Chapter 3

The State of Current Mistletoe Research

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"The words question *and* quest *are cognates. Only through inquiry can we discover truth."* —Carl Sagan

"By disregarding intuition in favor of science, or science in favor of instincts, we limit ourselves." —Bernie Siegel, MD

Mistletoe therapy is supported by a foundation of over one hundred years of research and safe clinical use, from initial studies looking at observed effects only, through current research elucidating complex immunological methods of action. This chapter shares only a handful of the most recent and compelling studies. We'll look at seven clinical studies, one case report series, and one qualitative study. It was challenging to limit our selection, but these are some of the most recent (2004–2020) leading-edge and informative studies in the growing pool of VAE research today. With each, we'll share a brief summary of the study and its findings, as well as our own observations about clinical implications.

This is by no means a full systematic review of all the existing research. Please see the Resources and Endnotes sections at the end of this book

to find many more studies. A comprehensive compilation of mistletoe research can be found at www.Mistletoe-Therapy.org. The authors of this book will also regularly update a list of VAE therapy case stories and links to published studies at www.TheMistletoeBook.com.

1. A. Longhi, et al. "Long-term follow-up of a randomized study of oral etoposide versus viscum album fermentatum pini as maintenance therapy in osteosarcoma patients in complete surgical remission after second relapse" (Sarcoma, *Apr. 2020)*

Background and Overview: Osteosarcoma (bone cancer) remains an especially challenging cancer when relapse occurs. Surgical treatment is often regarded as the primary standard of care (SOC) treatment. There are no standard post-surgery maintenance therapies recommended. Chemotherapy does not appear to convey any benefit that would outweigh its risks. Typically, the five-year post-relapse, disease-free survival (PRDFS) for this cancer is around 20 percent after a second recurrence.[1–4] There has been one randomized study evaluating metronomic chemotherapy (oral cyclophosphamide + methotrexate) as a maintenance strategy following surgical remission of osteosarcoma. But that study found that chemotherapy conveyed no benefit as far as disease-free survival or overall survival.[5]

With these concerns in mind, researchers in Italy set out in 2007 to test oral etoposide and VAE therapy as two possible maintenance therapies for osteosarcoma patients who are in surgical complete remission after a second relapse. There is not yet a broad scientific base for etoposide in this situation, but it is used as an adjuvant to help prevent further recurrences. We do know that oral etoposide (50 mg/m2/daily), as a 14-day monotherapy, has demonstrated a 15 percent response rate (RR) in relapsed pediatric patients with metastatic disease.[6]

This randomized study was small and should be considered a pilot study. However, its results were striking, and the long-term follow-up is highly valuable. Ten patients received daily etoposide for three-week stretches every 28 days for six months. Nine other patients received

subcutaneous VAE therapy three times per week for a year. Researchers checked all patients' white blood cell counts at baseline (beginning of study) and at three, six, nine, and twelve months.

Results and Conclusions: In 2019, 12 years after the study began, researchers found a median PRDFS of 106 months (more than eight years) among the patients who had been provided VAE therapy. The ten-year PRDFS was 55.6 percent in the VAE arm and zero in the etoposide arm. Thus, in this long-term evaluation, more than half of the patients in the subcutaneous mistletoe group had not relapsed, while 100 percent of the patients receiving chemotherapy relapsed. The ten-year overall survival forecast was 64 percent for VAE therapy and 33 percent for etoposide. Just as striking were the effects on white blood cells. At six months, the mistletoe group experienced an increase in T-cell categories (CD_3, CD_4, and NK cells), while the etoposide group experienced a decrease in those categories.

The study authors concluded that since chemotherapeutic maintenance therapies have so far proven ineffective when this cancer recurs, "an inexpensive maintenance treatment like *Viscum* should be...further evaluated in post-relapsed osteosarcoma." They ended with a call for a larger randomized controlled trial.

Implications: The five-year overall survival for patients with relapsed osteosarcoma is around 20 percent,[7] and that has remained unchanged for the past three decades.[8] The use of immune stimulating therapy for osteosarcoma was first pioneered by Coley who injected a mixture of streptococcal bacteria into unresectable bone sarcomas in 1891, achieving an immunological reaction and tumor regression.[9] Mistletoe acts similarly (minus the potential risks) to stimulate the immune system. This study also found that the T-cell and NK (natural killer) cell lymphocyte populations increased with mistletoe but decreased with chemotherapy.

This study compared mistletoe and etoposide as individual, separate treatments. It is fascinating to note that a previous preclinical study has shown that mistletoe has a synergistic action in osteosarcoma when *combined with* etoposide.[10] Regardless, subcutaneous mistletoe alone

was highly effective for this aggressive cancer and was safely administered for a year without serious side effects.

