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MISTLETOE IN CANCER
A SYSTEMATIC REVIEW ON CONTROLLED CLINICAL TRIALS

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Abstract

Background: Mistletoe preparations are among the most widely used unconventional cancer therapies in Central Europe. Their clinical effectiveness, however, is controversial.

Objective: To investigate whether prospective controlled clinical trials provide evidence for efficacy of mistletoe therapy in cancer.

Design: Systematic review.

Material and Methods: Search of 11 electronic databases, reference lists and expert consultations. Criteria based analysis was performed to assess methodological quality of the studies.

Results: Twenty-three studies were identified: 16 randomized, 2 quasi-randomized and 5 non-randomized. Cancer sites included breast, lung, stomach, colon, rectum, head and neck, kidney, bladder, melanoma, glioma, and genital. Among these studies, statistically significant positive outcomes were reported for survival (n = 8), tumor remission (n = 1), overall quality of life (QOL) (n = 3), and QOL in relation to side effects during cytoreductive therapy (n = 3). Further, positive trends were reported for survival (n = 8), disease-free-survival (n = 1), and tumor remission (n = 2). Several studies reported no effect on survival (n = 4), disease-free-survival (n = 1), recurrence (n = 2), remission (n = 3), and QOL (n = 1). One study showed a negative trend for disease-free-survival. However, methodological quality of the studies was sometimes far below the standard that is today regarded as optimal or necessary. In view of substantial heterogeneity of the studies and potential positive and negative biases, we considered effect size estimation by quantitative synthesis to be unreliable and decided on a non-quantitative synthesis and discussion. Mistletoe therapy was well tolerated, and no major side effects were noted.

Conclusions: Among 23 identified studies evaluated for clinically relevant outcome measures, 12 studies showed one or more statistically significant, positive results, another 7 studies showed at least one positive trend, 3 showed no effect and 1 had a negative trend. All studies, however, suffered from methodological shortcomings to some degree, and many of the studies are not conclusive. As several reasonably well conducted studies indicate beneficial effects, further properly designed trials should be encouraged. Future controlled studies should take into account the methodological limitations and potential biases of these past mistletoe trials.

Key words: Mistletoe; Viscum album L.; cancer; clinical trials; systematic review

INTRODUCTION

Mistletoe extracts (*Viscum album* L.) are the most frequently prescribed unconventional cancer therapies in Central Europe [61]. Up to two thirds of cancer patients in Germany and Austria receive alternative therapies, primarily mistletoe extracts [52, 72]. Mistletoe treatment for cancer was introduced in 1920 by Steiner and Wegman, founders of the anthroposophical medical method [65]. Anthroposophical mistletoe preparations - Abnobaviscum, Helixor, Iscador (labeled as "Iscar" in the US), Iscucin, Isorel - are extracts from defined parts of *Viscum album* L., i.e. fresh leafy shoots and berries. These preparations are available from different host trees such as oak, apple, pine and others. Harvesting procedure is standardized, and the juices from summer and winter harvests are mixed together. Route of application and dosage are varied individually, depending on the patient's reaction and stage of disease. Non-anthroposophical *Viscum album* extracts (VAEs) - Cefalektin, Eurixor, Lektinol - are harvested in winter from poplars; they are dosed according to mistletoe lectin content (ranging from 1 ng/kg up to 15 ng/kg bodyweight) on the premise that mistletoe lectin is the main active ingredient (see Table 1) [4]. Today, mistletoe is used in all stages of disease, either alone or in combination with chemotherapy, radiation therapy or hormone therapy.

During the last decades biological and pharmacological properties of VAE have been subject to extended scientific investigations (e.g. [4, 37]).

Several pharmacologically active compounds have been isolated, such as mistletoe lectins (ML I, II and III) [21], viscotoxins [74, 75], oligo- and polysaccharides [39, 47], and several others [4]. The most prominent properties of VAE are their cytotoxic and growth-inhibiting effects towards a variety of human tumor cell lines, lymphocytes and fibroblasts in vitro [4]. The cytotoxic effects of VAE are mainly due to the apoptosis-inducing mistletoe lectins [9, 10, 34], while the viscotoxins induce necrotic cell death [8, 10]. VAE are also recognized for their immune modulating activity. *In vitro* and *in vivo* studies have demonstrated activation of monocytes/macrophages, granulocytes, natural killer (NK) cells, T-cells (especially T-helper-cells) and the induction of various cytokines [4]. Apart from these cytotoxic and immunomodulating effects, VAE possess DNA stabilizing properties [5-7]. In animals, VAE displays antitumoral effects when administered either directly into the tumor or systemically [4, 37].

