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Review

Complementary Cancer Therapy: A Systematic Review of Prospective Clinical Trials on Anthroposophic Mistletoe Extracts

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Abstract

Background: Anthroposophic Mistletoe therapy is a widely used complementary cancer treatment.

Objective: To evaluate prospective clinical trials on the effectiveness of anthroposophic mistletoe therapy for cancer.

Design: Systematic review.

Material and Methods: Search of 9 electronic databases, reference lists and extensive expert consultations. Criteria-based assessment of methodological study quality.

Results: 16 randomized (RCT) and 9 non-randomized (N-RCT) controlled trials were identified that investigated mistletoe treatment of malignant diseases. Statistically significant benefit for survival was reported in 8 of 17 trials (in 5 of 10 RCTs), for disease-free survival and tumour recurrence in none of 2 RCTs, for remission of tumour and malignant effusion in 1 RCT and 1 N-RCT of 4 controlled trials, for quality of life (QoL) in 3 of 5 RCTs, and for QoL and reduction of side effects of cytoreductive therapies (chemotherapy, radiation or surgery) in 5 of 7 trials (3 of 5 RCTs). Methodological quality of the controlled trials differed substantially; some had major limitations while others were reasonably well conducted. 12 single-arm cohort studies were identified. 5 of 7 studies found substantial tumour remission in various cancers, one study reported remission of CIN, and 4 studies remission of malignant pleural effusion or ascites. Quality of reporting in cohort studies was mostly reasonably good. Mistletoe application was well tolerated.

Conclusions: Regarding quality of studies and consistency of results, the best evidence for efficacy of mistletoe therapy exists for improvement of QoL and reduction of side effects of cytotoxic therapies (chemotherapy, radiation). Survival benefit has been shown but not beyond critique. Tumour remissions are described in cohort studies that investigate the application of high dose or local mistletoe extracts. As several reasonably well-conducted studies indicate beneficial effects, further properly designed trials should be encouraged to investigate clinical efficacy and its possible dependency on the mode of application.

Key words: Clinical trials, systematic review, mistletoe, *Viscum album*, neoplasms

Introduction

Complementary and alternative medicine (CAM) is popular among cancer patients; across Europe 40% (15-73%) use some form of CAM, mostly herbal medicine. [1] Mistletoe extracts (*Viscum album* L., VAE) are the most frequently prescribed CAM cancer therapies in Central Europe [2]. Up to two thirds of cancer patients in Germany and Austria receive CAM, primarily mistletoe extracts. [3;4]

Mistletoe treatment for cancer was introduced in 1920 by Steiner and Wegman, founders of Anthroposophic Medicine (AM). [5] AM is a CAM system, and is practised worldwide, particularly in Central Europe. [6;7] AM mistletoe preparations – Abnobaviscum, Helixor, Iscador (labelled as "Iscar" in the US), Iscucin, Isorel – are used not only within but also widely outside AM. They 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 fir (Abies, A), oak (Quercus, Qu), apple tree (Malus, M), pine (Pinus, P), elm (Ulmus, U), and others. Route of application and dosage are varied individually, depending on the patient's reaction and stage of disease. AM mistletoe is used in all stages of disease, either alone or in combination with chemotherapy, radiation therapy, or hormone therapy.

Biological and pharmacological properties of VAE have been subject to extended scientific investigations (overview in [8;9]). Several pharmacologically active compounds have been isolated, such as mistletoe lectins (ML I, II and III) [10], viscotoxins [11;12], oligo- and polysaccharides [13;14], lipophilic extracts [15] and several others [8]. The most prominent properties of VAE are their cytotoxic and growth-inhibiting effects on a variety of human tumour cell lines, lymphocytes and fibroblasts in vitro [8]. The cytotoxic effects of VAE are mainly due to the apoptosis-inducing mistletoe lectins [16-18], while the viscotoxins induce necrotic cell death [18;19]. 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 [8]. VAE also possess DNA stabilizing properties. [20-22] In animals, VAE displays potent antitumoural effects when adminis-

tered either directly into the tumour or systemically. [8; 9]

Clinical efficacy of mistletoe therapy has been the subject of controversial debate. Because of its widespread use and because of increasing research activity, systematic review of clinical mistletoe studies is important. Most reviews are outdated or incomplete (e.g. [23-28]). Of the recently published reviews, one focused on non-AM mistletoe extracts only [27], one missed most of the RCTs on AM mistletoe extracts [28], and one [29] is being incorporated into the following.