2. M. Mabed, et al. "Phase II study of viscum fraxini-2 in patients with advanced hepatocellular carcinoma" (British Journal of Cancer *90 no. 1, Jan. 2004:65–9)*

Background and overview: Liver cancer, or hepatocellular carcinoma (HCC), is the sixth most common cancer (diagnosed in approximately half a million people per year)[11] and the second leading cause of cancer mortality worldwide.[12] With a five-year survival of 18 percent, liver cancer is the second most lethal tumor, after pancreatic cancer. Surgery is often the most effective treatment option, but HCC is frequently inoperable by the time it is diagnosed.

Since mistletoe extracts are immunologically active, the Hematology and Medical Oncology Unit at Mansoura University in Egypt sought to determine whether mistletoe therapy might be a viable alternative treatment option in advanced HCC. This was a small study (23 participants) of patients with advanced liver cancer who had not previously received systemic therapies. In all cases, their HCC was considered inoperable, and they were not candidates for transcatheter arterial chemoembolization (TACE) or percutaneous ethanol injection (PEI). All participants received a fixed dose of *Viscum album* extract from the ash (fraxini) host tree, administered subcutaneously once weekly.

Results and conclusions: While the study was small, three patients (13.1 percent) did experience a complete response (CR, defined as the complete disappearance of all known lesions on radiological imaging for at least four weeks). When evaluating all participants in this study who experienced either CR or partial response (PR), the total response rate came to 21.74 percent. This comes close to the response rate of the above mentioned atezolizumab plus bevacizumab which is 27.3 percent.[13] The median overall survival time was 29 months for the CR group.

Implications: Palliative treatment for HCC provides a modest survival benefit (two to three months) and today typically comprises

tyrosine kinase inhibitors—sorafenib (or lenvatinib) and others.[14] Immune therapies (checkpoint modification, vaccines, and cell-based therapies), either alone, or in combination with loco-regional therapies, are showing some promise in modifying the occurrence of metastatic disease and regressions.[15–17] Two extension trials (Keynote-240 and CheckMate 459) failed to show statistically significant survival benefit.[18,19] Recently though, combination therapy with atezolizumab plus bevacizumab was FDA-approved for patients with unresectable or metastatic HCC, who had no prior therapy. This Phase III trial showed significantly longer overall and progression-free survival, as well as better patient-reported outcomes than sorafenib. This combination is now a benchmark for first line treatment of advanced HCC.[20] That said, we do need to research additional adjuvants for this highly aggressive cancer.

Mistletoe is not a "protocol therapy." Ideally it is always provided at a highly personalized dosage and administration frequency, based on the individual patient's response. This foundational requirement for ideal VAE administration makes it inherently challenging to study in typical clinical study models—which depend on dosages that are identical for all study participants.

This study is a perfect example of this research challenge. The study was designed with a fixed dosage of mistletoe at a fixed interval of only once weekly. In actual clinical practice, the dosage of mistletoe is routinely escalated over time to maintain responsiveness and the interval of dosing is optimized based on patient tolerance and response. In this study, there were no measures of patient tolerance such as localized skin reaction (a hallmark of patient response used to guide clinical application), fever, or immune system response (such as lymphocyte subpopulations).

All those challenges noted, the less-than-ideal administration of mistletoe still elicited a significant positive response. It is likely that the impressive results in this study could have been even better if the design included a method of dose escalation and optimal timing similar to what is actually used in clinical practice. The study did present a

chance to observe the effects of VAE as a sole therapy in a very challenging cancer. Once again, the power of a simple, inexpensive, and well-tolerated therapy (even for those with advanced liver disease) was clearly demonstrated with subcutaneous mistletoe. Overall, *Viscum album fraxini* extract showed more than double the response rate (21.74 percent, versus less than 10 percent) compared to the usual response to chemotherapy (which was standard at the time of the study).[21–24] The response rate was similar to that achieved with expensive modern immunotherapies, which can cause serious side effects. A more recent case report series, with a similar patient population, also observed this activity of AbnobaViscum® Fraxini in advanced HCC.[25]

3. B. K. Piao BK, et al. "Impact of complementary mistletoe extract treatment on quality of life in breast, ovarian, and non-small cell lung cancer patients: A prospective randomized controlled clinical trial" (Anticancer Research *24 no. 1, Jan.–Feb. 2004:303–9)*

Background and overview: In Europe, *Viscum album* extract is often used as an adjuvant to chemotherapy, in part to improve quality of life (QOL) and to mitigate conventional treatment side effects. *Lentinan* is a shiitake mushroom preparation containing the immunomodulatory active ingredient β-1,3 beta-glucan. It is similarly used as a cancer treatment adjuvant in China, and has been the subject of numerous human clinical studies.[26–33] A 2019 review of 9,474 lentinan-associated cancer treatment cases concluded that the "overall clinical data show solid effect of lentinan on improving the QOL and on promoting the efficacy of chemotherapy and radiation therapy during cancer treatment."[34] Mistletoe therapy and lentinan are applied in similar ways and are known to convey some similar benefits.

