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Mistletoe Therapy

Improving Outcomes In Complementary Cancer Care

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ABSTRACT:

Mistletoe therapy is an herbal medicine best known for its role in complementary cancer care. Pioneered by Rudolf Steiner, mistletoe, also known as Viscum album L or European mistletoe, has its roots in anthroposophic medicine; today there is a large body of evidence supporting use of mistletoe injection therapy as an adjunctive cancer treatment. Lectins and viscotoxins found in mistletoe appear to be responsible for its antitumor and immune stimulating effects. Mistletoe therapy has been investigated for its effects on survival, quality of life, and tolerability of chemotherapy/ side effects associated with chemotherapy. Meta analyses and systematic reviews have demonstrated a survival benefit associated with use of mistletoe injection therapy alongside chemotherapy or as a supportive therapy. There is also a large body of evidence indicating that mistletoe therapy improves quality of life, with improvements in global quality of life as well as symptoms such as fatigue, nausea and vomiting, pain, sleep disturbances, loss of appetite, and constipation found in a preliminary study. Finally, mistletoe therapy appears to reduce side effects of chemotherapy without decreasing its effectiveness. This article will summarize the history of mistletoe therapy and assess the current evidence surrounding its use in the area of oncology, including breast, lung, and pancreatic cancers to name a few.

Introduction

Mistletoe therapy is a leading complementary or adjunctive cancer therapy, widely used by naturopathic doctors and medical doctors working in integrative oncology, with known immune stimulatory and antitumor effects. Today an advanced therapy most often administered as a subcutaneous injection, mistletoe has a long history of use and has undergone considerable development over that period of time.

Historically, mistletoe (Viscum album L, European mistletoe) has its roots in German anthroposophic medicine, developed by Rudolf Steiner (1861-1925) (Bar-Sela 2011). This system of medicine sought to "acknowledge a spiritual-existential dimension in humanity" (Hamre 2009) and its interaction with physical health and disease (Hamre 2009, Horneber 2010). Initially, mistletoe therapy was used in the treatment of menstrual disorders, epilepsy, high blood pressure, artherosclerosis, diabetes, asthma, migraines, neuralgias, haemorrhages, endometriosis, eczema, foot ulcers, and labour pains (Bar-Sela 2011, Ostermann 2009). In 1920, Steiner introduced mistletoe extract as a treatment for cancer, recommending an extract produced through a complex preparation method that combined sap from mistletoe harvested in the summer and in the winter (Ostermann 2009). Based on this, mistletoe therapy has been used as a cancer therapy for almost a century. During this time, additional types of extracts have been developed, and are in use today. Presently, mistletoe therapy enjoys a prominent role in complementary cancer therapy, and is the subject of a wealth of research evaluating its impact on cancer treatment outcomes including survival, side effects of chemotherapy, and quality of life. This paper will examine the current use of mistletoe therapy in oncology and discuss the research relating to its effects on cancer related outcomes.

Sources and extracts

European mistletoe (Viscum album, L) is a partially woody, semi-parasitic plant that grows on deciduous and coniferous trees including pine, apple, oak and spruce (Kelter 2007, Melzer 2009). The medicinal parts are the stems, including the sap, and the leaves (Melzer 2009). Mistletoe extracts vary according to the type of plant material used, extraction method, as well as the type of tree that the mistletoe used grows on. The host tree that the product is derived from is denoted by a suffix at the end of the preparation name, for instance, Helixor-M is from mistletoe growing on the apple tree (Malus). Older, anthroposophic extracts are produced through a standardized manufacturing method but are not standardized to their constituents; while newer, "phytotherapeutic" extracts are standardized to their mistletoe lectin (ML-1) content (Melzer 2009). For instance, Eurixor is reported to contain between 50-70ng ML-1 per mL (NCI 2013). Helixor is standardized to its biological activity: degree of cytotoxic effects against a specific leukemia cell line. Iscador may contain between 0.0001–20 mg per mL, however this content refers to the amount of plant material rather than specific constituents such as lectins (Mistel-therapie 2014). The best-known extracts in North America are Helixor and Iscador. Helixor is a cold-water extract, while Iscador is a fermented extract of fresh leafy shoots and fruits harvested in the summer and winter (Ostermann 2009). Other commercially available extracts include Abnoba, Isorel, and Iscucin. Iscucin is produced in accordance with the German Homeopathic Pharmacopoeia. Phytotherapeutic extracts include Eurixor and Lektinol. Table 1 compares the characteristics of selected mistletoe extracts (adapted from Melzer 2009).

