected several hours after injection and usually peaks around eight hours after the injection, but may persist for more than twelve hours.

If the temperature in the evening is elevated (>39°C), the dose the following morning remains the same as the previous morning. If the temperature in the evening is normal, then the dose the next morning is increased. If the temperature on the following morning, twenty four hours after the injection, remains elevated (>39°C), then no injection should be given that day. The peak fever can vary by several hours for individual animals. This fever response normally occurs at a dose of 2.5mg-5mg and may persist for two weeks until the dose has reached 10-15mg. The degree and duration of the fever, in association with the clinical demeanour of the patient, are the main parameters used to determine the progression of treatment. A persistent fever may reflect another cause, either a paraneoplastic condition, tumour necrosis or some other concurrent disease. During the reactive phase some loss of body weight may occur. Appetite and demeanour may be significantly enhanced following this phase. Once the reaction to injections has ceased, the dose is then increased by 5mg increments until a dose of 50mg has been achieved. The reactive phase seldom lasts longer than 2-3 weeks and it is during this time (a window of opportunity) that the immune cascade is best stimulated.

Concurrent drug treatment may affect the development of a fever response. Non steroidal anti-inflammatory drugs are effective anti-pyretics and corticosteroids may also interfere with the therapeutic benefit. It is advisable to stop this medication if possible, at least for the first 2-3 weeks during the reactive phase.

Once a dose of 50mg has been achieved a rhythmic dose sequence is instituted. The frequency of injections is reduced to every two or three days, and the dose is rotated from 50mg to 75mg to 100mg and repeated. Following several cycles, and depending on the response to therapy and the malignancy of the tumour/s, the frequency of injections is reduced to weekly, then to monthly, with the dose being maintained between 50mg and 100mg.

ADJUNCTIVE SUPPORT

It is helpful to provide additional support for the body, especially during the reactive phase, as this protects against free radical damage and encourages immune modulation. This is particularly important when concurrent chemotherapy is used. The author uses a comprehensive antioxidant formula, high levels of vitamin C, and a mushroom extract.

Dietary advice includes the use of a high protein, high fat and low carbohydrate foods preferably prepared at home from fresh raw meat and cooked or raw coloured vegetables (carrot, beetroot, broccoli, beans, pumpkin). Cold pressed oil can be used to increase the fat content of food (flax oil 5cc/10kg). Other modalities such as homoeopathy, acupuncture, herbal remedies and nutraceuticals can also be used.

MONITORING TREATMENT

In addition to measuring daily rectal temperature, local skin reaction and general demeanour, the monitoring of haematological indices is valuable. A complete blood count will often show a moderate leucocytosis with a left shift.

The rate at which the dose can be increased and the frequency at which injections can be given is determined by;

• The degree of fever and local reaction
• The tumour size; the rate of tumour growth and tumour malignancy
• The animal's health; any debilitating, paraneoplastic or concurrent disease.

A local swelling greater than 4cm in diameter or a fever over 39.5°C is excessive. Where there are prolonged and debilitating reactions and/or large local swellings over the injection sites, the following options can be considered:

- Reduce the incremental dose from 2.5mg to 1.25mg
- Miss a day or give injections every second or third day
- Change from Helixor® P to Helixor® A. Once the reactive phase is over Helixor® P can then be substituted.

These side effects of Helixor® treatment constitute an excessive manifestation of the desired inflammatory and immunostimulatory effect, and can be controlled by adjusting the dose and frequency of injections. Local subcutaneous swelling is indicative of delayed cellular responses and shows that the immune system is responding. A fever is an indirect indication of the release of interleukin-1 from macrophages, marking the start of the immune cascade. Occasionally there may be regional lymph node enlargement. Clients may regard these local reactions as debilitating for their animal; however, if they are made aware of what to expect, that the response to treatment is evidence of efficacy, and that the reaction is transient and should not last longer than 2-3 weeks, then most are willing to persevere.

The response to Helixor® therapy is primarily dependent on the patient's capacity for mustering an immune response. While there may be some direct effect on the tumour it is the stimulation of immunological, regulatory and regenerative processes that constitutes the main benefit of therapy. Significant individual differences in response and course of disease necessitate individualised treatment regimens.

Where an allergic reaction occurs, seen as generalised urticaria or persistent swelling at the injection site for more than two weeks, then desensitisation should be instituted. Desensitisation using Helixor® A in minute doses of 0.1mg should be given twice weekly until there is no appreciable skin swelling. To date the author has not seen any allergic reactions. Surveillance using radiography, sonography and digital palpation are useful for monitoring response to treatment. Where appropriate, callipers can be used to directly measure the size of superficial tumours.

The duration of treatment is variable and depends on:

- Other concurrent therapy being used
- The presence of secondaries
- The prior use of surgery and whether it was successful
- The malignancy of the tumour
- The degree of tumour reduction seen since treatment commenced

Where surgery has succeeded in complete removal of the tumour or tumours and there has been no recurrence, treatment may stop after twelve months. Where there has been incomplete surgical excision, tumour recurrence or continued growth, high malignancy or the presence of secondaries, then Helixor® treatment should be maintained indefinitely.

As well as the effect Helixor® has on the tumour it is important to recognise the benefits of enhanced well being. Patients often show improved appetite and demeanour and take up activities that they have not displayed for some time, such as chasing the ball or barking at visitors. Amelioration of the symptoms of concurrent diseases such as arthritis and dermatitis may also occur.

CASE REPORT - LIVER CARCINOMA IN A CAT

On the 16th October 1985 a 3cm diameter palpable liver tumour was diagnosed in Candy, a 13 year old cat. Candy's liver enzymes were elevated and weight loss and polydypsia were evident. Treatment with Helixor® A began on the 16th October 1985 commencing with a dose of 2.5mg and increased daily by increments of 2.5mg. When a dose of 50mg was reached the frequency of injections was reduced to every second or third day. Concurrent supportive treatment with the antioxidant selenium ACE and the homoeopathic remedy lycopodium was given. The owner administered a fresh extract of aloe vera regularly. After 2 weeks the cat's appetite was good and no increase in tumour size was palpable.

On the 13th November 1985, one month after commencing treatment, no hepatic mass could be palpated. The dose at this stage was 12.5mg. The tumour was again palpable on the 16th December 1985 but despite this Candy was in good health. On the 30th December 1985, the cat was operated on for the removal of a gastric furball. Observation of the tumour at surgery determined that it was inoperable and the prognosis was poor. The tumour continued to grow over the following four months reaching 4cm in diameter.

A year later in December 1986 Candy was again operated on to remove a gastric furball. A cystic 6cm mass was removed from the liver at the same time and was confirmed histologically as a hepatocellular carcinoma. Histologically there was extensive necrosis, vacuolation and degeneration with a mild to moderate host immune response. Multiple liver secondaries were also observed at this time. Extensive invasion of the portal fissure was observed and an extremely poor prognosis given. Helixor® was maintained at 50mg fortnightly and Candy`s condition remained surprisingly stable. No tumour was palpated in October 1988 but by February 1990 the tumour had regrown. The tumour continued to grow slowly over the following eight months during which time Candy received 50mg Helixor® every month. The frequency was increased to weekly but by the end of January 1991 the tumour had increased further in size. Candy died peacefully at home on the 10th February 1991 at the age of 18½ years of age, five and a half years after the diagnosis and commencement of Helixor® therapy.

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