Professional Resource: European Mistletoe

Proper name: *Viscum album* Loranthaecea, *Viscum album L.*
Common names: Mistletoe, European Mistletoe, VAE (Viscum album extracts)
Commercially available products: Helixor®, Iscador®, abnobaVISCUM® (Isorel®, Lektinol®, Eurixor® are no longer available)

Summary:

Mistletoe extracts (VAE) are used in integrative cancer care to support immune function, reduce side effects, improve quality of life, and possibly improve survival and recurrence. The most common routes of administration are subcutaneous injection and intravenous infusion, with the majority of research pertaining to subcutaneous administration. Proposed mechanisms of action include immunomodulation of both innate and adaptive immune response, and direct cytotoxicity. Increased lymphocytes (T cells, B cells, and NK cells), cytokines including INF-gamma and IL6, and presence of IgG antibodies to mistletoe lectins and viscotoxins have been observed. Subcutaneous and IV VAE are well tolerated; serious side effects such as allergy and anaphylaxis are rare but have been reported. Mild and self-limiting side effects including local injection site reactions (with subcutaneous use), fatigue, and mild fever are common. Studies in people with cancer have found that mistletoe is likely to support quality of life, improve symptom burden, and reduce side-effects associated with treatment when given alongside standard care. Studies on survival and tumor response are not conclusive; some studies find benefit and others find no difference compared to control groups. VAE is not a cancer cure and not an alternative to conventional care. Overall methodological quality is poor, and studies with better methodology are less likely to find benefit to survival. In conclusion, mistletoe is a promising adjunctive therapy for quality of life and side effect management, but more research is needed from well controlled studies to further elucidate its impact, and understand if it improves survival or recurrence risk for people with cancer.

Background

Preparations from European Mistletoe are sometimes recommended for people with cancer, most notably in Germany (1). Mistletoe, a parasitic plant from the Santalacea family, is commonly prepared as an extract containing various compounds which vary slightly based on host tree, harvest time, and extraction/preparation method. Available products often are named based on host tree, commonly including malus (apple tree: “M”), abies (fir tree: “A”), pinus (pine: “P”), and quercus (oak: “Qu”) (1, 2). Some mistletoe extracts are fermented (Iscador®), while others are unfermented (Helixor®, abnobaVISCUM®).

This monograph exclusively discusses evidence pertaining to the use of European mistletoe (Viscum album L) extracts in complementary cancer care, omitting American and Korean mistletoe, and pharmaceutical preparations (e.g. E coli-derived recombinant counterpart of mistletoe lectin-I known as rViscumin (Aviscumine)) (3, 4). Mistletoe will primarily be referred to as VAE (*Viscum album* extract).

Methods:

This monograph was prepared by conducting a systematic literature search of Medline and Cochrane library from inception to March 31 2019 for English-language, human studies of VAE for cancer. The systematic search was developed by a medical librarian, and executed by OICC research staff. Many studies have been published in German only; these will only be discussed within the context of systematic reviews and meta-analyses which included these trials (5-7). Scoping review was completed by OICC research staff for additional supporting information such as background, mechanism of action, and safety.

Common Purported Uses of VAE in Cancer Care:

- Enhance immune function
- Support quality of life
- Reduce cancer- and treatment-related symptoms
- Slow disease progression
- Reduce risk of recurrence
- Improve survival

Routes of Administration:

VAE can be administered via subcutaneous (SC), intramuscular, intrapleural, and intratumoral injections, as well as via intravenous infusion (IV) and intravesical instillation. This monograph will focus on the two most common routes: SC and IV. Safety and efficacy evidence is absent for oral administration of European mistletoe, and therefore will not be discussed.

Pharmacokinetics:

VAE pharmacokinetics information is limited. A phase I study evaluated the pharmacokinetics of subcutaneously administered VAE by administering a single injection of abnoba VISCUM Fraxini (20mg) to 15 healthy male volunteers (8). Mistletoe lectins were detected in all serum samples after injection, and mean and median peak concentrations reached 1 and 2 hours after injection, respectively. However, concentration-time profiles varied considerably, indicating non-linear kinetics, and thus half-

life could not be determined (8). Mistletoe lectins were detectable in 60% of the men after 14 days. Significant individual variability in subcutaneous mistletoe pharmacokinetics exists.

Pharmacokinetics of other VAE administration routes have not be studied.

Proposed Mechanisms of Action:

Identified active compounds include mistletoe lectins (ML) (I, II and III), viscotoxin (VT) proteins, flavonoids, phenylpropanoids, triterpenes, phytosterol, alkaloids, polyalcohols, and polysaccharides (9). The lectins and viscotoxins have received the most research attention (2, 10). Different VAE formulas contain different concentrations of MLs and VTs due to host tree, time of harvest, and extraction method, and thus the biological response is also expected to differ (2). The two primary mechanisms of action for VAE are immune system modulation and cytotoxicity.

Immunologic activity:

Lectins are proposed to be primarily responsible for the immunologic activity of VAE (11). While diverse effects have been noted, overall, most studies report immune function improvement with VAE administration (2). Immune parameters observed to increase or improve include granulocytes (neutrophils, eosinophils, basophils), lymphocytes (T cells, B cells, NK cells), cytokines and interleukins (including IFN-g, TNF-a, IL-1, IL-4, IL-5, IL-6), and IgG antibodies (2).

Randomized trials in healthy volunteers indicate that subcutaneous VAE stimulates both innate and adaptive immune responses (11-13). One study randomized 43 healthy volunteers to subcutaneous VAE, purified mistletoe lectin (ML), ML-free VAE, or placebo twice weekly for 8 weeks, and analyzed differential blood counts and peripheral blood mononuclear cells (PBMC) (11). Significant increases in leukocyte, granulocyte, and antigen-induced production of GM-CSF, IL-5, and IFN gamma by PBMC with VAE and ML treatment compared to placebo groups was observed. Another study compared SC injections of Iscucin Populi (IP), Visum Mali (VM), or placebo and demonstrated eosinophilia with both VAEs, increased CD4 T-lymphocytes in the VAE IP group, and no change in IL6 or CRP in any group (12). An adaptive immune response to VAE was demonstrated in a 12-week trial of 47 people randomized to Iscador Q (rich in ML), Iscador P (rich in viscotoxins, low in ML), or placebo (13). Anti-ML-1 IgG antibodies were present in all Iscador Q-treated subjects but only 6 exposed to Iscador P. Anti-VA2 IgG-antibodies were detected in all individuals in VAE groups, none of the participants receiving placebo developed antibodies.

Studies in cancer populations report similar results. A small RCT of women with breast cancer receiving adjuvant chemo-radiotherapy found that 7 weeks of VAE significantly increased IFN-g and IL-6 compared to control. (14). In a study of 98 women with breast cancer having surgery, a single infusion of 1mg Iscador M one-hour prior to anaesthetic prevented the surgical suppression of granulocyte function when compared to the control group (15). However, results of four controlled trials of VAE during

adjuvant chemotherapy for breast (n= 3) and gastric (n=1) cancer found that VAE did not improve neutrophil counts (the most abundant granulocyte) as there was no change compared to controls (16-19), thus VAE is not recommended for this purpose. Details of these four studies can be found in Table 1. Several other studies presented in tables 1-3 also provide information on the immune effects found from VAE administration.

Natural killer (NK) cells are of particular interest in cancer research. Two studies have found improvements in NK cell numbers or function in people treated with VAE peri-operatively. One RCT randomized 70 people undergoing surgery for digestive tract cancer to receive VAE for 4 weeks peri-operatively or control (20). The treatment group observed significantly decreased immunosuppressive effects of surgery compared to controls, in particular an increased number of lymphocytes including NK cells, T cells and B cells, and an increase in immunoglobulins. A study of patients undergoing surgery for colon cancer found similar results following perioperative infusion of VAE, showing that NK suppression 24h post-surgery was prevented in the mistletoe group (21).

Cytotoxic activity:

Mistletoe lectins, viscotoxins and alkaloids are believed to be responsible for mistletoe's cytotoxic activity (22). Proposed mechanisms include protein synthesis inhibition, triggering apoptosis and necrosis, indirect cytotoxic effects resulting from cytokine release, and increasing natural killer cell cytotoxicity and macrophage activity (22-24). Most studies on the cytotoxic activity of VAE come from preclinical data. It has been suggested that although low doses of VAE have been effective for supporting immune function, higher doses may be needed to exert cytotoxic effects which may also increase toxicity and side effects of the therapy (22).

