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Short Review

Evidence-based Complementary Oncology: Innovative Approaches to Optimise Standard Therapy Strategies

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Abstract. *Cancer diseases demand diagnostic and therapeutic measures with proven quality, safety and efficacy. Bases for evaluation of new clinical and therapeutic measures are clinical studies representing level I (randomised controlled trials [RCTs]) or level II (epidemiological cohort studies), in accordance with recommendations of the Centre for Evidence-Based Medicine, University of Oxford, UK. Evidence-based treatment of cancer follows recommendations of international expert panels and includes indication-based surgery, chemotherapy, radiotherapy, hormone and antibody therapy. These therapies have all proven their potency to destroy cancer and their curative feasibility. This review provides an overview of some of the complementary therapies that are also recommended to support and optimise the standard evidence based cancer treatments.*

Complementary medicine can be primarily regarded as an addition or optimisation of current standard and evidence-based treatment options in oncology (1, 2). It is very popular all over the world. In Germany, more than 80% of the cancer patients apply complementary medicine (1). In particular, young, female, educated and higher socioeconomic class patients show interest in methods that may optimise the standard treatment and protect quality of life (3).

The American Cancer Society defines complementary medicine or methods as those that are used along with regular medical care (4). If these treatments are chosen and managed carefully, they may add to enhanced comfort and well-being (2-4). Some complementary treatments have been tested scientifically, such as nutrition, sports and psycho-oncology (5), while others have not, *e.g.* cancer diets, non-specific immunotherapies, high-dose vitamin and trace element supplementation. Certain complementary medications such as sodium selenite, proteolytic enzymes and standardised mistletoe extracts have shown clinical benefits in level I and II evidence-based medicine (EBM) trials, where examples of the benefits include reduced adverse reactions to chemotherapy (CT) and radiotherapy (RT) and enhanced quality of life (2, 5), while others, such as *Lens culinaris* lectin, are traditional naturopathic remedies that stabilise the mucosal surfaces (6).

In this review, complementary medications that have been supported by biometrically secured data, either from randomised controlled trials (RCTs), EBM level I, or from epidemiological cohort studies according to good-epidemiological practice (GEP), EBM level II, are described.

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Nutrition

The National Cancer Institute (NCI) of the United States attributes a considerable number of all types of cancer to malnutrition (7). In this context, the potential for prevention of cancer is thus large, and according to the German Society of Nutrition (DGE) and the International Society for Nutrition and Cancer (8), general nutrition guidelines for primary and secondary prevention are of great value.

It is striking to see that both fruit and vegetables play a prominent role in the prevention of cancer (8, 9). For almost every type of cancer, there is evidence of protective nutritional factors (10). Among the cancer-promoting factors, obesity plays a major role, in addition to smoking and alcohol (7, 8). 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 for a causal relationship. This statement does not address the role of fats as energy source or their possible role in the development of obesity (9).

Once cancer becomes apparent, success of therapy or the healing process are influenced by the patient's nutritional state. A specific analysis of the patient's optimised nutritional regime 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% (9, 10) and cachexia worsens the prognosis of disease significantly, since it is associated with reduced response to treatment, increased complications and adverse reactions to treatment and prolonged hospitalization.

To date, no scientifically evidenced benefit to patients has been shown for so-called 'cancer diets' (*e.g.* Gerson, Budwig, Breuss diet; 11), however, they are known to bear the risk of delaying curative treatment options and of inducing a life threatening malnutrition. Accordingly, they cannot be recommended to cancer patients.

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 and spinal column gymnastics) have been proven to be beneficial in the prevention and follow-up of cancer (12), as well as during cancer destructive therapies (13, 14).

Cancer imposes an enormous psychological and physiological stress on the patient, thus weakening immune, hormone and other metabolic systems (15) Exercise, in contrast, ensures a certain tolerance to stress which can be developed, particularly through endurance training. Diagnosis and therapy of cancer exert 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, the cardiovascular, hormone and metabolic systems.