Some groups presume ML I to convey the main pharmacological properties of VAE. Some mistletoe preparations are standardized for ML I. Recombinant ML I is currently being investigated in clinical trials (e.g. EORTC-13001, -16002). However, in animal models adverse effects of low-dose isolated ML I on tumor development were reported [69]. Moreover, ML's are bound by serum glycoproteins, and by anti-ML antibodies that are physiologically produced within weeks of therapy [64, 66]. Thus, the biological effects of isolated ML products may diminish over time.

Clinical trials with mistletoe remedies have been subject to controversial debate. The last systematic reviews, published in 1991 [36] and 1994 [38], are outdated, and recent surveys (e.g. [49, 70] are incomplete. Therefore, a systematic review on clinical trials of mistletoe therapy in cancer was performed to answer the following questions:

Do prospective clinical trials provide stringent evidence for clinical effects of mistletoe therapy on survival, on tumor remissions, or on quality of life (QOL) in cancer patients? Can the effect size be estimated?

Methods

Search Strategy

We used a systematic process to search the following databases for clinical trials: AMED, BIOSIS Previews, CANCERLIT, Conference Papers Index, Cochrane Controlled Trials Register, Dissertation Abstracts, EMBASE, Extramed, MEDIKAT, MEDLINE, and Science Citation Index from inception of these databases to December 2002 using the terms "mistletoe", "viscum", "Mistel", "Misteltherapie", "Mistelextrakt", "Abnobaviscum", "Cefalektin", "Eurixor", "Helixor", "Iscador", "Iscucin", "Isorel", "Lektinol", "Vysorel". The reference list from each potentially eligible study, relevant review article and textbook was checked, and experts in the field and manufacturers of mistletoe preparations were contacted for additional reports.

Selection

The following selection criteria were used for inclusion of studies in the analysis: (I) Prospective controlled clinical trial, either randomized or non-randomized; (II) Study population with cancer, including cervical intraepithelial neoplasia (CIN); (III) Intervention group treated with mistletoe preparation; (IV) Measurement of clinically relevant outcome (i.e. overall or disease-free survival, remission, relapse, QOL, or reduction of side effects during cytoreductive therapy); (V) Completion of study; (VI) Publication as a manuscript or abstract (e.g. conference report). Studies were excluded if they: only measured toxicity or tolerability (Phase I), only measured immunological parameters, or were not conducted on cancer patients. There were no restrictions on language.

Validity Assessment and Data Abstraction

Criteria based analysis was performed on the selected studies to assess their methodological quality. Analyses were performed independently by two reviewers (GK, HK) and checked by others (FB, EP). There were no major differences in study assessment; disagreements were resolved by discussion. Criteria for assessing strength of evidence were adapted from National Health Service Centre for Reviews and Dissemination [35] and from criteria for good methodology as already applied in an earlier review on mistletoe trials [38]. Criteria were rated as "+" = adequately fulfilled, "(+)" = partly fulfilled, "(-)" = little fulfilled, "-" = not fulfilled. Data were abstracted by one reviewer and checked by a second reviewer.

For ranking the quality of the studies (see Tables 2-5) we computed a summary score with 3 for +, 2 for (+), 1 for (1) and 0 for - respectively. The function of this ranking is only to provide a quick, summary reference to the methodological quality of the studies. It does not claim precision since it neither presupposes equivalence of rating intervals nor numerical equality among the different criteria.

Results

Two hundred fifty two references were found, describing 138 clinical trials of mistletoe therapy. The following studies were then excluded from this initial pool: retrospective or uncontrolled studies (n=66), studies performed on populations other than cancer patients (n = 10), studies of immune modulation without clinically relevant outcome measures (n = 23), studies of tolerability without clinically relevant outcome measures (n = 7), uncompleted trials (n = 4) and unpublished studies (n = 5). Twenty-three prospective controlled studies remained for detailed analysis.

Table 1. Mistletoe Preparations used to treat cancer [4].

