Mistletoe therapy and Cancer – an Overview 2017

Mistletoe extracts (*Viscum album* L., VAE) are widely used integrative cancer care treatments, particularly in Europe [1-5]. They are an old herbal remedy [6, 7] and were introduced as cancer treatment in 1920 by Rudolf Steiner and Ita Wegman, founders of Anthroposophic Medicine [8]. Viscum album is a hemiparasitic shrub, growing on different host trees. Different preparations are available for the treatment of cancer (currently Abnobaviscum®, Helixor®, Iscador®, Iscucin® and Lektinol®). They are available from different host trees such as oak, apple, pine and many others. They are applied parenteral, particularly subcutaneous, but also intravenous, intratumoural, intrapleural, intraperitoneal and other sites.

Several pharmacologically active compounds have been isolated from VAE, such as mistletoe lectins (ML I, II and III) [9], viscotoxins [10, 11], oligo- and polysaccharides [12, 13], lipophilic extracts [14] and various others [6, 7]. Currently VAE triterpenes are gaining great interest. [15-19] The most prominent properties of VAE are their cytotoxic and growth-inhibiting effects, *in vitro*, on a variety of human tumour cell lines, lymphocytes and fibroblasts [6, 7]. The cytotoxic effects of VAE are mainly due to the apoptosis-inducing mistletoe lectins [20-22], while the viscotoxins induce necrotic cell death [21, 23]. VAE are also recognized for their immune-modulating activity: *In vitro* and *in vivo* studies have demonstrated activation of monocytes/macrophages, granulocytes, natural killer (NK) cells, NK-cell mediated tumor cell lysis, T-cells (especially T-helper-cells) and the induction of various cytokines [6, 7, 24]. VAE also downregulate tumor genes, reduce motility and invasiveness of tumor cells [24], and show antiangiogenetic effects [25]. They also possess DNA stabilizing properties, they reduce chromosome damage and improve DNA repair [26-29]. In animals, VAE displays potent antitumour effects when administered either directly into the tumour or systemically [6, 7, 30].

Clinical effectiveness of mistletoe extracts in cancer has been investigated in a great number of studies, among these 43 prospective randomized controlled trials [31-80]: They predominantly report significant clinical benefits. With regard to quality of studies and consistency of results, the best evidence concerning efficacy of mistletoe therapy exists for the improvement of *quality of life*, increase of weight, and *improved tolerability of cytoreductive therapies* (chemotherapy, radiotherapy, surgery) [33, 81, 82]. Regarding *survival,* a well-designed randomized controlled trial has recently shown a highly significant benefit in advanced pancreatic cancer [32]. Other studies showed similar results [30, 83-85]. Effectiveness seems to depend on the duration of the mistletoe therapy, in addition to factors relating to dosage, host tree and choice of preparation. *Tumour remissions* have been repeatedly observed after local application of high dose mistletoe extracts. This finding is consistent with the preclinical research on cytotoxicity and treatment of tumors in animals. During customary low-dose mistletoe therapy, tumour remissions are rare exceptions. Tumor remissions have therefore been reported primarily in small studies, case series and single cases. (e.g. [30, 84, 86-96])

According to highly experienced practitioners much improved outcomes are possible, with highly individualized and comprehensive treatment schedules – individually adjusted and with selected dosage, preparation, host tree, injection site, time schedule of administration, and supplementation with other interventions. This still needs to be investigated. [97, 98]

Currently, several interesting trials have been started: One large publicly funded confirmative (phase III) randomized controlled trial investigating the influence of mistletoe treatment on survival and health-related quality of life in patients with advanced pancreatic cancer, conducted at several cancer centers in Sweden (NCT02948309). One phase I trial on safety of intravenous mistletoe infusions in various cancers, conducted at the John Hopkins Hospital in Baltimore (NCT03051477 [99]), funded by the charity organization Believe Big (www.believebig.org). And one large confirmative (phase III) randomized controlled on the efficacy and

safety of intravesical mistletoe extract conpared to Mitomycin instillation in superficial bladder cancer, conducted in more than 30 German study sites. [100]

Clinical application of mistletoe extracts is safe, even in high dosages [6, 7, 101-106].

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Enclosed, exemplary literature:

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