

Healthcare Provider Resource

Developed by:

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Table of Contents

General information 3
Summary 3

Table 4: Observational research of subcutaneous or IV mistletoe for cancer23
Disclaimer29
References30

General information

Proper name:

Viscum album Loranthaceae, *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

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-

particularly in relation to chemotherapy (37, 46). Evidence from a range of study designs 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 (47-49), all of which used the EORTC QLQ-C30 for QOL assessment. Appetite loss significantly improved in four studies (17, 18, 20, 41). Fatigue scores significantly improved with VAE use in three-clinical-studies (20, 34, 41) and in one observational study (50), possibly W* n(4%)-36ETQq0.00000912 0 612 792 reW* nBT/F1 11.04 Tf1 0 0 1 42

long-term follow up results in 2020 (53). 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 Viscum arm and 33% in the etoposide arm (53).

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. A retrospective observational study of 240 patients with advanced stage pancreatic cancer compared survival time for those receiving VAE therapy and those not. 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 (supportive care only), patients receiving VAE lived significantly longer (5.4 vs 2.5 months, $p=0.006$) (57). A retrospective study of 158 patients with stage IV NSCLC, primarily receiving subcutaneous VAE, reported that compared to chemotherapy alone, those

availability of higher quality evidence. However, in areas where research is limited (as in subsequent sections), case reports have bee

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 (77). 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 (77). 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.

Reported serious adverse events are rare. They include urticaria and angioedema (37, 44), hypotension and loss of consciousness (78), anaphylaxis (<1%) (23, 78, 79), and severe delayed type hypersensitivity reaction (80).

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

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

Rare but serious (1-4%): Angioedema, allergic reactions

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 (52), 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 (82).

Although direct pharmacokinetic and pharmacodynamic studies evaluating for 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 0 Gd552 792 reW* nBT/F1 12 Tf1 0 0 1 42.6 296.93 Tm0 g0 G[()] Tgbutned use

Other treatments

VAE injections were combined with radiofrequency ablation (RFA) in a case report with encouraging results (88). As noted below, when immunosuppressive treatments are applied, mistletoe use should be avoided.

Cautions and Contraindications

Mistletoe should not be used by anyone with a known allergy or hypersensitivity to mistletoe. There is insufficient evidence regarding safety of mistletoe during pregnancy and lactation. Mistletoe should be used cautiously in people with autoimmune (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, 89). 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 it may stimulate the immune system and cause a flare-up of the disease. (27)

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

Reference	Study Design	Demographics	Intervention	Concomitant Treatment	Endpoints and Measures	Results
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	Oe298.97 112				

Longhi,
2020 (53)

See Longhi, 2014 (34)

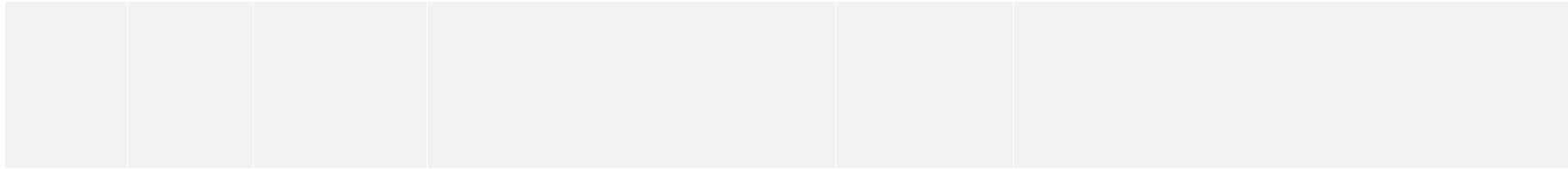


Table 4: Observational

			maintained or reduced to 1X/week in cases of remission Comparison: NA			
Axtner et al (2016) (103)	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			