This review was initiated by the Complementary Medicine Evaluation Programme (Programm Evaluation der Komplementärmedizin – PEK), a research initiative of the Swiss Parliament, covering HTA reports on five CAM methods, including AM [6;7]. Out of 197 clinical studies on AM therapies, 97 prospective and retrospective studies investigated mistletoe in cancer and other neoplasms [7]. The present review is restricted to prospective clinical studies on AM mistletoe application in cancer only, addressing the following questions:

Do prospective clinical trials provide evidence for the effectiveness of mistletoe therapy in relation to survival, tumour remissions (including malignant effusion), quality of life (QoL), or reduction of side effects from cytoreductive therapies in cancer patients? Can the effect size be estimated by quantitative data synthesis?

Material and Methods

Methods were predefined in a protocol.

Search Strategy

We used a systematic process to search the following databases for clinical trials: AMED, Biosis Previews, Cinahl, Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, The NHS Economic Evaluation Database, Health Technology Assessment Database), Embase, Medline/Premedline, NLM Gateway, Science Citation Index, National Centre for Complementary and Alternative Medicine, private databases; from inception of these databases to June 2006 using the terms (ANTHROPOS? OR MISTLETOE OR VISCUM? OR MISTEL? OR ISCADOR? OR ISCAR OR HELIXOR OR ABNOBA? OR ISCUCIN OR ISOREL OR VISOREL OR ?SOREL OR WELEDA OR WALA) AND (STUDY? OR STUDIE? OR TRIAL OR EVALUAT? OR RANDOM? OR INVESTIG? OR COHORT? OR KOHORT? OR OUTCOME? OR REVIEW OR UEBERSICHT OR METANALYS? OR META(W)ANALYS?) 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 randomized or non-randomized controlled clinical trial, or prospective single-arm cohort study (e.g. phase II trial); (II) study population with cancer, including cervical intra-epithelial neoplasm (CIN); (III) intervention group treated with anthroposophic mistletoe preparation; (IV) clinically relevant outcome (i.e. survival, disease-free interval, remission, relapse, QoL, or reduction of side effects or immune suppression during cytoreductive therapy); (V) completion of study; (VI) published or unpublished. Studies were excluded if they: only measured toxicity or tolerability (phase I trial), only measured stimulation of 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). There were no major differences in study assessment; disagreements were resolved by discussion. Criteria for assessing strength of evidence in controlled trials were adapted from the National Health Service Centre for Reviews and Dissemination [30] and from criteria for good methodology as already applied in earlier reviews on mistletoe trials [24;29]. Quality criteria were adjusted for cohort studies [6]. Criteria were rated as "+" = adequately fulfilled, "(+)" = partly fulfilled, "(-)" = little fulfilled, "-" = not fulfilled. Data were abstracted by one reviewer (GK) and checked by the second reviewer (HK). When necessary, primary authors of the trials were contacted for additional information.

For ranking the quality of the studies (cf. Table 1 and Table 2) we computed a summary score with 3 for +, 2 for (+), 1 for (-), 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

Figure 1 summarizes the process of identifying eligible clinical trials (for more details see [6;7]). 37 trials met the inclusion criteria: 16 RCTs, 9 N-RCTs, and 12 single-arm cohort studies. Of the 37 trials, 34 were published (three of these only as an abstract [31-33]), one study was retrieved as a doctoral dissertation [34], and two were unpublished reports [35;36]. Two further trials [37;38], conducted in Poland, were excluded from this review because of severe validity concerns: a collaborating scientist questioned the alleged randomization of treatment allocation, and no information could be received from the authors to clarify this question.

Characteristics of Included Trials

Table 1 - Table 6 show characteristics of the trials. Settings of the trials were academic hospitals, large community hospitals, and specialized cancer hospitals;

