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MISTLETOE FOR CANCER? A SYSTEMATIC REVIEW OF RANDOMISED CLINICAL TRIALS

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Mistletoe extracts are widely used in the treatment of cancer. The results of clinical trials are however highly inconsistent. We therefore conducted a systematic review of all randomised clinical trials of this unconventional therapy. Eight databases were searched to identify all studies that met our inclusion/exclusion criteria. Data were independently validated and extracted by 2 authors and checked by the 3rd according to predefined criteria. Statistical pooling was not possible because of the heterogeneity of the primary studies. Therefore a narrative systematic review was conducted. Ten trials could be included. Most of the studies had considerable weaknesses in terms of study design, reporting or both. Some of the weaker studies implied benefits of mistletoe extracts, particularly in terms of quality of life. None of the methodologically stronger trials exhibited efficacy in terms of quality of life, survival or other outcome measures. Rigorous trials of mistletoe extracts fail to demonstrate efficacy of this therapy.

Key words: *mistletoe; alternative medicine; viscum album; cancer*

"Alternative" cancer cures remain in widespread use.[1] Particularly in continental Europe, mistletoe (*viscum album*) extracts (anthroposophical or herbal remedies) are amongst the most popular such therapies.[2] More than US $30 million is spent on mistletoe extracts annually in Germany and the yearly increase in sales has been estimated at 20%.[3] It is therefore important to ask whether mistletoe extracts are of benefit to cancer patients. Numerous clinical trials have attempted to answer this question with highly varying rigour and results, *e.g.*, the study of Majewski and Bentele.[4] Several reviews have summarised the clinical evidence, for example, references 5–10. The only *systematic* review of the subject concluded in 1994 that "the use of mistletoe extracts in the treatment of cancer patients [cannot be recommended] with an exception for patients involved in clinical trials."[10] This review included nonrandomised studies and may therefore have been open to bias. Moreover, it is now outdated as several new trials have emerged.

The current article is aimed at critically evaluating the evidence for or against mistletoe extracts as a treatment of cancer from all randomised clinical trials available to date.

MATERIAL AND METHODS

Systematic literature searches of Medline, Embase, BIOSIS, AMED (British Library), Scirusa, Clinical trials.com, CISCOM (Research Council for Complementary Medicine, London, UK) and the Cochrane Library (all from their respective inception to July 2002) were performed to identify all randomised clinical trials of mistletoe for any type of human cancer. The search terms were alternative medicine, cancer, controlled clinical trial, Eurixor®, Helixor®, Iscador®, lectin, malignancy, Mistel, mistletoe and derivatives. In addition, manufacturers of commercial mistletoe products and other experts were asked to contribute published as well as unpublished material, and our own extensive files were hand-searched. A manual search was also performed of the bibliographies of studies and reviews located through the computer searches and through scanning our own files.

All prospective, randomised clinical trials (RCTs) conducted with human cancer patients were considered. RCTs were excluded if they only reported nonclinical outcome measures, *e.g.*, immunological parameters, or failed to include an adequate comparison group (*e.g.*, one mistletoe preparation *vs.* another). Dual publications were only included once. All mistletoe preparations were considered, including pure mistletoe lectin preparations. No language restrictions were imposed. Both adjuvant and mono-therapy trials of mistletoe extracts were considered. Data extraction and validation were performed by 2 authors and checked by the third author using standardised, predefined criteria: study design, sample size, patient description, interventions, primary endpoints and main results. The scoring system developed by Jadad *et al.*[11] was used to evaluate methodological quality (Table I). Statistical pooling of data had been anticipated, however, due to the heterogeneity of the primary studies, this plan had to be abandoned.

RESULTS

Ten RCTs met our inclusion criteria. Key data are summarised in Table I and described in narrative form below.