Proprietary Names	Host tree*	Harvest season	Extraction	Parts used	Dosage according to lectin content
Anthroposophical					
Abnobaviscum	A, Ac, Am, B, C, F, M, P, Qu	Winter and summer juices mixed	Pressing	Fresh leafy shoots, fruits	Seldom
Helixor	A, M, P		Aqueous	"	
Iscador (Iscar)	M, P, Qu, U		Aqueous fermentation	"	
Iscucin	A, C, M, P, Po, Qu, S, T		Aqueous	Dried leafy shoots fruits, sinker	
Isorel	A, M, P		Aqueous	Fresh leafy shoots, fruits, sinker	
Other					
Cefalektin	Po	Winter	Aqueous	Fresh leafy shoots	Yes
Eurixor	Po	"	"	Fresh leafy shoots	
Lektinol	Po	"	"	Fresh leafy shoots	

*A: Abies = fur; Ac: Acer = maple; Am: Amygdalus = almond tree; B: Betula = birch; C: Crataegus = whitethorn; F: Fraxinus = ash tree; M: Malus = appletree; P: Pinus = pine; Po, Populus = poplar; Qu: Quercus = oak; S: Salix = willow; T: Tilia = lime, U: Ulmus = elm

Sixteen of the studies were randomized, 2 quasi-randomized (alternating treatment allocation) and 5 non-randomized. One non-randomized trial was a matched pair study and another had a penalty design (prognostic disadvantage for mistletoe group). Three studies were nested in the same epidemiological cohort study [24].

Tables 2 and 3 summarize the validity assessment. Tables 4 and 5 describe the studies in terms of type of cancer, stage, intervention, and main results. Studies listed in Tables 2-5 have been ordered according to quality (see methods section).

Cancer sites studied were: breast (n = 4), lung (n = 4), colon and rectum (n = 3), melanoma (n = 2), stomach (n = 1), head and neck (n = 1), kidney (n = 1), bladder (n = 1), glioma (n = 1), gynecological (ovary, uterine, cervix, breast) (n=3), and mixed (breast, rectum, colon, stomach, lung) (n = 2). Intervention was Iscador (n = 14), Eurixor (n = 6), Helixor (n=3). Measured outcomes of mistletoe treatment included: overall survival (n = 20), remission (n = 6), disease-free survival and recurrence (n = 5), overall QOL (n = 5) and QOL and side effects during cytoreductive therapy (n = 3). Eighteen of the studies were conducted in an academic setting or within major community hospitals [3, 12, 15, 19, 23-25, 33, 42, 43, 45, 54-60, 67], 3 in rehabilitation centers [12-14], and 2 in major practices [29, 30]. One of the study reports was only available as an abstract [3, 44]. One other randomized placebo-controlled trial was published as an abstract [73] but was not included in this review because, according to the manufacturer, it has not yet been completed and the preliminary results are non-quantitative.

Five studies investigated mistletoe therapy as a co-intervention administered concurrently with conventional treatment (chemotherapy, radiotherapy, corticosteroids) [13, 14, 29, 30, 43]. Four of these studies were conducted on patients with advanced, metastatic disease [13, 14, 29, 30]; three primarily assessed reduction of side effects from cytoreductive therapy [29, 30, 43]. In 12 studies mistletoe therapy was used in an adjuvant setting with patients after surgery or radiotherapy [15, 19, 23, 25, 45, 54-60, 67]. In one study mistletoe therapy was used as primary treatment in CIN [33]. Four studies investigated mistletoe therapy independently from conventional treatments, including the palliative setting [12, 24]. One study had mistletoe as a control intervention for chemoimmunotherapy [3, 44].

We found substantial heterogeneity of the studies in terms of intervention, patients characteristics, clinical diagnosis, measured outcomes, design, methodological quality and potential positive and negative biases. We therefore considered a quantification of effect size by combining results to be unreliable and decided on a non-quantitative synthesis and discussion.

Altogether 12 studies had statistically significant positive results in at least one of the clinically relevant outcome measures [12, 13, 19, 24, 25, 29, 30, 42, 43, 55, 57-59], another 7 studies showed a positive trend [14, 33, 45, 54, 56, 60], 3 had no effect [3, 23, 44, 67], and 1 showed a negative trend [15]. In one trial that utilized mistletoe extract as a

Table 2. Quality of Randomized Controlled Mistletoe Trials.