This multi-center, randomized, open, prospective, clinical trial examined the QOL and tolerability of polychemotherapy in combination with mistletoe therapy. It compared the effects of standardized mistletoe extract (sME) Helixor® A to the effects of lentinan as an adjuvant to recommended chemotherapeutic treatment for 233 breast,

ovarian, and non-small cell lung cancer patients at three major cancer care centers in Beijing, Shenyang, and Tianjin. Both adjuvants were administered via injection. The lentinan group received daily 4 mg intramuscular injections. sME was administered via subcutaneous injections three times per week, administered in escalating dosages from 1 mg to a maximum of 200 mg, depending on patient response.

The study authors acknowledged that complete "blinding" was not possible for this comparative study, since most practitioners and many patients would be aware of the typical local inflammatory reaction associated with subcutaneous sME. The lentinan group also could not be considered a true control group, since lentinan conveys its own beneficial effects.[35]

Results and conclusions: Of the original 233 patients, 224 met the requirements for final analysis. Improvement of QOL was significantly better under adjuvant mistletoe therapy compared to control therapy with adjuvant lentinan ($p < 0.05$). There were also significantly fewer chemotherapy-related side effects under add-on mistletoe therapy. The Karnofsky index, which measures a patient's general condition (and therefore ability to tolerate chemotherapy), improved in 50.4 percent of patients in the mistletoe group and in 32.4 percent in the control group, which was statistically significant ($p = 0.002$).

As a result of mistletoe therapy, fatigue, insomnia, loss of appetite, nausea, and pain in particular improved. A total of 52 adverse events (AEs) occurred in the mistletoe therapy group and 90 in the lentinan group. Respectively, 28 and 77 were chemotherapy-related. In 5 and 10 cases, respectively, the AEs were considered severe. Most mistletoe therapy-specific AEs were overreactions at the injection site, which were self-limiting and did not need therapeutic intervention. Subcutaneous mistletoe was found to be generally safe and well-tolerated.[36]

Conclusion: In this study, patients with breast, ovarian, and non-small cell lung carcinoma showed a significant improvement in QOL and a reduction in chemotherapy-related side effects when treated with chemotherapy plus mistletoe therapy, when compared to chemotherapy plus lentinan.

Implications: This study is valuable for both its administration methods and its sheer number of participants. Many mistletoe studies do not utilize personalized escalating dosages. It's common to see a fixed-dose protocol, which generally does not work as optimally and skews the study results. It's refreshing to see that these researchers intentionally provided an escalating dosage schedule, basing the VAE dosage on patient response. This provides VAE therapy results and data that better reflect those seen in clinical practice. The larger data set is also appreciated. Mistletoe therapy is still growing its research base, and many clinical studies are admittedly small, often under 100 participants. This study's multicenter aspect and larger population (over 200 patients in the final analysis) have provided us with stronger statistics.

The primary challenge with this study, as noted by the authors themselves, is the issue with the "control group." This is more of a comparative study than a true controlled study. The substance used as a control in any study should be indistinguishable to both the participant and investigators, and it should also have a negligible effect on the study outcomes. In this study, the control has itself been shown to improve QOL and efficacy of chemotherapy, so the mistletoe extract had to overcome this positive effect in order to establish a statistical benefit. However, even with this stacked deck, the mistletoe extract was shown to significantly improve QOL and reduce AEs when compared to lentinan. Several other studies appear to observe similar results, including the study summarized next and a recent study by the Society for Cancer Research at the Hiscia Institute in Arlesheim, Switzerland.[37]

4. V. F. Semiglazov, et al. "Quality of life is improved in breast cancer patients by standardised mistletoe extract PS76A2 during chemotherapy and follow-up: A randomised, placebo-controlled, double-blind, multicentre clinical trial" (Anticancer Research *26, no. 2B, Mar.–Apr. 2006:1519–29)*

Background and overview: As we have seen in the previous study, which looked at multiple cancer types, mistletoe therapy appears to enhance QOL and mitigate side effects during chemotherapy. This

multi-center study further explored these benefits, focusing on the effects of mistletoe extract in breast cancer patients during chemotherapy and during a chemotherapy-free follow-up period. 331 patients from six cancer centers completed four to six cycles of chemotherapy (CMF: cyclophosphamide, methotrexate, fluorouracil) and began the follow-up period. Participants were women ages 18 to 55 with operable breast cancer (Stages II and III), who underwent surgery one to four weeks before starting adjuvant chemotherapy.

Because much attention has been given to the lectin component of mistletoe, the study authors selected a VAE product standardized to mistletoe lectin.[38–40] Participants were divided equally into two groups, one group receiving a placebo and the other receiving 0.5 mg of a VAE providing 30 ng mistletoe lectin/ml. Both the VAE and the placebo were administered subcutaneously, twice weekly for 16 to 24 weeks, depending on the patient's chemotherapy course. Mistletoe treatment or placebo were continued during a two-month chemotherapy-free follow-up phase.