Douwes and colleagues[12] randomised 60 patients with histologically verified metastatic colorectal carcinoma into 3 groups. Group A received only chemotherapy (5-fluoruracil and folinic acid), group B was treated with the mistletoe extract Helixor® (slow, insidious commencement up to a dose of 200 mg daily subcutaneous) plus chemotherapy and group C were treated with xenogenic peptides (Ney Tumorin®) plus chemotherapy. The frequencies of complete remission, partial remission, minimal response, tumour standstill and progression were similar in all groups. Mean survival time in groups A and B was about twice that of group C.

It is unclear which of these endpoints was the primary outcome measure; the text implies that remission rates were the primary and survival the secondary endpoints. The total number of chemotherapy cycles in each group was not adequately reported. It was not mentioned how many injections of Helixor® or Ney Tumorin® were actually administered and other concomitant biological treatments were administered but inadequately accounted for. Finally, this trial was not patient-blinded.

Dold *et al.*[13] assessed the effects of Iscador® (group A) compared to Polyerga® (group B), a glycopeptide extracted from the spleen of sheep, with a multi-vitamin "placebo" (group C) in 408 patients with histologically confirmed advanced nonsmall-cell carcinoma. Iscador® Q (oak tree) and Iscador® U (elm tree) were used both with Hydrargyrum D8 (dilution 10^{-8}). Patients were stratified according to clinical severity and stages groupings. The total drop-out rate was 17%, yet no intention-to-treat analysis was

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carried out. Median survival was 9.1 (95% CI: 6.8–10.7) months, 9.0 (7.1–11.5) months and 7.6 (6.0–8.9) months for groups A, B and C, respectively. Two-year survival was 11.5%, 13.9% and 10.1%, respectively. None of these differences was statistically significant. Quality of life (measured with the Karnofsky Index) was similar in all 3 groups. However, more patients in group A experienced improvement of their general well-being.

Even though this was a relatively rigorous trial, it is not flawless. The lack of patient-blinding renders the subjective endpoints of debatable value. The high dropout rate may have jeopardised comparability between groups. No intention-to-treat analysis was performed. There was no check of compliance, and the authors fail to mention the number of Iscador® injections that the patients actually received. The study was published in book form and has therefore not passed the usual peer-review process.

Salzer *et al.*[14] randomised 218 patients with histologically verified nonsmall-cell bronchial cancer to receive the mistletoe extract Iscador® (group A) or no treatment (group B) in addition to conventional care. The report lacks many methodological details essential for evaluation. The authors state that Iscador® is clinically "clearly advantageous, however, from a statistical point of view, there is no significant difference. . .." The Kaplan-Meier curves presented in the article suggest a better survival rate of the experimental compared to the control group, which becomes apparent after 2–4 years of therapy.

This report provides little data essential for critical evaluation. The most reliable hard endpoint is the rate of patients remaining free of recurrences, which does not show a statistically significant effect.

Lenartz and colleagues[15] randomised 35 patients with histologically verified glioma (stage grouping III or IV) to receive either a mistle lectin-1 (ML-1) standardised mistletoe extract (1 ng ML-1 per kg twice weekly for 3 months) or no such treatment in addition to conventional care (*e.g.*, surgery and radiation). A range of immunological parameters served as primary outcome measures and quality of life (Spitzer questionnaire) was quantified as a secondary endpoint. After 24 weeks of therapy, there was a difference between the 2 groups of about 1.5 points on the Spitzer scale. The authors report no statistical assessment (nor exact numbers with standard deviations) but note that there was "a considerable improvement for the verum group." Four years after their initial publication, a (not identical) team of authors reported the survival rates of this trial after a total follow-up of 50 months. No beneficial effect was noted in the total patient group. A subanalysis of stage grouping III/IV patients, however, demonstrated a significant prolongation of the overall survival in the therapy group (20.05 ± 3.5 months *vs*. 9.90 ± 2.1 months).[16]

This study has several obvious drawbacks. The clinical endpoints were employed as secondary outcome measures, and no evaluable results are presented for quality of life. Lack of patient-blinding, absence of adequate descriptions of randomisation or dropouts/withdrawals and the small sample size constitute further weaknesses. Most importantly, the 2 published reports of this study are highly inconsistent. In the first article,[15] the sample size is 35, while in the second,[16] it is 38. In the first article,[15] only stage grouping III/IV patients were mentioned, while in the second publication[16] the authors differentiate between analyses of all stages and one of stage grouping III/IV patients only.