Pharmacology

European mistletoe contains many constituents, including lectins, viscotoxins, amino acids, flavonoids, phenylpropanoids, triterpenes, phytosterol, alkaloids, polyalcohols, and polysaccharides (Melzer 2009). The active components thought to be responsible for mistletoe's antitumor effects are mistletoe lectins (ML), and less so, viscotoxins. Lectins are glycoproteins capable of binding to the outside of cells (NCI 2013). Three classes of lectins have been identified: ML-I, ML-II, and ML-III depending on what type of surface molecule they bind (Melzer 2009). Lectins possess direct cytotoxic effects, inhibiting protein synthesis and triggering apoptosis, as well as indirect antitumor effects through stimulation of cytokine release, and increasing NK cell and macrophages activity (Bar-Sela 2011, Kelter 2007). Viscotoxins are small polypeptides related to thionins and have cytotoxic effects (Bar-Sela 2011, Melzer 2009). Viscotoxins possess immunogenic effects, inducing production of anti-viscotoxin antibodies and causing rapid lysis of the cell membrane; and enhance cytotoxic T-cell activity, oxidative granulocyte bursting, and phagocytosis (Bar-Sela 2011, Klein 2002). Viscotoxins also inhibit cell division through inhibition of DNA and RNA synthesis (Bar-Sela 2011).

Tumour Cell Growth

Mistletoe therapy has been shown to inhibit tumour cell growth independently as a monotherapy as well as when used in conjunction with chemotherapy. This is effected both by direct cytotoxic effects mediated by the lectin- and viscotoxin- components as described above, as well as indirectly through immune stimulation (Bar-Sela 2011). Mistletoe therapy inhibits cell cycle progression, and induces tumour cell apoptosis and removal through phagocytosis (Friedel

Table 1. Characteristics of Select Mistletoe Extracts (adapted from Melzer 2009)

Preparation	Method	Host tree	Harvest	Administration	Dosage	Standardization
Anthroposophic extracts						
Helixor	aqueous (herb)	apple (M:Malus) fir (A: Abies) pine (P: Pinus)	summer and winter	SC	0.01–50 mg/amp (1 ml); or 100 mg (2 ml)	process
Iscador	aqueous lacto-fermented (herb)	M,A,P, elm (U: Ulmus) oak (Q: Quercus)	summer and winter	SC	0.0001–20 mg per amp (1 ml)	process
Isorel	aqueous (whole plant)	M, A, P	summer and winter	SC, IM	1–60 mg	process
Phytotherapeutic extracts						
Eurixor	aqueous (herb)	poplar	winter	SC, IC, IV	1mg or 70ng per amp (1 ml)	ML-I
Lektinol	aqueous (herb)	poplar	winter	SC, IV	0.02–0.07 mg or 15 ng per amp (0.5 ml)	ML-I

Legend: amp ampoule; IC intracoelomic (in the abdominal cavity); IM intramuscular; IV intravenous; ML mistletoe lectins; SC subcutaneous

2009). We describe two case reports of mistletoe therapy as monotherapy, followed by stronger evidence for its use as an adjunctive treatment alongside chemotherapy.

Two case reports describe decreases in tumour size in response to intratumoral mistletoe injections among patients not undergoing chemotherapy (Orange 2010). A patient diagnosed with Merkel cell cancer was treated with subcutaneous and intravenous mistletoe therapy over a period of 9.8 months, during which the patient received no other anti-cancer treatment (Orange 2010). A second patient diagnosed with bilateral breast cancer, who declined cancer staging and surgical treatment, received subcutaneous and intratumoral mistletoe injections over a period of 31 months. Both patients experienced complete and durable remissions following use of mistletoe as a monotherapy (Orange 2010).

