

Review

Evidence-based Complementary Oncology. Innovative Approaches to Optimize Standard Therapy Strategies

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Abstract. *Cancer diseases demand diagnostic and therapeutic measures with proven quality, safety and efficacy. The basis for evaluation is clinical studies representing levels I or II (randomized controlled trials (RCT) or epidemiological cohort studies) in accordance with recommendations of the Centre for Evidence-based Medicine, University of Oxford, UK. Regarding these claims, surgery, chemo-, radio- and hormone therapy have emerged as the gold standard in the treatment of carcinomas. These therapies have proven their cancer destructive potencies and their curative feasibilities, dependent on the particular cancer entity and stage. Complementary therapies are recommended to support and optimize the scientifically-based cancer standard treatment. Complementary medicine is currently widely debated by the oncological community, because the required scientific proof of safety and effectiveness for most of the therapeutic approaches has not yet been definitively provided. In the past years, basic research and clinical evaluation of defined complementary therapeutic concepts in oncology have been intensified in an attempt to integrate these procedures into evidence-based medicine. Scientifically-based therapies of complementary medicine cannot replace the well studied conventional cancer-destructive therapies such as surgery, chemo-, radio- or hormone therapy. Accordingly, they are by no means “alternative therapies”. Complementary approaches in oncology that are recommended as additional to standard cancer destructive therapies claim to optimize this therapy. A great body of data emerging from scientifically sound clinical trials prove that defined complementary procedures are beneficial for the patients.*

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Complementary Medicine: A Scientific Approach to Comprehensive Therapy in Oncology

New developments of complementary medicine in oncology have emerged out of a general disappointment with the results of more traditional treatment options. Despite innovative approaches towards cancer destruction, including surgery, chemo-, radio- or hormone therapy, cancer mortality rates have not been significantly reduced in the United States or other industrialized countries in the past twenty years. Notable treatment success, however, has been achieved in rare cancers such as testicular cancer, leukaemia and lymphoma (1).

Global analyses conducted independently by Abel (2) and Moss (3) dampened the optimism associated with chemotherapy for advanced carcinomas, especially when responses (temporary cancer shrinkage) are used as a measure of therapeutic success. These authors urged the medical community to think about new therapeutic strategies. While mainstream oncology has introduced promising therapeutic innovations (4), e.g. targeted antibody/antisense therapies, specific inhibitors of cancer cell growth factors, efficient but tolerable new chemotherapeutic agents, advanced concepts for radiotherapies, some non-toxic but promising complementary approaches (5, 6) have undergone scientific and clinical trials.

A statement made by the drug administration in Germany, about unconventional alternatives to aggressive cancer treatment, should be mentioned: “The practice of drug therapy as the main source of treatment offered in medicine by all industrialized nations is based on the scientific acknowledgement of certain laws (e.g. drug-receptor interactions; dose-response relationship; demonstrated effects on the disturbed regulation of biochemical and psychophysiological processes) and on the testing of these medicines according to internationally accepted clinical-pharmacological and biometric methods” (7). The consistent application of

this statement should result in an ethical consensus and lead to the following set of requirements: the scientific study and evaluation (proof of safety and efficacy) of all therapeutic concepts; the limitation to diagnostics and therapeutics with proved safety and efficacy and their inclusion into health insurance plans and the development of a comprehensive plan for adequate prevention, prophylaxis, diagnosis, therapy and follow-up of cancer.

While the importance of cancer prevention has moved into the forefront of public consciousness, due to intense awareness campaigns by the cancer societies, the areas that include diagnosis, therapy and follow-up need to achieve similar recognition. Widespread passive follow-up ought to be replaced by an active treatment plan tailored to the respective indications of the patient's disease. In order to reach this goal, oncologists should aim to expand on proven complementary medicinal approaches and optimize the timing and the benefits of therapy (4-6).