QOL was assessed in terms of physical, emotional, and functional wellbeing. Researchers used the FACT-G Scale (Functional Assessment of Cancer Therapy-General) as a primary assessment tool.[41–43] The GLQ-8 (Global Quality of Life Scale) and Spitzer's uniscale served as secondary evaluating tools.[44–48]

Results and Conclusions: Physical, emotional, and functional wellbeing improved by 9.5 percent in the mistletoe-treated group compared to an 11.1 percent decline with the placebo. Most of the GLQ-8 factors were better in the mistletoe group as well, particularly related to tiredness, anxiety, and depression. Nausea and vomiting, common chemotherapy side effects, were also improved in the mistletoe group. VAE therapy was found to be tolerable and safe. The only reactions noted were those associated with a normal, mild reaction at the mistletoe injection site. The only adverse events that were observed were those associated with CMF chemotherapy.

Implications: When looking at the supportive effect of VAE therapy and the decline in wellbeing in the placebo group, the difference

between the two groups is over 20 percent. This is a significant course-altering difference. The side effects of CMF chemotherapy can be harsh enough that patients discontinue their treatment plan. Improving general wellbeing by 20 percent can be the difference between staying the course or discontinuing conventional treatment.

We've witnessed this indirect benefit frequently in clinical practice. When wellbeing is bolstered and side effects are held at bay, patients are able to persist with more aggressive conventional treatment. Hopefully in the future we will see even larger studies that analyze this effect on treatment completion.

5. A. Rose, et al. "Mistletoe plant extract in patients with nonmuscle invasive bladder cancer: Results of a phase Ib/IIa single group dose escalation study" (Journal of Urology *194 no. 4, Oct. 2015:939–43)*

Background and overview: Most bladder cancer cases (75 to 85 percent) can be classified as nonmuscle invasive bladder cancer (NIBC), meaning limited to the mucosa inside the bladder and not invaded into surrounding muscle tissue.[49] Standard treatment focuses on surgery (transurethral bladder resection or TURB). Recurrence after TURB ranges from 50 to 70 percent depending on tumor stage and grading. Historically, intravesical chemotherapy (for intermediate and high-risk cases) or immunotherapy with Bacillus Calmette-Guerin (BCG, for high-risk) has been found to significantly reduce this risk of recurrence.[50,51] These therapies can have unwanted side effects (for example, generalized mycobacterial infection after BCG or severe symptoms of cystitis), which has motivated exploration of other adjuvant therapies that could possibly reduce recurrence.[52,53]

Mistletoe extract can be administered as an intravesical therapy (also referred to as bladder instillation). Intravesical therapies are administered directly into the bladder through a catheter. The therapeutic agent is held in the bladder for a planned duration of time, usually up to two hours, then released through urinating. This administration route can provide direct cytotoxic effects at the tumor site.

The focus of the study was to determine the upper-limit dosage (due to side effects or toxicity) of mistletoe that could be used in this manner. While this was a dose tolerance and safety study, some efficacy evaluation data were also provided "to be interpreted in a strictly exploratory sense." A standard 3 + 3 design was used to determine the upper-limit dose. In this design, three patients at a time were given a starting dosage (in this study, 45 mg for the first group) for six weeks, then if no toxicity was seen, another group of three patients were provided the next higher dose. This was repeated until the final group received the maximum dosage studied of 675 mg.

Before the study, all 36 participants had their bladder tumors removed, except for one small marker tumor that could be checked as a reference for treatment efficacy. Starting two weeks after the resection, patients were treated with weekly instillations of mistletoe extract for six weeks. Twelve weeks after the start of instillation therapy, the patients underwent transurethral resection of the marker tumor or a biopsy of the former marker tumor location, so they were tumor-free when entering the follow-up period, which lasted until week 48. During the follow up, cystoscopy was done every 12 weeks to monitor for recurrence.

Results and conclusions: The dosages ranged from 45 to 675 mg with no observed toxicity. Furthermore, it was concluded that a dose limiting toxicity "could not be expected at higher doses." Bladder instillation of VAE was determined to be safe and well-tolerated, even though the 3+3 study design meant that the dosages were provided in a fashion that was nothing like the individualized approach used in normal clinical practice.

After 12 weeks, the marker tumor had disappeared in 55.6 percent of the patients and, at a one-year follow-up, the recurrence rate for all the patients was 26.3 percent. According to European Association of Urology (EAU) guidelines, the forecasted one-year recurrence rate for these patients would have been 24 to 38 percent.[54,55] It seems even this very limited administration of mistletoe may have helped patients reach the low end of their typical recurrence range.