A much higher grade of evidence, a 2008 Cochrane review, analyzed twenty-one studies of mistletoe therapy in adult patients with cancer (Horneber 2008). Of these 21 studies, seven provided data on tumour response. Two of seven studies demonstrated additive benefit associated with combined mistletoe plus chemotherapy, compared to chemotherapy alone (Borrelli 2001, Lange 1993). The remaining five studies failed to demonstrate significant benefit on antitumor response compared to standard care alone, however there was no evidence of harm (Horneber 2008).

Survival

Data from several systematic reviews and meta-analysis indicate that mistletoe therapy has a survival benefit (Horneber 2008, Kienle 2009, Ostermann 2009, Ostermann 2012). These studies are summarized in Table 2. Ostermann et al performed two systematic reviews and meta analyses including over 50 studies and concluded that mistletoe therapy in addition to standard care resulted in approximately 40% improved survival, compared to standard care alone: HR 0.59 (95%CI 0.53- 0.66 and 0.50-0.70), where HR

<1.0 favours mistletoe (2009, 2012). There was evidence of publication bias, undermining the strength of these findings, however these are nonetheless notable findings. A third, 2009 systematic review assessing the effectiveness of mistletoe in 19 RCTs, 16 non-randomized studies, and 11 cohort studies of patients with breast or other gynaecological cancer found that 12 of 22 studies showed significant benefits on survival, and three of nine studies showed significant benefits for remission or time to relapse (Kienle 2009). Finally, the 2008 Cochrane review included twenty-one studies, of which thirteen evaluated survival as an endpoint (Horneber 2008). Six of these 13 studies showed a survival benefit associated with mistletoe therapy, although it was noted that they lacked methodological rigor. Collectively, the weight of data from these reviews suggests that despite certain limitations in the literature, mistletoe may have clinically important anticancer effects.

A 2013 randomized controlled trial recently assessed mistletoe therapy in 72 patients with advanced non-small-cell lung cancer (NSCLC) (Bar-Sela 2013). All patients received chemotherapy with carboplatin plus gemcitabine or pemetrexed, and were then randomized to receive either mistletoe or no additional treatment. Iscador was dosed three times weekly until progression. This study found a non-significant improvement in time to tumour progression and overall survival associated with mistletoe therapy. Time to tumour progression was 6.0 months in the mistletoe group compared to 4.8 months in the control group. Overall survival (OS) was 15.9 months in the mistletoe group compared to 13.3 months in the control group. Importantly, fewer patients in the mistletoe group required chemotherapy dose reductions (13% versus 44%, p=0.005), experienced grade 3-4 non-haematological toxicities (16% versus 41%, p=0.043), or had hospitalizations (24% versus 54%, p=0.016).

Another recently published randomized controlled trial assessed overall survival among 220 patients with advanced pancreatic cancer not receiving other cancer therapy (Troger 2013). Patients were randomized to treatment with mistletoe or no treatment, although both groups received the best available supportive care. Mistletoe was dosed subcutaneously three times per week, with the primary endpoint being overall survival (OS) at 12 months. At the time of this writing, interim results are available, showing median OS as 4.8 months for the mistletoe group, compared to 2.7 months for control patients (prognosis-adjusted hazard ratio, HR 0.49, p<0.0001). Among the subgroup of patients with a 'good' prognosis at baseline, median OS was 6.6 versus 3.2 months (HR 0.43, p<0.0001); while among the 'poor' prognosis subgroup, median OS was 3.4 versus 2.0 months, respectively (HR 0.55, p=0.0031). There were no side effects related to mistletoe. These interim results indicate a significant survival benefit associated with use of mistletoe, in this case even as a monotherapy in advanced cancer patients.

