Mistletoe Extracts in Cancer Care

Healthcare Provider Resource

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Developed by:
The Patterson Institute for Integrative Oncology Research
of the Canadian College of Naturopathic Medicine

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General information

Proper name:
Viscum album Loranthaecea, *Viscum album L.*

Common names:
Mistletoe, European Mistletoe, Viscum album extracts (VAE)

Routes of administration:
Subcutaneous (SC), intravenous (IV), intramuscular, intrapleural, intratumoral, and intravesical instillation. This monograph will focus on the two most common routes: SC and IV.

Commercially available products:
Helixor®, Iscador®, abnobaVISCUM® (Isorel®, Lektinol®, Eurixor® are no longer available)

Common uses in cancer care:
Mistletoe extracts are commonly used to enhance immune function, support quality of life, reduce cancer-related side effects and symptoms, slow disease progression, reduce risk of recurrence, and improve survival.

Summary

Viscum album extracts (VAE) are used in integrative cancer care to support immune function, reduce side effects, improve quality of life (QOL), and possibly improve survival and recurrence. The most common routes of administration are subcutaneous (SC) injection and intravenous (IV) infusion; most research pertains to SC 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), dendritic cells, cytokines including INF-gamma and IL6, and presence of IgG antibodies to mistletoe lectins and viscotoxins have been observed. SC 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 SC use), fatigue, and mild fever are common. Studies in people with cancer have found that mistletoe is likely to support QOL, reduce 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 QOL and side effect management, but more research is needed from well controlled studies to further elucidate its impact on survival and recurrence risk for people with cancer.

Background

Preparations from European Mistletoe are used as complementary treatment for people with cancer, most notably in Germany.[1] Mistletoe, a parasitic plant from the Santalacea family, is commonly prepared as an extract and is commercially available from several manufacturers. The extracts contain various compounds which vary slightly based on host tree, harvest time and preparation method. Available products are often 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 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] This monograph primarily discusses the subcutaneous and intravenous routes of administration, which are most often used in North America. Throughout this summary, mistletoe will be referred to as VAE (*Viscum album* extract) or mistletoe.

Methods

Monographs are created by the Patterson Institute for Integrative Oncology Research team and are updated approximately every two years. Comprehensive and structured literature searches were performed in Medline and Cochrane library from inception for English-language studies in people with cancer. The most recent search was completed on November 20, 2023. Additional scoping reviews were performed by research staff to obtain supporting information such as background information, mechanism of action, and safety data. Articles are duplicate-screened, data is extracted into standardized spreadsheets, and studies summarized.

Pharmacokinetics

Pharmacokinetic data on VAE is limited. A phase I study evaluated the pharmacokinetics of VAE by administering a single SC injection of abnobaVISCUM Fraxini (20 mg) to 15 healthy male volunteers.[5] Mistletoe lectins were detected in all serum samples after injection, with mean and median peak concentrations reached 1 and 2 hours after injection, respectively. Concentration-time profiles varied considerably, indicating non-linear kinetics, and thus half-life could not be determined.[5] 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 been studied. In vitro research has found no cytochrome P450 induction capacity of VAE, and no inhibition over 50% when concentrations equivalent to 100,000 times the clinically relevant dose in plasma were used. Thus, the authors concluded that herb-drug interactions due to P450 interactions were unlikely.[6]

Mechanism of Action

Active compounds of VAE include mistletoe lectins (ML) (I, II and III), viscotoxin (VT) proteins, flavonoids, phenylpropanoids, triterpenes, phytosterol, alkaloids, polyalcohols, and polysaccharides.[7] Lectins and viscotoxins have been studied the most.[2,8] Different VAE formulas contain varied 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.[9] 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), dendritic cells, cytokines and interleukins (including IFN-g, TNF-a, IL-1, IL-4, IL-5, IL-6), and IgG antibodies.[2,10-12]

Randomized trials in healthy volunteers indicate that SC VAE stimulates both innate and adaptive immune responses.[9,13,14] One study randomized 43 healthy volunteers to SC 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).[9] 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), Viscum 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.[13] 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.[14] 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.[15] In a study of 98 women with breast cancer having surgery, a single infusion of 1mg Iscador M one-hour prior to anesthesia prevented the surgical suppression of granulocyte function when compared to the control group.[16] 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 (the most abundant granulocyte) count as there was no change compared to controls.[17-20] Details of these four studies can be found in Table 1.

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.[21] The treatment group had significantly less immunosuppressive effects from surgery compared to controls, with 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, showing that perioperative infusion of VAE prevented NK suppression 24h post-surgery in the mistletoe group.[22]

Lastly, VAE may exert effects on dendritic cells (DCs). VAE stimulates both the maturation and the activity of DCs and counteracts the immunosuppressive effect of tumour cells on DCs as evident from in vitro and in vivo studies.[10-12] Several other studies presented in tables 1-3 provide additional information on the immune effects of VAE administration.

Cytotoxic activity

Mistletoe lectins, viscotoxins and alkaloids are believed to be responsible for mistletoe's cytotoxic activity.[23] 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.[23-25] 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.[23]

Other actions

Mistletoe may attenuate markers of inflammation, which may result in improved fatigue, as demonstrated by one study in women with early-stage breast cancer.[26]

Clinical Evidence Related to Effectiveness

There are 14 clinical trials (18 publications) for SC VAE in cancer (Table 1), 3 clinical trials for IV VAE in cancer (Table 2), 8 studies using other routes of VAE administration (Table 3), and 27 observational studies (Table 4) identified from the literature search. These studies are discussed below based on administration route and outcomes assessed. The most up to date systematic reviews and meta-analyses are also discussed, as in many cases they contain data from studies not meeting our inclusion criteria (e.g. German-language, or journals not indexed by Medline or Cochrane), and thus provide additional information.

Subcutaneous injections

There are a diverse number of human studies using SC VAE injections, though they vary in quality and design. There are 14 clinical trials described in 18 publications (Table 1), as well as several observational studies (Table 4). Overall, VAE appears to likely benefit immune function, QOL, and reduce disease and treatment-related symptoms. Results are mixed regarding tumour response and survival. Variance in survival studies may be attributed to differences in VAE preparations, dosing, cancer types, administration schedules and study design. Several systematic reviews report methodological concerns within published clinical trials.[8,27-31]

Quality of Life

Of the 14 subcutaneous VAE clinical trials identified, 12 investigated endpoints related to QOL, side-effects and/or toxicity of cancer treatments.[17-21,32-38]. Eleven were randomised controlled trials,[17-21,32-35,37,38] only one of which was placebo-controlled.[35] Five studies included patients with breast cancer,[17,18,20,35,37] four studied patients with pancreatic cancer,[21,33,38,39] two each with colorectal cancer,[21,36] lung cancer,[32,37] and gastric cancer,[19,21] and one each with relapsed osteosarcoma,[34] esophageal cancer, [21] and ovarian cancer.[37]

The majority of studies report that VAE improves QOL endpoints observed across different cancer types, conventional treatments, and stages of disease. Only one study reported that VAE did not improve QOL but did reduce treatment related toxicity,[32] Most studies report mixed QOL benefit, with some endpoints significantly improving while others did not. While VAE appears to consistently improve aspects of QOL, predictions of which specific endpoints will be improved vary between patients. Due to methodological issues and trial heterogeneity, the exact type and magnitude of benefit warrants further investigation.

Nine studies used the same validated standardized QOL assessment tool (EORTC QLQ-C30),[17-20,32-34,40,41] allowing for inter-study QOL endpoint comparison. VAE significantly improved global health in relapsed osteosarcoma patients,[34] gastric cancer patients receiving chemotherapy,[19] advanced pancreatic cancer patients receiving supportive care,[41] breast cancer patients receiving chemotherapy.[17,18,20,40,42] In one study, no benefit was seen in QOL for patients with lung cancer receiving carboplatin chemotherapy.[32] Two studies reported that VAE application resulted in significant benefit for physical functioning.[20,38] VAE significantly benefited role functioning in four studies, three of which included patients with breast cancer receiving chemotherapy,[17,18,20] and one which evaluated patients with advanced pancreatic cancer.[41] Five studies observed significant benefit of VAE application for emotional functioning, including three for breast cancer patients receiving chemotherapy,[17,18,20] one with relapsed osteosarcoma patients post-surgery,[34] and one in advanced pancreatic cancer receiving best supportive care.[38] Lastly, social and cognitive function were significantly improved compared to controls in a study of patients with advanced pancreatic cancer.[38]

Ten studies reported use of VAE during different chemotherapy treatments,[17-20,32-34,37,40,42] of which only one reported that no significant benefit was noted for QOL.[32] Chemotherapy agents included carboplatin based treatments,[32] cyclophosphamide, doxorubicin plus 5-Fluorouracil (5FU),[17,18,20] cyclophosphamide, methotrexate, and 5-FU, [40,42] doxifluridine (5-DFUR), [19] and "mixed/multiple" types.[37]

A systematic review and meta-analysis published in 2020 of VAE for QOL in patients with cancer, [43] included 25 RCTs and 5 clinical trials. Compared to control groups, the post-treatment standardized mean difference in global QoL was d = 0.61 (95% CI 0.41-0.81, $p < 0.00001$), indicating a medium-sized, clinically meaningful effect favoring mistletoe. Studies included various types of cancer, conventional treatments, and brands of subcutaneous mistletoe preparations. There was a high risk of bias due to lack of blinding and heterogeneity across studies. Other systematic reviews show similar results,[1,8,29,30,44-47] with one exception which concluded no benefit from mistletoe.[28]

Symptom management and treatment toxicity

It is likely that at least part of the documented improvements in QOL is attributable to the effects of mistletoe on managing symptoms and toxicities, particularly in relation to chemotherapy.[37,48] Evidence from a range of studies suggests a benefit for VAE treatment in symptom management and chemotherapy toxicity. Side effects and toxicities which may be improved include nausea, vomiting, diarrhea, appetite loss, pain, fatigue, weight loss, non-hematological toxicities in general, and need for chemotherapy dose-reductions. Further research from high quality studies is needed, as methodological quality continues to be a concern.

