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Professional Resource: Mistletoe

Brief Background

Mistletoe is a parasitic plant from the Santalacea family that attaches to and penetrates the branches of a tree or shrub in order to absorb water and nutrients from the host plant. There are three main types of mistletoe: European Mistletoe (*Viscum album*), Korean Mistletoe (*Viscum album var. coloratum*) and American Mistletoe (*Phoradendron leucarpum*). Preparations from European Mistletoe are some of the most commonly prescribed substances internationally in out-patient cancer clinics [1], where they are provided either in injectable form or as an intravenous infusion. Mistletoe berries and raw plant are toxic; however, when sterile extracts are injected or infused side effects are rare and typically mild.

Proper Names

Viscum album Loranthaceae, Malus (mistletoe of the apple tree), Abies (mistletoe of the fir), Pinus (mistletoe of the pine)

Common Names

Mistletoe, mistletoe extract, mistletoe lectin, mistrel, ML-1, aviscumine

Commonly used mistletoe products include: Helixor®, Eurixor®, Iscador®, Isorel® and Lektinol®, and abnobaVISCUM®. They are made as extracts, prepared in either water- or water and alcohol-based solutions. Commercially prepared mistletoe extracts are most commonly standardized to the lectin content. Products are often named based on the type of host tree on which the plant grows, usually abbreviated as A for the fir tree, P for the pine tree, and M for the apple tree, for example.

Common Uses in Cancer Care

Mistletoe is most commonly prescribed in cancer care to:

- Stimulate the immune system

- Improve quality of life
- Improve cancer- and treatment-related symptoms
- Reduce tumour size
- Slow disease progression

Route of Administration

Mistletoe preparations are most commonly administered as a subcutaneous, intramuscular, or intrapleural injections, or as an intravenous infusion.

Pharmacokinetics

In one Phase I trial, people with solid tumours were treated with weekly 24 h IV infusions. In this study, plasma levels above 2 ng/ml were maintained throughout the infusion in the majority of cases [2]. The maximum median concentration was 5.4 ng/ml using a 5 ug/kg dose level. The median time with a plasma concentration above 2 ng/ml was 24 h. At the end of the infusion, plasma concentrations decreased rapidly with an initial alpha (distribution) half-life of 13.8 minutes, and a median (elimination) beta half-life of 3.8h.

In a separate phase I trial [3] that had as one objective to evaluate pharmacokinetics, people with a range of solid tumours were treated with twice weekly 1 h IV infusions of aviscumine (rViscumin). The pharmacokinetic evaluation revealed a short a half-life of 13 min with linear kinetics on dose levels >1600 ng/kg.

Mechanism of Action

Mistletoe contains a variety of biologically active compounds, including lectin (I, II and III), viscotoxin (a protein), amino acids, flavonoids, phenylpropanoids, triterpenes, phytosterol, alkaloids, polyalcohols, and polysaccharides [4], [5]. Of these, the lectins—in particular lectin I—have been the most intensively studied. Most commercial products are standardized to lectin content. The principal anticancer mechanisms of action attributed to mistletoe come from its ability to have both cytotoxic and immunologic activity.

The immunologic activity of mistletoe is attributed primarily to lectins and polysaccharides. Lectins have been shown to induce increased macrophage cytotoxic activity, stimulate phagocytosis by immune cells, increase cytokine secretion (TNF-alpha, IL-1, IL-2, and IL-6), and enhance cytotoxic effects on various cell lines in vitro [6]. In addition, preclinical laboratory studies suggest that mistletoe supports the immune system by increasing the number and activity of various types of white blood cells, particularly the natural killer cell subset, including their ability to interact and more effectively recognize cancer cells [6]–[9].

The lectins, viscotoxins and alkaloids are believed to be responsible for mistletoe's cytotoxic activity. A number of processes appear to be involved, including the inhibition of protein synthesis, triggering apoptosis and necrotis, in addition to indirect cytotoxic effects resulting from stimulating cytokine release, and increasing natural killer cell and macrophage activity [10]–[12].

Clinical Evidence related to Effectiveness

Many clinical studies have been conducted over the past several decades to assess the effectiveness of mistletoe as a treatment in cancer care. Human level evidence varies in quality and ranges from individual case reports, to randomized controlled trials (RCTs). The evidence has also been reviewed and pooled in systematic reviews and meta-analyses. Overall, mistletoe therapy appears to be effective in particular for improving immune response, quality of life and symptom management. Results are mixed in terms of tumour response and survival. Inconsistent study results might be attributed to the range of mistletoe preparations used across studies, as the effects of the therapy might vary depending on the extract and dose used, how it is administered, the subspecies used, manufacturing process, and time of harvest. Further, authors of several systematic reviews refer to poor methodological quality within published clinical trials [13]–[15] for reasons such as lack of blinding, and poor methods of randomization and matched-pair building for example. The methodological quality of mistletoe research is improving, however, as research designs become more refined to account for many sources of risk of bias. A summary of the best available evidence by clinical outcome is provided below.