Heiny and Albrecht[17] randomised 79 patients with advanced colorectal cancer into 2 groups. The control group received standard care (5-fluorouracil), while the experimental group received in addition Eurixor® (0.5–1 ng ML-1 per kg every 72 hr for 8 weeks, followed by 4 weeks no treatment and repeat of cycle). The results showed that significantly fewer patients in the experimental group suffered from mucositis stage III. Similarly, the average length of this complication was significantly shorter in this group. There were no significant differences for remission rates, length of remission, recurrence-free interval or survival time. The primary endpoint of this study was quality of life that was quantified with a visual analogue scale (VAS). This parameter significantly favoured mistletoe. After 7 weeks of therapy, the difference amounted to 18 mm on a 100 mm VAS.

This study is burdened with several problems. The authors state that 107 patients participated in the trial but only 79 were randomised. They note that the study was randomised but continue to explain that it followed a matched pair design. As the numbers in the 2 groups were not equal, a proper matching seems implausible. They also mention that quality of life was measured with a verbal rating scale but present the results of a VAS in mm. The study was not patient-blinded and subjective outcome measures could therefore be unreliable.

Kleeberg *et al.*[18] reported results for the EORTC Melanoma Cooperative Group (so far only) in the form of an abstract. Melanoma patients were randomised into 3 groups: low dose r IFN-α2 (iMU) or r IFN-γ (0.2 mg) both subcutaneous qod for 12 months or to placebo. All patients received standard care in addition. The German Association of Medical Oncology added a 4th group to this trial. It consisted of patients treated with Iscador® (subcutaneous twice per week) and monitored every second month with a quality of life measurement. Time to progression and length of survival were the primary outcome measures. Analysis was by intention to treat. Eight hundred thirty patients were followed for 5.5 years on average. Comparisons were stratified by melanoma stage grouping at randomisation. Compared to placebo, the relative risk in the Iscador® group for disease-free interval was 1.33 (95% CI 0.93–1.89). The authors conclude that "the clinical benefits of . . . Iscador are most likely not important." This study is difficult to evaluate because the abstract lacks sufficient detail.

A widely mailed document from Madaus, Germany described the following multicentre trial of Lektinol®, a ML-1 standardised preparation.[19] Two hundred seventy-nine women with breast cancer (T1-3 NO-N+ MO) were randomised after surgery into 4 groups: 5, 15 and 35 ng ML twice weekly for 15 weeks or placebo. The study was double-blind. Two hundred sixty-two patients were included in the intention-to-treat analysis. The treatment group receiving the intermediate dose showed a significant advantage in terms of quality of life (VAS, GLQ8 and Spitzer Scale). The 2 other experimental groups yielded results that were similar to those of placebo.

The results of this study look encouraging. Unfortunately it has not yet been published in a peer-reviewed journal (the manufacturer informed us that publication of this trial is not planned). As the frequency of local adverse reactions increased with increasing doses, patient-blinding may have been inadequate, which would seriously weaken the quality of life results. The short promotional text from the manufacturer may not be the best source of reliable information, and critical evaluation of these data is therefore not possible.

Grossarth-Maticek *et al.*[20] reported 2 RCTs including 49 and 17 matched pairs of patients with various cancers with various stage groupings. These patients received either Iscador® (no mention of host tree) or no such adjuvant therapy. Neither the dose, the type of Iscador® injected nor the treatment schedules were documented. The authors report significantly longer survival times (3.5 *vs* 2.5 years and 4.8 *vs*. 2.4 years, no standard deviations provided) for the experimental groups.