EVIDENCE RELATED TO CLINICAL EFFICACY

Subcutaneous injections:

Diverse human level studies exist that vary in both study design and quality. Overall, VAE appears to likely benefit immune function, quality of life and reduce disease and treatment related symptoms. Results are mixed regarding tumour response and survival. Variance in survival studies is attributed to differences in VAE preparations, dosing, cancer types, administration schedules and study design. Further, several systematic reviews report poor methodological quality within published clinical trials (5-7, 10, 25). In the most recent systematic review (published in two parts) data is presented for a possible beneficial effect of VAE, especially for quality of life parameters, however, authors bring forth concerns regarding methodological issues which led the authors to conclude that evidence of VAE efficacy is lacking (5, 6). This systematic review has been criticised by some for the interpretation and conclusions it draws; the letter to the editor and the author's responses can be reviewed for further commentary (26, 27).

Quality of Life

Of the 14 subcutaneous VAE clinical trials identified, 11 investigated endpoints related to quality of life, side-effects and/or toxicity of cancer treatments (16-20, 28-33). Ten were randomised controlled trials (16-20, 28-31, 33), only one of which was placebo-controlled (31). Five studies included patients with breast cancer (16, 17, 19, 31, 33), two each with colorectal cancer (20, 32), lung cancer (28, 33), pancreatic cancer (20, 29), and gastric cancer (18, 20), and one each with relapsed osteosarcoma (30), esophageal cancer (20) and ovarian cancer (33). Table 1 presents details of prospective clinical trials for subcutaneous mistletoe which met our inclusion criteria.

The majority of studies report that VAE improves quality of life endpoints observed across different cancer types, conventional treatments, and stages of disease. Only one study reported that VAE did not improve quality of life, but did reduce treatment related toxicity (28). Regarding specific quality of life endpoints, differences in particular outcomes are present, as illustrated by two similar breast cancer trials (16, 17). The first study (16) found that VAE significantly improved cognitive function, anorexia, nausea/vomiting and pain, with no significant effects on global health, physical function, fatigue or dyspnea. The second study (17), found no significant benefit for cognitive functioning, anorexia and nausea/vomiting, but found significant improvements for role functioning, pain and diarrhea. Most studies report mixed QOL benefit, with some endpoints significantly improving while others do not. While VAE appears to consistently improve aspects of QOL, predictions of which *specific* endpoints will be improved may vary between patients, even with similar case presentations.

Seven studies implemented the same validated standardized QOL assessment tool (EORTC-QLQ-C30) (16-19, 28, 30, 34), allowing for inter-study QOL endpoint comparison. VAE significantly improved global health in relapsed osteosarcoma patients (30) and gastric cancer patients receiving chemotherapy (18), with no significant benefit for patients with breast cancer receiving chemotherapy (16, 17, 19, 34) or patients with lung cancer receiving carboplatin chemotherapy (28). Only one study reported that VAE application resulted in significant benefit for physical functioning (19). VAE significantly benefited role functioning in three studies, all of which included patients with breast cancer receiving chemotherapy (16, 17, 19). Four studies observed significant benefit of VAE application regarding emotional functioning, including three with breast cancer patients receiving chemotherapy (16, 17, 19) and one with relapsed osteosarcoma patients post-surgery (30).

Seven studies reported use of VAE during different chemotherapy treatments (16-19, 28-31, 33), of which only one reported that no significant benefit was noted for quality of life (28). Chemotherapy agents included carboplatin based treatments (28), CAF (cyclophosphamide, Adriamycin and 5-FU) (16, 17, 19), CMF (cyclophosphamide, methotrexate, 5-FU)(31), 5-DFUR(18) and “mixed/multiple” types(33).

A 2008 Cochrane review found 14/16 RCTs demonstrated QOL benefit, but only two were of high methodological quality (1). Other systematic reviews show similar results (7, 10, 25, 35, 36). One 2012 meta-analysis (n= 13 studies), reported an estimated overall treatment QOL effect as a standard mean difference of 0.56 (CI: 0.41 to 0.71), indicating a moderate effect. The most recent systematic review (2019) identified 17 randomized controlled studies (both English & German language) with quality of life endpoints (6). Regarding general QOL presented in 11 of the studies, 7 publications showed significant benefit of VAE for the majority of items measured for breast, pancreatic and colorectal cancer patients(6). Study methodology varied extensively, with notable heterogeneity. While the majority of studies ranked low for reporting bias, major methodological concerns in most studies included selection bias, performance bias, attrition bias and the issue of multiple testing (5).

Based on multiple positive outcomes seen across randomized controlled studies and reviews, it is likely that VAE provides some benefit for QOL for patients with cancer. However, due to methodological issues and trial heterogeneity, the exact type and magnitude of benefit warrants further investigation.

Symptom Management

It is likely that at least part of the documented improvements in quality of life is attributable to the effects of mistletoe on managing symptoms, particularly in relation to chemotherapy (33, 37). Evidence from a range of study designs suggests a benefit for VAE treatment in symptom management, although further studies are needed (38).

A randomized controlled study of patients with stage III and IV lung cancer receiving carboplatin based chemotherapy found that VAE reduced the frequency of chemotherapy dose reductions (44% vs 13%, p= 0.005), grade 3-4 non-hematological toxicities (41% vs 16%, p= 0.043) and hospitalisations (54% vs 24%, p=0.016). No benefit was found for hematological toxicities (grade 3-4) (28). An open label study of patients with metastatic treatment-resistant colorectal cancer initiating VAE reported that 40% of participants experienced symptomatic relief of nausea, vomiting, diarrhea, constipation, fatigue and dyspnea (32). One RCT administering VAE during 5-DFUR to patients with early stage gastric cancer reported a significantly lower rate of diarrhea in the intervention group compared to control (p=0.014) (18).

Seven studies implemented the same validated standardized QOL assessment tool (EORTC-QLQ-C30) (16-19, 28, 30, 34). Pain scores significantly improved in four studies (16, 17, 19, 30). Fatigue scores significantly improved in two studies (19, 30). Appetite loss significantly improved in three studies (16, 17, 19). One observational study of 324 patients with stage I-III colorectal cancer receiving either chemotherapy or chemo-radiotherapy, found the addition of VAE significantly improved cancer-related fatigue (p <0.001) (39).

One systematic review included seven studies which assessed chemotherapy-related side effects. Five of seven studies documented significant benefit with VAE (7). Another systematic review published in German included 10 studies that assessed mistletoe in combination with chemotherapy (38) and documents inconsistent results ranging from no effect to positive effects. The most recent systematic review (2019) presents data from seven studies (both English and German language) evaluating the effects of VAE on chemotherapy tolerance and toxicity (6). The review reports that most studies included found some positive effects of VAE pertaining to toxicities and side-effects of chemotherapy (6).

In summary, VAE administration appears to improve symptom burden, side-effects and toxicities associated with treatment when given alongside standard care. In particular, side effects and toxicities which may be improved include nausea, vomiting, diarrhea, appetite loss, pain, fatigue, non-hematological toxicities in general, and need for chemotherapy dose-reductions.

Survival

Six of the clinical trials described in table 1 investigated survival and/or tumor response endpoints in different cancer populations (17, 28-30, 32, 40). The studies evaluated patients with lung cancer (28, 40), breast cancer (17, 40), pancreatic cancer (29, 40), colorectal cancer (32, 40) and relapsed osteosarcoma (30).

From English-language clinical trials (Table 1), survival outcomes are mixed, with two trials reporting a survival benefit (29, 30), two reporting no effect (17, 28) and two studies having no comparison measure to determine effect (32, 40). Several systematic reviews and meta-analyses of mistletoe for survival have been published; all reporting that some, but not all studies, show a survival benefit (1, 5, 7, 35, 36, 41-43). Notably, methodological quality is a concern, and studies with better methodologies are less likely to find a significant benefit.

Regarding the two studies showing a significant survival benefit, one investigated patients with advanced pancreatic cancer (29) and the other patients with relapsed osteosarcoma (30). In a Phase III RCT, 220 patients with stage III or IV pancreatic cancer, receiving standard supportive care were randomized to VAE or control. Median overall survival was 4.8 months in the VAE group and 2.7 months in control ($p < 0.0001$).(29). An RCT of 20 patients with relapsed osteosarcoma (stages I-III) randomized participants to VAE or etoposide after surgery. Post-relapse disease free survival (PRDFS) at 1 year was 55.6% in the VAE group compared to 12% in historical controls, and 27.3% in the etoposide group. Median PRDFS was 39 months (2-73 months) in the VAE group and 4 months (1-47 months) in the etoposide group (30).