Author, Year	Results[I]	Quality Criteria Fulfilled in Studies[II]											Sample Size	AR[III]
		A)	B)	C)	D)	E)	F)	G)	H)	I)	J)	K)		
Studies of anthroposophical mistletoe preparations														
Grossarth 2001 [24]	s	+	+	-	(-)	+	+	+	(-)	+	+	-	34	0%
Dold 1991 [12]	t, t, s	+	+	-	-	+	(-)	+	(+)	+	+	(-)	337	17%
Grossarth 2001 [24]	s	+	+	-	(-)	+	(-)	+	(-)	+	+	-	78	20%
Salzer 1991 [56]	t	+	(+)	-	(-)	(+)	(-)	+	(+)	(+)	+	-	210	16%
Douwes 1986 [14]	t	+	-	-	(-)	+	+	+	+	-	(+)	-	60	0%
Gutsch 1988 [25]	s	+	-	-	(-)	+	(-)	+	+	(+)	+	-	677	20%
Jach 1999 [33]	t	+	-	-	(-)	+	+	+	(+)	(-)	(-)	-	60	0%
Salzer 1979, 1988 [55, 57, 59]	s	+	-	-	(-)	+	-	+	+	(+)	(+)	-	137	57%
Salzer 1987 [54]	t	+	(+)	-	(-)	+	-	+	-	-	-	-	50	48%
Eggermont 2001 [15, 16]	-t	+	-	-	(-)	(-)	(-)	(+)	-	-	-	(+)	[IV]	ns (I: 21%)[V]
Studies of other mistletoe preparations														
Steuer-Vogt 2001 [67]	0	+	(+)	-	+	+	(-)	+	+	+	(+)	(+)	477	29%
Goebell 2002 [23]	0	+	-	-	(+)	+	+	+	(+)	+	+	-	45	2%
Heiny 1991 [29]	s	+	-	(-)	(-)	+	(+)	+	(+)	+	+	-	40	13%
Heiny 1997 [30]	s, 0	+	-	-	(-)	+	-	+	+	(+)	(+)	-	79	26%
Lenartz 1996, 2000 [42, 43]	s	+	-	-	(-)	+	-	+	-	(+)	(+)	-	35 (38)	26%
Brinkmann 2000 [3, 44]	0[VI]	+	ns	-	ns	ns	ns	ns	ns	ns	ns	ns	176	ns

I t: trend, s: significant, 0: no effect;

II A) Protection against selection bias, especially by adequate randomization
B) Minimization of heterogeneity by prestratification or matching
C) Protection against observer bias by blinding of patient, care provider, and outcome assessor
D) Protection against performance (treatment) bias by standardization of care protocol, documentation of all co-interventions, blinding of patients and care providers
E) Protection against measurement (detection) bias by standardization of outcome assessment
F) Protection against attrition (exclusion) bias, lost patients < 10% or by intention-to-treat and per-protocol analysis in combination with sensitivity analysis, and by comparison of prognostic characteristics of lost patients and compliers
G) Effect measurement relevant and well described
H) Well described intervention, patient characteristics, disease (diagnosis, stage, duration), previous therapy
I) Well described study design
J) Well described results
K) Data quality assured by GCP-ICH-guidelines, especially by monitoring

III AR: attrition rate (dropouts, protocol deviations, withdrawals).

IV Number of study patients not indicated; publication refers to two studies including altogether 830 patients; mistletoe group included 102 patients.

V ns: not stated for total study population, only for Iscador group (I).

VI Mistletoe extract was control therapy for chemoimmunotherapy.

Table 3. Quality of Quasi-randomized and Non-randomized Controlled Mistletoe Trials.

Author, Year	Results[I]	Quality Criteria Fulfilled in Studies[II]											Sample Size	AR[III]
		A)	B)	C)	D)	E)	F)	G)	H)	I)	J)	K)		
Quasi-Randomized Controlled Trials														
Salzer 1987 [54]	t	(+)	-	-	(-)	+	-	+	-	-	(+)	-	155	ns
Majewski 1963 [45]	t	(+)	-	-	(-)	+	-	+	-	-	-	-	[VII]	ns (I: 15%)[V]
Non-Randomized Controlled Trials														
Grossarth 2001 [24]	s	(+)	+	-	(-)	+	+	+	-	+	+	-	792	3.5%
Salzer 1978 [58]	s	-	-	-	(-)	+	+	+	(+)	+	(+)	-	77	0%
Douwes 1988 [13]	t, s	-	-	-	(-)	+	+	+	+	-	+	-	39	3%
Schuppli 1990 [60]	t	(+)	-	-	(-)	+	(-)	+	(-)	-	-	-	198	ns
Fellmer 1966 [19]	s	-	-	-	(-)	+	-	+	+	-	-	-	790	16%