Implications: Bladder instillation of VAE is considered a novel administration method in the U.S. (see chapter 10). This tolerable dose study helps to establish the credibility and safety of this alternate administration route. This study highlights the versatility of mistletoe, since we now have reviewed studies that show a dramatic impact on cancer using subcutaneous, IV, and now bladder instillation. Keep in mind that, in clinical practice, these various routes of administration are often combined to achieve maximal benefit for the patient.

Despite the fact that VAE was not administered in a typical clinical fashion, participants still experienced some benefit from the therapy. This is a remarkable result given the wide range of dosages. The study did not report response-dosage correlation since that was not the intent. A confirmatory Phase III trial is currently underway.

6. W. Tröger, et al. "Viscum album (L.) extract therapy in patients with locally advanced or metastatic pancreatic cancer: A randomised clinical trial on overall survival" (European Journal of Cancer *49, no. 18, Dec. 2013:3788–97)*

Background and overview: Patients with late-stage pancreatic cancer have few treatment options. Possible chemotherapies typically include FOLFIRINOX, gemcitabine and nab-paclitaxel, which show some benefit in terms of disease control, but side effects can be severe, and treatment is not possible or effective in many of the patients.[56,57] The research community has been exploring therapeutic alternatives that may be gentler, but still provide some level of efficacy. As far as VAE's effects in pancreatic cancer, at the time of this 2013 study, one animal study and one human study had already seen some benefits, but these studies focused on intratumoral injection. Little was known about the effects of subcutaneous VAE in pancreatic cancer care.[58,59]

This study looked at the effects of subcutaneous VAE (Iscador® Quercus) in locally advanced (Stage III) or metastatic (Stage IV) pancreatic cancer, compared to a control group that was provided "best supportive care." Study participants had at least a one-month life expectancy but were determined ineligible for any chemotherapeutic

options. While randomized and controlled, the study was open label (not blinded). Per FDA guidelines, blinding is not necessary in "studies with overall survival as a primary end point."

The mistletoe was administered three times per week in a fixed escalation schedule up to a maximum of 10 mg per injection. If patient reaction to the VAE therapy exceeded clinically expected parameters (for injection site reaction or body temperature), the dosage for that patient "was to be reduced to the last well-tolerated dosage."

Results and conclusions: 220 patients were analyzed at the interim (mid-study) evaluation. The median overall survival (OS) in the mistletoe group was 4.8 months compared to 2.7 months in the control group (hazard ratio [HR] = 0.49; $p < 0.0001$)—with control group OS found to be consistent with life expectancy for similar pancreatic cancer cases in the literature. In two following subgroup analyses, in which the patients were divided according to a prognosis index, the median survival time in the group with "good prognosis" was 6.6 months for the patients with mistletoe therapy and 3.2 months for the control group (HR = 0.43; $p < 0.0001$). In the group of patients with "poor prognosis" the corresponding survival times were 3.4 and 2.0 months respectively (HR = 0.55; $p < 0.0031$). Additionally, 15 percent of the mistletoe treated group were able to finish the 12-month study with a regular follow-up visit, while none of the placebo group were well enough to do this.

The interim results were so dramatic that the independent reviewing organization stopped recruitment into the study early due to the proven effectiveness of the mistletoe. *They also decided to provide mistletoe to all the remaining patients in the study, since it was deemed "medically unethical" to not provide mistletoe to everyone.*

Most of the parameters for QOL were also significantly different between the two groups. For example, a QOL questionnaire designed for patients with cancer (the EORTC QLQ-C30) showed a significant and clinically relevant advantage in the mistletoe therapy group in 13 of its 15 dimensions. The significant improvement was also reflected in the reduced number and severity of cancer-related symptoms during

treatment. In particular, cancer-related pain was significantly lower, which was accompanied by a significant reduction in analgesics. In addition, nausea and vomiting as well as loss of energy and appetite were significantly less severe. Despite all expectations, the investigators even observed a slight weight gain in patients of the mistletoe therapy group.[60]

Implications: This study found that, even with one of the most aggressive forms of cancer, VAE therapy can improve OS. The positive effects on tumor-related symptoms, notably pain and weight loss, were striking. It is good to see that the personalized escalating-dosage method typically used in clinical practice was indeed applied in this study, though the study design did limit the maximum dosage to 10 mg per injection. In actual clinical practice, the dosage would likely be increased over time to maintain patient response. Regardless, the findings in this study are striking and the larger participant base affords us some stronger statistics.