Overview of Complementary Therapies in Oncology

Complementary medicine should primarily be regarded as an addition to or enhancement of current standard treatment options in oncology (5, 6). It should be differentiated from "alternative medicine", which seeks to find replacements for conventional toxic approaches. Although complementary and alternative medicines are grouped together in the popular acronym "CAM", they are in fact quite different in their aims. Since many alternative treatments are still poorly documented, equating the two could lead to a misguided and undeserved rejection of all complementary medicine. That many of the methods discussed in this paper can optimize standard treatment has been proved in clinical studies that have shown an increase in quality of life as well as in overall survival. Biometrically secured and prospectively randomized data for these approaches, for the most part from randomized controlled trials (RCTs) and epidemiological cohort studies according to good-epidemiological practice (GEP), are presented.

Nutrition

The National Cancer Institute (NCI) of the United States attributes about 35% of all types of cancer to malnutrition (8). The potential for prevention of cancer is thus large and general nutrition guidelines for primary and secondary prevention are of much value, according to the German Society of Nutrition (DGE) and the International Society for Nutrition and Cancer (9).

It is striking to see that both fruit and vegetables play a prominent role in the prevention of cancer. For almost every type of cancer, there is evidence of protective nutritional factors. Among the cancer promoting factors, obesity plays a

major role in addition to smoking and alcohol. The role of animal fats as a carcinogenic factor remains unclear. Although fats are considered to increase the risk of cancer, there is neither compelling evidence from epidemiological studies nor any other indication that a causal relationship exists. This statement does not address the role of fats as an energy source or their possible role in the development of obesity (5, 9, 10).

Once cancer becomes apparent, the success of therapy and the healing process, are decisively determined by the patients nutritional state. Fundamentally, a specific advisory for the patient's optimized nutrition is of great importance at this point, since malnutrition and cachexia can have a significant effect on the quality and duration of life. Malnutrition increases cancer mortality by about 30% (11) and cachexia worsens the prognosis of disease significantly, since it is associated with reduced response to treatment, more complications from and adverse reactions to the treatment and prolonged hospitalization.

So called "cancer diets" (such as the Gerson-, Budwig- and Breuss diets) have not yet shown any scientifically sound benefit for patients, however, they bear the risk of delaying curative treatment options and of inducing life threatening malnutrition. Accordingly, they cannot be recommended to cancer patients (12).

Exercise; Physical Activity

Exercise in the form of "moderate endurance training" (such as walking, jogging, swimming and cycling, all under strict aerobic conditions) and "focused gymnastics" (such as stretching, functional, water, spinal column gymnastics) have proved to be beneficial in the prevention and follow-up of cancer (13) as well as during cancer destructive therapies (14, 15).

Cancer imposes an enormous psychological and physiological stress on those afflicted, weakening the immune, hormone and other metabolic systems (16). Exercise, in contrast, ensures a certain tolerance to stress which can be developed particularly through endurance training. The diagnosis and therapy of cancer exert a maximum of stress that is processed in a variety of ways. Stress entails an adaption syndrome of neurovegetative and psychoimmunological regulatory circuits as a result of an acute or chronic challenge to the physical and psychological capabilities of the afflicted person. The patient can be trained to adapt to this burden by means of a coping strategy which includes physical activity.

Endurance exercise induces stress resistance and has beneficial effects on the psyche, thereby strengthening immune defences and the cardio-vascular, hormone and metabolic systems.

Recently published clinical studies (RCTs, representing level I of the Evidence-based Medicine classification) proved

Table I. Components and pharmacological effects of mistletoe extracts.

Active substances of <i>Viscum album</i> L.			
Structural types	Substances	Effects on cancer cells	Effects on the immune system
Glycoproteins	Mistletoe lectins ML, I, II, III	Cytotoxicity by inhibition of the ribosomal protein synthesis + induction of apoptosis	Release of TNF- α , IL-1, IL-2, IL-6
	Visalb CBA		Stimulation of lymphocytes
Polypeptides	Viscotoxins A ₁₋₃ , B, 1-PS, U-PS	Cytotoxicity by lysis of cell membrane	Activation of macrophages Enhanced phagocytosis activity of granulocytes
Peptides	Peptide 5000 D [Kuttan <i>et al.</i> (37)]	Cytotoxicity Cancer inhibition in animals	Activation of macrophages Increase of cytotoxic activity
Oligo- and Polysaccharides	Arabinogalactane Rhamno- galacturonane		Stimulation of T-helper-cells (TH ₁ \uparrow , IFN γ \uparrow) Enhanced NK-cell activity
Flavonoids	Derivates of quercetine	Induction of apoptosis	Antioxidative + Cell protective effects

the beneficial effects of moderate endurance exercises to cancer patients in the follow-up period (13, 17, 18; enhanced quality of life) and during standard therapies (13, 14, 17; significantly reduced frequency and severity of fatigue syndrome and other therapy related adverse reactions).