Immune system response

Most published studies document that mistletoe can effectively stimulate the immune system, with most studies detailing positive effects on various immune parameters but no effect on others. For example, one RCT in stomach cancer documented significantly higher white blood cell and eosinophil counts in those treated with mistletoe plus 5FU, but no significant difference in CD16+/CD56+ and CD 19+ lymphocytes, TNF-α and IL-2 (135). A separate RCT in glioma patients documented significant up regulation of CD-3, CD-4 and CD-8 cell counts and activities, as well as CD-25, and HLA/DR positive cells after 3 months of mistletoe treatment alongside standard care [16]. In a multicentre RCT in head and neck cancer, there was an increase in CD3+DR+, CD16+56+3+, and CD25+ positive cells in the mistletoe group, but also a decrease in CD3+ positive lymphocytes [17]. Observational studies similarly document consistent immune response with mistletoe treatment, including significant increases in leukocyte [18], lymphocyte [18]–[20], natural killer cell [21] and eosinophil [18] counts. Longer term therapy (e.g., 2 or more years) might have a greater impact on immune function than shorter term therapy [22]. Pure mistletoe appears to have a similar effect on immune function as mistletoe extract standardized for lectin content [23].

Mistletoe has also been studied in relation to immune response around surgery. For example, one RCT [24] included 70 people undergoing digestive tract cancer surgery who were treated with mistletoe for 6 weeks: 2 weeks before surgery until 4 weeks after. People in the treatment group observed significantly decreased immunosuppressive effects of surgery as compared to the control group, and observed an

increased number of lymphocytes, including natural killer (NK) cells, T cells and B cells, as well as an increase in immunoglobulin values. Similarly, another RCT studied a single mistletoe infusion immediately post-surgery, and documented that this infusion prevented the typical suppression of NK cell activity [25]. In a smaller RCT in breast cancer patients, people were treated with mistletoe extract after surgery followed by standard chemotherapy and radiation treatment [26]. In this study, most immune parameters remained unchanged before and after treatment in both study groups, but the concentration of IFN-g was significantly increased in the mistletoe group after treatment.

Quality of Life

Numerous studies have assessed the impact of mistletoe treatment on quality of life. The primarily positive results have been summarized through several systematic reviews.

A recent Cochrane review [1] included 21 RCTs, of which 16 provided measures of quality of life or psychological outcomes. Of the 16 trials, 14 showed some evidence of a benefit. The authors note that only two of the 14 studies that demonstrated a benefit were of high methodological quality. Another systematic review included 15 RCTs and 9 non-RCTs that assessed quality of life outcomes [27]. Twenty-one of these 24 studies reported a significant positive result. A further systematic review included 10 RCTs, 8 of which examined quality of life as an outcome [28]. Of these 8 studies, five documented improved quality of life with mistletoe treatment and three documented no difference as compared to a control group. Another systematic review of controlled clinical studies focused on the effectiveness of mistletoe treatment for quality of life [29]. This study reviewed 26 RCTs and 10 non-RCTs; all but one reported quality of life outcomes. All of the non-RCTs reported improvements in quality of life with mistletoe treatment. Of the 25 RCTs that reported relevant outcomes, 22 indicated a quality of life benefit for mistletoe, 2 indicated no difference, and one had mixed results. Importantly, none found a quality of life disadvantage for mistletoe. Another systematic review included four studies that reported quality of life outcomes [14]. Of the four studies, three reported favourable results for overall quality of life, and one reported no effect. A further review included 5 RCTs that assess quality of life [15]. Of the 5 studies, 3 reported a quality of life benefit with mistletoe treatment.

One meta-analysis was conducted using data from 13 studies, including 9 RCTs, all of which reported positive outcomes for quality of life with no difference between randomized and non-randomized studies [30]. A random-effect meta-analysis estimated the overall treatment effect as a standard mean difference of = 0.56 (CI: 0.41 to 0.71), indicating a moderate effect.

Symptom Management

It is likely that at least part of the documented improvements in quality of life (as described above) is attributable to the effects of mistletoe on managing symptoms, particularly in relation to chemotherapy [31], [32]. Evidence from a range of study designs suggests a benefit for mistletoe treatment in symptom management, although further studies are needed [33].