Recently published clinical studies (RCTs, representing level I of the EBM classification) documented beneficial effects of moderate endurance exercises for cancer patients during standard therapies namely, significantly reduced frequency and severity of fatigue syndrome and other therapy related adverse reactions) (13, 14), and during the follow-up period, enhanced quality of life (16, 17).

Psycho-oncological Support

Psychotherapy is an integral part of acute and rehabilitative treatment in oncology with proven beneficial effects, such asimprovement of quality of life, especially for breast cancer patients in well-designed RCTs and meta-analyses (18, 19). Psycho-oncological treatment options (such as visualisation, relaxation, creativity training and discourse) should be recommended individually and were recently published (15). It is also widely recognised that physical handicaps 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 disease in 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.

Selenium

Selenium is an essential trace element recognised as a cancer-protective agent and it is increasingly administered as a complementary cancer therapy. Whereas organic nutritional forms of selenium are used for cancer prevention, sodium selenite (Se) is the preferred form of selenium for therapeutic applications (*e.g.* Cefasel®, Selenase®). Sodium selenite is administered as a complementary treatment mainly in order to reduce side effects of CT and RT. Patients are typically treated with 300 μg Se/day, orally or by infusion, for one to five days prior to and during CT and RT, and subsequently with oral doses of 100-150 μg Se/day on demand for maintenance. Sodium selenite is also used complementarily with standard therapies in the management of secondary or postoperative lymphedema (20-22).

Experimental *in vitro* data showed that Se can enhance the efficacy of CT and RT (23, 24). Since the molecular basis of the mode of action of Se was demonstrated in detail (2), discussions on its potency to inhibit standard therapies have ceased. Randomised controlled clinical trials demonstrate benefits for cancer patients receiving Se during CT and RT, namely reduction of lymphedema in head and neck- and breast cancer patients (20-22, 25). In 2007, the German Society of Radiooncology (DEGRO) approved a clinical trial on the complementary Se administration in gynaecological radiation oncology, since it improved the quality of life significantly (25).

Proteolytic Enzymes

A standardised combination of proteolytic enzymes (papain, trypsin, and chymotrypsin; Wobe Mugos® E, not available anymore) results in a significant reduction of disease- and therapy-induced symptoms, such as nausea, vomiting, cachexia and mucosal ulceration in cancer patients treated with CT and RT. Depending on the type and stage of cancer, quality of life has been shown to be improved significantly in

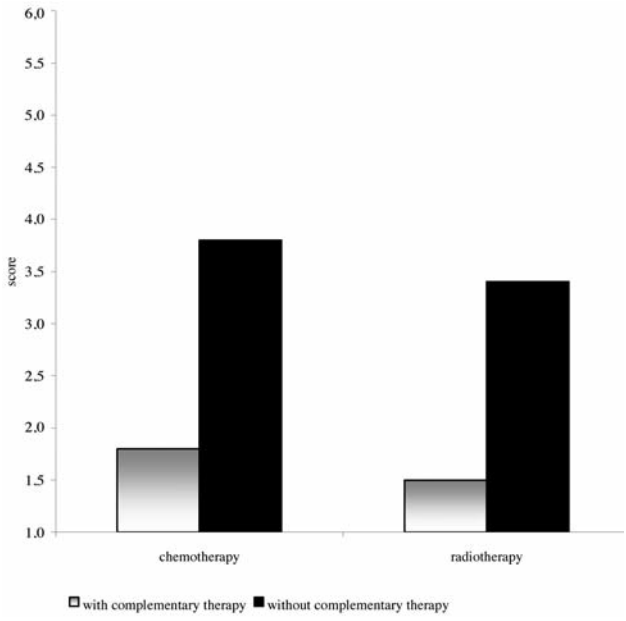

Figure 1. *Tolerability of adjuvant chemotherapy in breast cancer patients, quantified by scoring from 1 (optimal tolerability) to 6 (extremely bad tolerability. Score data as described above and published elsewhere (30). Complementary treatment comprised sodium selenite, proteolytic enzymes and Lens culinaris lectin.*