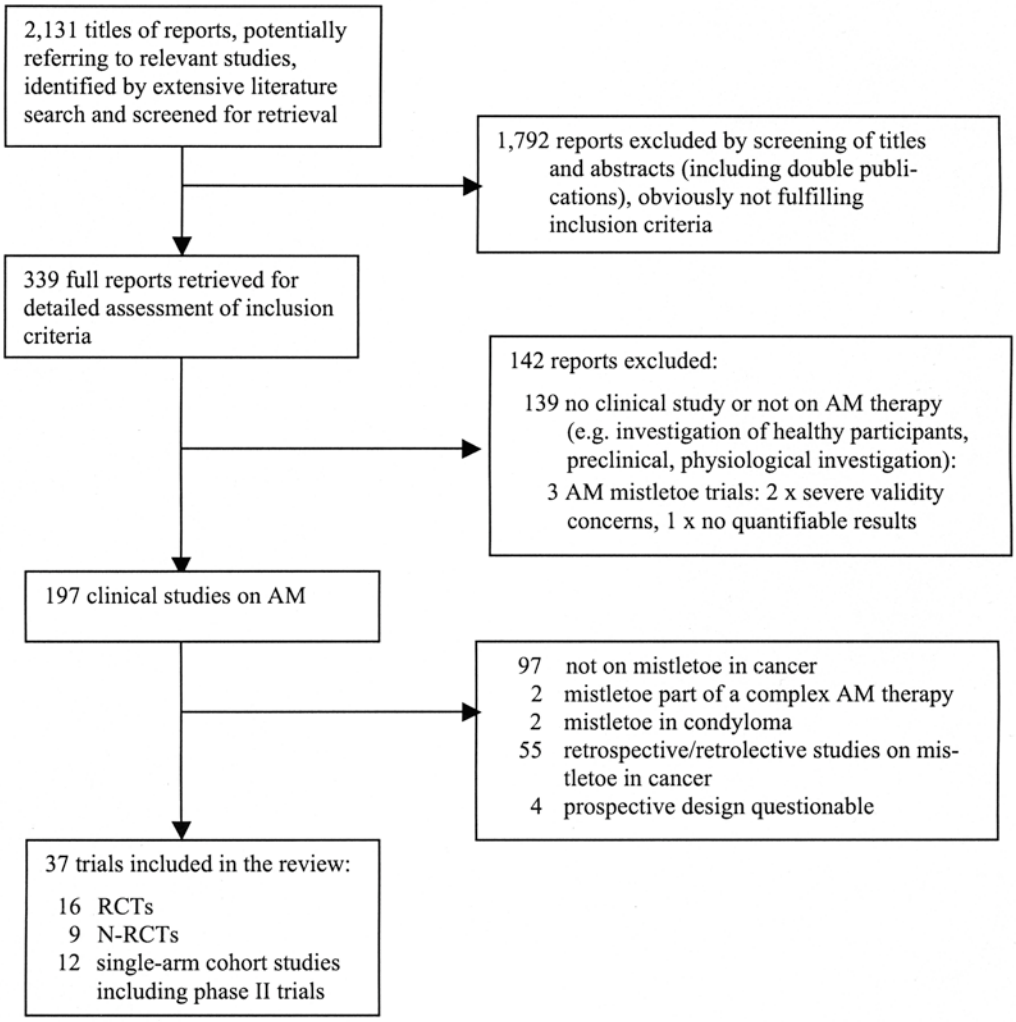

Fig. 1. Identification of eligible prospective clinical cancer trials on anthroposophic mistletoe preparations (updated HTA-report [6; 7])

three trials were done in cancer rehabilitation centres. The studies were conducted in Germany (n = 14), Austria (n = 6), Egypt (n = 4), Italy (n = 2), Israel (n = 2), Switzerland (n = 2), Romania (n = 2), China (n = 1), Denmark (n = 1), South Korea (n = 1), or in more than one European country (n = 2). 22 trials were conducted in one, 15 in more than one centre. One of the controlled [39] and four of the cohort studies [33;36;40;41] were conducted in an AM hospital, the other ones in non-AM institutions.

Controlled trials:
16 RCTs (see Table 1) included 2602 participants, 9 N-RCTs (see Table 2) included more than 2512 participants (the sample size of one control group was not published). Cancer sites studied were: breast (n = 10), lung (n = 8), colon and rectum (n = 5), stomach (n = 3), melanoma (n = 2), ovary (n = 2), genital (n = 2), head and neck (n = 1), gastrointestinal (n = 1), and malignant pleural effusion (n = 1). Stages ranged from early detected to advanced disease. 20 trials had two arms, four trials had three arms, one trial consisted of two overlapping parts with three and four arms respectively, with two of the four arms used for analysis of mistletoe efficacy. Endpoints were: survival (n = 17), tumour remission or recurrence (n = 5), pleurodesis (n=1), quality of life or coping with disease (QoL, n = 5), QoL, physical condition and reduction of side effects of chemotherapy, radiotherapy or surgery (n = 7). Length of follow-up depended on primary outcome, varying from three days in one trial [39] to usually months or years (survival).