		Stage: Moste were I or II	Dose: not reported Route: variable and uncertain Administration: not reported Comparison: Standard breast cancer treatment alone			No survival benefit when mistletoe is added to conventional treatment. No QOL benefit observed when mistletoe compared to conventional treatment.
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Schad et al (2018) (58) Retrospective N: 158

			dose and administration were varied Comparison: None			No patient had to stop mistletoe therapy. In a subgroup analysis of 30 patients with long-term mistletoe therapy, none experienced a flare up/exacerbation of their auto-immune condition.
Oei et al (2020) (65)	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 ×6'y ggm Comparison: Chemotherapy alone, mistletoe alone, combined therapy, or no mistletoe or chemotherapy (control ó this group could receive endocrine therapy/immunotherapy)	All patients offered standard oncology therapies		

			Route: SC route or by off-label IV administration (52.6% of patients) Administration: duration for $\times 6$ y g_{gm} Comparison: Standard oncological treatment alone			
Baek et al (2021) (59)	Retrospective	N: 52 Ca type: rectal adenocarcinoma Stage: II-III				

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.

References

1. Horneber MA, Bueschel G, Huber R, Linde K, Rostock M. Mistletoe therapy in oncology. The Cochrane database of systematic reviews. 2008(2):Cd003297.
2. Kienle GS, Grugel R, Kiene H. Safety of higher dosages of *Viscum album* L. in animals and humans--systematic review of immune changes and safety parameters. BMC complementary and alternative medicine. 2011;11:72.
3. Schoffski P, Breidenbach I Fau - Krauter J, Krauter J Fau - Bolte O, Bolte O Fau - Stadler M, Stadler M Fau - Ganser A, Ganser A Fau - Wilhelm-Ogunbiyi K, et al. Weekly 24 h infusion of aviscumine (rViscumine): a phase I study in patients with solid tumours. European journal of cancer (Oxford, England : 1990). 2005(0959-8049 (Print)).
4. Schoffski P, Riggert S Fau - Fumoleau P, Fumoleau P Fau - Campone M, Campone M Fau - Bolte O, Bolte O Fau - Marreaud S, Marreaud S Fau -

