Healthcare Provider Resource

Developed by:
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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

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 (e.g., swelling, erythema, pruritus, warmth, and induration).

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

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

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 [illegible] 0.37fhs2 reW*BTn12 11.04 369(Th)11 0 0 1 k88.41 538.54 Tm0 g0 G[( )] TETQq0.00000912 0 612 792 rsW

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: v**ariable and uncertain **Administration**: not reported **Comparison: S**tandard breast cancer treatment alone			No survival benefit when mistletoe is added to conventional treatment. No QOL benefit observed when mistletoe compared to conventional treatment.
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 Ó4 weeks **Comparison**: Chemotherapy alone, mistletoe alone, combined therapy, or no mistletoe or chemotherapy (control ï this group could receive endocrine therapy/immunotherapy)	All patients offered standard oncology therapies	[redacted]	

			Route: SC route or by off-label IV administration (52.6% of patients) **Administration:** duration for Ó4 weeks **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.

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