A study of patients with stage III and IV non-small-cell lung cancer receiving carboplatin based chemotherapy found no significant benefit of VAE on survival; median OS was 11 months in both groups.(28). A study in patients with non-metastatic breast cancer receiving surgery and adjuvant chemotherapy found no significant disease free survival benefit of VAE (15/56 of VAE participants relapsing compared to 8/29 of controls) (17).

Observational data, while more susceptible to bias than controlled clinical trials, supplements clinical trial findings. A retrospective observational study of 240 patients with advanced stage pancreatic cancer, primarily receiving subcutaneous VAE showed VAE + chemotherapy for >4 weeks significantly improved survival compared to chemotherapy alone (p=0.014). Compared to best supportive care, patients receiving only VAE lived significantly longer (p=0.006) (44). A retrospective study of 158 patients with stage IV NSCLC, primarily receiving subcutaneous VAE, reported that compared to chemotherapy alone, those receiving concomitant VAE had a significantly better median survival (17 months compared to 8 months) (p=0.007) (45) .

The 2008 Cochrane review reported that 6/13 RCTs demonstrated survival benefit of VAE, however, none were of high methodological quality (1). Four studies that were judged as having high methodological quality did not provide any evidence of survival benefit (1). A 2009 meta-analysis (n= 35 controlled trials) (41) used data from studies that compare mistletoe versus no treatment, estimates the overall hazard ratio at 0.59 (CI: 0.53 to 0.66). Using data from studies that compare mistletoe versus other treatments, the meta-analysis demonstrated no effect (HR = 0.95, CI: 0.81 to 1.12, p = 0.56). Funnel plot analysis found a likely publication bias, and the authors noted that the effect of mistletoe was less pronounced when looking only at randomized studies. Thus, results should be interpreted cautiously.

The most recent systematic review (2019) identified 14 randomized controlled studies (both English & German language) assessing survival (5). Five of fourteen studies reported significant benefit for breast cancer, advanced staged glioma, non-metastatic corpus uteri cancer and pancreatic cancer. Nine studies were identified that found no overall survival benefit in patients with breast cancer, colorectal cancer, gynecological cancer, lung cancer and melanoma. It also reported that the majority of studies showed no significant effect for progression free survival, disease specific survival or disease free survival (5). Study methodology varied extensively, with notable heterogeneity observed between trials for cancer type, stage of disease, VAE administration, concomitant treatments and survival measures. The majority of studies ranked low for reporting bias, however, major methodological concerns including selection bias, performance bias, attrition bias and the issue of multiple testing were identified in most studies (5).

Taken together, while both positive and neutral data exists, due to inter-study heterogeneity and notable methodological issues, no conclusive summary can be made regarding the benefit of VAE for cancer survival. However, the research on mistletoe for survival outcomes in pancreatic cancer (29, 44)

and osteosarcoma (30) is compelling. It may be possible that mistletoe could improve disease outcomes given certain clinical scenarios such as type of cancer, stage of disease, and adjunctive treatments. More research is needed to determine this.

Intravenous infusion

Evidence of Clinical Efficacy

Two clinical trials investigated the effects of intravenous VAE administration; one phase I study primarily pertaining to safety (46) and one RCT evaluating survival (47) (Table 2). The phase 1 clinical study investigated escalating doses (200mg-2000mg) of VAE in people with varied advanced cancers, but no concurrent cancer treatment. There were no serious AEs related to the IV VAE. The authors report that 2/21 patients had an unexpected clinical response observed by tumor marker changes and 1/21 had slowed progression (46). The study reporting on survival was a 3-arm RCT (N = 64) of patients with advanced colorectal cancer comparing adjuvant chemotherapy to adjuvant chemotherapy + VAE to surgery without adjuvant treatment (47). Median survival in the VAE group was significantly longer (757 days) compared to both the chemotherapy group (545 days) ($p < 0.05$) and the surgery alone group (502 days) ($p < 0.05$). There were fewer side effects in the VAE group compared to chemotherapy alone group (0% vs 19%).

No prospective intravenous VAE clinical trial was identified with QOL related endpoints for review.

Other routes of administration

VAE has been applied through other routes aside from subcutaneous and intravenous administration including: intravesicular, intratumoral, intrapleural and intraperitoneal applications. The related research is not described in this monograph; however, details for prospective trials for these alternate routes are listed in Table 3, and observational studies in Table 4. Some case reports exist, but are not reviewed in this monograph.

Applications with limited research

Hematological malignancies:

Two case reports and one observational study were identified. One case report describes a 65 year old male with diffuse B-cell lymphoma who received R-CHOP chemotherapy, initially experiencing a minor response. The addition of VAE to chemotherapy, and then continuation of application afterwards, is reported to have resulted in further regression, with the patient in complete remission at time of publication (48). A 2012 case report of two patients with primary cutaneous B-cell lymphoma describes regression of disease (with no conventional treatment provided) with the combined use of high dose IV,

subcutaneous and intra-tumoral VAE administration (49). Authors report that both patients remain in remission 3.5 years after commencement of VAE treatment. A German language retrospective observational study reported that patients with hematological cancers receiving VAE did not differ from the small control group not receiving VAE (50). Although the 205 patients who received VAE had a reported median survival of 11.4 years compared to 8.6 years reported for the 9 control patients, these results were not statistically significant. Authors note that given no evidence of worsening outcomes, future clinical trials are warranted.

Data is very limited regarding both the safety and efficacy of VAE use for hematological cancers at this time, and caution is warranted with its use due to theoretical concerns of immune stimulation in hematological cancers (5, 22).

Children:

Two retrospective studies were identified. One was a retrospective case series of ten children with varied relapsed or advanced cancers treated with IV VAE in which it was deemed safe and feasible, with more research warranted (51). Patients were treated for an average of 48 days; with a maximum dose of 2000 mg, and mean survival was 130 days. Partial remission was seen in four patients, slowed disease progression in two, and progression of disease in two. Fever and fatigue were the most common side effects, with all side effects resolving spontaneously after a treatment break. A retrospective matched-pair analysis of children with medulloblastoma treated with standard care, with or without anthroposophic medicine (including VAE), found no difference in 10-year survival and recurrence between groups. Authors conclude that while treatment appeared to be safe, no survival benefit was found (52). Lastly, in a study of 92 children with recurrent respiratory infections (non-cancer patients) treated with VAE injections twice weekly for 5 weeks, there was evidence of immune response, reduced frequency of infections, and no safety concerns (53). In summary, while available evidence indicates no safety concerns beyond what is known from adult population studies, there is very little specific evidence for the use of VAE in children with cancer.

Adverse Events and Side Effects

VAE administered subcutaneously or intravenously is generally well tolerated (1, 2, 7, 10, 22, 35, 46, 54, 55). Overall, side effects are generally mild and self-limiting. Serious AEs have been documented, but are rare. Certain side effects such as mild fever and local injection-site reactions may be considered desirable by some, as a surrogate marker for physiological response to treatment (22). Side effects of subcutaneous and IV applications differ, and are discussed below.

Subcutaneous injections:

Side effects are fairly common and expected, and are mostly minor, dose-dependent, and self-limiting within a few days of treatment (2, 22, 55). Common side effects include local reactions at the injection

site (e.g., swelling, erythema, local pain, pruritus, induration, warmth), fatigue, mild flu-like symptoms, headache, mild fever, chills, flatulence and loose stools (2, 10, 22, 35). Localized reactions can sometimes appear at former injection sites for pre-exposed patients (2) and dose reductions might be required if reactions are severe (56). The side effect rate for mistletoe injections based on systematic reviews has ranged from 17.5% to 21.5%, with the vast majority being expected local reactions (22, 55). Severe localized reactions (>5 cm diameter) occur in less than 1% of cases (19). One study reported two cases of injection site cellulitis (40).

Reported serious adverse events are rare. They include urticaria and angioedema (33, 35), hypotension and loss of consciousness (57), anaphylaxis (<1%) (22, 57, 58), and severe delayed type hypersensitivity reaction (59).

Common (>5%): local injection-site reactions (e.g. swelling, erythema, pruritus, warmth, and induration).

Rare (<5%): fatigue, fever, chills, headache, flu-like symptoms, diarrhea/flatulence, and severe local reactions.

Rare but serious (1-4%): Angioedema, allergic reactions including anaphylaxis (<1%), hypotension and loss of consciousness, delayed hypersensitivity reaction, cellulitis at injection site.