14. Klein R, Classen K, Berg PA, Lüdtkke R, Werner M, Huber R. In vivo-induction of antibodies to mistletoe lectin-

60. Huber R, Schlodder D, Effertz C, Rieger S, Troger W. Safety of intravenously applied mistletoe extract - results from a phase I dose escalation study in patients with advanced cancer. *BMC complementary and alternative medicine*. 2017;17(1):465.
61. Cazacu M, Oniu T Fau - Lungoci C, Lungoci C Fau - Mihailov A, Mihailov A Fau - Cipak A, Cipak A Fau - Klinger R, Klinger R Fau - Weiss T, et al. The influence of isorel on the advanced colorectal cancer. *Cancer Biother Radiopharm*. 2003(1084-9785 (Print)).
62. Thronicke A, Reinhold T, von Trott P, Matthes H, Schad F. Cost-Effectiveness of Real-World Administration of Concomitant *Viscum album* L. Therapy for the Treatment of Stage IV Pancreatic Cancer. *Evidence-based complementary and alternative medicine : eCAM*. 2020;2020:3543568.
63. Thronicke A, Reinhold T, von Trott P, Grah C, Matthes B, Matthes H, et al. Cost-effectiveness of real-world administration of chemotherapy and add-on *Viscum album* L. therapy compared to chemotherapy in the treatment of stage IV NSCLC patients. *PloS one*. 2020;15(7):e0236426.
64. Thronicke A, Matthes B, von Trott P, Schad F, Grah C. Overall Survival of Nonmetastasized NSCLC Patients Treated With Add-On *Viscum album* L: A Multicenter Real-World Study. *Integrative cancer therapies*. 2020;19:1534735420940384.
65. Oei SL, Thronicke A, Kröz M, von Trott P, Schad F, Matthes H. Impact of Oncological Therapy and *Viscum album* L Treatment on Cancer-Related Fatigue and Internal Coherence in Nonmetastasized Breast Cancer Patients. *Integrative cancer therapies*. 2020;19:1534735420917211.
66. Werthmann PG, Kindermann L, Kienle GS. Chemoimmunotherapy in Advanced Renal Cell Carcinoma: A Case Report of a Long-Term Survivor Adjunctly Treated with *Viscum album* Extracts. *Complementary medicine research*. 2019;26(4):276-9.
67. Reynel M, Villegas Y, Kiene H, Werthmann PG, Kienle GS. Bilateral Asynchronous Renal Cell Carcinoma With Lung Metastases: A Case Report of a Patient Treated Solely With High-dose Intravenous and Subcutaneous *Viscum album* Extract for a Second Renal Lesion. *Anticancer research*. 2019;39(10):5597-604.
68. Reynel M, Villegas Y, Werthmann PG, Kiene H, Kienle GS. Long-Term Survival of a Patient with Recurrent Dedifferentiated High-Grade Liposarcoma of the Retroperitoneum Under Adjuvant Treatment with *Viscum album* L. Extract: A Case Report. *Integrative cancer therapies*. 2021;20:1534735421995258.
69. Gutsch J, Werthmann PG, Rosenwald A, Kienle GS. Complete Remission and Long-term Survival of a Patient with a Diffuse Large B-cell Lymphoma Under *Viscum album* Extracts After Resistance to R-CHOP: A Case Report. *Anticancer research*. 2018;38(9):5363-9.
70. Orange M, Lacey A, Fonseca MP, von Laue BH, Geider S, Kienle GS. Durable Regression of Primary Cutaneous B-Cell Lymphoma Following Fever-inducing Mistletoe Treatment: Two Case Reports. *Glob Adv Health Med*. 2012;1(1):18-25.
71. Stumpf C, Rosenberger A, Rieger S, Tröger W, Schietzel M. Mistletoe extracts in the therapy of malignant, hematological and lymphatic diseases--a monocentric, retrospective analysis over 16 years. *Forschende Komplementärmedizin und klassische Naturheilkunde = Research in complementary and natural classical medicine*. 2000;7(3):139-46.
72. Zuzak TJ, Wasmuth A, Bernitzki S, Schwermer M, Langler A. Safety of high-dose intravenous mistletoe therapy in pediatric cancer patients: A case series. *Complementary therapies in medicine*. 2018;40:198-202.
73. Seifert G, Rutkowski S, Jesse P, Madeleyn R, Reif M, Henze G, et al. Anthroposophic supportive treatment in children with medulloblastoma receiving first-line therapy. *J Pediatr Hematol Oncol*. 2011;33(3):e105-e8.
74. Chernyshov VP, Heusser P, Omelchenko LI, Chernyshova LI, Vodyanik MA, Vykhovanets EV, et al. Immunomodulatory and clinical effects of *Viscum album* (*Isador M* and *Isador P*) in children with

recurrent respiratory infections as a result of the Chernobyl nuclear accident. *Am J Ther.* 2000;7(3):195-203.

75. Steele ML, Axtner J, Happe A, Kroz M, Matthes H, Schad F. Safety of Intravenous Application of Mistletoe (*Viscum album L.*) Preparations in Oncology: An Observational Study. *Evidence-based complementary and alternative medicine : eCAM.* 2014;2014:236310.

76. Steele ML, Axtner J, Happe A, Kroz M, Matthes H, Schad F. Adverse Drug Reactions and Expected Effects to Therapy with Subcutaneous Mistletoe Extracts (*Viscum album L.*) in Cancer Patients. *Evidence-based complementary and alternative medicine : eCAM.* 2014;2014:724258.

77. Bussing A, Stumpf C Fau - Troger W, Troger W Fau - Schietzel M, Schietzel M. Course of mitogen-

105. Fritz P, Dippon J, Muller S, Goletz S, Trautmann C, Pappas X, et al. Is Mistletoe Treatment Beneficial in Invasive Breast Cancer? A New Approach to an Unresolved Problem. *Anticancer research*. 2018;38(3):1585-93.
106. Hamrin E, Ernerudh J, Rosen A. Immunological and Quality-of-Life Profiles in Women with Breast Cancer: Complementary versus Conventional Care. *Complementary medicine research*. 2018;25(6):391-7.