This study is either poorly reported or poorly conducted or both. A detailed commentary is available elsewhere and casts serious doubt on the rigour of this study.[21] The data provided are incomplete, confusing, contradictory and therefore of debatable value. Information is insufficient in respect of informed consent, study design, randomisation and treatment schedule. No entry has therefore been made of this study in Table I.

Steuer-Vogt and colleagues[22] studied a total of 477 patients with head and neck squamous cell carcinoma. Patients in the experimental group received subcutaneous injections of a mistletoe extract (Eurixor®) with a standardised amount of mistletoe lectin 1 (1 ng/kg bodyweight, twice weekly over a 60-week period). Treat-

TABLE I – RANDOMISED CLINICAL TRIALS OF MISTLETOE FOR CANCER[1]

First author (year)	Jadad score	Study design	Sample size	Patient description	Experimental interventions* (host tree)	Control interventions	Primary outcome measures	Main results	Comments
Douwes (1986)	3	Three parallel groups	60	Metastatic, colorectal CA, histologically confirmed	A) Helixor® (apple or fir) B) Ney Tumorin®	C) No such treatment	Remission rate, survival time	No significant inter-group differences	Survival favoured groups A and B
Dold (1991)	3	Multicentre, 3 parallel groups	408	Advanced, nonsmall-cell bronchial CA, histologically confirmed	A) Iscador® Q and Iscador® U with Hydrargyrum D8 (elm and oak) B) Polyerga®	C) Placebo (multi-vitamin)	Survival time, tumor growth, well-being	No significant inter-group differences in terms of survival, well-being favoured Iscador® therapy	Rigorous study but not free from flaws, subjective results (wellbeing), not reliable (no patient blinding), authors' conclusions negative
Salzer (1991)	2	Two parallel groups	218	Nonsmall-cell bronchial CA, histologically confirmed	A) Iscador® (unclear)	B) No such adjuvant therapy	Percentage of patients free from recurrences, mortality	No significant inter-group differences (50 *vs.* 55%), mortality 59% *vs.* 56%	Report lacks essential details
Heiny (1991)	3	Two parallel groups	46	Advanced breast CA	A) Eurixor® (poplar)	B) Placebo injections	Leukocyte and platelet counts; quality of life and anxiety were secondary endpoints	Significant advantage for A in terms of wellbeing and anxiety	No patient blinding, thus subjective endpoints not reliable
Lenartz (1996 and 2000)	1	Two parallel groups	35	Glioma, all stage groupings (histologically confirmed)	A) Eurixor® (poplar)	B) No such adjuvant therapy	Leukocyte count and other surrogate variables; quality of life was a secondary endpoint; relapse free and overall survival was reported in a 2nd publication	"Considerable improvement in quality of life"; no survival differences in total sample, for stage grouping III–IV patients, a significant effect on survival was shown in the experimental group (20.1 *vs.* 9.9 months)	No test statistics for quality of life
Heiny (1997)	1	Two parallel groups	79	Advanced colorectal CA	A) Eurixor® (poplar)	C) No such adjuvant therapy	Quality of life	Significant inter-group difference in favour of mistletoe	Multiple problems raise concern about the validity of this study
Kleeberg (1999)	n.a.	Four parallel groups	830	Melanoma after curative resection of high risk primary (> 3 mm)	A) r IFN-α2	D) Placebo	Disease-free survival, length of survival, relapse rate	No differences that indicate efficacy of Iscador®	Trial so far only reported as an abstract