A randomized controlled study of patients with stage III and IV lung cancer receiving carboplatin-based chemotherapy found that VAE decreased 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).[32] No benefit was found for hematological toxicities (grade 3-4). 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.[36] 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).[19]

Several specific symptoms have been improved with the use of VAE in clinical trials. Pain scores significantly improved in five studies (published in 6 reports) [17,18,20,34,39,41] and failed to improve in three,[49-51] all of which used the EORTC QLQ-C30 for QOL assessment. Appetite loss significantly improved in four studies. [17,18,20,41] Finally, insomnia and weight loss improved with the use of VAE compared to a control group in patients with advanced pancreatic cancer,[41] in this study weight increased by 5.3% in the VAE arm compared to a 3.2 % weight loss in the control arm.

Cancer-related fatigue (CRF) has been assessed in three clinical trials,[20,34,41] one observational study,[52] and two recent systematic reviews with meta-analysis.[55,56] The systematic reviews reported different findings. The first evaluated different modalities, either pharmacological or nonpharmacological, one of which was VAE. Three RCTs that used SC VAE injections were included.[55] There was no significant reduction of CRF with VAE injections. A random effects model treatment effect of −0.76 (−2.00, 0.48), P = 0.33 was calculated. The second systematic review and meta-analysis included 12 RCTs and 7 non-randomized studies, half of which included breast cancer patients.[56] The meta-analysis included 1494 participants from the 12 RCTs and 2668 from the 7 non-randomized trials. Heterogeneity between the studies was high, and most studies had a high risk of bias. A random-effects model revealed for RCTs, a standardized mean difference of – 0.48 (95% CI – 0.82 to – 0.14; P = 0.006), and for non-randomized trials, an odds ratio of 0.36 (95% CI 0.20 to 0.66; P = 0.0008). This was deemed to cause a moderate beneficial effect on CRF using VAE. One possible mechanism by which VAE may improve cancer-related fatigue is by attenuating markers of inflammation.[26]

The 2020 systematic review discussed previously[43] included a meta-analysis on QOL subdomains including specific symptoms across 10 studies. The standardized mean difference (SMD) of VAE compared to control in seven of 14 QOL dimensions were statistically significant in favor of mistletoe ($p < 0.05$). Although all symptoms improved with VAE, only nausea and vomiting, pain, dyspnea and diarrhea met statistical significance (fatigue, insomnia, appetite loss and constipation did not). One systematic review included seven studies which specifically assessed chemotherapy-related side effects. Five of seven studies documented significant benefit with VAE.[30] Another systematic review published in German included 10 studies that assessed mistletoe in combination with chemotherapy,[53] and documents inconsistent results ranging from no effect to positive effects. Other systematic reviews have found similar findings regarding chemotherapy toxicity.[28]

Survival and tumor response

Six of the clinical trials described in table 1 investigated survival and/or tumor response endpoints in different cancer populations.[18,32-34,36,54] The studies evaluated patients with lung cancer,[32,54] breast cancer,[18,54] pancreatic cancer,[33,54] colorectal cancer, [36,54] and relapsed osteosarcoma.[34,55] Several observational studies and systematic reviews have also been published and are briefly described.

From English-language clinical trials (Table 1), survival outcomes are mixed, with two trials and a long-term follow-up on one reporting a survival benefit,[33,34,55] two reporting no effect,[18,32] and two studies having no comparator to determine effect.[36,54] 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 [1,27,30,31,44,45,56-58]. Notably, methodological quality is a concern, and studies with better methodologies were less likely to find a significant benefit.

The two studies showing a significant survival benefit investigated patients with advanced pancreatic cancer [33] and relapsed osteosarcoma,[34] which published long-term follow up results in 2020.[55] 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 and 2.7 months in the VAE and control groups, respectively ($p < 0.0001$).[33] An RCT of 20 patients with relapsed osteosarcoma (stages I-III) randomized participants to VAE or etoposide after surgery.[34] 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.[34] A 2020 follow-up on this RCT assessed PRDFS 144 months later. The median PRDFS was 106 months and 7 months, in the VAE and etoposide groups, respectively. The 10-year overall survival (OS) rates were estimated to be 64% in the VAE arm and 33% in the etoposide arm.[55]

The two studies that did not show a survival benefit from the use of mistletoe included a study of patients with stage III and IV non-small-cell lung cancer receiving carboplatin based chemotherapy,[32] and a study in patients with non-metastatic breast cancer receiving surgery and adjuvant chemotherapy.[18]

Several observational studies have reported benefit with VAE, including two retrospective studies in pancreatic cancer. The first was a study of 240 patients with advanced-stage pancreatic cancer. The study found that the combination of VAE and chemotherapy significantly improved survival compared to chemotherapy alone (12.1 vs 7.3 months, $p = 0.014$). In patients not receiving chemotherapy but receiving supportive care only, patients receiving VAE lived significantly longer (5.4 vs 2.5 months, $P = 0.006$).[59] The second study was a retrospective analysis of patients with advanced or metastatic pancreatic cancer who received either palliative chemotherapy alone or with additional VAE and/ or hyperthermia. [60] Survival time for chemotherapy alone was 8.6 months (95% CI 4.7–15.4), for chemotherapy and VAE was 11.2 months (95% CI 7.1–14.2, $P = 0.02$, in comparison to chemotherapy alone), and for a combination of chemotherapy with VAE and hyperthermia was 18.9 months (95% CI 15.2–24.5, $P < 0.001$, in comparison to chemotherapy alone).

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) ($P = 0.007$).[61] A retrospective cohort study looked at the use of SC VAE alongside neoadjuvant chemoradiotherapy pre-operatively, in patients with stage II-III rectal adenocarcinoma.[62] In the mistletoe group ($n = 15$) compared to the control group ($n = 37$) there were significantly better outcomes for pathologic complete response rate (53.5% vs 21.6%, $P = 0.044$), tumor regression grade (66.7% vs 32.4%, $P = 0.024$), T downstaging (86.7% vs 43.2%, $P = 0.004$), overall TNM downstaging (86.7% vs 56.8%, $P = 0.040$), and presence of lymphovascular invasion (13.3% vs 32.4%, $P = 0.04$).

Several systematic reviews and meta-analysis have evaluated VAE for cancer survival; only the most recent reviews will be discussed. A systematic review and meta-analysis from 2020 included 32 controlled trials (13, 745 patients) reporting on survival from studies on Iscador (fermented VAE) published from 1963-2014.[31] The overall survival hazard ratio (HR) was 0.59 (95% CI 0.53 to 0.65, $P < 0.0001$), favouring Iscador treatment. None of the studies were blinded, and funnel plot analysis found a moderate performance bias, thus, results should be interpreted with caution. On subgroup analysis, hazard ratios for survival were statistically significantly in favor of Iscardor in breast, cervical, colorectal, liver metastases, uterine, ovarian, pancreatic, and stomach cancer, and not significantly improved in lung, osteosarcoma, or skin cancer.

Similarly, a systematic review and meta-analysis was published in 2022 which evaluated only non-fermented

VAE (Helixor and Eurixor) on survival in different cancer populations (about half were breast and colorectal cancer patients).[63] Eleven RCTs and eight non-randomized studies were included. The pooled effect estimate of non-fermented VAE on survival was HR 0.81 (95% CI 0.69-0.95, P = 0.01) with corresponding heterogeneity of I^2 = 0%. For non-randomized studies the pooled effect size was HR 0.63 (95% CI 0.4-1.01, P = 0.05), and the heterogeneity was I^2 = 89%. When active comparators were included in the analysis, the effect estimates became non-significant, with HR 0.90 (95% CI 0.71-1.25, P = 0.68), for RCTs and HR 0.68 (95% CI 0.45-1.03, P = 0.07), for non-randomized trials.

Finally, the most recent systematic review to evaluate all types of subcutaneous mistletoe was published in 2019.[27] Fourteen randomized controlled trials were included, and 5/14 studies found significant benefit for survival in breast cancer, advanced stage glioma, non-metastatic uterine cancer and pancreatic cancer. Nine studies found no overall survival benefit in patients with breast cancer, colorectal cancer, gynecological cancer, lung cancer and melanoma. Most studies found no significant effect for progression free survival, disease specific survival or disease-free survival. Similar to findings of other reviews, study methodology varied extensively. While most studies ranked low for reporting bias, major methodological concerns including selection bias, performance bias, attrition bias and the issue of multiple testing were identified in most studies.

In addition to the above-mentioned data, there are many case reports and case series that have been published. These are not reported in this monograph given the availability of higher quality evidence. However, in areas where research is limited (as in subsequent sections), case reports have been included given the paucity of data.