Abbreviations as in Table 2. VII Number of study patients not indicated: mistletoe group included 155 patients

control intervention for chemoimmunotherapy, remission rates were lower for the mistletoe group, while overall survival was slightly higher [3, 44]. Clinical outcomes are summarized in Table 4 and Table 5. Regarding overall survival, 8 studies showed statistically significant positive results [19, 24, 25, 42, 43, 55, 57-59], an additional 8 studies demonstrated positive trends that were not statistically significant [12-14, 45, 54, 56, 60], and 4 studies showed no effect [3, 15, 30, 44, 67]. Regarding disease-free survival and recurrence, no studies demonstrated statistically significant effects: 1 study showed a positive trend [42, 43], 3 showed no effect [23, 56, 67], and 1 showed a negative trend [15]. Regarding remission, 1 showed a statistically significant positive result [13], 2 studies showed a positive trend [12, 33], and 3 showed no effect [3, 14, 30, 44]. Regarding QOL, 3 showed a statistically significant positive result [12, 24], 1 showed no effect [67], 1 result was not reported [15]. In regard to QOL in relation to reduction of side effects during cytoreductive therapy, 3 showed a statistically significant positive effect [29, 30, 42, 43]. Methodological quality of the studies was sometimes far below the standard that is today regarded as optimal or necessary (Tables 2 and 3); only a few studies seemed reasonably well conducted.

No major side effects were reported. Minor symptoms included rubor, pruritus and/or induration at the injection site, and also mild flu-like symptoms.

Discussion

Several key issues emerged through this review: First, even though use of mistletoe therapy is longstanding and widespread, few controlled clinical trials have been performed. Second, although many of the studies were conducted in academic centers, they mostly do not meet contemporary methodological standards for clinical trials (see Tables 2 and 3). Third, study results are positive in most cases; however, a pooled estimation of effect size is not sensible because of substantial heterogenity in regard to quality, design, preparation, dosage, duration of treatment, and even assessment of outcomes (such as measuring survival time from diagnosis [24] or from study entry [12]).

Several of the methodological shortcomings are avoidable, particularly in respect to transparency and completeness of data reporting. However, other criteria are more difficult to fulfill. Blinding, for instance, was not done in any of the trials, including the two with placebo controls [12, 29]. Reliable blinding would be hard to assure since subcutaneous mistletoe injections initially induce local skin reactions (rubor, pruritus, induration) and mild flu-like symptoms that potentially lead to unblinding in most cases. For this reason, the ethics committee for one of the recent studies did not approve a double-blind design [67]. Still, studies without blinding do not deviate from most other oncological drug trials, as chemotherapy studies are essentially never blinded [50]. After all, susceptibility for observer bias depends on the type of outcome measure and is likely negligible for survival studies. Nevertheless, non-blinded trials require especially careful preparation to protect against potential biases.

Performance bias (systematic difference in care provided apart from the intervention under investigation) must be regarded for most of the mistletoe trials. In the study by Dold et al. on non-small cell lung cancer (see Table 4) unusually high tumor remission rates were reported in all treatment groups. This study included particularly patients with advanced disease and substantial comorbidity, who had no additional conventional treatment options [12]. Yet, even in the placebo group there was a remarkable 3% rate of complete tumor remission and 20% rate of overall tumor regression. These rates are far higher than reported for spontaneous remissions in lung cancer [28, 51] and raise important questions. It is likely that patients who receive placebo or other experimental therapy, and consider it non-effective, seek out additional active co-interventions. Such performance bias can impair efficacy estimation, as the verum-placebo comparison is contaminated [31]. Relevant details on this issue, however, are only seldom documented and published, as for instance in a four-armed randomized trial on persistent back and neck complaints: The less effective the primary treatment, the more contamination and co-therapy: 17% in the most effectively treated group (manipulative therapy), 24% in the second effectively treated group (physiotherapy), 44% and 45% in the control groups (general practitioner and placebo respectively) [40]. As a consequence effect sizes become diluted, and efficacy assessment can be falsely negative. This might also account for the study of Dold et al.: While remissions during mistletoe therapy may occur [2, 68] (although the rate is unclear), the unexplained high remission rate under placebo suggests an undocumented performance bias, and the study result may therefore be unreliable.

Most mistletoe studies were not susceptible for detection bias, as outcome was survival, or measurements were standardized. Still, detection bias might have been relevant in the melanoma trial by Eggermont et al. [15], who reported a reduction in disease-free survival and an increase in brain metastases in the mistletoe group. In general, brain metastases in melanoma are frequent, though clinically occult in most cases, and found three times as often in autopsies [1]. Since the study by Eggermont et al. [15] included no general protocol obligation for computed tomography (CT scan) or nuclear magnetic resonance (NMR) of the brain, and since brain metastases are contraindications for the mistletoe intervention (Iscador), relatively more brain scans might have been done in the mistletoe group, leading to an increased detection of otherwise clinically occult brain metastases. Additionally, a significantly decreased overall

Table 4. Randomized Controlled Trials on Mistletoe Treatment in Cancer (ordered by decreasing quality).