					B) r IFN-γ C) Iscador® (unclear)				
Schaefer (2000)	n.a.	Four parallel groups, double-blind	272	Breast cancer (T 1–3 NO-N+MO)	A) Lektinol® low dose	D) Placebo	Quality of life (and immunological variables)	Significant advantage for B versus D in terms of quality of life	Only manufacturers' brochure available, no dose response relationship
					B) Lektinol® intermediate dose C) Lektinol® high dose (poplar)				
Steuer-Vogt (2001)	3	Two parallel groups, stratified for conventional therapy	477	Head and neck squamous cell CA	A) Eurixor® (poplar)	B) No such adjuvant therapy	Disease-free survival, 5-year survival rates, relapse rates, quality of life	No significant inter-group differences	Details regarding quality of life to be published
Kleeberg (1999)	n.a.	Four parallel groups	830	Melanoma after curative resection of high risk primary (> 3 mm)	A) r IFN-α2	D) Placebo	Disease-free survival, length of survival, relapse rate	No differences that indicate efficacy of Iscador®	Trial so far only reported as an abstract
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					B) Lektinol® intermediate dose C) Lektinol® high dose (poplar)				
Steuer-Vogt (2001)	3	Two parallel groups, stratified for conventional therapy	477	Head and neck squamous cell CA	A) Eurixor® (poplar)	B) No such adjuvant therapy	Disease-free survival, 5-year survival rates, relapse rates, quality of life	No significant inter-group differences	Details regarding quality of life to be published
Goebell (2002)	3	Two parallel groups	45	Superficial bladder CA (pTaG1-2)	A) Lektinol® (poplar)	B) No such adjuvant therapy	Recurrence-free survival, total number of recurrences during 18 months of follow-up	No significant inter-group differences	No quality of life data, small sample size

[1]CA, cancer.–*, treatment schedules are usually complex, conventional care was always given in parallel.–ML-1, mistletoe lectin 1.

ment cycles lasted 12 weeks followed by a mistletoe-free interval of 4 weeks. Three cycles were given in total. The primary endpoint was disease-free survival (DFS). Disease-specific survival (DSS) was a secondary endpoint. The adjusted hazard ratio for DFS was 0.959 (95% CI 0.725–1.268). Five-year survival and quality of life also did not significantly favour mistletoe. The authors concluded that "the used mistletoe preparation has no indication in the adjuvant treatment of patients with head and neck squamous cell carcinoma."

This study is probably the most rigorous mistletoe-trial published to date. It includes a formal power calculation, adequate follow-up and stratification for conventional treatments. One weakness is the lack of placebo and thus patient-blinding.

The most recent RCT of mistletoe was published by Goebell *et al*.[23] Forty-five patients with pTa G 1–2 bladder cancer were randomised after transurethral resection into receiving adjuvant therapy with 0.1 ml mistletoe lectin or no such therapy. The mistletoe treatment schedule commenced 2 weeks after surgery and involved twice weekly subcutaneous injections of 1 ml extract standardised for the galactoside-specific ML I for 3 months. Subsequently there were 3 months of no such injections followed by a second cycle. Recurrence-free interval and the total number of recurrences were the endpoints during 18 months of follow-up. Both variables did not differ significantly between groups: there were 30 and 31 recurrences, and the recurrence free intervals averaged 9.0 and 10.5 months, respectively. Similarly, secondary outcome variables did not demonstrate statistically significant or clinically relevant differences between the 2 groups.

Even though relatively rigorous, this study has several limitations: it did not report quality of life, it was neither placebo-controlled nor double-blind and, perhaps most importantly, its sample size was small.

DISCUSSION

The collective evidence reviewed above does not lend strong support to the efficacy/effectiveness of mistletoe extracts as a curative or supportive cancer therapy. In reviewing 11 controlled clinical trials, Kleijnen and Knipschild came to similar conclusions.[10] Only 4 of the 11 studies in their review were adequately randomised. In 1989, Kiene reviewed 46 clinical studies of mistletoe and arrived at a much more encouraging overall result.[5] This review included uncontrolled, historically controlled and retrospective studies. As it is important to eliminate selection bias in clinical trials; our emphasis was on randomised studies only. Apart from one study,[22] none of the included RCTs have carried out a power calculation to estimate how many participants are needed to be sure of finding something important. Numerous other weaknesses of the primary studies are mentioned above. The overall picture that emerges shows that those trials that are insufficiently vigorous to be conclusive do not demonstrate the effectiveness of mistletoe extracts.