In summary, while both positive and neutral data exists, due to inter-study heterogeneity and methodological issues, no conclusive statement can be made regarding the benefit of VAE for cancer survival. However, the research on mistletoe for survival outcomes in pancreatic cancer [33,59,60] and osteosarcoma [34,55] is compelling. More research is needed.

Other outcomes

Cost analysis was evaluated in one systematic review including three observational studies.[46] For comparative cost analysis from Germany, there were lower medical costs within five years after surgery for patients with VAE than those without VAE (4,504 euros versus 9,996 euros, respectively).

Intravenous infusion

Three clinical trials investigated the effects of intravenous VAE administration; two phase I [64,65] and one RCT [66] (Table 2).

The RCT was a 3-arm trial of 64 patients with advanced colorectal cancer which compared adjuvant chemotherapy, adjuvant chemotherapy + VAE, and surgery without adjuvant treatment for survival outcomes.[66] Median survival in the adjuvant VAE group was significantly longer (757 days) compared to both the chemotherapy alone 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%).

One phase I study, included 21 patients with progressing solid tumors (about one-third had colorectal cancer) after multiple lines of systemic treatments.[65] Patients received escalating doses (150, 300, 600, and 900 mg) of IV Helixor M 3 times weekly. Objective responses were not detected; however, five patients achieved stable disease, and in 3 patients, reductions in baseline target lesions were detected. Furthermore, assessment of serum tumor markers (cancer antigen-125 and carcinoembryonic antigen) revealed a slower rate of increase at higher doses of VAE. The median OS was 10.1 months (95% CI 3.5 months – not reached), the median PFS was 46 days (95% CI 44 – 48 days), and the disease control rate (complete/partial response and

stable disease) was 23.8%. The median QoL measured by Functional Assessment of Cancer Therapy scale was improved from 79.7 at week 1 to 93 at week 4, then slightly decreased to 89 at the end of treatment. The authors commented that IV VAE demonstrated manageable toxicities with disease control and improved QoL in a heavily pretreated solid tumor population.

The second phase 1 clinical study investigated escalating doses (200 mg to 2000 mg) 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 positive clinical response observed by tumor marker changes and 1/21 had slowed progression.[64]

Mixed routes of administration

Five observational studies and one systematic review with meta-analysis combined data on patients administered VAE using different routes of administration, commonly SC, IV, and intratumoral. Of the observational studies, three included NSCLC patients, one included pancreatic cancer patients, and the fifth looked at patients with breast cancer.[67-71] The pancreatic and NSCLC studies used mistletoe (either SC, IV, intratumoral or combined) plus standard oncologic treatment, and found survival outcomes favoring the combined approach which were also cost-effective compared to standard oncologic treatment alone.[67,68] The second study among NSCLC patients yielded non-significant overall survival benefits, however, subgroup analysis revealed that patients with unresected tumours were more likely to benefit.[69] The third study was among lung cancer patients (mainly NSCLC), where 68% were stage III and IV.[71] Compared to patients who received no radiation or VAE, patients who received VAE had improvements in several EORTC scales including role functioning (P = 0.03), physical functioning (P = 0.02), cognitive functioning (P = 0.04), and social functioning (P = 0.04) at a 1-year follow-up. Another observational study in women with breast cancer was identified through our search, but due to methodological limitations it will not be discussed as it does not add meaningful information to our understanding of mistletoe.[70]

A systematic review and meta-analysis was conducted to evaluate the safety and efficacy of VAE, administered by various routes, during the oncological perioperative period. The study revealed preliminary but encouraging data for VAE usage, particularly in the context of the immune system in colorectal cancer; however, survival results were inconsistent. Seven RCTs (comprising 663 participants; five of which used SC route, one each used IV and intravesical routes) and three non-RCT studies were included. More than half of the RCTs applied VAE postoperatively. VAE was used as adjunctive care and compared to no further treatment in 5 RCTs, while in two RCTs, VAE was compared against standard cancer treatment. Meta-analyses found no evidence for a difference between VAE and no added therapy for mortality and recurrence including metastasis (RR = 1.00, 95% CI 0.79 – 1.27; and RR = 1.03, 95% CI 0.79–1.33, respectively). Two RCTs reported positive effects of VAE on immune cells (natural killer cells), and one RCT reported quality of life improvement, both were among colorectal cancer patients. However, the evidence found is tempered by the small number of studies, different outcomes evaluated, and methodological limitations, as quality appraisal revealed a substantial risk of bias.

Four case reports described outcomes for patients treated with both IV and SC mistletoe. Two cases showed long-term disease-free survival in patients with stage IV renal cell carcinoma. In one, VAE was used alongside chemoimmunotherapy,[72] and in the other VAE was applied as monotherapy.[73] One case report described a patient with relapsing hepatocellular carcinoma who received IV VAE in conjunction with IV L-ornithine L-aspartate (LOLA) but without any active oncological treatment.[74]The patient sustained a complete remission for three and half years. The fourth case report was in a patient with dedifferentiated high-grade liposarcoma in the retroperitoneum who survived 10.5 years with good QOL with conventional treatments in addition to IV and SC VAE.[75]

Other routes of administration (excluding IV and SC)

VAE has been applied by 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, some details for these alternate routes in studies are listed in Table 3.

Applications with limited research

Hematological malignancies

Two case reports and one observational study were identified for VAE in hematological malignancies. One case report describes a 65-year-old male with diffuse B-cell lymphoma who received R-CHOP chemotherapy, initially experiencing a minor response.[76] The addition of VAE to chemotherapy, and then continuation of application afterwards resulted in further regression, with the patient in complete remission at the time of publication. A second case report on two patients with primary cutaneous B-cell lymphoma describes regression of disease (no conventional treatment provided) with the combined use of high dose IV, subcutaneous and intra-tumoral VAE administration.[77] Authors report that both patients were in remission 3.5 years after commencement of VAE treatment. A German language retrospective observational study reported that patients with a hematological malignancy (types not specified) who received VAE (n = 205) had a median survival of 11.4 years compared to 8.6 years from the controls used (n = 9), these results were not statistically significant.[78] There were no cases where mistletoe was associated with deterioration.

Pediatric use

Two retrospective studies were identified related to pediatric application of mistletoe. One was a retrospective case series of ten children with varied relapsed or advanced cancers treated with IV VAE.[79] 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, progression of disease in two, and data was unavailable for two. Fever and fatigue were the most common side effects, with all side effects resolving after a treatment break. In the second study, a retrospective analysis was completed of matched-pairs for children with medulloblastoma treated with standard care, with or without anthroposophic medicine (including VAE). The study found no difference in 10-year survival nor recurrence between the groups. The authors concluded that while treatment appeared to be safe, there was no survival benefit to be seen.[80] Although not related to cancer but relevant from a safety perspective, mistletoe has also been used in children for other conditions, such as respiratory infections.[81] While the evidence for benefit is thin in a pediatric cancer setting, available evidence indicates no safety concerns beyond what is known from adult populations. Given the potential for impact and low toxicity, selective use of mistletoe in a pediatric setting may be warranted.

Adverse Events and Side Effects

VAE administered subcutaneously or intravenously is typically well tolerated.[1,2,8,23,30,44,64,82,83] 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 treatmen.[23] Side effects of subcutaneous and IV applications differ and are discussed below.

Subcutaneous injections

Side effects are common and expected, and mostly minor, dose-dependent, and self-limiting within a few days of treatment.[2,23,75,83] 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.[2,8,23,44] Localized reactions can sometimes appear at former injection sites for pre-exposed patients, [2] and dose reductions might be

required if reactions are severe.[84] 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.[46,84] More intense local skin reactions (> 5 cm diameter) occur in less than 1% of cases, [20] and are typically avoidable if a moderately progressive dosing approach is applied. One systematic review reported on treatment discontinuations due to adverse events from two RCTs. In these two studies, rates of discontinuation due to grade 3/4 toxicities ranged from 5-15%.[47]

Reported serious adverse events are rare. They include urticaria and angioedema,[37,44] hypotension and loss of consciousness,[85] anaphylaxis (< 1%),[23,85,86] and severe delayed type hypersensitivity reaction.[87]

Adverse reactions as reported in clinical trials and observational studies are reported below.

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, anorexia, depressive mood, 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

Data from two clinical trials and two observational studies of IV mistletoe indicate that IV mistletoe is generally safe and well tolerated.[64,65,82,88] No serious adverse reactions have been reported. Fever and chills are the most common adverse reactions; however, the incidence has varied substantially between studies, ranging from 1.7% to 76%.[64,65,82,88] This likely has to do with the dose and type of VAE (host tree and fermentation status), as for example Iscador (fermented) VAE has been reported to elicit greater adverse reactions than unfermented forms.[82,88] Fatigue and nausea are the next most common adverse reactions reported. One large observational study reported that compared to subcutaneous use, the adverse reaction frequency of IV VAE was significantly lower (4.6% vs 8.4%, P = 0.005) mostly accounted for by the expected adverse skin reactions from SC injections.[89]

Adverse reactions as reported in the five studies previously mentioned are summarized below.

Common (>5%): Mild fever and related symptoms (headache, shivering, chills), nausea, fatigue.