Intravenous infusions:

A phase I study investigated escalating doses (200-2000mg) in a variety of cancer types (46). The highest dose (2000 mg) was reported to have the same tolerability as the second lowest dose (400 mg). No serious AEs were deemed related to VAE. Twenty of 155 adverse events were related to VAE, and included allergic reaction, fever, weakness, eosinophilia and minor temporary ALT elevation. An observational study evaluated safety of IV VAE in 475 people (54). Twenty-two patients reported 32 ADRs, and none were serious. The most common was fever occurring in 8 people, followed by pruritus in 6. Other less common ADRs included urticaria, inflammation of prior subcutaneous injection sites, vomiting, fatigue, infusion site irritation, myalgia, headache, paraesthesia, and rash. Compared to subcutaneous use, the ADR frequency of IV VAE was significantly lower (4.6% vs 8.4%, $p = 0.005$). Iscador preparation had a higher frequency of ADRs compared with Helixor. Another retrospective observational study evaluated fever reactions in 59 patients receiving a total of 567 IV treatments (60). Forty-five (76%) of patients achieved a fever after at least 1 treatment, no AEs over grade 2 occurred.

Common (>5%): Mild fever

Rare (<5%): Pruritus, weakness, eosinophilia, minor temporary ALT elevation, urticaria, re-inflammation of prior subcutaneous injection sites, vomiting, fatigue, infusion site irritation, myalgia, headache, paraesthesia, rash

Rare but serious (1-4%): Allergic reaction (urticaria, angioedema)

Interactions

Chemotherapy and radiotherapy:

VAE has been studied alongside a variety of chemotherapy agents including carboplatin, gemcitabine, cyclophosphamide, adriamycin, 5FU, methotrexate, and doxorubicin as outlined in Tables 1-4. None of these studies reported a worsening of treatment outcomes for survival, tumor response, or increased toxicity with the addition of VAE. As discussed in the prior sections on efficacy, some studies actually reported better outcomes with the addition of VAE therapy. However, pharmacological studies to evaluate for interactions are lacking (22). A phase 1 pharmacokinetic study of VAE and gemcitabine found the combination was well tolerated, and no botanical/drug interactions were observed (40), but similar studies have not been performed for other chemotherapy agents. In vitro studies corroborate the findings from human studies that have used VAE alongside chemotherapy without any worsening of treatment outcomes or toxicity. A study in 2017 found no induction or major inhibition of nine major cytochrome P450 isoenzymes with Helixor VAE products, making a clinically relevant pharmacokinetic herb-drug interaction unlikely (61).

Although direct pharmacokinetic and pharmacodynamics studies to evaluate for interactions are lacking, the totality of evidence supports the premise that it is unlikely that there is any negative interaction with combined use of these commonly used chemotherapy drugs.

There is no known interaction of VAE with radiation therapy. Some Studies in table 1 and 2 included people receiving radiation therapy without any negative interaction noted.

Immunotherapy and targeted therapies

Due to the immunomodulatory properties of VAE, there has been some concern about the safety of combined use of VAE and immunotherapies and targeted therapies due to a theoretical additive effect. However, available evidence thus far has not demonstrated an increase in toxicity with combined use (62-65).

A multicentre observational trial evaluated the safety of targeted therapies with add-on VAE therapy compared to targeted therapy alone in 310 people (64). Targeted therapies included a variety of monoclonal antibodies (mAbs), immune checkpoint inhibitors (ICIs), and tyrosine kinase inhibitors (TKIs), but the majority of participants were using bevacizumab, rituximab, trastuzumab, or erlotinib. There

was a significantly lower AE rate in the combined group compared to control (20.1% vs 30.2%, p = 0.04) and a lower rate of discontinuation of standard oncology treatment in the combined vs control group (35% vs 60.5%, p =0.03). A pilot study evaluated sixteen patients treated with ICI (Nivolumab, ipilimumab, pemprolizumab), of whom nine were treated with concomitant VAE. There was no statistically significant difference between groups with respect to AEs (67% in ICI plus VA, vs 71% ICI monotherapy) (62). A retrospective study of 56 patients was conducted to evaluate the safety of combined mAb and intravenous Helixor VAE (63). Forty-three patients received combined therapy (defined as mAB and VAE administered on the same day), 12 received VAE therapy alone (no mAb within 1 month of VAE administration), and 8 received mAB therapy alone (no VAE within 1 month of mAb administration) (Seven patients were included in more than one treatment group). Given the small number of people treated only with VAE or mAb, caution in interpretation is warranted. However, the incidence of AEs was highest in the mAB monotherapy group (63%), followed by combined group (56%), and lowest in the VAE monotherapy group (42%). A multivariate analysis found increased odds of experiencing an AE following mAB therapy compared to combined therapy (OR = 4.97, P = 0.008). Rates of serious AEs were similar for combined therapy (2%), mAB therapy (3%), and lower for VAE therapy (0.8%). Lastly, a small study of 15 patients with metastatic lung cancer treated with nivolumab alone (n=7) compared to nivolumab with VAE therapy (n=8) evaluated toxicity rates between groups (65). The toxicity rate in nivolmab-alone group was 71.4% (5/7 participants) compared to 37.5% (3/8) in the combined group.

Given the studies are preliminary and are mostly observational, clinicians should weigh possible risks and benefits with patients considering VAE therapy alongside targeted therapy or immunotherapy.

Other Medications

Because mistletoe has been shown to modulate the immune system (2, 11-13), it should not be used in combination with immunosuppressant medications when the goal of the medication is immune suppression.

Cautions and Contraindications

Mistletoe should not be used by anyone with a known allergy or hypersensitivity to mistletoe. There is insufficient evidence regarding safety of mistletoe during pregnancy and lactation. Mistletoe should be used cautiously in people with autoimmune conditions although this is not a contraindication. Use should be avoided if immune suppressant medication is required to manage the autoimmune condition due to the immune-stimulating properties of mistletoe (2, 11, 12, 66). Given the need for immune suppression, mistletoe should not be used following a recent organ or bone marrow transplant. Mistletoe should be used cautiously in patients with brain tumors or metastases if there is unmanaged cerebral edema due to possible peri-tumoral inflammation with VAE, although evidence of harm from

clinical studies is lacking (5). There are no clinical trials of mistletoe for management of leukemia, however some suggest it should be considered a contraindication until more is known (particularly for acute leukemias), given the possibility of leukocyte stimulation (6, 22).

Concomitant autoimmune conditions:

Given the immunomodulatory properties of mistletoe, it has been theorized that it may exacerbate autoimmune conditions. However, a recent uncontrolled observational study evaluated the safety of VAE therapy (IV, SC, IT) in people with cancer with pre-existing autoimmune conditions and failed to find an increased risk (67). In the cohort of 106 patients treated with VAE extracts, 17 patients (16%) experienced a VAE-related AE which is consistent with expected AE rate of other VAE-treated cancer patients. In a subgroup of 30 patients receiving long-term VAE therapy (>6 months), no exacerbations or flares of underlying AI disease were recorded. The most common AI conditions were Hashimoto's thyroiditis, psoriasis, ulcerative colitis, Grave's disease, and Sjogren's syndrome. There were insufficient patients with Crohn's disease or multiple sclerosis to comment. Observational, uncontrolled studies must always be interpreted with caution. Clinicians are recommended to discuss the theoretical possibility of AI condition flares with mistletoe use and consider the severity of the AI condition. It is recommended to not use mistletoe if the patient is using systemic immune suppressants to manage their condition.

Brain tumors or metastases:

There is no published literature to confirm a safety concern for VAE use in people with brain tumors. Many experts and VAE manufacturers recommend using only in the absence of uncontrolled cerebral edema (5). The reason for the concern is due to the possible risk of peri-tumoral inflammation caused by mistletoe injections or infusions (5).

Acute leukemias:

There is no published literature to demonstrate a safety concern for VAE use in people with acute leukemia. However, some experts recommend caution based on the possibility of VAE stimulating the immune system (5, 22).

Dosing, frequency and length of treatment

Maximum tolerated dose of IV VAE has not been established. In a phase I study, Helixor P (pine) was found to be well tolerated up to the predefined maximum dose of 2000mg, with one dose limiting event occurring at this amount (46). IV mistletoe has been administered from 1-3 times weekly, over a duration of a few weeks to over a year in some observational studies. The optimal dose and length of administration is unknown.

Dose of subcutaneous injections varies based on VAE formulation, cancer stage, cancer type, and patient tolerance. It is typically recommended to use a dose escalation protocol starting with 0.01-1mg injections depending on the product, and increase based on tolerance. In Canada, Helixor (Viscosan) is the most common product; doses range from 0.1mg - 200mg, with administration most often 3 times weekly, and duration of use is most often several months (14, 16, 17, 33, 40). Although most clinical trials of VAE are a few months in duration, mistletoe has been used up to several years in observational studies and case reports, and examined in systematic reviews, without any apparent safety concerns (9, 49, 54, 55, 68, 69).