Author, Year	Site	Stage	Intervention (Sample Size)	Survival		Tumor	Other outcomes
Studies of anthroposophical mistletoe preparations							
Grossarth 2001 [24]	Breast	IIIA-IIIB	• Iscador (17) • None (17)	Mean survival (months)	• 57.5 * • 28.9		Psychosomatic selfregulation ↑*
Dold 1991 [12]	Lung	All stages	• Iscador (114) • Vit B as placebo (113) • Polyerga (110)	Median survival (months)	• 9.1 • 7.6 • 9.0	Complete resp. | overall regr.II • 4% | 26% • 3% | 20% • 2% | 19%	Patients subjectively improved • 59% * • 45% • 43%
Grossarth 2001 [24]	Breast, lung, rectum, colon, stomach	All stages	• Iscador (39) • None (39)	Mean survival (months)	• 42 * • 29		Psychosomatic selfregulation ↑*
Salzer 1991 [56]	Lung	I-IV	• Iscador, surgery (87) • Surgery (96)	Median survival (months)	• 33 • 31	Recurrence • 50% • 55%	
Douwes 1986 [14]	Colon, rectum	Advanced	• Helixor, 5FU/FA (20) • 5FU/FA (20) • Ney Tumorin, 5FU/FA (20)	Mean survival (months)	Responder | non-resp • 27 | 12 • 14 | 5 • 24 | 12	Complete resp. | partial response • 15% | 35% • 15% | 30% • 15% | 25%	
Gutsch 1988 [25]	Breast	T1-3, N0-3, M0	• Helixor, surgery, radiationI (192) • Surgery, radiationI (274) • CMF, surgery, radiationI (177)	5-year survival	• 69.1% * • 59.7% • 67.7% *		
Jach 1999 [33]	CIN, HPV-associated	I-II	• Iscador QuS (30) • None (20) • IFN-α (10)			Complete resp. | progressive disease • 60% | 7% • 50% | 20% • 80% | 0%	
Salzer 1979, 1988 [55, 57, 59]	Stomach	II-III	• Iscador, surgery (62) • Surgery (75)	Mean survival (months)	Lymph node: + | – • 25 * | 55 • 18 | 45		
Salzer 1987 [54]	Lung	I (II)	• Iscador, surgery (12) • Surgery (14)	Median survival (months)	• 117 • 34.5		
Eggermont 2001 [15, 16]	Melanoma	High risk primary (≥3MM) or LN+	• Iscador, surgery (102) • IFN-α, surgery (ns) • IFN-γ, surgery (ns) • Surgery (ns)	Overall survival (hazard-ratio)	• 1.2 • 1 • 1.1	Disease-free survival (hazard-ratio) • 1.3 • 0.9 • 1	QOL: no result reported
Studies of other mistletoe preparations							
Steuer-Vogt 2001 [67]	Head and neck	I-IV, T1-4, N0-3, G1-3	• Eurixor, surgery, radiationI (235) • Surgery, radiationI (242)	Disease-specific survival (adjusted hazard-ratio)	• 1.07	Disease-free survival (adjusted hazard-ratio) • 0.96	No effect on QOL, not specified
Goebell 2002 [23]	Bladder	pTa G1-2	• Eurixor, transurethral resection (23) • Transurethral resection (22)			Number of recurrences • 31 • 30	
Heiny 1991 [29]	Breast	Advanced	• Eurixor, VEC (21) • Placebo, VEC (19)				QOL ↑*, anxiety ↓*, leukopenia↑* No effect on platelets
Heiny 1997 [30]	Colon, rectum	Advanced	• Eurixor, 5FU/FA (38) • 5FU/FA (41)	Mean survival (months)	• 12.1 • 11.5	Response (CR + PR) | progressive disease • 21% | 36% • 23% | 36%	QOL↑*, leukopenia↓*, mucositis↑* No effect on platelets
Lenartz 1996, 2000 [42, 43]	Glioma	III-IV	• Eurixor, surgery, radiation, dexa (18) • Surgery, radiation, dexa (7)	Adjusted mean survival (months)	• 20 * • 10	Adjusted disease-free survival (months) • 17 • 10	QOL ↑*
Brinkmann 2000 [3, 44]	Kidney	Advanced	• Eurixor (control) (88) • IL-2 IFN-α, 5FU (88)	Median survival (months)	• 21 • 13	Complete | partial response • 0% | 2% • 8% | 17%	

Abbreviations: CMF: cyclophosphamide, methotrexate, 5FU; 5FU: 5-fluorouracil; FA: folinic acid; VEC: vindesine, epirubicin, cyclophosphamide; dexa: dexamethasone; ns: not stated; QOL: quality of life.
* Statistically significant superiority compared to comparison-group. I Co-intervention (i.e. radiation) applied to part of the group. II Not corresponding to WHO-definition of tumor response.