One problem with our systematic review is that a diverse variety of mistletoe extracts (different mistletoe species, different forms of extraction and different host trees) and treatment regimen exist. These had to be assessed together for the purpose of this article. It is not always clear which extracts have been tested (Table I), and the number of trials on each extract is not sufficiently large to conduct separate systematic reviews. However, no clear evidence emerges from this review that one extract might be superior to another. "Claims about health effects must ideally be sustained . . . for every single mistletoe extract,"[10] and the burden of proof clearly rests with those who manufacture and promote these treatments. A further problem is that mistletoe extracts are used for most forms of cancer. For the purpose of this review, we therefore pooled the data relating to different types of malignancy. Again, the information currently available is too scant to allow subanalyses for different cancers. All one can therefore state with confidence is that the existing evidence does not imply that mistletoe extracts are more effective for one type of malignancy than for another.

Our systematic review was hampered by several other factors. Some trials of mistletoe appear in relatively obscure journals; even though our search strategy was thorough, we cannot be absolutely certain that all relevant RCTs were included. Many of the retrieved RCTs are poorly reported. Some have been published 2–4 times with considerable contradictions between these reports. Some manufacturers were less than helpful in assisting our efforts, even doubting our motivation in conducting this review. We therefore fear that unpublished trials, if they exist, may not have been included in our analysis. For obvious reasons, these would be studies with a negative result.

The treatment of cancer with mistletoe extracts was suggested by R. Steiner, the founder of anthropological medicine.[24] Steiner was guided by philosophy rather than science. Considering this history it seems surprising that mistletoe extracts do, in fact, possess several immunological effects that could be useful in the treatment of cancer. Most importantly, mistletoe extracts have been shown to increase the severity of tumour necrosis factor α, interleukin-1 and interleukin-6.[25] These could decrease cancer cell viability,[26] influence their migratory behaviour[27] and render cancer cells more sensitive to induction of apoptosis.[28] While these effects appear encouraging, one has to consider that they are based on *in vitro* experiments. Proponents of mistletoe therapy tend to extrapolate too optimistically from the preclinical findings to the clinical situation.[29] Furthermore, Gabius and Gabius have pointed out that several *in vitro*, *in vivo* and clinical studies suggest that interleukins can also stimulate (rather than suppress) the proliferation of certain cancer cells.[8] In other words, mistletoe therapy has the potential to harm cancer patients.

The notion that mistletoe extracts may not always be harmless is further supported by the fact that they are contra-indicated for patients with primary or secondary brain tumours, leukaemias or malignant lymphoma.[30] Adverse effects occur in up to 45%[31] and include local reactions at the site of injection, fever, elevation of intracerebral pressure, swelling of lymph nodes, thrombophlebitis, headache, circulatory problems and allergic reactions including anaphylaxis.[30] This high frequency of adverse effects renders placebo-controlled trials a near impossibility—a fact that deserves consideration when evaluating or planning future clinical trials in this area.

The issue arises of how to definitively answer the question whether mistletoe extracts are clinically effective. Obviously, we need high quality trials conducted by trustworthy experts and monitored according to GCP guidelines. No less than 30 different mistletoe preparations are on the German market.[31] As these vastly differ (for instance, in lectin content), each preparation should be tested and evaluated separately. As one cannot necessarily extrapolate from one type of cancer to another, each extract should be tested in each cancer for which it is claimed to be effective. The research effort thus needed is huge, and it seems unrealistic to expect the necessary data to emerge in the foreseeable future. The most reasonable alternative is therefore to insist that manufacturers' claims are supported by convincing data or they are not deemed acceptable.

In conclusion, the evidence from rigorous RCTs of mistletoe extract does not imply that this widespread and collectively costly therapy has any benefit for cancer patients.

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