All treatment groups received conventional care (COM) when indicated. In nine trials mistletoe was administered concurrently with chemotherapy, radiotherapy or surgery [35;39;42-48]; seven of the trials assessed reduction of side effects from these cytoreductive therapies [35;39;44-48]. In 18 trials mistletoe therapy was used at least partly in an adjuvant setting after surgery or radiotherapy [39;44-46;48-60].

The applied mistletoe remedies were Iscador, Helixor, or Isorel. Host tree specification of these remedies (usually depending on cancer site, and sex of patient) was often not mentioned. Dosage mostly followed recommendations of the manufacturer, starting with low doses and increasing to the maximum tolerated dosage; one trial treated according to lectin-content (1ng/kgKG) [61]. Mistletoe was injected subcuta-

Table 1. Quality of Randomized Controlled Mistletoe Trials (ordered by decreasing quality).

Author, Year	Quality Criteria Fulfilled in Studies[I]											Participants	AR[II]
	A)	B)	C)	D)	E)	F)	G)	H)	I)	J)	K)		
Piao 2004 [45]	+	+	-	(-)	+	+	+	(+)	+	+	+	233	4%
Auerbach 2005 [46]	+	-	(+)	(+)	+	-	+	(+)	+	(+)	+	23	17-30%
Grossarth 2001 [59]	+	+	-	(-)	+	+	+	(-)	+	+	-	34	0%
Dold 1991 [66]	+	+	-	-	+	(-)	+	(+)	+	+	(-)	408	17%
Lange 1985 [35]	+	+	-	(-)	+	(-)	+	(+)	+	+	-	68	35%
Borrelli 2001 [61]	+	-	(+)	(+)	+	+	(+)	+	(-)	(+)	-	30	0%
Grossarth 2001 [59]	+	+	-	(-)	+	(-)	+	(-)	+	+	-	98	20%
Kleeberg 2004 [60;67]	+	+	-	(-)	(-)[III]	(-)	(+)	+	(+)	(+)	(+)	204 (830)	24%
Salzer 1991 [49]	+	(+)	-	(-)	(+)	(-)	+	(+)	(+)	+	-	218	16%
Douwes 1986 [42]	+	-	-	(-)	+	+	+	+	-	(+)	-	60	0%
Gutsch 1988 [51]	+	-	-	(-)	+	(-)	+	+	(+)	+	-	692	20%
Salzer 1979, 1983 [56-58]	+	-	-	(-)	+	-	+	+	(+)	(+)	-	320	57%
Cazacu 2003 [44]	(+)	-	-	(-)	+	+	(+)	(+)	(-)	-	-	64	not shown
Salzer 1987 [55]	+	(+)	-	(-)	+	-	+	-	-	-	-	50	48%
Enesel 2005 [47][IV]	+	-	-	-	(+)	-	(+)	(-)	(-)	(-)	-	70	45%
Kim 1999 [32]	+	-	-	-	(-)	-	(+)	(+)	(-)	(-)	-	30[V]	13%

[I] A) Protection against selection bias, especially by adequate randomization
B) Minimization of heterogeneity by pre-stratification 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 analysis (including non-adherers as randomized) plus per-protocol analysis (excluding non-adherers) 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

[II] AR: attrition rate (dropouts, protocol deviations, withdrawals, patients did not receive treatment as allocated).

[III] Primary endpoint (disease-free survival) was prone to measurement bias (see discussion or [29]); secondary endpoints were resistant to measurement bias (overall survival), or were not published (quality of life).

[IV] Essential information in a supplementary statement

[V] Discrepancy in patient numbers in two presentations (30 and 33), with corresponding discrepancy of results

neously except in three studies employing intravenous infusion [39;44] or intrapleural instillation [32]. Treatment duration depended on primary endpoint and related follow-up, ranging from one single application (in one trial [39]) to repeated applications over months and years, often with individually varying length within trials. Exact treatment duration, however, was often not specified. Control groups received either no further treatment (n = 18), additional placebo application (n = 3), doxycyclin (n = 1), Lentinan (n = 1), BCG (n = 1), or partly hormones (n = 1). Two trials had double-blinded treatment application [46;61]. Besides the mistletoe extracts, AM was not part of any study treatment except perhaps in one N-RCT on surgery-associated inhibition of granulocyte function [39] that was partly conducted in an AM hospital.