Table 5. Quasi-Randomized and Non-Randomized Controlled Trials on Mistletoe Treatment in Cancer (ordered by decreasing quality).

Autor, Jahr	Site	Stage	Intervention (Sample Size)	Survival		Tumor	Other outcomes
Quasi-Randomized Controlled Trials							
Salzer 1987 [54]	Breast	I-III	• Iscador, surgery (76) • Radiation, surgery, hormone (79)	Alive 1985 (after 11-14 years)	• 29% • 24%		
Majewski 1963 [45]	Genital	All stages	• Iscador, surgery[1], radiation[1] (155) • Surgery[1], radiation[1] (ns)	Disease-specific survival partly improved			
Non-Randomized Controlled Trials							
Grossarth 2001 [24]	Breast, colon, rectum, stomach, lung	All stages	• Iscador (396) • None (396)	Mean survival (months)	• 50.8 * • 36.6		
Salzer 1978 [58]	Lung	I-III	• Iscador, surgery (37) • Surgery (40)	6-year survival	• 38% * • 15%		
Douwes 1988 [13]	Colon, rectum	Advanced	• Helixor, 5FU/FA (19) • 5FU/FA (20)	Median survival (months)	• 26 • 14	Complete | partial | minimal response • 16% | 37% | 26% * • 0% | 30% | 20%	
Schuppli 1990 [60]	Melanoma	Not specified	• Iscador, surgery (84) • BCG, surgery (114)	5-year survival	• ~ 86% • ~ 72%		
Fellmer 1966 [19]	Cervix	I-III	• Iscador, radiation (81) • Radiation (709)	5-year survival	• 83% * • 69%		

Abbreviations as in Table 4.

survival was mentioned for a subgroup of mistletoe patients (with lymph node metastases). However, as the publication [15] does not report details (e.g. on patient numbers or exact results) and altogether contains only sparse information, validity remains unclear.

Post-randomization dropouts, protocol deviations, and withdrawals are a major threat to clinical trials in general. To estimate and reduce subsequent attrition bias, the reasons for these losses should be reported as well as the prognostic characteristics of the lost patients in comparison to adherers, and both per-protocol analysis (excluding non-adherers) and intention-to-treat analysis (including non-adherers) should be conducted. Still, large attrition rates affect the reliability of effect size estimation, and even an intention-to-treat analysis does not prevent potential bias [62]. An attrition rate lower than 10% is reported only for seven of the mistletoe studies. Even the otherwise well conducted trial by Steuer-Vogt et al. [67], which found no effect of lectin-standardized mistletoe on disease-free and overall survival and QOL, reported 18 dropouts after primary randomization of 495 patients; an additional 63 of 235 patients entering the mistletoe arm did not receive intervention as allocated, and 12 more withdrew from this arm. This resulted in an attrition rate of 32% in the mistletoe arm (20% in control group) over and above the initial dropouts. Intention-to-treat and per-protocol analyses were done according to current standards; however, no additional comparative analysis of prognostic factors (adherers vs. non-adherers) was performed. Room is left, therefore, for speculations about how these exclusions may have biased the results. The same issue applies to the study of Dold et al. [12], where 17% of the patients (71 of 408) were excluded. Gutsch et al. [25], showing a significant survival advantage for mistletoe group, had a 20% attrition rate, mostly due to protocol violations; they analyzed "as-treated" (analyzing non-adherers according to the treatment they actually received, regardless of the initial random treatment allocation) and included a stratified risk adjustment in the final analysis. As no additional intention-to-treat analysis was done, however, the potential effect of an attrition bias again cannot be estimated.

A different approach is presented by the trials of Grossarth et al. [24]: The trials (one non-randomized and two randomized, both with matched pairs) were nested in a large-scale epidemiologic cohort study (n = 10,226) that investigated the influence of various factors on survival in cancer, one of these being mistletoe treatment. For the non-randomized trial (Table 5) matched pairs were defined from patients who had either already received or not received mistletoe therapy. For the two RCTs (Table 4), matched pairs were defined among registered patients that had no prior mistletoe therapy. One patient of each such pair was then randomly selected as candidate for mistletoe treatment and was suggested to ask his/her

physician for mistletoe therapy. In contrast to common RCTs, randomization units were the individual pairs of patients, and any sub-combination of these randomized pairs was regarded as a fully matched and randomized group. Therefore, different tumor stages could be included in one of the studies. Also, when registered patients declined to participate and dropped out after randomization (but before treatment was started), the complete randomization unit (i.e. drop-out plus corresponding twin) was deleted in order to maintain the randomized matched pair study structure and assure internal validity.