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 with cancer treatments

Chemotherapy and radiotherapy

VAE has been studied alongside a variety of chemotherapy agents including carboplatin, gemcitabine, cyclophosphamide, 5-fluorouracil, 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 reported better outcomes with the addition of VAE therapy. However, pharmacological studies to evaluate for interactions are lacking.[23] A phase 1 pharmacokinetic study of VAE and gemcitabine found the combination was well tolerated, and no botanical/drug interactions were observed,[54] but similar studies have not been performed for other chemotherapy agents. In vitro research corroborates 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.[90]

Although direct pharmacokinetic and pharmacodynamic studies evaluating interactions are lacking, the totality of evidence supports the premise that it is unlikely that there is any negative interaction with combined use with cytotoxic chemotherapy.

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 interactions 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, and in fact has generally reported lower rates of adverse effects with combined use.[91-96]

Several observational studies assessed the safety of VAE (IV or SC) alongside targeted therapies including monoclonal antibodies (mAB), immune checkpoint inhibitors (ICIs), CDK 4/6 inhibitors (CDKi), and tyrosine kinase inhibitors (TKIs). The first included 242 patients with breast and gynecological cancer receiving targeted therapies with or without Helixor primarily administered SC.[96] Targeted therapies included mAB (79.8%), CDKi (10.7%), and ICIs (5.4%). Add-on VAE did not negatively alter targeted therapies' safety profile ($\chi 2 = 0.107$, P = 0.99). No adverse events were reported, and a trend toward improved adherence to targeted therapy usage was observed in the combination group. The second study included 310 patients receiving a variety of mAbs, ICIs, and TKIs (primarily bevacizumab, rituximab, trastuzumab, or erlotinib).[93] 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). Thirdly, a small pilot study evaluated sixteen patients treated with ICI (Nivolumab, ipilimumab, pemprolizumab), of whom nine were treated with concomitant VAE.[91] There was no statistically significant difference between groups with respect to AEs (67% in ICI plus VAE, vs 71% ICI monotherapy).

A fourth study included 43 patients who received combined mAB and VAE treatment, 12 who received VAE only, and 8 who received mAB only.[92] The incidence of AEs was highest in the mAB monotherapy group (63%), followed by combined group (56%), then 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%). Finally, a small study of 15 patients with metastatic lung cancer treated with nivolumab alone (n = 7) compared to nivolumab with VAE therapy (n = 8) found a lower toxicity rate with combined treatment compared to nivolumab alone (37.5% vs 71.4%). [94]

An interim analysis of an ongoing prospective cohort study in patients with NSCLC was published as a conference abstract. In an interim sample size of 20 the authors reported no clinically relevant increase in AEs due to VAE.[95]

Finally, a case report of a patient with metastatic clear cell renal cell carcinoma in the lung demonstrated no adverse effects from the combination of chemoimmunotherapy (interferon-α2a, interleukin-2, fluorouracil, isotretinoin) and mistletoe treatment administered both IV and SC.[72]

Other treatments

VAE injections were combined with radiofrequency ablation (RFA) in a case report with encouraging

results.[97] As noted below, when immunosuppressive treatments are applied, mistletoe use should be avoided.

Interactions with other medications:

Warfarin:

A case report describing a possible interaction between warfarin and VAE was published.[98] The patient was treated with warfarin for atrial fibrillation, and upon initiating nab-paclitaxel and gemcitabine chemotherapy he experienced melena and an INR of 7.3. The patient revealed that he used SC injections of VAE. The authors hypothesized that VAE may inhibit cytochrome P450 (CYP) isoforms;1A2, 2C9, and 3A4, which metabolize warfarin. Additionally, nab-paclitaxel may interact with warfarin and thus the combination of both may have been involved. However, other research has indicated that VAE is not an inhibitor or inducer of major CYP P450 isoforms,[99] thus what contribution VAE made in this scenario is unclear.

Cautions and Contraindications

Mistletoe should not be used by anyone with a known allergy or hypersensitivity to mistletoe. There is insufficient evidence regarding the safety of mistletoe during pregnancy and lactation. Mistletoe should be used cautiously in people with autoimmune (AI) conditions although this is not a contraindication. Use should be avoided if immune suppressant medication is required to manage the AI condition due to the immune-stimulating properties of mistletoe.[2,9,13,100] 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.[27] There is no clinical data or case reports using mistletoe for management of acute leukemias, however some suggest it should be considered a contraindication until more is known, given the possibility of leukocyte stimulation.[23,28] Although data from peer-reviewed sources is absent, there is some concern among practitioners about the use of fermented mistletoe products intravenously. The concern is that fermented products may increase the risk of allergic reactions, thus many clinicians use fresh unfermented aqueous extracts for IV use. There is an ongoing phase I clinical trial of IV fermented Iscador which should help to clarify whether there is any reason for concern.[101]

Autoimmune conditions

Given the immunomodulatory properties of mistletoe, it has been theorized that it may exacerbate AI conditions. However, an uncontrolled observational study evaluated the safety of VAE therapy (IV, SC, IT) in people with cancer with pre-existing AI conditions and failed to find an increased risk.[102] 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. 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

Many experts and VAE manufacturers recommend only using VAE in the absence of uncontrolled cerebral edema.[27]. The reason is due to the possible risk of peri-tumoral inflammation caused by mistletoe injections or infusions.[27] There is no published data to confirm or refute this recommendation.

Acute leukemias

There is no published literature to demonstrate or refute 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.[23,27]

Dosing, frequency and length of treatment

The maximum tolerated dose of IV VAE has not been established. In a phase I study, Helixor P (pine) was well tolerated up to the predefined maximum dose of 2000 mg, with one dose limiting event occurring at this dose.[64] Another phase I study concluded that the MTD of IV Helixor M was 600 mg. 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.

The 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. Helixor (or aqueous mistletoe extract) is a common formulation used; doses range from 0.1mg – 400 mg, with administration most often 3 times weekly, and duration of use is most often several months.[15,17,18,37,54] 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 without any apparent safety concerns.[7,48,72,77,82,83,97,103-105] In addition, long term usage of combined IV and SC VAE has been reported in case reports.[73,75]

Disclaimer

This monograph provides a summary of available evidence 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.

Table 1: Clinical trials of subcutaneous (SC) mistletoe for cancer

Reference	Study Design	Demographics	Intervention	Concomitant Treatment	Endpoints and Measures	Results
Longhi et al (2020) [55]	See Longhi, 2014 [34]				**PRDFS** (long-term follow up)	**i)**The mistletoe arm saw a median PRDFS of 106 months compared to 7 months in the etoposide arm (HR 0.287, 95% CI 0.076-0.884, P = 0.03). 5 of 9 patients never relapsed in the VAE arm, compared to the etoposide group in which all patients relapsed. **ii)**Through a model, the estimated 10-year overall survival rates were 64% and 33% in the mistletoe and etoposide arms, respectively (statistical significance not calculated).
Reif et al (2019) [39]	See Troger, 2013 [33] (post-hoc analysis)				**Pain** (EORTC QLQ-C30) and consumption of analgesics	**i)**Patients in the control group received more potent and frequent analgesics than those in the VAE group (OR 0.005, 95%CI0.001- 0.014). **ii)** Post-baseline pain EORTC QLQ-C30 scores were lower in the VAE arm than in the control arm: mean OR 0.013, 95%CI 0.006- 0.028). **iii)** investigators reported lower pain levels in VAE group (mean OR 0.034, 95%CI 0.009-0.123) than in the control group.
Reif M et al (2019) [26]	See Troger et al (2009) (re-analysis of data for additional outcomes). *Only the abstract was available				**Correlation between Cancer related fatigue (CRF)** (EORTC QLQ-C30) and **immunological inflammatory markers**	**i)** Absolute T4, monocyte, and absolute NK cell counts, and absolute T8 cell counts were correlated with CRF with statistical significance ($P \leq 0.05$) or tendency ($0.05 < P < 0.1$). in the control arm. However, these correlations in the Iscador M arm were weaker and not significant. May indicate that VAE attenuates inflammatory immune response which contributes to effect on CRF.
Pelzer et al (2018) [18]	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:** SC **Admin:**	CAF chemotherapy (6 cycles)	**Temperature** **Neutropenia** **Quality of Life** (EORTC QLQ-C30) **Relapse** (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 affect global health status, physical functioning, cognitive functioning, social