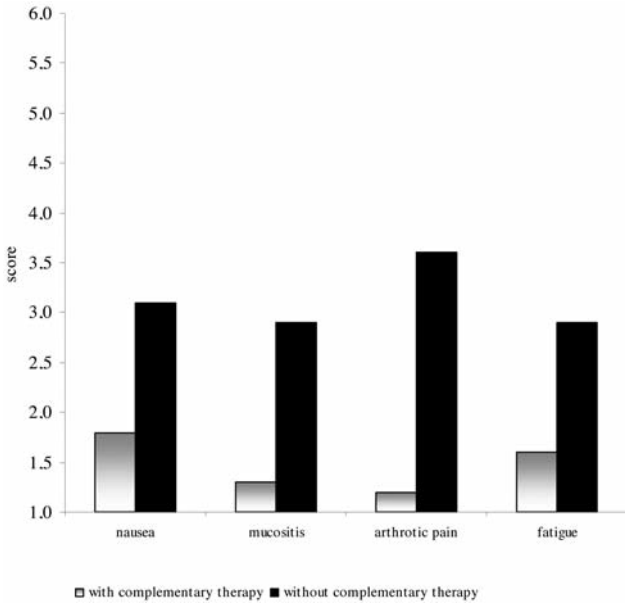

Figure 2. *Adverse reactions of adjuvant CT and RT in breast cancer patients, quantified by scoring from 1 (no side-effects) to 6 (extreme side-effects). Score data as described above and published elsewhere (30). Complementary treatment comprised sodium selenite, proteolytic enzymes and Lens culinaris lectin.*

breast and colorectal cancer and plasmocytoma patients, whereas relapse free survival is significantly prolonged only in plasmocytoma patients treated complementarily with proteolytic enzymes (26-28).

As EBM-relevant cohort studies (level II) have shown that complementary treatment of patients with breast cancer and other tumour entities with proteolytic enzymes improved the quality of life and enhanced the efficacy of standard therapies, proteolytic enzymes were designated an orphan drug status by the U.S. Food and Drug Administration for the indication plasmocytoma (29).

Selenium-Enzyme-*Lens culinaris* Lectin Combination

An observational trial (30) evaluated the benefit of complementary treatment comprising a combination of sodium selenite, proteolytic enzymes and *Lens culinaris* lectin (Equizym® MCA) in breast cancer patients undergoing adjuvant CT and RT.

The patients (n=60) were treated according to the guidelines of St. Gallen and San Antonio (n=30; control group) and complementarily (n=30; study group) with a combination of sodium selenite (300 μg/day), proteolytic enzymes (bromelaine and papain; 4000 FIP units/day) and *Lens culinaris* lectin (20 mg/day) in certified breast cancer centres in hospitals in Cologne and Iserlohn, Germany. For each patient a self assessment of tolerability and side-effects of CT, RT, and complementary treatment, including gastrointestinal tract disorders such as nausea, vomiting, mucositis, mucosal dryness, arthritic pain, fatigue, and inflammation was documented. Validation was performed by scoring from 1 (no side-effects/optimal tolerability) to 6 (extreme side-effects/extremely bad tolerability).

Compared to the control group (mean score: 3.8 CT; 3.4 RT), the tolerability of the adjuvant treatment was better in the study group (mean score: 1.8 CT; 1.5 RT; Figure 1). As shown in Figure 2 enhanced tolerability of adjuvant CT and RT resulted from reduced side-effects, especially nausea (mean score: 3.1 control; 1.8 study), mucositis (mean score: 2.9 control; 1.3 study), arthritic pain (mean score: 3.6 control; 1.2 study), fatigue (mean score: 2.9 control; 1.6 study). No adverse reactions of the complementary treatment were documented confirming the data from the literature.

This observational trial demonstrated benefits of indication-based complementary treatment in breast cancer patients, namely a reduction of side-effects and enhancement of tolerability of adjuvant CT and RT. A randomised controlled trial confirming these clinical findings is currently planned to integrate the complementary treatment with the combination of sodium selenite, proteolytic enzymes and *Lens culinaris* lectin into (BM).