Quality of Life

Quality of life (QOL) has proved to be a very important component in terms of cancer treatment. At certain stages of disease, patients are no longer candidates for curative treatment. As a result, practitioners and members of the health care team focus on prolonging life without compromising quality of life, and on relieving symptoms (Bar-Sela 2012).

Clinical data derived from studies of mistletoe therapy indicates an improvement in quality of life and decrease in side effects when used alongside chemotherapy (Bar-Sela 2013, Bussing 2012, Kim 2012). A 2012 RCT found that mistletoe significantly improved QOL (global health) (p <0.01), and increased leukocyte- and eosinophil counts (p ≤0.01) in 32 resected gastric cancer patients starting chemotherapy with doxifluridine, a 5-fluorouracil prodrug, compared to chemotherapy alone (Kim 2012). Diarrhea was also less frequently reported (7% vs. 50%, p=0.014) in the mistletoe group. A cohort study of 25 patients with various cancers reported similar findings, with improvements in QOL as measured by the EORTC QLQ-C30 questionnaire following three months of mistletoe therapy (Brandenberger 2012).

In a 2012 meta analysis, Bussing found a moderate effect size for Iscador in improving quality of life when used alongside chemotherapy, standardized mean difference 0.56 (95%CI 0.41-0.71) (Bussing 2012). Similarly, a 2010 systematic review by Kienle found that of the 26 RCTs included, 22 reported a QOL benefit associated with use of mistletoe extracts, with the remaining four studies showing either no benefit or not reporting results (2010). Improvement was seen for coping, fatigue, sleep, exhaustion, energy, nausea, vomiting, appetite, depression, anxiety, ability to work, and emotional and functional well-being. The 2008 Cochrane review found that of 16 trials evaluating these outcomes, 14 showed significant benefits on QOL, performance score, or side effects of chemotherapy (Horneber 2008).

Side Effects of Chemotherapy

Mistletoe therapy may improve the tolerability of treatment and offset the need for dose reductions among patients undergoing chemotherapy. Most of the clinical research on mistletoe in oncology has been

Table 1. Evidence on Mistletoe in Oncology from Systematic Reviews of the Literature

Ref	Design	Cancer type(s)	Intervention	Endpoint	Results
Meta Analysis					
Büssing 2012	Meta analysis N=13 prospective & controlled studies (9 randomized)	NR	Mistletoe (Iscador) in addition to standard care, compared to standard care alone	QOL	Overall treatment effect favoured Iscador. Standardized mean difference = 0.56 (95%CI 0.41-0.71), indicating a moderate effect. However, the methodological quality of the studies was poor.
Ostermann 2012	Retrolective meta analysis of data derived from N= 4 German cohort studies (N=3324 patients)	Breast Melanoma Colorectal Pancreatic	Mistletoe (Iscador) in addition to standard cancer therapy (chemo, surgery, etc), compared to standard therapy alone	Survival	HR survival: HR 0.59 (95%CI 0.50-0.70). (HR <1.0 favours mistletoe therapy.)
Ostermann 2009	Systematic review (n=49 studies) and meta analysis of N= 41 RCTs and non-randomized studies	Breast Ovarian Colorectal Lung Skin GI cancers Renal	Mistletoe (Iscador) in addition to standard cancer therapy (chemo, surgery, etc), compared to standard therapy alone	Survival	Overall, HR survival 0.59 (95%CI 0.53- 0.66). Randomized studies showed less effect than non-randomized studies (ratio of HRs: 1.24, CI: 0.79 to 1.92, p = 0.35). There was suggestion of publication bias on funnel plot analysis.
Systematic Reviews					
Kienle 2010	Systematic review N=26 RCTs and 10 non-randomized controlled trials	Breast & gynaecological cancers GI cancer Lung Head & neck	Mistletoe extracts in addition to standard care, compared to standard care alone. 6 different mistletoe extracts were investigated, in order of most studies to least: Iscador, Helixor, Eurixor, Isorel, Lektinol, Abnoba	QOL & reduction of SE of chemo	Of the 26 RCTs, 22 reported a QoL benefit for VAE, 2 indicated no difference, 1 had mixed results, and 1 did not present the QoL results. Improvement was seen for the following: coping, fatigue, sleep, exhaustion, energy, nausea, vomiting, appetite, depression, anxiety, ability to work, and emotional and functional well-being in general. Less consistent improvement was seen for pain, diarrhea, general performance, and side effects of conventional treatments.
Kienle 2009	Systematic review N=19 RCTs, 16 non-randomized, controlled studies, 11 cohort studies. Total of 2420, 6399 and 1130 patients, respectively.	Breast & gynaecological cancers	Mistletoe (*Viscum album*) extracts in addition to standard care, compared to standard care alone.	Survival Remission or time to relapse SE of chemo QOL	12 of 22 studies showed significant benefits on survival. 3 of 9 studies showed significant benefits for remission or time to relapse. 21 of 24 studies showed significant benefits for QOL and/ or tolerability of chemotherapy. Tumour regression was observed in cohort studies following high dose, local application. Study quality was better for more recent studies assessing quality of life, and lower for RCTs on survival and tumour behaviour that had small sample sizes.
Horneber 2008; Cochrane review	Systematic review N= 21 RCTs including 3484 patients	Adults with cancer of any type	Mistletoe extracts given as sole treatment, or given concomitantly with chemo- or radiotherapy compared with chemo or radiation alone. 5 different mistletoe extracts were investigated.	Survival Tumour response QOL SE of chemo Safety	Of the 13 trials investigating survival, 6 showed evidence of benefit, although they lacked high methodological quality. Of the 16 trials investigating the efficacy of mistletoe extracts for either improving QOL, performance score, or side effects of chemotherapy, 14 showed evidence of benefit. Mistletoe extracts were "usually well tolerated and had few side effects." RCT reporting was deemed generally poor.