This study validates VAE therapy as an extremely valuable therapy, with minimal side effects, for one of the most difficult cancers. A study designed in a similar way to investigate these results is currently underway in Sweden.[61]

7. F. Schad, et al. Overall survival of stage IV non-small cell lung cancer patients treated with Viscum album L. in addition to chemotherapy, a real-world observational multicenter analysis (PLoS One, *Aug. 2018)*

Background and overview: Accounting for 25.9 percent of all cancer-related deaths in 2017, lung and bronchial cancer ranks first position, followed by breast, colon and rectum, prostate, and pancreatic cancer. Over one half of primary non-small cell lung cancer (NSCLC) patients are already diagnosed with Stage IV lung cancer. Median overall survival (OS) for these patients ranges between 7.0 and 12.2 months.[62]

The authors of this study noted that "stage IV NSCLC is one of the most devastating diagnoses of lung cancer, [and so] worldwide great

effort is done in the search for new treatment solutions—i.e., reflected by the vast clinical research on CTX-combinations in the past and accelerated approval of new immuno-oncological treatment in the U.S. and Europe in recent years."[63,64] Despite reported efficacy, the tolerability of current modern oncological treatment with respect to side effects, QOL, and palliative care, remains an important issue.[65] The medical community continues to look for a treatment regimen that is both effective and safe.

Mistletoe extracts are applied in integrative oncology alongside conventional SOC to improve QOL. The potential beneficial effects on cancer patient survival are accumulating.[66] This observational study aimed to evaluate the effect of adjuvant mistletoe therapy on the survival of Stage IV NSCLC patients who also received SOC treatment.

This non-randomized, multi-center, observational study analyzed 158 patients with histologically confirmed Stage IV NSCLC. The data were obtained from the clinical register of the Network Oncology (NO) database. To determine the influence of mistletoe therapy on survival time, data from two patient groups were included. One group of 108 patients received only chemotherapy, and the other group of 50 patients received a combination of chemotherapy and mistletoe therapy. Only patients who were still alive for at least 28 days after diagnosis were analyzed. The average age was about 64 years; there were no statistically significant differences between the two groups.

First-line chemotherapy consisted of platinum compounds (73.4 percent), often in combination with gemcitabine, pemetrexed, vinorelbine or etoposide. Patients receiving additional mistletoe therapy (with AbnobaViscum, Helixor, or Iscador) typically received subcutaneous administration, sometimes in combination with IV infusions (off-label).[67]

Results and conclusion: Median overall survival was 17 months in the group with additional mistletoe therapy compared to 8 months in the group receiving chemotherapy alone. The difference was statistically significant ($p = 0.007$). The one-year survival rate was 35.5 percent in the chemotherapy group compared to 60.2 percent in the group

with additional mistletoe therapy, and the three-year survival rate was 14.2 percent compared to 25.7 percent.

The results of this real-world data study suggest that patients with Stage IV NSCLC who received combined chemotherapy and mistletoe therapy have a significantly longer survival than patients who received chemotherapy alone. The authors suggest that these real-world observational findings should be complemented by prospective randomized studies.

Implications: The merit of this study is the fact that it examines findings from everyday clinical practice. It's not a randomized trial, which would be affected by inclusion and exclusion criteria. This was not a selected population, rather it looked at the overall effects of adjuvant mistletoe therapy as applied by clinicians.

The statistics were calculated in a conservative manner, and the authors were astonished to find a survival benefit this significant. Palliative chemotherapy for metastasized lung cancer, on average, improves survival by two months. That is a modest benefit. When speaking with an individual patient, it is powerful to be able to offer a simple therapy in this palliative situation that could significantly enhance the chance of one-year and three-year survival.

8. M. Orange, et al., "Durable regression of primary cutaneous b-cell lymphoma following fever-inducing mistletoe treatment: Two case reports" (Phytomedicine *20, Issues 3-4, Feb. 2013: 324–27)*

Background and overview: Primary cutaneous lymphomas account for 5 percent of non-Hodgkin's lymphoma. Among the subtypes, primary cutaneous B-cell lymphomas (PCBCL) are even less common, accounting for up to 25 percent of primary cutaneous lymphomas.[68–70] Some of the subtypes occur alongside an autoimmune tendency (i.e., rheumatoid arthritis).[71–75] These lymphomas respond best to immunological treatments such as intratumoral injections of interferon-α.[76] Intratumoral therapies, in which a therapeutic agent is injected into the tumor itself, are occasionally seen to convey an

abscopal effect—when treatment of a primary tumor results in reduction or full remission of other lesions.[77]

Mistletoe therapy is typically administered via subcutaneous (SC) injections, but it has also been studied and administered as an intratumoral (IT) therapy (see chapter 10). Higher doses, through IT, SC, and intravenous (IV) therapy, have been shown to induce therapeutic fever in *mistletoe-naïve patients* (those who have not received VAE therapy before). These fever-inducing dosages have been associated with tumor reduction and remission.

In 2008, two patients with primary cutaneous lymphoma sought integrative treatment at Park Attwood Clinic (PAC) in England. Both patients had, of their own volition, decided to forego or delay conventional treatment options, wishing to try mistletoe therapy first.