			3X/ week during 6 cycles of chemotherapy. Stopped within 3 weeks of chemo discontinuation **Comparison:** chemotherapy alone		**Metastasis** (5 year follow-up)	functioning, fatigue, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation and financial difficulties. **v)** Other than local skin reactions, no AEs were observed for mistletoe therapy. **vi)** 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 = 0.76). Median DFS could not be calculated.
Longhi et al (2014) [34]	Randomized Controlled Open-Label	**N:** 20 **Ca Type** Relapsed Osteosarcoma **Stage:** 1 stage 1B 14 stage IIA/B 5 stage III/A/B **Priox Tx:** Prior surgery and chemo, no prior radiotherapy.	**Agent:** Iscador P **Dose:** escalating dose (0.01 mg - 20 mg). **Route:** SC **Admin:** 3X/week for 12 months **Comparison:** oral etoposide daily for 21d of 28d cycle (total of 6 cycles) (historical controls were also used to evaluate each treatment arm)	None	**1-year PRDFS (primary)** **Quality of Life** (EORTC QOL-C30, PedsQL) **Safety** (CTCAE)	**i)** 1-year PRDFS was 55.6% in mistletoe arm compared to 12% in historical controls (P = 0.004, 95% CI 21.2%-86.3%). The rate in the etoposide group was 27.3% compared to 12% in historical controls (p = 0.272, 95% CI 6.0%-61.0%). **ii)** The median PRDFS at the time of analysis was 39 months in the mistletoe group (range 2-73 months) and 4 months in the etoposide group (range 1-47 months), no statistical analysis applied, however the follow up was ongoing. **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 et al (2014) [38]	See Troger 2013 [33] (Data from 96 patients in the mistletoe group and 72 patients in the control group).				**QOL and symptoms** (EORTC QLQ-C30) **Body weight**	Compared to control, Iscador Q: **i)** Had improved global health and functional scales. **ii)** Improved symptom scale in 6 out of 9, including pain (95% CI −29 to –17), fatigue (95% CI –36.1 to –25.0), appetite loss (95% CI −51 to −36.7), and insomnia (95% CI –45.8 to –28.6). **iii)** increased body weight (5.3% increase vs 3.2% decrease, P < 0.001).
Troger et al (2014) [17]	Randomized Open-Label	**N:** 65 **Ca Type:** Non-metastatic Breast **Prior Tx:**	**Agent:** Helixor A **Dose:** escalating dose of 1 mg-50mg **Route:** SC	Adjuvant chemotherapy (6 cycles CAF)	**Quality of Life** (EORTC QLQ-C30) **Neutropenia**	**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),

		Surgery	**Admin:** 3X/week during 6 cycles of chemotherapy **Comparison:** chemotherapy alone		(neutrophil count) **AEs** (CTCAE-v3)	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). **iv)** Overall, VAE was well tolerated. The only notable adverse events were erythema >5 cm (42 events, 2.7% of injections), and. one participant experienced rhinoconjunctivitis and withdrew from the study.
Bar-Sela, (2013)[32]	Phase II, randomized	**N:** 72 **Ca Type:** NSCLC (squamous cell carcinoma and adenocarcinoma) **Stage:** IIIA-IV (majority stage IV) **Prior Tx:** No prior chemo	**Agent:** Iscador Q **Dose:** 0.01-10 mg **Route:** SC **Admin:** dose escalation from 0.01 to 10 mg of mistletoe, given every other day **Comparison:** chemotherapy alone	Carboplatin-based combination chemotherapy given in 21-day cycles	**Toxicity** (CTCAE) **Quality of life** (EORTC QLQ-C30 and QLQ-LC13) **Tumor response** (RECIST criteria) **Overall Survival**	**i)** Control group had more chemotherapy dose reductions (44% vs 13% P = 0.005). **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 et al (2013)[54]	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:** SC **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 et al (2013) [33]	Phase III Randomized Controlled Open-Label	**N:** 220 **Ca Type:** Pancreatic Cancer **Stage:** III (n= 121) IV (n= 99) **ECOG** 1 (n=112) 2-4 (n=108) **Prior Tx:** 205 had surgery	**Agent:** Iscador Q **Dose:** escalating dose (0.01 mg - 10 mg) **Route:** SC **Admin:** 3X/week up to 12 months **Comparison:** supportive care only	Standard supportive care only No anti-neoplastic therapies provided	**Overall Survival** **QOL** **Vital Signs** **Performance Status** **Weight** **Medication Use** **Safety** (CTCAE)	**i)** mOS was 4.8 months in the intervention group compared to 2.7 months in control group (HR 0.49, 95% CI 0.36-0.65, P < 0.0001). **ii)** No adverse events related to mistletoe, and fewer AEs in treatment vs control group (17 vs 53 respectively) **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).
Kim et al (2012) [19]	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:** SC **Admin:** dose escalating, 3X/week beginning 7 days after surgery, for 24 weeks. **Comparison:** standard treatment alone	5-DFUR (chemo)	**QOL** (EORTC QLQ-C30, 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). **ii)** Significantly higher WBCs (P = 0.0101) and eosinophil counts (P = 0.0036) were observed in the intervention group. **iii)** No differences were noted for CD16/CD56, CD19 lymphocytes, TNF-a and IL2. **iv)** No serious AEs attributed to mistletoe.
Soo Son et al (2010) [14]	Randomized Controlled Open	**N: 20** **Ca Type:** Stage I/II breast, post-treatment	**Agent:** Helixor **Dose:** 1-100 mg **Route:** SC **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 SC 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.
Troger et al (2009) [20]	Randomized Controlled Open	**N:** 61 **Ca Type:** non-metastatic breast	**Agent:** Iscador M **Dose:** 0.01-5 mg **Route:** SC **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 in the mistletoe group compared to control (range: p = 0.017 to P < 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).

Semiglazov et al (2006) [42]	Randomized Placebo Controlled Double-Blind	**N:** 352 **Ca Type:** Breast, stage II/III	**Agent:** Lektinol **(**PS76A2, an aqueous mistletoe extract) **Dose:** 15 ng mistletoe lectin/0.5 ml **Route:** SC **Admin:** 2x/week for 4-6 cycles of chemotherapy **Comparison:** placebo injection	4-6 cycles of CMF chemotherapy (cyclophosphamide, methotrexate, fluorouracil)	**QOL** (FACT-G, GLQ-8, Spitzer's uniscale) **Safety** (Adverse events)	**i**) FACT-G total score increased by 4.40 ± 11.28 in ME group and decreased by 5.11 ± 11.77 in placebo ($p < 0.0001$). **ii**) GLQ-5 sub-score was significantly better (lower) in ME compared to control group (42.9 ± 125.0 vs 60.3 ± 94.0 $P < 0.0001$), GLQ3 score worsened in both groups but more in placebo group than ME group ($P = 0.0007$). **iii**) Spitzer's uniscale improved in ME group compared to placebo (12.2 ± 30.7 vs 10.8 ± 26.1 $Pp < 0.0001$). **iv**) Well tolerated, local reactions occurred in 17.6% of participants.
Enesel at al (2005) [21]	Randomized Controlled	**N:** 70 **Ca Type:** mixed gastroesophageal and abdominal cancers (esophageal, gastric, pancreatic, colorectal, ileac)	**Agent:** Isorel A **Dose:** 60 mg/ml **Route:** SC **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 ($p < 0.001$). **ii)** KPS score significantly increased in the intervention group ($p < 0.01$) compared to a significant decrease in the control group ($p \leq 0.05$).
Bar-sela et al (2004) [36]	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:** SC **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 which lasted a median of 2.5 months. **iv)** Median survival 5.5 months. **v)** Symptomatic relief observed in 10 (40%) of participants for: 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) [37]	Randomized Controlled Open label	**N:** 233 **Ca Type:** Breast, ovarian, NSCLC **Stage:** All	**Agent:** Helixor A **Dose:** 1-200 mg **Route:** SC **Amin:**	Conventional chemotherapy (mixed type)	**QOL** (FLIC, KPI) **Safety**	**i)** KPI scores significantly improved in the intervention group compared to control ($p = 0.002$). **ii)** Functional Living Index-Cancer (FLIC) scores significantly improved in the intervention group compared to control ($P = 0.0141$).

			3 times weekly with dose escalation during chemotherapy **Comparison:** control group receiving 4 mg Lentinan injection daily			**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 VAE group: angioedema and urticaria.
Semiglasov et al (2004) [40]	Randomized Placebo Controlled Double-Blind	**N:** 272 **Ca Type:** Breast, stage II/III **Prior Tx:** Mastectomy	**Agent:** Lektinol **(**PS76A2, an aqueous mistletoe extract) **Dose:** 10 or 30 or 70 ng/ml **Route:** SC **Admin:** 2x/week for 15 weeks during chemotherapy **Comparison:** placebo injection	4 cycles CMF chemotherapy (cyclophosphamide, methotrexate, fluorouracil)	**QOL** (EORTC QLQ-C30) **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 for VAE group in CD4 count 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.

Add; additional**, Admin;** administration, **AE;** adverse event, **Ca;** cancer, **CAF;** cyclophosphamide/doxorubicin (Adriamycin)/fluorouracil, **Chemo;** chemotherapy, **Clin. Eval;** clinical evaluation, **CMF;** cyclophosphamide/methotrexate/fluorouracil, CRF;cancer related fatigue; **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 Treatment of Cancer Quality of Life Questionnaire, **KPI;** key performance indicators, **KPS;** Karnofsky performance status, **LCV;** leucovorin, **ME;** Mistletoe extract, **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, **SC;** subcutaneous, **Surg;** surgery, **Tx;** treatment, **VAE;** Viscum album extract, **yoa;** years of age, **5-FU;** fluorouracil