Psycho-oncological Support

Psychotherapeutic measures should be an integral part of any acute treatment or rehabilitation of cancer patients. It is widely known that disabilities may lead to psychosomatic diseases and that these can be relieved or even cured with appropriate psychological aid or therapeutic modalities.

In addition, psychotherapeutic measures are indicated for dealing with the following types of problems or symptoms: emotional disturbances, such as fear or depression; conflicts within a relationship or family; impairment in social behaviour; social withdrawal tendencies; psychological impairment with physical decline or deterioration; problems in accepting the disease; discrepancies between therapeutic expectancy and actual treatment options and inadequate behaviour towards the disease.

Psychotherapy is an integral part of acute and rehabilitative treatment in oncology and it has proved its beneficial effects (for example improvement of quality of life and prolongation of disease free intervals) especially for breast cancer patients in well designed RCTs (19, 20). Psycho-oncological treatment options (such as visualization, relaxation, creativity training and discourse) should be recommended individually and have recently been published (16).

Phytotherapy

Treatment with mistletoe extracts is the most common complementary therapy in Central European oncology. Mistletoe extracts are used as complementary treatment in addition to chemotherapy and radiation treatment and show immunostimulatory, cytotoxic and pain-relieving effects (5, 6).

In several *in vitro* and *in vivo* studies activation of NK-cells, monocytes, macrophages and T-cells, cytokine release as well as antiangiogenic effects, induction of apoptosis and protection against sister chromatid exchange inducing DNA-damage were demonstrated (21).

The best researched components and their pharmacological effects on tumour or immune cells are summarised in Table I. The contribution of the other mistletoe components to the efficacy of the total extract is still open to further research.

As a result of the over 85 years of experience, mistletoe therapy is indicated for all stages of malignant non-systemic tumours. It is used complementarily to the individually necessary oncologically therapeutic measures. The contraindications are all acute inflammatory and hyperpyrexial conditions, where symptoms are aggravated by the inflammation stimulating effect of mistletoe.

Mistletoe extracts are generally well tolerated and do not show any toxic reactions even in highly dosed, long-term therapy in cancer patients.

In a systemic review of studies of mistletoe therapy Kienle *et al.* (22) investigated 66 retrospective and non-controlled