At the OICC, mistletoe (Helixor) is available as subcutaneous injections or intravenous infusion. Route of administration, maximum dose, and length of use is determined based on cancer type, stage, medical history, and other concurrent treatments. For both IV and subcutaneous use, treatment begins with an induction phase at a lower dose to assess tolerability (1mg for subcutaneous; 50mg for IV), and if well tolerated doses can increase up to 200mg for subcutaneous and 1000mg for IV. The process of informed consent and discussion of patient preferences, which outlines realistic expected benefits, as well as risks and costs is an important aspect of VAE application.

Treatment may be used for a few months to support people during active treatment, and in some instances may be used for one or more years if well-tolerated and positive outcomes are observed.

Table 1: Prospective clinical trials of subcutaneous mistletoe for cancer outcomes and quality of life

Reference	Study Design	Demographics	Intervention	Concomitant Treatment	Endpoints and Measures	Results
Bar-sela et al (2004) (32)	Phase II	**N:** 25 **Ca Type:** Metastatic Colorectal Cancer **Prior Tx:** Chemotherapy (resistant to 5FU/LCV)	**Agent:** Abnoba-viscum Q **Dose:** Target 15 mg **Route:** Subcu **Admin:** Dose escalating, 3 injections a week until toxicity or patient bedridden **Comparison:** None	None	**Time to progression** **Survival** **Toxicity** (CTCAE)	**ii)** No objective tumor response observed **iii)** Stable disease in 21 (84%) of participants and lasted a median of 2.5 months **iv)** Median survival 5.5 months **v)** Symptomatic relief observed in 10 (40%) participants, which included nausea, vomiting, diarrhea, constipation, fatigue and dyspnea **vi)** All AEs deemed mild, included local reaction, 2 participants had mild transient temperature elevation
Piao et al (2004) (33)	Randomized Controlled Open label	**N:** 233 **Ca Type:** Breast, ovarian, NSCLC **Stage:** All	**Agent:** Helixor A **Dose:** 1-200 mg **Route:** Subcu **Amin:** 3 times weekly with dose escalation during chemotherapy **Comparison:** Control group receiving 4 mg Lentinan injection daily	Conventional chemotherapy (mixed type)	**QOL** (FLIC, KPI) **Safety**	**i)** KPI scores was significantly improved in the intervention group compared to control (p=0.002) **ii)** Functional Living Index-Cancer (FLIC) scores were significantly improved in the intervention group compared to control (p=0.0141) **iii)** Fewer AEs in intervention compared to control group (52 events in the intervention group compared to 90 in control) **iv)** One serious AE was noted in the study group: angioedema and urticaria
Semiglasov et al (2004) (34)	Randomized Placebo Controlled Double-Blind	**N=** 272 **Ca Type:** Stage II/III Breast **Prior Tx:** Mastectomy	**Agent:** Lektinol PS76A2 **Dose:** 10 or 30 or 70 ng/ml **Route:** Subcu **Admin:** 2x/week for 15 weeks during chemotherapy **Comparison:** Placebo injection	4 cycles CMF chemotherapy	**QOL** (QLQ C-30, EORTC) **Adverse Events** **Immune markers**	**i)** 15 ng/0.5 ml given twice a week (30 ng/ml total)was found to be the dose which significantly improved QOL **ii)** Significant increase in CD4 and CD4/CD8 ratio was observed (p=<0.05) **iii)** VAE was very well tolerated, with local reaction being the only adverse event related to the intervention
Enesel at al (2005) (20)	Randomized Controlled	**N=** 70 **Ca Type:** mixed gastroesophageal and abdominal cancers (esophageal, gastric, pancreatic, colorectal, ileac)	**Agent:** Isorel A **Dose:** 60 mg/ml **Route:** Subcu **Admin:** Every second day from 2 weeks before to 2 weeks after surgery **Comparison:** Surgery alone	Surgery	**Cellular Immunity** (CD2, CD3, CD19, CD4, CD8, NK) **Humoral Immunity** (IgG, IgA, IgM, complement) **QOL (**KPS)	**i)** Compared to controls, treatment arm had significantly higher: WBC counts before and after surgery ($p < 0.001$), lymphocytes after surgery ($p < 0.001$), complement post-surgery (C3 and C4) ($p < 0.001$), immunoglobulins post-surgery (particularly IgA and IgM), ($p<0.05$), CD4/CD8 ratio before and after surgery ($p<0.05$), and NK cell levels significantly increased overall ($p<0.001$) **vii)** KPS score significantly increased in the intervention group ($p<0.01$) compared to a significant decrease in the control group (p=<0.05)

Bar-sela et al (2006) (70)	Open	**N=** 25 (23 evaluable) **Ca Type:** mixed stage IV cancers, mostly gastrointestinal	**Agent:** Iscador M **Dose:** 10 mg diluted in 10-15 ml saline **Route:** Peritoneal catheter used for drainage (injection) **Admin:** Following abdominal punctures for drainage **Comparison:** Previous drainage parameters	Peritoneal puncture	**Drainage Time Intervals** **Abdominal Circumference** **Drainage Volume** **Symptoms**	**i)** Paracentesis interval was 7 days prior to mistletoe, and extended to 12 days after the first instillation (p=0.001) **ii)** No differences in abdominal circumference, volume drained or symptom scores noted. Transient abdominal pain was noted in one participant for 1 hour which self-resolved. No other AEs were noted during the trial
Troger et al (2009) (19)	Randomized Controlled Open	**N:** 61 **Ca Type:** non-metastatic breast	**Agent:** Iscador M **Dose:** 0.01-5 mg **Route:** Subcu **Admin:** Dose escalating, 3 times/ week during adjuvant chemotherapy **Comparison:** Adjuvant chemotherapy alone	6 cycles CAF chemo	**QOL** (EORTC-QLQ-C30) **Neutropenia**	**i)** Mean differences were significantly better for 12 of the 15 QOL endpoints for the mistletoe group compared to control (range: p= 0.017-<0.001). Clinically relevant changes (5 point differences) were noted for 9 QOL endpoints **ii)** Neutropenia occurred non-significantly less in the intervention group compared to control (p=0.182)
Soo Son et al (2010) (14)	Randomized Controlled Open	**N=** 20 **Ca Type:** Stage I/II breast, finished	**Agent:** Helixor **Dose:** 1-100 mg **Route:** Subcu **Admin:** Dose escalating, 3 injections a week, from 1 mg to 100mg, for a total of 7 weeks beginning 2 weeks after completing cancer treatment (surgery, chemo radiation) **Comparison:** Standard treatment alone	None, VAE was initiated 2 weeks post-treatment completion	**Cytokines** (IL2, IL4, IL6, IL10, TGF-b, IFN-y)	**i)** Concentrations of IL6 and IFN-y significantly increased from baseline after treatment compared to control (p=0.013 and p=0.009, respectively) **ii)** No significant changes from baseline were noted for IL2, IL4, IL10, TGF-b **(NS)**
Kim et al (2012) (18)	Randomized Controlled Open Pilot	**N=** 32 **Ca Type:** Gastric (stage Ib primarily) **Prior Tx:** Surgery	**Agent:** abnobaVISCUM "Q" **Dose:** 0.02 mg- 20 mg **Route:** Subcu **Admin:** Dose escalating, 3 injections per week beginning 7 days after surgery, alongside chemotherapy for 24 weeks. **Comparison:** Standard treatment alone	5-DFUR (chemo)	**QOL** (EORTC QLQ-30, ST022) **Liver Function** **Immune Markers** (TNF-a, Il2, CD16/CD56, CD19	**i)** QOL: Compared to control, the following improved in the mistletoe group: Global health status (p=0.0098), pain: p=0.038, eating restriction: p=0.037 and hair loss: p=0.023. **iii)** Significantly higher WBCs (p=0.0101) and eosinophil counts (p=0.0036) were observed in the intervention group **iv)** No differences were noted for CD16/CD56, CD19 lymphocytes, TNF-a and IL2 **v)** No serious AEs attributed to mistletoe
Bar-Sela, 2013 (71)	Phase II, randomized	**N:** 72 **Ca Type:** NSCLC	**Agent:** Iscador Q **Dose:** 0.01-10 mg	Carboplatin-based combination	**Toxicity** (CTCAE)	**i)** Control group had more chemotherapy dose reductions (44% vs 13% p = 0.005)