CASE 1

A 51-year-old female, in good health otherwise, presented with two lesions on the lower part of her left leg. One lesion had developed smaller satellite lesions. This was confirmed as grade 1 follicular B-cell lymphoma. The patient was generally healthy with no allergies or history of infections. She did not smoke or drink and wasn't taking any medications. A bone marrow biopsy was normal, but she did have one swollen inguinal lymph node. SOC recommendations were: systemic immunochemotherapy followed by radiation. The patient came to PAC wishing to delay the SOC plan and "keep it in reserve," while trying VAE therapies first.

Treatment and Outcomes: The patient and her practitioner team developed a plan combining IV, IT, and SC mistletoe over the course of one year, and then continued IV and SC mistletoe for another eight months (*AbnobaViscum Fraxini*). She also received multiple treatments of whole-body hyperthermia (WBHT, medical hyperthermia; see chapter 9). No other cancer treatments were administered during this time.

IT injections were administered from the margins of the lesions, to avoid the very thin skin over the tumors. The patient experienced four febrile (fever) responses during the initial fever induction phase. The lesions swelled (as expected) initially, then

began to regress. Regression accelerated with WBHT, and after four months the lesions were significantly reduced. Remission was assessed by three independent clinicians and confirmed by scans in May 2009. IT therapy was stopped at this time, and the patient continued with the eight months of IV and SC therapy along with WBHT. Complete remission had been maintained as of reviews in both June and December 2011.

All therapies were generally well tolerated. IV and IT therapies caused some transient fatigue, and swelling from the IT injections caused discomfort, but not enough to warrant analgesics. The patient referred to the fever therapies as intense and "the only thing I could do during that time." She also stated that, "During one of the high fevers an old traumatic experience became disentangled, and I have felt freed up since; I now feel better than before my cancer, physically and emotionally."

CASE 2

A 52-year-old male was diagnosed with stage 2A primary cutaneous marginal zone B-cell lymphoma (PCMZL). An initial lesion on the inside of his left elbow (left antecubital fossa) was excised and found to show evidence of nodal marginal zone lymphoma. Shortly thereafter, another lesion formed on his chest, near his right shoulder. The patient was otherwise asymptomatic with no signs of systemic disease on a CT scan. However, he did have a history of other conditions including: two basal cell carcinomas (excised), actinic keratoses (precancerous condition) on his back, rosacea, and keratitis, as well as facial cutaneous scleroderma (autoimmune condition). He reported no allergies or recent infections and was not taking any medications. He did use nicotine and drank moderately. SOC recommended either R-CVP chemotherapy followed by radiation or six months of pulsed chlorambucil. The patient had declined both options.

Treatment: The patient and his practitioner team decided on combined IV, IT, and SC mistletoe therapy (AbnobaViscum Fraxini). The patient understood that mistletoe could possibly aggravate his autoimmune condition. The combination therapy schedule lasted a little over eight months, and no signs of autoimmune reactivation or hypersensitivity were observed. During the induction

phase, the patient experienced six febrile responses. The lymphoma lesion showed expected swelling after IT injections. The lesion initially increased in size (referred to as *pseudo progression*, see appendix B) and then, when the IT dose reached 100 mg, the tumor began to regress. Complete remission was reached at 8.5 months and confirmed by three independent clinicians. IT injections were discontinued in April 2009, while IV and SC mistletoe continued until November 2010.

The patient described the first three months of fever therapies and inflammatory responses as challenging and fatiguing. But after six months, he was stronger and regularly reported "improved vitality and wellbeing." When commenting on his treatment choice, he said, "The treatment itself, whilst challenging, confirmed my feeling that it was the bedrock, the main stay [sic] of being healed."

***Implications** (Contributed by Dr. Nasha Winters)*: Both patients were still in remission three years later when these case reports were published. This response seems quite consistent with every person with lymphoma whom I have supported. Most patients and practitioners are under the impression that solid tumor types are the only cancers that best respond to mistletoe therapy. However, in my personal clinical experience, along with that of many of my colleagues, lymphomas seem to respond beautifully to this powerful remedy.

VAE is normally used alongside conventional treatment. I have also seen it offer some rather extraordinary outcomes with lymphoma, both as a treatment *after* SOC has failed the patient, and *before* SOC is initiated. When I first used VAE therapy in a lymphoma case, patients wanted to prepare and support their body for chemotherapy by using subcutaneous mistletoe for two months prior to SOC treatment. Instead, toward the end of their VAE course, the enlarged lymph nodes and other symptoms had resolved and were no longer visible on scans. All the Terrain-based Core Lab Tests (see chapter 5) had normalized, including LDH (which can be elevated in more aggressive lymphomas).[78] None of us had expected that. This experience, and case stories like those above, have led me to use VAE therapy as a "first resort" in

patients rather than a last. Each patient reports improved QOL in addition to symptom resolution and reduction in tumor burden. It is highly unusual for mistletoe therapy to be used as a stand-alone therapy, but we do see some preliminary successes like these with B-cell lymphoma cases. Much more research is clearly needed.