Table 2: Clinical trials of intravenous mistletoe for cancer

Reference	Study design	Participants	Intervention	Concomitant treatment	Outcomes and measures	Results
Paller et al (2023) [65]	Phase I Safety Study	**N:** 21 **Ca Type:** mixed (about 1/3 were colorectal) **Stage:** advanced and progressing **Prior Tx:** multiple lines of systemic treatments	**Agent:** Helixor M **Dose:** Escalating doses (150, 300, 600, and 900 mg) **Route:** Intravenous **Admin**: 3x weeks until DLTs, disease progression, or intercurrent illnesses were observed **Comparison:** Phase 1 internal comparison – Safety of different mistletoe infusion doses	None	**Safety** (revised CTCAE version 4.03, clinical, blood work and imaging studies) **MTD** **Phase II recommended dose** **QoL** (FACTG) **Efficacy** Imaging and tumor marker kinetics	**i)** Objective responses were not detected. **ii)** Serum Ca125 and CEA revealed a slower rate of increase at higher dose levels of VAE. iii) The median OS was 10.1 months (95% CI 3.5 months- not reached), the median PFS was 46 days (95% CI 44–48 days), and the DCR (percentage of complete/partial response and stable disease) was 23.8%. **iv)** The median QoL improved from 79.7 at week 1 to 93 at week 4. **v)** The MTD was 600 mg, and one patient discontinued treatment within this dose level due to treatment-related fatigue. **vi**) AEs occurred in 13 patients (61.9%), with the most reported being fatigue (28.6%), nausea (9.5%), and chills (9.5%). **vii)** Most AEs (76.9%) were grade 1, with grade 3 events noted in 14.8% of patients. No grade 4 or 5 treatment-related AEs were reported. viii) Three patients discontinued treatment because of DLTs across all doses.
Huber et al, (2017) [64]	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 weekly for 3 weeks. A 3+3 dose design was implemented until the maximum dose (2000 mg). If the max dose was achieved, it was applied for 9 more weeks **Comparison:** Phase 1 internal comparison – Safety of different mistletoe infusion doses	None	**MTD** **DLT** (AE >/= grade 2) **Safety** (CTCAE, physical exam, blood work) **Tolerability**	**i)** Tolerability of 2000 mg did not differ from 400 mg. **ii)** 6 serious AEs occurred during the study, none attributed to mistletoe. **iii)** 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). **iv)** 2 patients had unexpected temporary tumor marker improvement. One patient had a slowed progression. v) 0 drop outs. One DLT occurred at the 2000 mg dose – generalized urticaria allergic reaction requiring IV anti-histamines.

Cazacu et al (2003) [66]	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)** Median survival was significantly better in the mistletoe group compared to the surgery + chemotherapy alone group ($p < 0.05$). **ii** 4 treatment AEs in the surgery + chemotherapy group compared to none in the surgery + chemotherapy + mistletoe group.

AE; adverse event **, Admin;** administration, **Adv/mets;** advanced and/or metastatic disease, **ALT;** Alanine-transaminase, **Ca;** cancer, **CA 125**; cancer antigen 125, **CEA**; Carcinoembryonic antigen, **CTCAE;** common terminology for adverse events, **DCR**; disease control rate, **DLT;** dose limiting toxicity, FACTG; Functional Assessment of Cancer Therapy-General, **MTD;** maximum tolerated dose, **OS**; overall survival, **PFS;** progression free survival**, QoL;** quality of life, **temp;** temperature, **Tx;** treatment, **WBC;** white blood cell count, **5-FU;** fluorouracil

Table 3: Clinical trials or observational studies of intratumoral, intravesicular, intrapleural, or transcatheter mistletoe

Reference	Study design	Participants	Intervention	Concomitant treatment	Outcomes and measures	Results
Han et al (2023) [106]	Retrospective	**N**: 137 **Ca type**: 52% were primary lung cancer **Stage**: with malignant pleural effusion	**Agent**: ABNOVA viscum **Route**: VATS surgical procedure or bedside procedure using chest tube (pleurodesis) **Dose**: 20-mg ampules were mixed with 50 mL of normal saline **Administration**: 1-5 treatments as needed (every other day for repeat instillations) **Comparison:** Talc (large particle) pleurodesis through VATS	Drainage catheter/ chest tube	**Clinical responses** **Disease progression** **Safety**	**i)** The tube insertion duration and the total drainage amount in both Viscum groups were more effective than in the talc group $P \leq 0.001$. **ii)** The success rate was not significantly different among the V. album surgical procedures (91.7%), V. album bedside procedures (83.6%), and talc surgical procedures (91.2%), $P = 0.680$. **iii)**The bedside Viscum group showed significantly lower post-pleurodesis pain scores than the other two groups, $P = 0.012$ **iv)** The authors reported that Viscum pleurodesis showed safer outcomes in ensuring quality of life than talc
Galun et al, (2019) [107]	Conference abstract: Prospective cohort analysis	**N:** 107 **Ca Type:** non-resectable hepatocellular carcinoma	**Agent**: Iscador Qu **Dose**: unknown **Route**: hepatocellular transcatheter **Administration**: unknown	Lipitol and cisplatin	**Survival time**	**i)** A significantly better median survival time was found in the mistletoe group who received Iscador Qu in addition to standard treatment, compared to the control group, at 430 and 246 days, respectively (HR 0.36; 95% CI 95% 0.23-0.57). ii) Participants in the mistletoe group who developed a fever had a slightly better survival time than those who did not, though the difference was not statistically significant.
Lee et al (2019) [108]	Retrospective	**N**: 52 **Ca type**: Lung Cancer **Stage**: With malignant pleural effusion	**Agent**: Helixor M **Route**: Pleural Catheter (pleurodesis) **Dose**: 100mg, if ineffective the dose increased by 100mg each instillation **Administration**: 1-5 treatments as needed (every other day for repeat instillations) **Comparison:** None	Drainage catheter	**Malignant pleural effusion control** **Safety**	**i)** The one month recurrence rate of malignant pleural effusion was 48%. **ii)** 25% of patients experienced pain related to the procedure and 15% had fever > 38 C^{o}.
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	Pleural effusion drainage	**Pleural Effusion** **QOL** (KPS score)	**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.

			Administration: after pleural effusion drainage, injection administered with dosing schedule based on newly-generated pleural effusion		**Safety**	**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.
Rose et al, (2015) [109]	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%.
Gaafar, (2014) [110]	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, however the difference was not significant (P = 0.21). **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.
Bar-sela et al (2006) [111]	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.
Elsasser-Beile et al (2005) [112]	Phase I/II	**N:** 30 **Ca Type:** Bladder **Prior Tx:** Transurethral resection	**Agent:** aqueous mistletoe extract **Dose:** 10-5000 ng/ml **Route:** intravesicular **Administration:**	None	**Recurrence** (Cytology, ureterocystoscopy)	**i)** No local or systemic side effects noted. **ii)** At the 12-month mark, 30% developed recurrence. No clear association between dosage and recurrence rate was found. **iii)** Recurrence rate was comparable to historical controls.

			6 weekly instillations. Extract retained 2 hours in bladder.			

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

Table 4: Observational research of subcutaneous or IV mistletoe for cancer

Reference	Study design	Participants	Intervention	Concomitant Tx	Endpoints and Measures	Results
Hohneck et al (2023) [60]	Retrospective	**N:** 206 **Ca type:** advanced or metastatic pancreatic cancer, not candidates for curative treatment	**Agent:** unspecified V **Dose:** not reported **Route:** SC **Administration:** 2 to 3 times weekly. The median treatment duration for VAE was 41 days (range: 8.0 - 213). **Comparison:** palliative chemotherapy and/or hyperthermia	Palliative chemotherapy and/or hyperthermia	Survival time	**i)** Survival times: chemotherapy alone 8.6 months (CI 4.7–15.4), chemotherapy and only VAE 11.2 months (95% CI 7.1–14.2) P = 0.02, or chemotherapy with VAE and hyperthermia 18.9 months (95% CI 15.2–24.5) P < 0.001.
Schad et al (2023) [71]	A real-world data using registry data	**N**: 112 **Ca type**: primary Lung cancer (all stages, 68% stage III & IV, 92% were NSCLC)	**Agent:** unspecified **Dose:** not reported **Route:** SC (92%), IV (66%), Intra tumoral (3%) **Administration:** not reported **Comparison**: combination of radiation and VAE	Neither radiation therapy nor VAE, or radiation therapy alone	QOL (EORTC QLQ-C30)	At 12 months: **i)** Significant improvement in pain (p = 0.006) and nausea/vomiting (P = 0.005) of 27 points and 17 points, respectively, in patients who received combined radiation and VAE versus no treatment (no comparison was made to the group who received radiation alone). . **ii)** Significant improvements of 15 - 21 points for the role (P = 0.03), physical (P = 0.02), cognitive (P = 0.04), and social functioning (P = 0.04) observed in patients who received VAE but no radiation therapy compared to those who received no VAE or radiation.
Schad et al (2022) [96]	Real-world demographic and treatment data collection	**N**: 242 **Ca type**: all stages of breast and gynecological (mainly ovarian cancer)	**Agent:** Helixor® **Dose:** at the physician's discretion **Route:** SC or IV off label in selected cases **Administration:** not reported **Comparison**: Targeted therapy without VAE	Targeted therapies (79.8% monoclonal antibodies, mAB)	Safety	**i)** The addition of Helixor® does not negatively alter targeted therapies' safety profile in breast and gynecological cancer patients ($\chi 2 = 0.107$, P = 0.99) **ii)** No adverse events were reported, **iii)** A trend toward improved adherence to targeted therapy usage was observed in the combination group.
Baek et al (2021) [62]	Retrospective	**N**: 52 **Ca type**: rectal adenocarcinoma **Stage**: II-III	**Agent:** Abnoba Viscum Q **Dose:** dose escalation every 3 weeks from 0.02mg to 20mg **Route:** SC **Administration**: 3X/week for 3 weeks **Comparison**: neoadjuvant chemoradiotherapy alone	Neoadjuvant chemoradiotherapy	Tumor response	**i)** Tumor response was significantly better in the VAE group compared to the no-VAE group, meeting statistical significance in pCR rate (53.5% vs 21.6%, P = 0.044), tumor regression grade (66.7% vs 32.4%, P = 0.024), T downstaging (86.7% vs 43.2%, P = 0.004), overall TNM downstaging (86.7% vs 56.8%, P = 0.040). **ii)** Lymphovascular invasion was more common in the no VAE group (32.4% vs 13.3%, P = 0.04). **iii)** No significant differences seen in adverse effects, with the most common toxicity in both groups being stage 1 proctitis.