conducted among patients also undergoing standard care. For instance, the study by Bar-Sela cited above showed that there were significantly fewer dose reductions as well as non-hematological toxicities among NSCLC patients receiving mistletoe (2013). The study by Kim showed a reduction in the incidence of diarrhea among patients on doxifluridine (2012). In addition, several systematic reviews indicate a reduction in side effects of chemotherapy, although in most reviews, this was an endpoint combined with quality of life (Kienle 2010, 2009).

Mistletoe therapy has also been shown to improve symptoms during cancer patients' aftercare, defined as the five years following the completion of standard care (Beuth 2008). Data from a cohort of 681 breast cancer patients found that use of mistletoe was associated with decreased overall symptoms (56% versus 70%) as well as a reduction in specific symptoms including mucositis, fatigue, pain, and headache during aftercare, compared to patients not using mistletoe (Beuth 2008).

Safety

Mistletoe therapy has a good safety profile, with most side effects being mild to moderate soreness and inflammation at injection sites, headache, fever, and chills (NCI 2013). Although rare, allergic reactions and anaphylaxis are possible. Dose escalation strategies are used to prevent such reactions.

Interactions

Based on a large volume of data evaluating the use of mistletoe alongside standard care including chemotherapy, and the existence of several meta analyses showing survival benefits (Table 1), mistletoe appears to have a good safety profile alongside chemotherapy. If anything, there appear to be beneficial interactions such that mistletoe reduced side effects of chemo, while improving cancer treatment outcomes such as survival and time to tumour progression (Bar-Sela 2013, Ostermann 2012).