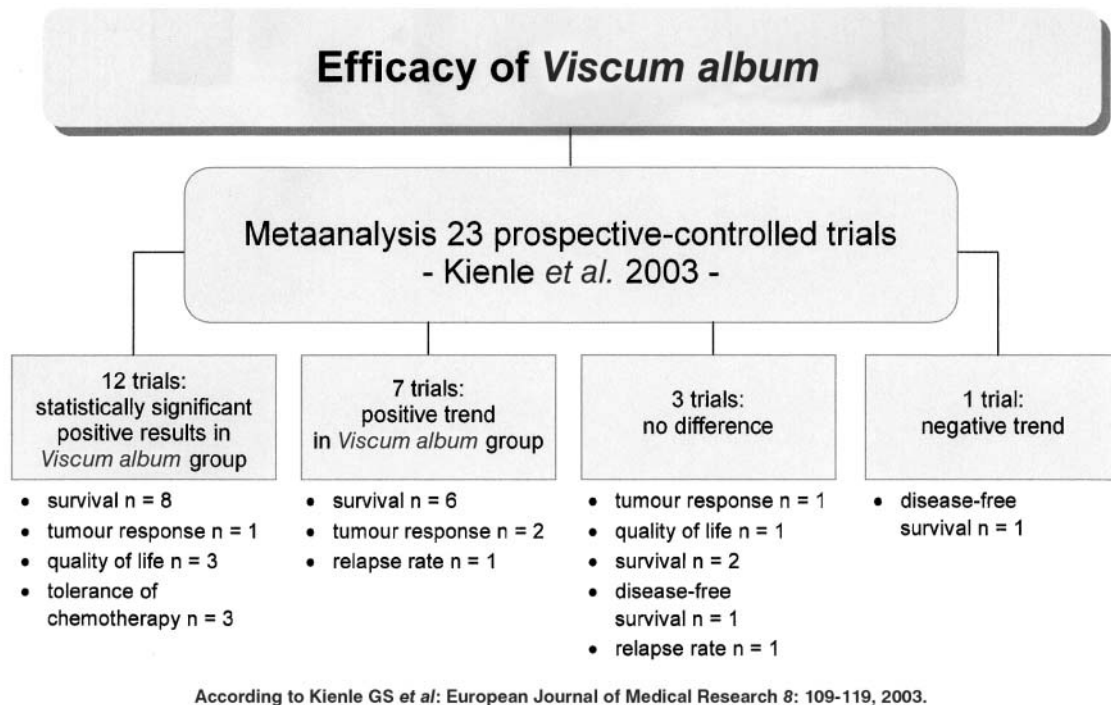


Figure 1. *Oncological relevance of mistletoe therapy.*

studies as well as 23 controlled clinical studies. In the majority of the studies a statistically significant proof for it to be an oncologically relevant therapy for patients could be achieved (Figure 1).

Most of the methodological problems of these studies mentioned by Kienle *et al.* (38) were now overcome in two recently performed prospective randomised clinical multicentre trials. In one study 233 male and female patients (lung, breast and ovarian cancer) received, complementary to the standard chemotherapy, a standardised mistletoe total extract (Helixor® A) in individual optimal dosages or lentinan, a widely known phytotherapeutic agent in Asia with proven efficacy with respect to immune function and quality of life under chemotherapy. In comparison to the control, the complementary mistletoe therapy led to a significant reduction in the number and degree of severity of chemotherapy associated side-effects. Three different systems to measure quality of life [Karnofsky performance index, functional living index-cancer (FLIC) questionnaire and traditional Chinese medicine index (TCM) score] resulted concordantly in a statistically significant improvement in quality of life, with respect to the reduction of pain and fatigue, physical status, physical activity, well-being, and appetite (23). The blinding problem was elegantly solved in the following way, in that the patients of the control group with lentinan received a well-known in China and Japan immune stimulating agent, whereby the probability of a

relevant performance and information bias was markedly reduced.

In a second, placebo-controlled, double-blind, multicentre trial a statistically significant effect was achieved with three FACT-6 questionnaire subscales with a dosage of 15 ng mistletoe lectin/0.5 ml (24).

Within an overall therapeutic concept, consisting of a combination of tumour effective (destructive) methods of standard oncology (surgery, radiation, chemo, and hormone therapy) and bordering measures such as diet, physical therapy and mental-spiritual activation, mistletoe therapy has become the lynchpin of a human tumour therapy, in which the needs of the individual human being suffering from cancer is the centre of attention.

Balanced Vitamin/Trace Element Mixtures

Cancer patients have an increased requirement for essential micronutrients that are rarely adequately supplied even through a wholesome and balanced diet. This especially holds true before or during cancer destructive therapy, since the need for micronutrients in these phases is increased due to side-effects such as reduced appetite, nausea, vomiting, diarrhea, and perspiration (9). It has been demonstrated that a deficit in micronutrients (vitamins, trace elements and minerals) results in a reduced tolerance of current standard cancer therapy (25).

The role of micronutrients in the primary and secondary prevention of cancer is multifunctional. Vitamins, trace elements, and minerals can inhibit the activation of cancer-causing substances as well as the inflammatory processes. Other micronutrients can prevent the reuptake of cancer-inducing substances into the cell and protect cellular DNA by disabling the adhesion of cancerous compounds (26).

Indication-specific substitution with balanced micronutrients (combination of balanced vitamins, trace elements, and minerals, according to the recommended daily allowances specified by specialized societies such as the International Society for Nutrition and Cancer) as a prevention of cancer as well as a compensation for therapy-induced nutritive deficits has proved beneficial in intervention studies and controlled clinical trials (25, 26).