		(squamous cell carcinoma and adenocarcinoma) **Stage:** IIIA-IV (majority stage IV) **Prior Tx:** No prior chemo	**Route:** Subcu **Admin:** Dose escalation from 0.01 to 10 mg of mistletoe, given every other day. **Comparison:** Chemotherapy alone **Timing:** Iscador injections began on day 1 of chemotherapy initiation and continued until disease progression	chemotherapy given in 21 day cycles	**Quality of life** (EORTC QLQ-C30 and QLQ-LC13) **Tumor response** (RECIST criteria) **Overall Survival**	**ii)** Treatment group had fewer grade 3-4 non-hematological toxicities (41% vs 16%, p = 0.043), hospitalizations (54% vs 24%, p = 0.016), and rate of peripheral neuropathy (p=0.03) **iv)** No difference in grade 3-4 hematological toxicity or total grade 3-4 toxicity (48% vs 57%, NS) **v)** No difference in primary QoL questionnaires **vii)** mOS in both groups was 11 months **viii)** Median TTP was 4.8 months for control vs. 6 months in iscador (**NS**)
Mansky, 2013 (40)	Phase I Uncontrolled 2 Stage Design	**N:** 44 **Ca Type:** Mixed (colorectal. Breast, pancreatic, lung) **Stage:** IV **Prior Tx:** 10 No prior Tx 34 pre-treated	**Agent:** Helixor A **Dose:** Stage I: Escalating dose 1mg – 250mg Stage II: Dose right below MTD in stage I **Route:** Subcu **Admin:** Stage I: Dose escalation of mistletoe, fixed dose gemcitabine Stage II: Fixed dose mistletoe, escalating gemcitabine	**Stage I:** Gemcitabine dose (750 mg/m^2) IV on day 1 & 8 of a 3-week cycle **Stage II:** Escalating IV gemcitabine (20% increments) dosing	**CT scan** - baseline and every 3 cycles **Adverse Events** (CTCAEv3) **Lab Values** **Clin. Eval.** **MTD & DLT** **Survival** **Clinical Response**	**i)** 112 AEs attributed to mistletoe. Most common: injection site reaction (42 events), localized induration (20 events), grade 1-2 non-neutropenic fever (22 events) and grade 1-2 flu-like symptoms (10 events). 2 grade 3 events - cellulitis at injection site **ii)** MTD was 250 mg for mistletoe **iii)** Mistletoe did not affect gemcitabine pharmacokinetics. Clinical response similar to gemcitabine alone **iv)** 33 completed 3 cycles. 6% achieved partial response, 42% achieved stable disease and 43% progressed (9% not evaluable) **v)** All developed ML-3 IgG antibodies, with higher levels achieved with increasing doses of mistletoe. Cytokines were not affected
Troger, 2013 (29)	Phase III Randomized Controlled Open-Label	**N:** 220 **Ca Type:** Pancreatic Cancer **Stage:** III (n= 121) IV (n= 99) **ECOG** 0-1 (n=112) 2-4 (n= 108) **Prior Tx:** 205 had surgery	**Agent:** Iscador Q **Dose:** Escalating dose (0.01 mg - 10 mg) **Route:** Subcu **Admin:** 3 injections/week up to 12 months **Comparison:** Supportive care only	Standard supportive care only No anti-neoplastic therapies provided	**Overall Survival** **Quality of Life** **Vital Signs** **Performance Status** **Weight** **Medication Use** **Safety** (CTCAE)	**i)** mOS 4.8 months in the intervention group compared to 2.7 months in control (HR: 0.49, 95% CI: 0.36-0.65, p<0.0001) **ii)** No adverse events related to mistletoe, and fewer AEs in tx (17) vs control group (53) **iii)** Frequency and severity of symptoms were significantly lower in the intervention group compared to control for pain (p<0.0001), weight loss (p<0.0001), energy (p<0.0001), nausea/vomiting (p<0.0001), diarrhea (p=0.0033) and anxiety (p=0.046)
Longhi, 2014 (72)	Randomized Controlled Open-Label	**N:** 20 **Ca Type** Relapsed Osteosarcoma **Stage:** 1 stage 1B 14 stage IIA/B	**Agent:** Iscador P **Dose:** Escalating dose (0.01 mg - 20 mg). **Route:** Subcu (abdominal) **Admin:** 3 times a week for 12 months **Comparison:**	None	**PRDFS** **Quality of Life** (EORTC QOL-C30, PedsQL) **Safety**	**i)** 1-year PRDFS was 55.6% in mistletoe arm compared to 12% in historical controls (p=0.0041, 95% CI: 21.2%-86.3%). The rate in the etoposide group was 27.3% compared to 12% historical controls (p=-.2724, 95% CI: 6.0%-61.0%) (**NS)** **ii)** The median PRDFS was 39 months in the mistletoe group (range 2-73 months) and 4 months in the etoposide group (range 1-47 months)

		5 stage III/A/B **Priox Tx:** Prior surgery and chemo, no prior radiotherapy.	Oral etoposide daily for 21d of 28d cycle (total of 6 cycles) (Historical controls were also used to evaluate each treatment arm)		(CTCAE)	**iii)** Compared to baseline, mistletoe therapy significantly improved QOL measures of physical functioning (p=0.046), emotional functioning (p=0.014), social functioning (p=0.003), global health (p=0.013), fatigue (p=0.005), pain (p=0.012), dyspnea (p<0.0001), insomnia (p=0.020) and financial strain (p<0.0001) **iv)** No toxicity was noted for VAE other than minor local erythema after injection and hypotension in one patient
Troger, 2014 (16)	Randomized Open-Label	**N:** 65 **Ca Type:** Non-metastatic Breast **Prior Tx:** Surgery	**Agent:** Helixor A **Dose:** Escalating dose of 1 mg-50mg **Route:** Subcu (abdominal) **Admin:** 3 times a week during 6 cycles of chemotherapy **Comparison:** Chemotherapy alone	Adjuvant chemotherapy (6 cycles CAF)	**Quality of Life** (EORTC QLQ-C30 **Neutropenia** (neutrophil count) **AEs** (CTCAE-v3)	**i)** Compared to control, mistletoe improved QOL from baseline significantly more for role function (p<0.001) emotional function (p<0.001), social function (p<0.05), cognitive function (p<0.01), pain (p<0.001), anorexia (p<0.001), diarrhea (p<0.001), insomnia (p<0.05), nausea/vomiting (p<0.001), and constipation (p<0.05) **ii)** Compared to control, mistletoe did not improve QOL parameters from baseline for global health, physical function, fatigue, dyspnea and financial strain **iii)** No significant change in neutropenia occurrence (p=0.628) **(NS)** **iv)** Overall VAE was well tolerated. Notable adverse events were erythema >5 cm (events). One participants experienced rhinoconjunctivitis and withdrew from the study
Pelzer, 2018 (17)	Randomized Controlled Open-Label	**N=** 95 **Ca Type:** non-metastatic Breast **Prior Tx:** Surgery	**Agent:** Helixor A **or** Iscador M **Dose:** Helixor A: Escalating dose of 1 mg-50 mg **OR** Iscador M: Escalating dose of 0.01 mg, 0.1 mg-5 mg **Route:** Subcu (abdominal) **Admin:** 3 times a week during 6 cycles of chemotherapy. Stopped within 3 weeks of chemo discontinuation **Comparison:** Chemotherapy alone	CAF chemotherapy (6 cycles)	**Temperature** **Neutropenia** **Quality of Life** (EORTC QLQ-C30) **Relapse** (5 year follow-up) **Metastasis** (5 year follow-up)	**i)** 2 fevers observed, neither were long-lasting **ii)** No significant differences in neutropenia between groups (p=0.178) **iii)** Compared to control, mistletoe significantly improved role functioning (p<0.0001), emotional functioning (p=0.0226), pain (p<0.0001) and diarrhea (p=0.0311) **iv)** Compared to control, mistletoe did not significantly differ on global health status, physical functioning, cognitive functioning, social functioning, fatigue, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation and financial difficulties **iiv)** Other than local skin reactions, no AEs were observed for mistletoe therapy **iiv)** 56/65 tx group and 29/31 controls were evaluable for DFS. 15/56 in tx arm developed relapse or metastasis compared to 8/29 controls (p=0.7637). Median DFS could not be calculated

