Mistletoe Therapy

Improving Outcomes In Complementary Cancer Care

By Sarah Vanderheyden, RPN and Heidi Fritz, MA, ND

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; Horneker 2010). Initially, mistletoe therapy was used in the treatment of menstrual disorders, epilepsy, high blood pressure, artherosclerosis, diabetes, asthma, migraines, neuralgias, haemorrhages, endometiosis, 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, the host tree that the product is derived from is denoted by a suffix at the end of the preparation name, the host tree that the product is derived from is denoted by a suffix at the end of the preparation name.

Pharmacology
European mistletoe contains many constituents, including lectins, viscositoxins, amino acids, flavonoids, phenylpropanoids, triterpenes, 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, viscositoxins. 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). Viscositoxins are small polypeptides related to thionins and have cytotoxic effects (Bar-Sela 2011, Melzer 2009). Viscositoxins possess immunogenic effects, inducing production of anti-viscositin antibodies and causing rapid lysis of the cell membrane; and enhancing cytotoxic T-cell activity, oxidative granulocyte bursting, and phagocytosis (Bar-Sela 2011, Klein 2002). Viscositoxins 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 tumor cell apoptosis and removal through phagocytosis (Friedel 2009). We describe two case reports of mistletoe therapy as monotherapy, followed by stronger evidence for its use as an adjunctive treatment alongside chemotherapy.

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

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Method</th>
<th>Host tree</th>
<th>Harvest</th>
<th>Administra- tion</th>
<th>Dosage</th>
<th>Standardi- zation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helixor</td>
<td>aqueous (herb)</td>
<td>apple (Malus)</td>
<td>summe r and winter</td>
<td>SC</td>
<td>0.01–50 ng per amp (1 ml)</td>
<td>process</td>
</tr>
<tr>
<td>Iscador</td>
<td>aqueous (herb)</td>
<td>elm (U: Ulmus)</td>
<td>summe r and winter</td>
<td>SC</td>
<td>0.001–20 mg per amp (1 ml)</td>
<td>process</td>
</tr>
<tr>
<td>Isorel</td>
<td>aqueous (whole plant)</td>
<td>M. A. P</td>
<td>summe r and winter</td>
<td>IM</td>
<td>1–60 mg</td>
<td>process</td>
</tr>
<tr>
<td>Lektinol</td>
<td>aqueous (herb)</td>
<td>popular</td>
<td>winter</td>
<td>SC, IV</td>
<td>0.02–0.07 mg or 15 ng per amp (0.5 ml)</td>
<td>ML-I</td>
</tr>
<tr>
<td>Helixor</td>
<td>aqueous (whole plant)</td>
<td>M. A. P</td>
<td>summer</td>
<td>SC</td>
<td>100–300 mg per amp (1 ml)</td>
<td>process</td>
</tr>
</tbody>
</table>

Legend: amp: ampoule; IC intracavitary (in the abdominal cavity); IM intramuscular; IV intravenous; ML mistletoe lectins; SC subcutaneous; ML-I...
<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, 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 (Kienele 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 placebo, 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 docetaxel, a 5-fluorouracil prodrg, compared to chemotherapy alone (Kim 2012). Diarrhea was also less frequently reported (7% vs. 50%, p=0.034) in the mistletoe group. A cohort study of 25 patients with various cancers reported similar findings, with improvement 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 Kienele 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.

Of the 26 RCTs, 22 reported a QoL benefit for mistletoe in 19 RCTs, 16 non-randomized studies and three of nine studies showed significant benefits for survival. Overall, HR survival 0.59 (95%CI 0.53-0.66). Standardized mean difference = 0.56 (95%CI 0.41-0.71), indicating a moderate effect.

Publication bias was assessed using funnel plot analysis. The methodological quality of the studies was assessed using the Jadad score. Six of 22 studies showed less effect than non-randomized studies (ratio of HRs: 1.24, CI 0.79 to 1.92, p = 0.35). There was no suggestion of publication bias on funnel plot analysis.

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

<table>
<thead>
<tr>
<th>Ref</th>
<th>Year</th>
<th>Cancer Type(s)</th>
<th>Intervention/Outcome</th>
<th>Study quality</th>
<th>Publication bias</th>
<th>SE of survival</th>
<th>SE of chemo</th>
<th>SE of QOL</th>
<th>SE of chemo QOL</th>
<th>SE of survival QOL</th>
<th>SE of chemo QOL</th>
<th>SE of chemo QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kienele 2010</td>
<td>Systematic review</td>
<td>N= 26 RCTs and 10 non-randomized controlled trials</td>
<td>Breast &amp; gynaecological cancers</td>
<td>Overall treatment effect favoured Iscador. Standardized mean difference = 0.56 (95%CI 0.41-0.71), indicating a moderate effect.</td>
<td>No evidence of publication bias, although they lacked high quality.</td>
<td>0.84</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Kienle 2008</td>
<td>Systematic review</td>
<td>N= 19 RCTs, 16 non-randomized, controlled studies</td>
<td>Breast &amp; gynaecological cancers</td>
<td>Mistletoe (Viscum album) extracts in addition to standard care, compared to standard care alone.</td>
<td>No evidence of publication bias, although they lacked high quality.</td>
<td>0.84</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Bussing 2012</td>
<td>Systematic review</td>
<td>N= 13 prospective &amp; controlled studies (9 randomized)</td>
<td>NMSC</td>
<td>Mistletoe (Viscum album) in addition to standard care, compared to standard care alone.</td>
<td>No evidence of publication bias, although they lacked high quality.</td>
<td>0.84</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Ostermann 2008;</td>
<td>Cochrane review</td>
<td>N= 26 RCTs and 10 non-randomized controlled trials</td>
<td>Lung cancer</td>
<td>Mistletoe extracts in addition to standard care, compared to standard care alone.</td>
<td>No evidence of publication bias, although they lacked high quality.</td>
<td>0.84</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Hornbichler 2008</td>
<td>Cochrane review</td>
<td>N= 21 RCTs including 1548 patients</td>
<td>Lung cancer</td>
<td>Mistletoe extracts given as sole treatment, or given concomitantly with chemotherapy or radiotherapy compared with chemotherapy or radiation alone.</td>
<td>No evidence of publication bias, although they lacked high quality.</td>
<td>0.84</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>

The Journal of IHP – Continuing Education

www.ihpmagazine.com | February / March 2014 | www.ihpmagazine.com
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 Kienle showed a reduction in incidence of diarrhea among patients on oxaliplatin (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 showed that use of mistletoe was associated with decreased overall symptoms (56% versus 70%) as well as a reduction in specific symptoms including maculosis, 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 studying 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 chemotherapies, while improving cancer treatment outcomes such as survival. 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 treated with carboplatin-based chemotherapy. There are several different mistletoe extracts commercially available, however the best-known and the most researched extracts are Isocad® and Heilos®. Mistletoe constituents, namely lectins and viscositoxins, exert direct and indirect cytotoxic effects and act as an immune stimulant. There is a wealth of clinical data on European mistletoe, including several reviews and meta-analyses; however, there is still a need for more rigorous study design and trial reporting in future research on this agent.

References


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 requiring 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

Fax or Email Answers to: 416.703.6392 or philip@ihpmagazine.com

Name:
Address:
City:
Province: Postal Code:
Phone:
Email: Fax:
Practice Registration #: Area of Clinical Focus:
Size of Practice (# of Doctors): □ 0-5 □ 5-10 □ 10 & up Years of Practice: □ 0-5 □ 5-10 □ 10 & up