Balanced Vitamin / Trace Element Mixtures

Cancer patients have an increased requirement for essential micronutrients (such as vitamins, trace elements and minerals) 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, diarrhoea, and perspiration (31). It has been demonstrated that a deficit in micronutrients results in a reduced tolerance of current standard cancer therapy (32).

The role of micronutrients in the primary and secondary prevention of cancer is multifunctional. Vitamins, trace elements, and minerals inhibit the activation of cancer-causing substances as well as inflammatory processes. Other micronutrients can prevent the re-uptake of cancer-inducing substances into the cell and protect cellular DNA by disabling the adhesion of cancerous compounds (33).

The indication-dependent supplementation with micronutrients (combination of balanced vitamins, trace elements, and minerals, according to the recommended daily allowances recommended by the German Society for Nutrition (DGE) or the International Society for Nutrition and Cancer; *e.g.* CAREIMMUN® Basic, Immunwell®) for the prevention of cancer or for the compensation of therapy-induced nutritive deficits has proven to be beneficial in intervention studies and controlled clinical trials (32).

Mistletoe Extract

Standardised mistletoe extracts (*e.g.* Eurixor®, Helixor®, Iscador®, Lektinol®) have been applied to cancer patients for several decades as complementary medications (34). They were introduced into oncological treatment by Steiner around 1920 and there are many reports on their clinical efficacy (35). However, the acceptance of these results is still controversial since the problem of adequate methodology in testing safety and efficacy of complementary medicine is still a matter of discussion.

Mistletoe extracts with defined amounts of mistletoe lectin-I (ML-I) have yielded promising experimental and clinical results (34, 36-38). Recent research shows that the same can be found with standardised mistletoe extracts with a predominant content of ML-III (34, 35, 39). Initial clinical studies of EBM levels I and II have shown that complementary application of standardised mistletoe extract can reduce side effects of CT and improve the quality of life (QoL) in cancer patients (36-39). However, further studies of adequate methodology are urgently needed to prove this clinical benefit definitively.

This conclusion was recently confirmed by the 2008 Cochrane Database of Systematic Reviews: "There is evidence that mistletoe extracts may offer benefits on measures of QoL during chemotherapy for breast cancer, but these results need replication. Overall, more high quality, independent clinical research is needed to truly assess the safety and effectiveness of mistletoe extracts. Patients receiving mistletoe therapy should be encouraged to take part in future trails" (40).

Following the recommendation of the responsible German Health Authority (Gemeinsamer Bundesausschuß, GemBA), administration of standardised mistletoe extract has been proven to improve the QoL in palliative care (41). There are scientifically sound clinical studies that prove significant benefits for patients with advanced cancers, which were the basis for the positive validation of this therapy by the GemBA.

Hyperthermia

Hyperthermia is a therapy based on external physical heat application to the patient and can be categorised according to its focus and extent of expansion into (2): whole body hyperthermia: treatment of advanced-stage cancer; deep hyperthermia: treatment of localised cancer, *e.g.* of internal organs; superficial hyperthermia: treatment of skin cancer/metastases; perfusion hyperthermia: treatment of cancerous/metastatic invasion of cavital organs and interstitial hyperthermia: treatment of regional cancer.

A combination of hyperthermia with standard therapies is expected to result in additive or synergistic effects. Hyperthermia in combination with CT or RT is currently being subjected to scientific testing worldwide. Initial controlled clinical trials have been 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 (42).

Quackery

It is imperative to be aware of non-safety and non-efficacy proven diagnostic and therapeutic approaches, which are sometimes erroneously associated with complementary medicine. Non-evaluated diagnostic and therapeutic measures are extensively advertised and wrongly suggest that their application may achieve: inhibition of cancer growth and reduction of cancer mass; prolongation of relapse-free and metastasis-free survival; prolongation of overall survival; intensified effectiveness of CT and RT; delay of the necessity of CT or RT; curation, even if all standard options have failed.

Although innovative concepts are appreciated, therapeutic procedures that are not based on sound scientific principles may ultimately be life-threatening for cancer patients since they may delay curative treatment options (43).

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