In particular, human studies have evaluated mistletoe therapy alongside the following chemotherapy regimens, finding that there was no evidence of mistletoe reducing the anticancer effectiveness of chemotherapy: gemcitabine (Mansky 2013), carboplatin plus gemcitabine or pemetrexed (Bar-Sela 2013), CMF (cyclophosphamide, methotrexate and fluorouracil) (Auerbach 2005, Horneber 2008), 5-fluorouracil (Heiny 1997, Horneber 2008), and cisplatin and ifosfamide (Lange 1993, Horneber 2008) (Lange 1993 is an unpublished study cited by Horneber 2008). Newly published in vitro experiments suggest that mistletoe is unlikely to reduce the effectiveness of the following chemotherapy drugs: doxorubicin, gemcitabine, docetaxel and mitoxantrone,

and docetaxel and cisplatin (Weissenstein 2014). The study reported that "VAE [Viscum album extract] did not inhibit chemotherapy induced cytostasis and cytotoxicity in any of our experimental settings. At higher concentrations VAE showed an additive inhibitory effect [with chemotherapy drugs]" (Weissenstein 2014).

Conclusion

Mistletoe therapy has a long history of use as a complementary cancer therapy, dating from the 1920s. This therapy demonstrates a good safety profile as well as important benefit on several endpoints related to cancer, including up to 40% improvement in survival, as well as benefits tof quality of life and tolerability of chemotherapy. There are several different mistletoe extracts commercially available, however the best-known and the most researched extracts are Iscador and Helixor. Mistletoe constituents, namely lectins and viscotoxins, exert direct and indirect cytotoxic effects and acts as an immune stimulant. There is a wealth of clinical data on European mistletoe, including several systematic reviews and meta-analyses; however, there is still a need for more rigorous study design and trial reporting in future research on this agent.

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Questions

1. The use of mistletoe therapy in the area of cancer was first developed by:
a) Sir Frederik Banting
b) Linus Pauling
c) Rudolf Steiner
d) Nicolaus Copernicus

2. Mistletoe is a semi-parasitic plant, growing upon other trees, including apple, fir, pine, oak, and others. The letter A at the end of Helixor-A designates an extract derived from mistletoe growing on which type of tree?
a) Apple
b) Fir
c) Poplar
d) Quercus

3. Phytotherapeutic mistletoe extracts are produced through a standardized manufacturing method but are not standardized to their constituents.
a) True
b) False

4. Which of the following is true about specific mistletoe extracts?
a) Eurixor contains between 25-50ng ML-1 per mL
b) Helixor is standardized to its biological activity against a breast cancer cell line
c) Iscador is a fermented extract of leafy shoots and fruits harvested in the summer and winter
d) All of the above

5. One of the two main active constituents in mistletoe thought to be responsible for its anticancer effects is which of the following:
a) saponins
b) alkaloids
c) lectins
d) beta-glucans

6. In a 2008 Cochrane review, 2 of 7 studies demonstrated an additive survival benefit associated with use of mistletoe in combination with chemotherapy, compared to chemotherapy alone.
a)True
b) False

7. A 2013 randomized controlled trial by Bar-Sela et al. reported that use of Iscador in patients with advanced non-small cell lung cancer (NSCLC) resulted in which of the following?
a) a non-significant trend in time to tumour progression favouring the mistletoe group;
b) evident lack of deleterious interactions between Iscador and the chemotherapy regimen: carboplatin plus gemcitabine or pemetrexed;
c) fewer patients in the mistletoe group requing chemotherapy dose reductions, 13% versus 44%;
d) All of the above

8. A 2012 systematic review by Bussing et al. reported that mistletoe was associated with a large effect size with respect to improving quality of life (QOL).
a) True
b) False

9. Subcutaneous mistletoe injections carry the potential risk for allergic reaction and anaphylaxis. As a result, gradual dose escalating strategies are used to minimize this risk.
a) True
b) False

10. Which of the following is true about the potential interactions between mistletoe and chemotherapy?
a) Given that an additive survival benefit is shown by some studies, null effects by other, but no studies show harm on survival parameters associated with mistletoe therapy alongside chemotherapy, it appears that mistletoe does not reduce the effectiveness of chemotherapy;
b) Mistletoe has been studied alongside the following regimens: gemcitabine; carboplatin with gemcitabine or pemetrexed; 5-fluorouracil; and cisplatin.
c) In vitro studies report that combination of mistletoe with various chemotherapy drugs "did not inhibit chemotherapy induced cytostasis and cytotoxicity"
d) All of the above

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