Oei et al (2020) [70]	Retrospective	**N**: 319 **Ca type**: Breast cancer **Stage**: Non-metastatic	**Agent:** AbnobaViscum, Helixor, Iscador, and Iscucin **Dose:** Not reported **Route:** SC and IV **Administration:** Either alone or with chemotherapy. Duration ≥ 4 weeks **Comparison**: Chemotherapy alone, mistletoe alone, combined therapy, or no mistletoe or chemotherapy (control – this group could receive endocrine therapy/immunotherapy)	All patients offered standard oncology therapies	Internal coherence (marker of resilience, optimism, sense of control) (ICS questionnaire) Cancer-related fatigue (EORTC QLQ C30) QOL (EORTC QLQ C30)	**i)** Patients receiving VAE but no chemotherapy experienced significant beneficial effects on thermo-coherence ($p < 0.05$), affective fatigue ($p < 0.05$), and seven EORTC subscales at 24 months (all $p < 0.05$). Note these changes are within-group, not between group comparisons. **ii)** Chemo-, immuno- and endocrine therapies had a 17-, 17- and 6-point decline, respectively, for EORTC fatigue ($P = 0.0004$), whereas the VAE group improved 12 points. **iii)** VAE group improved in insomnia and physical functioning scores while these scores worsened in conventional care groups ($p = 0.009$ and $p = 0.005$, respectively). **iv)** Caution is advised when reviewing these results given the possibility of selective reporting and questionable statistical analysis. Additionally, note that most positive results were for the VAE-only group not VAE + chemotherapy.
Thronicke et al (2020) [69]	Retrospective	**N**: 275 **Ca type**: NSCLC patients **Stage**: I -IIIA	**Agent:** Abnobaviscum, Helixor, and Iscador **Dose:** **Route:** SC route or by off-label IV administration (52.6% of patients) **Administration:** duration for ≥ 4 weeks **Comparison**: Standard oncological treatment alone	Standard oncological treatment	Overall survival (OS)	**i)** There was no significant difference in OS between the VAE + standard care and standard care alone groups.
Thronicke et al (2020) [68]	Retrospective	**N**: 118 **Ca Type**: NSCLC **Stage**: IV	**Agent:** Abnobaviscum, Helixor, and Iscador **Dose:** Not reported **Route:** Mainly SC (20 and 2 patients also received IV and intratumoral, respectively) **Administration:** Duration for ≥ 4 weeks **Comparison**: Chemotherapy alone	chemotherapy	Cost-effectiveness (CE) of VAE Overall survival (OS)	**i)** VAE + standard care group had longer age-adjusted mean overall survival (OS) than standard care alone group (19.1 months versus 13.4 months, respectively). No statistical analysis was applied to determine significance. **ii)** Compared to the control group, patients in the VAE group had a lower cost per mean months OS. No statistical analysis was applied to determine significance.
Thronicke et al (2020) [67]	Retrospective	**N**: 88 **Ca type**: pancreatic cancer **Stage:** IV	**Agent:** Abnobaviscum, Helixor, and Iscador **Dose:** Not reported **Route:** Mainly SC. IV and intratumoral was performed in individual cases **Administration:** Duration for ≥ 4 weeks **Comparison**: Standard care alone	Standard of care	Cost-effectiveness of VAE Overall survival (OS)	**i)** Median OS was 2.8 months longer in mistletoe group compared to standard care alone ($p = 0.008$), mean OS was 3.5 months longer in the mistletoe group (no P value provided). **ii)** The addition of the VAE to standard treatment resulted in 1.16 days and 1.43 days longer for mean hospital stays and mean hospitalization length however the results were not statistically significant ($P > 0.05$). **iii)** Costs per mean month of OS and per mean hospital stay were lower for VAE + standard care compared to standard treatment, however, there was no statistical analysis for this outcome.

Oei et al (2019) [102]	Retrospective	**N**: 106 **Ca type**: Multiple Cancer Types & Multiple Auto-Immune Diseases **Stage**:0-IV (most were early stages)	**Agent:** Abnoba, Iscador and Helixor **Dose:** varied, escalating **Route:** SC (+/- IV) or IV alone or intratumoral **Administration:** SC, 2 or 3 times per week. For IV, the dose and administration were varied **Comparison:** None	Most received chemotherapy with IV applications	Safety AEs	**i)** 84% of the study population reported 0 adverse events related to mistletoe. **ii)** 15% of patients had 1-3 adverse events related to mistletoe and 1 patient experienced 10. **iii)** Of the 37 mistletoe related AEs, 20 were expected (local reaction < 5 cm, indurations, local injection site reaction). 17 were considered unexpected. **iv)** No patient had to stop mistletoe therapy. **v)** In a subgroup analysis of 30 patients with long-term mistletoe therapy, none experienced a flare up/exacerbation of their auto-immune condition.
Hamrin et al (2018) [113]	Prospective	**N**: 52 **Ca type**: Breast Cancer **Stage**: Not specified	**Agent:** Not reported **Dose:** Not reported **Route:** Not reported **Administration:** For at least 2 weeks **Comparison**: Conventional care alone	Conventional care	Immune Response	**i)** Mistletoe group had significantly less CD8 T-cells compared to control (P = 0.05), no other immune parameters differed between groups. **ii)** Anxiety decreased (P = 0.04), physical symptoms improved (P = 0.05) in the mistletoe group.
Fritz, et al (2018) [114]	Retrospective Case-Controlled	**N**: 18,528 **Ca type**: Breast Cancer **Stage**: Most were I or II	**Agent:** Lectinol[R], Abnoba, Helixo, Iscador, and Aviscumine **Dose:** not reported **Route: v**ariable and uncertain **Administration**: not reported **Comparison: S**tandard breast cancer treatment alone	Standard breast cancer treatment	Survival QOL	**i)** Multiple types of mistletoe preparations, doses, administrations, etc. **ii)** No survival benefit when mistletoe is added to conventional treatment. **iii)** No QOL benefit observed when mistletoe compared to conventional treatment.
Schad et al (2018) [92]	Retrospective	**N**: 56 **Ca type**: Multiple types **Stage**: I-IV	**Agent:** Helixor **Dose:** Not reported **Route:** Intravenous **Administration:** Varied **Comparison:** Monoclonal antibody alone (n = 8), mistletoe alone (n = 12), combined (n = 43)	Most received chemotherapy or supportive therapy	Safety of VAE with monoclonal antibody therapy	**i)** Overall, 34 patients experienced 142 adverse events. **ii)** Highest incidence of AEs occurred in the monoclonal antibody group (63% of patients) compared to the combination mistletoe group (56% of patients). Five times higher OR of an AE after treatment with mAB compared to mAB plus VAE (95% CI 1.53-16.14). **iii)** Rates of serious AEs were similar between groups (2% for mistletoe combination group and 3% for monoclonal antibody alone group).
Schad et al (2018) [61]	Retrospective	**N**: 158 **Ca type**: NSCLC **Stage**: IV	**Agent:** Abnobaviscum, Helixor and Iscador **Dose:** Not reported **Route:** SC, IV, intratumoral **Administration**: Not reported **Comparison**: Chemotherapy alone	Chemotherapy	Survival	**i)** Median survival for patients receiving mistletoe + chemotherapy was 17.0 months compared to 8.0 months in the chemotherapy group alone (P = 0.007). **ii)** Overall survival was significantly prolonged in the mistletoe combination group (HR 0.44, 95% CI 0.26-0.74, P = 0.002). **iii)** 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.