Several cases have been documented that demonstrate a reduction in cancer-treatment related symptoms, weight gain, return to work and psychological well-being [34]. Further, authors of a large multi-center cohort study [32] and a separate retrospective cohort study [35] report that people who were treated with mistletoe described significantly fewer complaints as compared to those who were not, including mucositis, fatigue, pain and headache [32].

Results from observational studies been replicated through RCTs and summarized through systematic reviews. For example, one systematic review included 25 studies (16 RCTs and 9 non-RCTs) [15], seven of which assessed reduction of chemotherapy-related side effects as an outcome. Five of the seven studies documented significant benefit with mistletoe treatment. Another systematic review included 10 RCTs, studying mistletoe in various cancer types [28]. Symptom management was assessed in only one of the included RCTs. In this RCT, significantly fewer patients in the experimental group suffered from stage III mucositis and the average length of this complication was significantly shorter in this group. Another systematic review published in German included 10 studies that assessed mistletoe in combination with chemotherapy [33] and documents inconsistent results ranging from no effect to positive effects (i. e. reduction in side effects). The authors conclude that RCTs with treatment toxicity as the primary outcome are needed to answer the question of whether the addition of mistletoe extracts to chemotherapy regimes can be beneficial. Finally, a further systematic review of controlled clinical studies focused on the effectiveness of mistletoe treatment for quality of life [29]. This study reviewed 26 RCTs and 10 non-RCTs. While symptom management was not specifically studied in this review, the authors note frequent improvement in relation to fatigue, exhaustion, and sleep; nausea, vomiting, and appetite; and emotional well-being, sadness, anxiety, depression, irritability, and concentration difficulties.

Survival

Several systematic reviews and meta-analyses have summarized data on the impact of mistletoe treatment on survival. While there is some potential for positive impact on survival, these findings are still inconclusive and need additional clinical research.

A recent Cochrane systematic review [1] included 21 RCTs, of which 13 provided data on survival. Of the 13 trials, 6 showed some evidence of a benefit, but none of them was of high methodological quality. The 4 studies that were judged as being of high methodological quality did not provide any evidence of survival benefit. Another systematic review included 25 studies (16 RCTs and 9 non-RCTs) [15]. A statistically significant benefit for survival was reported in 8 of 17 trials (including 5 of 10 RCTs) that assessed this outcome, but neither of the 2 included RCTs that assessed disease free survival found a benefit. A further study systematically reviewed clinical and preclinical studies in breast and gynaecological cancers [27] including 9 RCTs and 13 non-RCTs that assessed survival. Of these studies, 12 reported a statistically significant benefit, the others either a trend or no difference. Another systematic review included 10 RCTs, 8 of which assessed some aspect of survival as a primary outcome [28]. As with other reviews, results were mixed. Five of the 8 RCTs that assess survival documented

comparable survival rates between study groups, while three documented improved survival with mistletoe treatment.

A few meta-analyses have helped to quantify any potential survival benefit. One individual patient data meta-analysis [36] included data from two randomized studies and four non-randomized studies with the goal to compare treatment with mistletoe plus standard care versus standard care alone. Overall survival was highly significant in the combined data set of the non-randomized studies, with the estimate of the hazard ratio at 0.43 (95% CI: 0.34, 0.56). Overall survival approached significance in favor of the mistletoe group in the combined data set of the randomized studies: 0.59 (95% CI: 0.34, 1.02). Another meta-analysis of retrospective studies included data from 4 studies that each independently suggest a moderate increase in survival with mistletoe therapy [37]. The meta-analysis indicates a moderate overall effect of 0.59 (95% CI 0.50-0.70) in favour of mistletoe treatment. A further meta-analysis included data from 35 controlled clinical studies [38]. Using data from studies that compare mistletoe versus no treatment, the meta-analysis estimates the overall hazard ratio at 0.59 (CI: 0.53 to 0.66). Using data from studies that compare mistletoe versus other treatments, the meta-analysis demonstrated no effect (HR = 0.95, CI: 0.81 to 1.12, p = 0.56).

Tumour Response

Studies that document the effect of mistletoe treatment on tumour response, including recurrence and remission, are inconclusive.