Selenium

Selenium is an essential trace element recognized as a cancer-protective agent and is increasingly employed as an adjuvant in cancer therapy. Whereas for cancer prevention organic nutritional forms of selenium (Se) are used, sodium selenite is the preferred form of selenium for therapeutic applications. Sodium selenite is administered primarily to reduce the side-effects of chemo- and radiotherapy. Patients typically receive 300-1000 mcg Se/day as sodium selenite orally or by infusion for one to five days prior to and during chemo- and radiotherapy, and subsequently oral doses of 100-200 mcg/day on demand for maintenance. Sodium selenite is also used in conjunction with biological therapies and in the management of secondary or postoperative lymphedema (5, 6, 27-29).

Experimental *in vitro* data have proved that Se can definitely enhance the efficacy of chemo- and radiotherapy (30, 31). Since the molecular basis of the mode of action of Se was demonstrated in detail (5), discussions on its potential for inhibiting standard therapies stopped. Randomized controlled clinical trials have demonstrated significant benefits for cancer patients receiving Se during chemo and radiotherapy, such as reduction of lymphedema in head and neck and breast cancer patients (27-29).

Proteolytic Enzymes

A standard combination of proteolytic enzymes (papain, trypsin, and chymotrypsin) resulted in a significant reduction of disease and therapy-induced symptoms, such as nausea, vomiting, cachexia and mucosal ulceration in cancer patients treated with chemo- and radiotherapy. Depending on the type of cancer (breast or colorectal cancer or plasmocytoma) and stage of disease, the quality of life was significantly improved and relapse free survival was significantly prolonged in patients complementarily treated with proteolytic enzymes (32-34).

As EBM-relevant (level II) clinical trials proved, complementary treatment with proteolytic enzymes adapted to the respective stage and type of cancer may improve the quality of life and may enhance the efficacy of standard therapy and thus qualifies as evidence-based medicine.

Hyperthermia

Hyperthermia is based on external physical heat application and can be categorized according to its focus and extent of expansion into: whole body hyperthermia: for the treatment of advanced-stage cancer; deep hyperthermia for the treatment of localized cancer, such as of the internal organs; superficial hyperthermia: treatment of skin cancer and metastases; perfusion hyperthermia for the treatment of cancer or metastatic invasion of the cavital organs and interstitial hyperthermia for the treatment of regional cancer (5).

A combination of hyperthermia with standard or immune therapies may be expected to result in additive or synergistic effects. Hyperthermia in combination with chemo- or radiotherapy is currently being subjected to scientific testing worldwide (35). It is absolutely vital for evaluations of this therapeutic measure to be performed without preconceived notions. Hyperthermia has been used for many centuries as a cancer-reductive therapy. Although there are many clinical trials (PubMed cites about 400 references to RCTs), there is still a lack of definitive clinical results. Initial controlled clinical trials have been very promising and seem to point to hyperthermia as a complementary treatment measure that enhances standard cancer-destructive therapies, for example in patients suffering from cervical cancer (35).

All of the aforementioned therapeutic approaches are currently being evaluated further, and exaggerated claims are unwarranted. Proof of efficacy for specific cancer types and stages must be completed so that defined complementary medicinal concepts may be integrated into evidence-based oncology. Concerning the scientific recommendations of EBM, relevant clinical studies of levels I or II are missing for hyperthermia. Accordingly, this complementary approach is still experimental and should be applied in well designed clinical studies only.

Fringe Methods

It is imperative to beware of unsound therapeutic and diagnostic measures that have not undergone any scientific testing for safety and efficacy, but are sometimes erroneously associated with scientifically proven complementary medicine. These procedures are extensively advertised and wrongly suggest the following after application: reduction of cancer growth and mass; slowing of growth of metastases; prolongation of survival time; intensified chemo- and

radiotherapy effectiveness; delay of the necessity for chemoradiotherapy and that they are beneficial treatment modalities after all options have failed.

Although new concepts should always be openly received, such procedures are usually not based on sound scientific principles and may ultimately prove life-threatening for the patient, if possibly curative measures are delayed (36).

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