Several authors extensively discuss their difficulties conducting the trials [12, 25, 54-56, 71]. Some studies did not reach the planned sample size. For instance, Dold et al. revised power calculations twice in order to reduce sample size, but still needed 9 ½ years for patient recruitment [12]. Other studies, too, needed considerably more time for completion than anticipated [15, 67]. Several randomized mistletoe trials had to be stopped because of failure to enroll appropriate patient numbers within reasonable time. (e.g. [22, 71]). In Germany, willingness to participate in clinical trials is generally low [20], but is even lower for mistletoe studies. Mistletoe is an emotional topic, and many patients as well as physicians have definite preferences, pro or con; patients and physicians with strong preferences tend to refuse participation in randomized trials [17].

Long study duration can result in unavoidable protocol deviations because of changes in conventional cancer treatments, as in the study of Salzer [59]. Additionally, quality standards of clinical research continue to develop, and standards had often changed between the time of enrolment of first patient and study publication (in some cases 15-20 years). Even recently published mistletoe studies were begun before the implementation of GCP- resp. ICH-guidelines [15, 24]. In general, systematic internal quality control of clinical trials, such as monitoring and auditing, was probably rare, and was not even mentioned in the most recent publications (e.g. [23, 67]).

Mistletoe therapy was well tolerated in the reviewed trials, which is in accordance with other investigations [63]. Although not reported in any of these trials, allergic reactions to mistletoe extracts can occur, and a few case reports of anaphylactic reactions have been published [32, 63]. Recently, concerns were expressed regarding serious complications after mistletoe therapy [18]. However, original data did not refer to therapeutic mistletoe application but instead to animal toxicity experiments (of viscotoxins and lectins), to accidental ingestions of leaves and berries especially of *Phoradendron* [26] (generally harmless [41]) not used in mistletoe remedies, and to a case of "mistletoe" hepatitis [27] after intake of herbal tablets which, after all, did not contain mistletoe [11].

Most of the trials concentrated on assessment of survival or remission, while QOL, being more susceptible to observer bias, was included in only a few. However, in clinical reality the primary reasons for mistletoe use are not necessarily survival advantage or remission, but improvements in overall performance, mood, and disease coping, reduced frequency of infections, reduced side effects of conventional antitumor therapies, and reduced cancer pain with decreased need for analgesics. These issues, which are important from a patient's perspective, should also find consideration in future mistletoe research.

General problems and potentials of research in complementary medicine [48] also apply to mistletoe treatment: Mistletoe is generally prescribed in a complex clinical setting, including not only conventional agents, other botanical medicines, and nutritional supplements, but often also non-pharmacological interventions such as art or music therapy, occupational therapy, movement therapy, therapeutic massage and counseling regarding physical, mental, social and spiritual issues. Complementary multi-modal treatments claim to focus on the "whole" patient, trying to improve his or her inherent self-healing abilities, whereas most studies follow the conventional research approach by examining only one or two isolated intervention elements intended to modify a specific pathogenic process [46, 48, 53]. In order to gather reliable information on patients receiving these multi-modal interventions, alternative study designs should also be considered. These may include comparison trials of different complex treatment systems, high quality observational studies, or carefully performed qualitative research [48]. Mistletoe research would benefit from these additional research strategies. Complex approaches, however, require strong commitment by the research community, and often require even greater preparation than conventional clinical trials [48].

Conclusions

In 23 prospective controlled clinical studies on mistletoe therapy in cancer, 12 studies had a statistically significant positive result in at least one clinically relevant outcome measure, another 7 studies showed positive trends, 3 showed no effect and 1 demonstrated a negative trend. However, some of the studies suffered from significant methodological shortcomings (see Table 2 and 3), or predated current methodological standards, and therefore are not conclusive. Calculation of effect size by pooling data is inappropriate because of the heterogeneity of methodology, quality, population, outcome assessment, and type of mistletoe preparations studied. Because there are a small number of relatively well conducted trials with positive clinical outcomes, further research is warranted. Future controlled studies should be well designed and carefully conducted to improve methodological quality, and should reflect the clinical reality of mistletoe therapy that emphasizes QOL and symptom management, and is frequent-

ly incorporated within multi-modal, complementary treatment.

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