A recent Cochrane review [1] included 21 RCTs, of which 7 included an analysis of tumour response. Of the 7 studies, two reported results that suggest a benefit, while the other five reported no benefit. The one trial that was judged to be of high methodological quality did not report a benefit. In another systematic review of clinical and preclinical studies in breast and gynaecological cancers [27], 3 RCTs and 6 non-RCTs assessed tumour behaviour (remission or time to relapse). Of these, 3 reported a significant benefit and the others reported either a trend, no difference or mixed results. Another systematic review included 25 studies, (16 RCTs and 9 non-RCTs) [15], 2 of which assessed disease-free interval and one which assessed tumour remission. No significant benefit was documented in any of these studies. A further systematic review that included 10 RCTs, no difference in remission or recurrence rates was documented between mistletoe and control groups [28]. A final systematic review assessed whether prospective controlled clinical trials provide evidence for efficacy of mistletoe therapy in cancer [14]. This review included 23 studies, 6 of which studied tumour remission. One of these studies reported a significant benefit with mistletoe treatment, two reported positive trends, and three reported no effect.

Adverse Events and Side Effects

Mistletoe is generally well tolerated [1], [15], [27], [29], [39], [40]. Some side effects are common, but most are minor, dose-dependent and subside on their own within a few days after treatment. Common side effects include local reactions at the injection site (e.g., swelling, redness, local pain, itchiness, rash, warmth), fatigue, mild flu-like symptoms, anemia, fever and diarrhea [3], [18], [27], [29], [34], [39], [41]–

[47]. Localized reactions can sometimes appear at former injection sites for pre-exposed patients [39] and dose reductions might be required if reactions are severe [48]. Severe localized reactions (>5 cm diameter) occur in less than 1% of cases [44]. Less severe localized reactions (<5 cm diameter) are more common and might be expected to occur in approximately 25% of cases [18], [49]–[51].

The risk of chemotherapy associated adverse events might be reduced if people are treated with mistletoe alongside chemotherapy [31], [49], [52] .

A few adverse events have been documented through case reports, case series and other clinical studies, but serious adverse events are rare. Reported adverse events include urticaria and angioedema [27], hypotension and loss of consciousness [41], anaphylaxis [2], [53], hypereosinophilia [54], severe delayed type hypersensitivity reaction [55] and liver toxicity [2]. In a phase I dose-escalation trial, dose limiting toxicities included grade 3 fatigue at a dose of 4,000 ng/kg (1 of 6 participants) reversible grade 3 liver toxicity at 4800 ng/kg (1 of 10 participants) and reversible grade 3 liver toxicity at 6,400 ng/kg (2 of 5 participants).

Interactions with other Therapies, including Drugs and Natural Health Products

Chemotherapy

Several studies (including RCTs, retrospective controlled studies and systematic reviews) have explored the use of mistletoe in combination a range of chemotherapies [15], [33], [35], [56], [57]. In these studies, no adverse events attributable to the combination were documented. Instead, the combination of chemotherapy plus mistletoe seems to contribute to reduced chemotherapy-related reactions, including nausea and vomiting, diarrhea, fatigue and psychological conditions [35], [42], [46], [57], and improved recovery from side effects [39], [57].

There has been one report of organ fibrosis and death with the combination of busulfan and mistletoe [58].

Other Drugs

Because mistletoe has been shown to stimulate the immune system, it should not be used in combination with immunosuppressants. Further, mistletoe should be used with caution alongside insulin and oral hypoglycemic, due to a potential to stimulate insulin secretion [59]. Caution is also warranted alongside antihypertensive drugs, because mistletoe could lower blood pressure thus compounding the effect of the antihypertensive.

Cautions and Contraindications

Raw European and American Mistletoe leaves and berries are toxic. Raw leaves and berries, or tea brewed from raw leaves or berries, should never be ingested.

Mistletoe should not be used by anyone with a known allergy or hypersensitivity to mistletoe, including any of its constituents, or other members of the Viscaceae or Loranthaceae families.

It should be avoided by people with seizure disorders, due to an increased risk of seizures, and should be used cautiously by people with diabetes, as insulin levels may be altered [59].

While there is a lack of solid data, mistletoe could potentially stimulate the uterus, and therefore should be used with caution in pregnancy and breast feeding [10].

Dosing, frequency and length of treatment

Mistletoe is prescribed to people at the OICC via subcutaneous injections. Prescriptions are based on cancer type, stage, metastasis, other concurrent treatments and gender. Treatment typically begins with an induction phase at a lower dose to assess tolerability. If injections during the induction phase are well tolerated (determined by absence of local skin reaction > 5 cm or other serious side effects), people move on to a maintenance dose, which also consists of ampules of increasing dosages. Some authors have advocated for dosing based on response to local reactions, due to an observed relationship between pre-existing T-cell activity and localized reactions [60]; however, this dosing method is not yet common in clinical practice. Phase I studies have determined a maximum tolerated dose to be between 5-6μg/kg body weight [2], [3].

Some people continue treatment for many years, if well-tolerated and positive outcomes are observed.

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