Thronicke et al (2018) [93]	Retrospective	**N**: 310 **Ca type**: Multiple types **Stage**: 0-IV	**Agent:** Fraxini, Quercus, Mali **Dose:** Not reported **Route:** SC **Administration:** Median duration was 3.8 months (114 days) **Comparison**: Targeted therapy alone	Targeted therapy	Safety with targeted therapy	**i)** 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). **ii)** Odds ratio of discontinuation of treatment was 0.30 for the mistletoe + conventional care group (P = 0.02).
Schad et al (2017) [115]	Retrospective	**N:** 1361 **Ca type:** Multiple types **Stage**: varied	**Agent:** Abnobaviscum Fraxini (44%), Mali (22.3%), Quercus (22.1%), other (11.6%) **Route**: SC **Administration**: duration not reported **Comparison**: low initial dose group ≤ 0.02mg (516 patients) vs. high initial dose group >0.02mg (845 patients)	Not reported	Safety: AEs & ADRs (high vs low starting dose)	**i)** 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). **ii)** No serious ADRs occurred.
Schlappi et al (2017) [88]	Retrospective	**N**: 59 **Ca type**: Multiple types **Stage**: 59% advanced or metastatic disease	**Agent:** most frequently used was Iscador M **Dose; v**aried **Route**: IV **Administration:** varied considerably **Comparison:** NA	None	Fever (≥ 38.5 C^o) Safety (CTCAE v 4.0)	**i)** Out of 59 patients, receiving a total of 567 intravenous infusions, 45 patients (76%) achieved a fever after at least 1 treatment. **ii)** Mean temperature increase 1.5 C^0 +/- 0.8 C^o. **iii)** No AEs over grade 2 occurred. One grade I allergic reaction occurred.
Thronicke et al (2017) [91]	Retrospective	**N**: 16 **Ca type**: Primarily lung cancers (69%) **Stage**: IIIA/IV(Progressive or metastatic)	**Agent:** Varied: Abnobaviscum,Helixor P Iscador Q **Dose**: varied **Route:** Varied (SC or IV or both) **Administration**: median duration was 84 days (range of 1-196 days) **Comparison**: ICI alone	Immune checkpoint inhibitors (ICI)	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)** 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). **v)** Progressive disease was observed in 71.7% of participants in the immunotherapy alone group, compared to 44.4% in the combined treatment group (p = 0.36). Stable disease was observed in 28.6% of participants in the immunotherapy alone group, compared to 22.2% in the combined treatment group (p: not available). Overall, no statistically significant differences were found between groups.
Axtner et al (2016) [116]	Retrospective	**N**: 240 **Ca Type**: Advanced Pancreatic Cancer **Stage**: stage IV	**Agent:** mixed **Dose:** not reported **Route**: SC (89.2%), IV (35.2), intratumoral (19.3%) **Administration:** alongside chemotherapy, durations not reported	Chemotherapy	Feasibility Survival	**iii)** Patients receiving >4 weeks of mistletoe in addition to chemotherapy had longer survival compared to those who only had chemotherapy (12.1 vs 7.3 months) (log rank test, $X^2 = 6$, P = 0.014). **iv)** Patients receiving VA only had longer survival than those receiving neither chemotherapy nor VA therapy (5.4 compared to 2.5 months) (log rank test $X^2 = 7.6$, P = 0.006).

			Comparison: chemotherapy only and VA only			
Steele et al (2015) [117]	Retrospective	**N:** 123 **Ca Type:** multiple types **Stage:** mixed and some unknown, but 47.2% stage IV	**Agent**: Helixor, Abnoba, Iscucin **Dose:** 0.02 to 250mg, median dose 60mg **Route**: intratumoral **Administration:** varied, majority received 2-6 applications, up to 1 month **Comparison:** NA	Mixed (SC, IV, both)	Safety: AE's & ADRs	**i)** 26 patients experienced a total of 74 ADRs (21.1%). **ii)** Most common ADRs were body temperature increase or immune related effect, of which 83.8% were mild and 14.9% moderate. **iii)** One possible severe ADR occurred (hypertension) with no serious ADRs occurring. **iv)** Intratumoral ADR rates were 3x higher than SC and 5x higher than intravenous application rates when compared with external data.
Sunjic et al (2015) [103]	Retrospective Case-report series	**N:** 74 **Ca Type:** multiple Types **Stage**: majority were advanced stages	**Agent**: Isorel (A, M & P) **Dose:** not reported, as per manufacturers guidelines **Route:** SC, IM, IV **Administration:** 3X/week first year after diagnosis, then maintained or reduced to 1X/week in cases of remission **Comparison:** NA	Conventional care (primarily surgery and radiation)	Clinical Effect (not adequately described)	**i)** There was no tumor recurrence in 47% of cases, partial cancer regression in 38% of cases, and no cases of worsening condition. **ii)** Not much can be stated from this study due to poor methodology.
Von Schoen-Angerer (2015) [104]	Retrospective Case-series	**N:** 8 **Ca Type:** Bladder Cancer **Stage**: Majority were non-muscle invasive cancer.	**Agent**: Iscucin Salicis **Route**: SC **Dose:** strengths F (0.125mg), G (2.5mg) and H (50mg) **Administration:** varied from 1x/week to daily based on fever and inflammatory reactions **Comparison: NA**	Mixed	Recurrence	**i)** Median tumor-free duration was 48.5 months. **ii)** High dose mistletoe showed possible benefit in 5 of 8 patients, 2 patients could not be assessed and 1 showed uncertain effects of mistletoe. **iii)** No tumor progression was observed in any of the 8 patients. **iv)** No patient stopped treatment due to intolerance/side-effects.
Bock et al (2014) [52]	Retrospective	**N:** 324 **Ca Type:** Colorectal **Stage:** non-metastasized CRC, stages I-III	**Agent**: Iscador Q **Dose:** total 16 to 20mg per week **Route:** SC **Administration:** daily doses were left up to physician's discretion **Comparison:** NA	Chemotherapy or radio-chemotherapy	Cancer Related Fatigue	**i)** 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) [118]	Retrospective	**N:** 39 **Ca Type:** Advanced Inoperable Pancreatic Cancer **Stage:** II-IV	**Agent**: Helixor, Abnoba **Dose:** escalating doses up to 160mg (Abnoba) or 1400mg (Helixor) **Route:** intratumoral **Administration:** alternately to chemotherapy in 4-week intervals or more **Comparison: NA**	Chemotherapy	Safety Survival	**i)** No serious intervention-related adverse effects. Increased body temperature was seen in 14% and fever in 11%. **ii)** Median survival 11 months (11.8 for stage III and 8.3 for stage IV). **iii)** Considered feasible, well-tolerated and safe.

Steele et al (2014) [82]	Retrospective	**N:** 475 **Ca Type:** multiple types **Stages:** I-IV	**Agent**: Helixor, Abnoba, Iscador **Dose:** ranged 10 to 400mg **Route**: IV and SC **Administration:** mixed **Comparison:** NA	Conventional care	Safety: AE's & ADRs	**i)** No serious ADRs occurred. **ii)** 22 patients reported 32 ADRs (59.4% mild, 40.6% moderate). **iii)** Iscador brand showed relative higher frequency of ADRs compared to the other products. **iv)** Intravenous mistletoe had significantly less ADRs than subcutaneous administration (4.6% vs 8.4%, P = 0.005).
Steele et al (2014) [83]	Observational	**N:** 1923 **Ca Type:** multiple types **Stage:** 0-IV	**Agent**: mixed **Dose:** varied, ≤0.02 to 60mg **Route:** SC **Administration:** varied, most often 3X/week, median length of mistletoe therapy 4.6 months **Comparison:** NA	Conventional care	Safety: AEs & ADRs	**iv)** 21.5% experienced either an expected effect or an adverse drug reaction. **v)** 264 ADRs in 162 patients (8.4%). 42.1% were possibly related, 53.4% were probably related and 4.5% were certainly related to mistletoe treatment. **vi)**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. **vii)** 11 severe ADRs which included 8 patients 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. **viii)** No life threatening ADRs occurred. **ix)** ADRs in general appeared lower with the combination of mistletoe therapy and conventional care. **xi)** Mistletoe ADR rate increased as dose increased.
Beuth et al (2008) [48]	Retrospective Cohort	**N:** 681 (167 mistletoe, 514 control) **Ca Type:** Breast **Stages**: I-III	**Agent:** Helixor **Dose:** not specified **Route:** not specified **Administration**: frequency not specified, used for up to 5 years post-cancer treatment **Comparison**: No mistletoe	Standard cancer treatments (surgery +/- chemotherapy, radiation, endocrine therapy)	Safety during aftercare (post-cancer treatment) (medical records) Symptoms (obtained from medical records) during aftercare (post-cancer treatment)	**ii)** Adverse drug reactions to mistletoe in the treatment group were 10% (local reactions, erythema, pruritus, flu-like symptoms, one case of generalized reaction). **ii)** In the aftercare period (after surgery, chemo, radiation were completed), disease or treatment-related symptoms were significantly lower in the mistletoe vs control group (56.3% vs 70%, P < 0.001). **iii)** Adjusted odds ratio of symptoms for mistletoe treated group was 0.51 (95% CI 0.32-0.81). **iv)** There was no difference between groups for rates of relapse, metastases, or death.
Bussing et al (2007) [84]	Prospective Cohort	**N:** 71 **Ca Type:** Breast, Prostate, Colorectal **Stages:** I-IV	**Agent:** Iscador **Dose:** 0.01mg – 20mg **Route: SC** **Administration**: 2x/week, over 6 months **Comparison**: slow incremental increase vs. rapid dose escalation	None	Immune Effects QOL	**i)** Swift escalation of dose resulted in more local reactions compared to slow incremental increase. **ii)** No differences were noted between groups regarding body temperature and QOL. **iii)** No differences between dosing schedules were noted for CD3, CD4, CD8 or CD4/CD8 ratio. **iv)** Swift escalation group had a significant decrease in HLA-DR+ T-Cells compared to a slight increase in the slow escalation group (P < 0.05).

ADR; adverse drug reaction, **AE;** adverse event, **Ca**; cancer, **CTCAE;** common terminology for adverse events, **HR;** hazard ratio, **HT**; Hyperthermia, **IV;** intravenous, **N;** number**, NSCLC;** non-small cell lung cancer**, OR;** odds ratio, **OS;** overall survival, **QOL;** quality of life**, SC;** subcutaneous, **Tx;** treatment, **VAE;** viscum album extract

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