Add; additional**, Admin;** administration, **AE;** adverse event, **Ca;** cancer, **CAF;** cyclophosphamide/doxorubicin (Adriamycin)/fluorouracil, **Chemo;** chemotherapy, **Clin. Eval;** clinical evaluation, **CMF;** cyclophosphamide/methotrexate/fluorouracil, **CTCAE;** common terminology for adverse events, **CT;** computerized tomography, **DFUR;** Docetaxel/epirubicin/doxifluridine, **DLT;** dose limiting toxicities, **EORTC-QLQ-C30;** European Organization for the Research and Treatement of Cancer Quality of Life Questionnaire, **KPI;** key performance indicators, **KPS;** Karnofsky performance status, **LCV;** leucovorin, **ML;** mistletoe lectin, **MTD:** maximum tolerated dose, **N;** number of participants **NR;** not reported, **NS;** non-significant, **NSCLC;** non-small cell lung cancer, **PRDFS;** Post-Relapse-Disease-Free-Survival**, QOL;** quality of life, **Rad;** radiation, **Subcu;** subcutaneous, **Surg;** surgery, **Tx;** treatment, **VAE;** Viscum album extract, **yoa;** years of age, **5-FU;** fluorouracil

Table 2: Prospective clinical trials of intravenous mistletoe for cancer

Reference	Study design	Participants	Intervention	Concomitant treatment	Outcomes and measures	Results
Cazacu et al (2003) (47)	Randomized Controlled Open	**N=** 64 **Ca Type:** Advanced colorectal **Prior Tx:** Surgery	**Agent:** Isorel **Dose:** 5 mg/kg in saline infusion (500 ml) **Route:** intravenous **Admin:** 3 infusions weekly after surgery alongside adjuvant chemotherapy **Comparison groups:** Surgery alone (no adjuvant treatment), surgery + adjuvant chemotherapy	Chemotherapy (5-FU)	**Survival**	**i)** 4 treatment AEs in the surgery + chemotherapy group compared to none in the surgery + chemotherapy + mistletoe group. **ii)** Median survival was significantly better in the mistletoe group compared to the surgery + chemotherapy alone group ($p< 0.05$)
Huber et al, 2017 (46)	Phase I Safety Study	**N=** 21 **Ca Type:** mixed **Stage:** advanced/ metastatic **Prior Tx:** 15 Surgery 14 Chemotherapy 9 Radiotherapy 4 Immunotherapy	**Agent:** Helixor P **Dose:** Phase I dose finding design: 200mg, 400 mg, 700 mg, 1200 mg and 2000 mg **Route:** Intravenous **Admin**: 1 infusion/week for 3 weeks. A 3+3 dose design was implemented until the maximum dose (2000 mg). If the max dose was achieved, it was used for 9 more weeks **Comparison:** Safety of different mistletoe infusion dose	None	**MTD** **DLT** (AE >/= grade 2) **Safety** (CTCAE, physical exam, blood work) **Tolerability**	**i)** 0 drop outs. One DLT occurred 2000 mg dose - generalized urticaria allergic reaction requiring IV anti-histamines **ii)** Tolerability of 2000 mg did not differ from 400 mg **iii)** 6 serious AEs occurred during the study, none attributed to mistletoe. **iv)** 25 AEs were deemed possibly related to the intervention (all occurring at 2000 mg dose). Allergic reaction (1), grade 1 fever (4), weakness (3), eosinophilia (2), and temporary minor ALT elevation (2) **v)** 2 patients had unexpected temporary tumor marker improvement. One patient showed sowed progression.

AE; adverse event **, Admin;** administration, **Adv/mets;** advanced and/or metastatic disease, **ALT;** Alanine-transaminase, **Ca;** cancer, **CTCAE;** common terminology for adverse events, **DLT;** dose limiting toxicity, **MTD;** maximum tolerated dose, , **temp;** temperature, **Tx;** treatment, **WBC;** white blood cell count, **5-FU;** fluorouracil

Table 3: Prospective clinical trials of intratumoral, intravesicular, or intrapleural instillation of mistletoe for cancer

Reference	Study design	Participants	Intervention	Concomitant treatment	Outcomes and measures	Results
Elasser-Beile et al (2005) (73)	Phase I/II	**N=** 30 **Ca Type:** Bladder **Prior Tx:** Transurethral resection	**Agent:** Aqueous mistletoe extract **Dose:** 10-5000 ng/ml **Route:** Intravesicular **Administration:** 6 weekly instillations. Extract retained 2 hours in bladder.	None	**Recurrence** (Cytology, ureterocystoscopy)	**i)** No local or systemic side effects noted **ii)** At 12 month mark, 30% developed recurrence. No clear association between dosage and recurrence rate was found **iii)** Recurrence rate was comparable to historical controls
Gaafar, 2014 (74)	Randomized Controlled	**N=** 23 **Ca Type:** lung (mixed types)	**Agent:** Viscum Fraxini-2 **Dose:** 5 ampoules in 10 cc glucose 5% **Route:** Intrapleural, via chest tube **Administration:** Up to once weekly for 6 weeks if needed until dryness of pleura **Comparison:** Bleomycin (60 units) once intrapleurally	Fluid drainage	**Physical Exam** **Chest Radiography (**Pleural effusion evaluation) **Adverse Event** (CTCAE v4.0)	**i)** Overall clinical response was 61.5% in the mistletoe group and 30% in the bleomycin group (p=0.21) **(NS)** **ii)** Adverse events reported in the mistletoe group included fever, chills, headache, malaise and allergic reaction (requiring discontinuation and steroid injection). No hospitalization was required for any of the adverse events.
Rose et al, 2015 (75)	Phase Ib/IIa	**N:** 36 **Ca Type:** Bladder Cancer **Prior Tx:** Surgery (transurethral resection)	**Agent:** Abnoba viscum Fraxini 2 **Dose:** Range from 45 – 675 mg **Route:** Intravesicular **Administration:** weekly for 6 weeks, dose escalating to find tolerable dose.	None	**Safety** **Recurrence**	**i)** No dose limiting toxicity was found up to 675mg **ii)** A total of 214 AEs were reported, 76 were deemed possibly or probably related to intervention. Most common were local skin reaction, urinary tract infection, and pyrexia. All participants recovered fully **iv)** Based on 30 evaluable patients, at the 12 week mark, 66.7% had no visible "marker" tumor (remnant of tumor purposely left over after surgery to assess intervention) remaining and negative biopsy. Based on 19 evaluable participants, the recurrence rate was 26.3%
Cho et al, 2016 (11)	Open-Label Phase III Single Arm Multicenter	**N=** 62 **Ca Type:** mixed. Large proportion were lung cancer	**Agent:** Abnovaviscum **Dose:** 20 mg **Route:** Direct injection into pleural space **Administration**: After pleural effusion drainage, injection administered with dosing schedule based on newly-generated pleural effusion	Pleural effusion drainage	**Pleural Effusion** **QOL** (KPS score) **Safety**	**i)** Complete pleural effusion response rate 79.0%, compared to historical reference of 64.0% (p <0.0001) **ii)** No significant changes in KPS scores were noted compared to baseline **iii)** 309 AEs occurred. 42 could not be excluded as causal with intervention; most frequent were localized reaction, pyrexia, chills, fatigue and pain. All AEs fully resolved. 2 serious AEs occurred that could not be excluded which included serious pleuritic and pain in one patient

Ca; cancer,**Tx;** treatment,**AE;** adverse event, **CTCAE;** common terminology for adverse events,**KPS;** Karnofsky performance status,**NS;** non-significant,**QOL;** quality of life