9. G. S. Kienle, et al. "Intravenous mistletoe treatment in integrative cancer care: A qualitative study exploring the procedures, concepts, and observations of expert doctors" (Evidence-based Complementary Alternative Medicine, *2016, ePub, Apr. 2016)*

Background and Overview: Mistletoe therapy is innately difficult to research because it is the most effective when administered in a highly individualized fashion. As mentioned earlier, quantitative clinical research models frequently depend on fixed dosages and treatment timelines for all study participants—the opposite of individualized dosing. In contrast, this particular research initiative was a qualitative study, meaning the researchers interviewed doctors who provide mistletoe therapy, to learn more about the actual use and possible effects of VAE therapy in clinical practice. The research team hoped to discover commonalities in administration choices and possible treatment effects that are harder to draw out of randomized, controlled trials.

Originally the team sought to explore more broadly "the concepts, goals, procedures, and observations associated with individualized cancer care" as well as specific uses of mistletoe therapy in practice. Initial inquiries yielded the finding that "physicians often stress the importance and potential of intravenous application of [VAE], which differs from normal subcutaneous...treatment." That discovery led to the development of this focused inquiry regarding intravenous (IV) administration of mistletoe extracts.

Interview subjects came from a pool of doctors highly experienced in the use of IV mistletoe therapy for cancer. They were selected through purposive sampling to ensure a broad range of specializations and countries. Intensive interviews (up to five hours) were conducted

with 35 physicians between 2009 and 2012. Interviews began with a warm-up question, then commenced with the subjects first providing un-influenced case stories, then completing a consistent checklist interview. The interviews were transcribed and charted to find thematic repetitions. Two members of the research team conducted data analysis using MAXQDA (qualitative data analysis software).

Findings: The research team found a consensus on the reasons for applying IV mistletoe. Reasons focused on the IV therapy's ability to:

- address diminished responsiveness to subcutaneous mistletoe injections;
- stimulate the immune system with induction of a fever reaction;
- support patients who have a high risk of recurrent disease;
- improve tolerability of chemotherapy and enhance overall QOL;
- stabilize the patient during advanced or progressive disease;
- address specific tumor situations that have responded poorly to other treatments.

As far as the effects of IV mistletoe, physicians were careful about pinpointing specific causal relationships. This is, indeed, hard to do within a truly integrative setting: *Did the patient's improvement occur because of mistletoe or some other therapy, or the synergy of multiple therapies?* Still, several observed benefits were noted repeatedly throughout the interviews, namely: overall improved QOL and patient vitality demonstrated through improved day-to-day activities (i.e., walking farther or with less assistance); increased strength, energy, and focus; improved appetite and sleep; and often improved toleration of chemotherapy. Interestingly, IV mistletoe was not regarded as a pain-reducing therapy unless pain was associated with bone metastases, in which case it did seem to help. Physicians also did not regard IV mistletoe as a specific therapy for tumor reduction or remission. However, they consistently shared examples of IV mistletoe helping with "long-term disease stabilization." It appeared to help people live longer with greater QOL, while managing an aggressive disease.

Implications: Mistletoe therapy is best utilized as a therapeutic system that synergizes with all other aspects of integrative care. It needs to be individually applied, personalizing dosage and dosage rhythm, as well as administration route. In this way, physicians tailor VAE therapy to the specific medical condition and complaints of the patient; to his or her emotional, mental, spiritual, and social needs; and to his or her respective goals. Experienced doctors recognize that IV mistletoe should not be used in a formulaic or highly standardized manner (i.e., "green chemo"), but must be incorporated within a holistic approach to healing.

This on-the-ground patient-centric understanding is crucial for any new mistletoe practitioner. Such nuances are impossible to learn from reading quantitative study findings only. New practitioners become skillful in mistletoe therapy through long-term mentoring. As stated by the authors, "The main strength of this study is the richness of information, arising directly from everyday clinical practice and from doctors who took care of their patients, often over years or even decades." Such narrative knowledge is invaluable when learning how to effectively administer such a nuanced therapy.

Still, both quantitative and qualitative research findings are needed. Both approaches help grow mistletoe's research base and our own understanding of its effects. Indeed, the study authors ended with a call for more *quantitative* clinical studies focused on some of the specific topics that emerged from their interviews. This includes exploring whether and how VAE might mitigate: cancer-related fatigue, weakness, and cachexia; pain from bone metastases; and chemotherapy side effects. As future researchers continue to explore these lines of inquiry, through both quantitative and qualitative means, new findings will empower practitioners to administer mistletoe with even greater insight and skill.

PART 2:

MISTLETOE IN CLINICAL PRACTICE

"If we treat people as they are, we make them worse. If we treat people as they ought to be, we help them become what they are capable of becoming."

—JOHANN WOLFGANG VON GOETHE