Table 4: Observational Research of mistletoe for cancer

Reference & Type	Population	Intervention	Endpoints	Primary Takeaways
Bussing et al (2007) (56) **Prospective Cohort**	Breast, Prostate, Colorectal (n=71)	**Type:** Iscador **Dose:** Slow or rapid escalation from 0.01mg – 20mg **Tx Duration**: Unknown **Follow up:** at least 5 years	Immune Effects	- Swift escalation of dose resulted in more local reactions compared to slow increment increase - No differences were noted between groups regarding body temperature and QOL - No differences between dosing schedules were noted for CD3, CD4, CD8 or CD4/CD8 ratio - Swift escalation group a significant decrease in HLA-DR+ T-Cells compared to a slight increase in the slow escalation group ($p > 0.05$)
Bock et al (2014) (39) **Retrospective**	Colorectal (n=324)	Type: Iscador Q	Cancer Related Fatigue	- Those who received mistletoe in addition to standard care had a cancer-related fatigue rate of 8.8% compared to 60.1% in the control group ($p< 0.001$)
Schad et al (2014) (76) **Retrospective**	Advanced Inoperable Pancreatic Cancer (n=39)	Type: variable Admin: Intratumoral Concomitant tx: chemotherapy	Safety Survival	- No serious intervention-related adverse effects. Increased body temperature was seen in 14% and fever in 11%. - Median survival 11 months (11.8 for stage III and 8.3 month stage IV)
Steele et al (2014) (55) **Retrospective**	Multiple types (n=1923)	Type: Subcu mistletoe, variable	Safety: AEs & ADRs	- 21.5% experienced either an expected effect or an adverse drug reaction - 264 ADRs in 162 patients (8.4%). 42.1% were possibly related, 53.4% were probably related and 4.5% were certain related to mistletoe treatment. - ADRs included: local skin reaction >5cm, >38 C temp, chills, fatigue and malaise. 50.8% of ADRs were classified as mild and 45.1% moderate. - 11 severe ADRs which included 8 patient with temp >40C for less than 24 h, 1 with severe injection site swelling, 1 with general urticaria and 1 with syncope. All patients fully recovered. - No life threatening ADRs occurred - ADRs in general appeared lower with the combination of mistletoe therapy and conventional care - Mistletoe ADR rate increased as dose increased
Steele et al (2014) (54) **Retrospective**	Multiple types (n=475)	Type: Helixor, Abnoba, Iscador Route: IV	Safety: AE's & ADRs	- No serious ADRs occurred - 22 patients reported 32 ADRs (59.4% mild, 40.6% moderate) - Iscador brand showed relative higher frequency of ADRs compared to the other products - Compared to the frequency of ADRs, intravenous mistletoe had significantly less than subcutaneous (4.6% vs 8.4%, $p=0.005$)
Steele et al (2015) (77) **Retrospective**	Multiple types (n=123)	Type: Helixor, Abnoba, Iscucin Route: Intratumoral	Safety: AE's & ADRs	- 26 patients experienced a total of 74 ADRs (21.1%) - Most common ADRs were body temperature increase or immune related effect, of which 83.8% were mild and 14.9% moderate - One possible severe ADR occurred (hypertension) with no serious ADRs occurring - ADR rate was 3x higher than subcu and 5x higher than intravenous application rates
Von Schoen-Angerer (2015) (69) **Retrospective Case-series**	Bladder Cancer (n=8)	Type: Iscucin Route: Subcu	Recurrence	- Median tumor-free duration was 48.5 months. - High dose mistletoe showed possible benefit in 5 of 8 patients, 2 patients could not be assessed and 1 showed uncertain effects of mistletoe. - No tumor progression was observed - No patient stopped treatment due to intolerance/side-effects

Sunjic et al (2015) (68) **Retrospective Case-report series**	Multiple Types (n=74)	Type: Isorel	Clinical Effect	- The addition of mistletoe therapy to conventional care was associated with no major therapeutic improvement in 15% of patients, prevention of tumor recurrence in 47% of patients and regression of cancer in 38% of patients
Axtner et al (2016) (78) **Retrospective**	Advanced Pancreatic Cancer (n=240)	Route: Subcu, IV, intratumoral	Feasibility Survival	- Patients receiving mistletoe in addition to chemotherapy had longer survival compared to those who did chemotherapy alone (12.1 vs 7.3 months)
Schad et al (2017) (79) **Retrospective**	Multiple types (n=1361)	Route: Subcu	Safety: AEs & ADRs (high vs low starting dose)	- Initiation of a high dose was associated with a significantly higher risk of ADR compared to initiation of treatment with low dose (20.7% vs 0.8%, p=<0.001) - No serious ADRs occurred
Schlappi et al (2017) (60) **Retrospective**	Multiple types (n= 59)	Route: IV	Fever (>/= 38.5 C^{o}) Safety (CTCAE v 4.0)	- Out of 59 patients, receiving a total of 567 intravenous infusions, 45 patients (76%) achieved a fever after at least 1 treatment. - Mean temperature increase 1.5 C^{0} +/- 0.8 C^{o} - No AE's over grade 2 occurred. One grade I allergic reaction occurred.
Thronicke et al 2017 (62) **Retrospective**	Stage IIIA/IV lung cancers (n=16)	**Agent:** Varied Abnoviscum Helixor P Iscador Q **Route:** Varied (subcu or IV or both) **Comparison**: 9 who received mistletoe vs 7 who did not	**Response Rate** **AEs** (CTCAE)	**i)** AE frequency rate was 68%, with 11 participants experiencing at least 1 AE **ii)** No grade 3 or 4 AEs occurred **iii)** Most frequent AEs reported were malaise, pyrexia, bronchitis and skin reaction **iv)** The AE rate was non-significantly lower in the mistletoe + immunotherapy group (p >0.99) **v)** Multivariate regression showed no significant association between the combination of mistletoe and immunotherapy for AE rate (OR: 1.467, 95% CI: 0.183-11.693, p=0.720) **vi)** Progressive disease was observed in 71.7% of participants in the immunotherapy alone group, compared to 44.4% in the combined treatment group. Stable disease was observed in 28.6% of participants in the immunotherapy alone group, compared to 22.2% in the combined treatment group. Overall, no statistically significant differences were found between groups.
Fritz, et al (2018) (80) **Retrospective Case-Controlled**	Breast Cancer (n=18, 528)	Route: variable and uncertain	Survival QOL	- Multiple types of mistletoe preparations, doses, administrations, etc. - No survival benefit of mistletoe when added to conventional treatment found. No QOL benefit observed
Schad et al (2018) (45) **Retrospective**	Stage IV NSCLC (n=158)	Route: subcu, IV, intratumoral	Survival	- Median survival for patients receiving mistletoe + chemotherapy was 17.0 months compared to 8.0 months in the chemotherapy group alone (p=0.007) - Overall survival was significantly prolonged in the mistletoe combination group (HR: 0.44, 95% CI: 0.26-0.74, p=0.002) - 1 year survival was 60.2% in mistletoe group compared to 35.5% in the chemotherapy alone group, and 3 year survival was 25.7% in the mistletoe group compared to 14.2% in the chemotherapy alone group.
Hamrin et al (2018) (81)	Breast Cancer (n=52)	*Anthroposophic* care which included mistletoe (Iscador) + conventional care	Immune Response	- Mistletoe group had significantly less CD8 T-cells compared to control (p=0.05), no other immune parameters differed between groups - Anxiety decreased (p=0.04), physical symptoms improved (p=0.05) in the mistletoe group

Prospective				
Schad et al (2018) (63) **Retrospectve**	Multiple Types (stages I-IV) (n=56)	Type: Helixor Route: Intravenous	Safety with monoclonal antibody therapy	- 34 patients experienced 142 adverse events - Rates of serious AEs were similar between groups (2% for mistletoe combination group and 3% for monoclonal antibody alone group) - Highest incidence of AEs occurred in the monoclonal antibody group (63% of patients) compared to the combination mistletoe group (56% of patients)
Thronicke et al (2018) (64) **Retrospective**	Multiple Types (stages 0-IV) (n=310)	Primarily subcu	Safety with targeted therapy	- Mistletoe + targeted therapy, compared to targeted therapy alone, was associated with a significant reduction in overall AE rate (20.1% vs 35%, p=0.04) and a significant reduction in therapy discontinuation rate (30.2% vs 60.5%, p=0.03) - Odds ratio of discontinuation of treatment was 0.30 for the mistletoe + conventional care group (p=0.02)
Lee et al (2019) (82) **Retrospective**	Lung Cancer with Malignant Pleural Effusion (n=52)	Type: Helixor M Route: Intercostal Catheter	Malignant Pleural Effusion Control	- The one month recurrence rate of malignant pleural effusion was 48% - 25% of patients experienced pain associated with treatment - 15% had fever >38 C^{o}
Li Oei et al (2019) (67) **Retrospective**	Multiple Cancer Types & Multiple Auto-Immune Disease (n=106)	Type: Abnoba, Iscador and Helixor Route: Subcu (+/- IV) or IV alone or intratumoral	Safety AEs	- 84% of the study population was reported to have 0 adverse events related to mistletoe - 15% of patients had 1-3 adverse events related to mistletoe and 1 patient experienced 10. - Of the 37 mistletoe related AEs, 20 were expected (local reaction < 5 cm, indurations, local injection site reaction). 17 were considered unexpected - No patient had to stop mistletoe therapy - Subgroup analysis of 30 patients with long-term mistletoe therapy, none experienced a flare up/exacerbation in auto-immune condition.
ADR; adverse drug reaction, **AE;** adverse event, **CTCAE;** common terminology for adverse events, **QOL;** quality of life**, Subcu;** subcutaneous , **Tx;** treatment,				

Disclaimer

The OICC has prepared this monograph, as part of a series of monographs, to share a review of the medical literature related to common therapies and products used within integrative cancer care. The monograph is designed to provide evidence-based research and neither advocates for nor against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published. Prior to using a new therapy or product, always consult a licensed health care provider. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a qualified health care provider.

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