We found substantial heterogeneity of the studies in terms of intervention, patient 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.

Single-arm cohort studies:

Twelve prospective cohort studies (see Table 6) included 251 patients. Cancer sites studied were colorectal (n = 1), pancreas (n = 1), hepatocellular carcinoma (HCC, n = 1), breast (n = 2), brain (n = 1), kidney (n = 1), follicular Non-Hodgkin's lymphoma (FL, n = 1), and CIN (n = 1). Furthermore, malignant pleural effusion (n = 2) and malignant ascites (n = 2) were investigated. Tumour stages were advanced or inoperable, except in FL (all stages) or CIN. Six trials were on solid tumours and one on FL; four of these included patients who all [31;62;63], or some of whom [41], had received conventional pre-treatment, and had mostly been resistant especially to chemotherapy; the two other trials included patients with inoperable or disseminated disease who had received no prior chemo- or hormone therapy [64;65]. One trial combined mistletoe extract with gemcitabine in inoperable pancreatic cancer [33]. All 12 studies assessed remission of solid tumours, of FL, or of malignant effusion; eight of them also reported QoL or symptomatic relief. The mistletoe remedies

Table 2. Quality of Non-randomized Controlled Mistletoe Trials (ordered by decreasing quality).

Author, Year	Quality Criteria Fulfilled in Studies[I]											Partici-pants	AR[II]	Design/control for confounding
	A)	B)	C)	D)	E)	F)	G)	H)	I)	J)	K)			
Grossarth 2001 [59]	(+)	+	-	(-)	+	+	+	-	+	+	-	792	3.5%	Prospective pair -matching
Büssing 2004 [39]	(-)[VI]	-	-	(-)	+	+	(+)	(+)	(+)	+	+	105	7%	Comparison of two different hospitals. Pair-matching for analysis
Salzer 1978 [53]	-	-	-	(-)	+	+	+	(+)	+	(+)	-	77	0%	Treatment allocation by type of hospital referring the patient to surgery
Douwes 1988 [43]	-	-	-	(-)	+	+	+	+	-	+	-	40	3%	Planned as an RCT, however, computer error occurred
Von Hagens 2005 [48]	-	-	-	(-)	+	(-)	+	+	(+)	(+)	-	66	11%	Self-selected treatment allocation
Schuppli 1990 [52]	(+)	-	-	(-)	+	(-)	+	(-)	-	-	-	198	not shown	Prognostic disadvantage for mistletoe group at study begin
Salzer 1987 [55]	(+)	-	-	(-)	+	-	+	-	-	(+)	-	155	not shown	Alternating treatment allocation
Fellmer 1966 [54]	-	-	-	(-)	+	-	+	+	-	-	-	924	16%	Treatment allocation by neutral attending physician
Majewski 1963 [50]	(+)	-	-	(-)	+	-	+	-	-	-	-	[VII]	not shown (I: 15%) [VIII]	Alternating treatment allocation

Abbreviations as in Table 1. [VI]Propensity Score and Matching for final analysis [VII]Number of study patients not indicated; mistletoe group included 155 patients [VIII]Numbers are given only for mistletoe group

were Abnobaviscum (partly Viscum fraxini), Iscador, or Helixor. They were applied subcutaneously (n = 7), intratumourally (n = 2), intrapleurally (n = 2), or intraperitoneally (n = 2). Dosage depended on mode of application. Of the seven trials on solid tumours or FL, three started with high dosage and applied it constantly once per week; three other trials started with low dosages, increasing them successively, and the seventh trial applied increasing dosages intratoumorally by endoscopic, ultrasound-guided, fine-needle injection [33]. The trial on CIN constantly applied a lower dosage. For intrapleural and intraperitoneal (repeated) application, mistletoe extracts were diluted in 5-15 or 100 ml solution respectively. Treatment durations and follow-up ranged from weeks to, most commonly, months or years.

Quality of Studies

Table 1, Table 2 and Table 6 summarize the validity assessment. Methodological quality differed substantially. Some studies had major limitations in quality of design, conducting and reporting, while others were reasonably well conducted (Table 1, Table 2). During recent years study quality has markedly increased in most trials. In the cohort studies, study quality was reasonably good except in an unpublished report [36] and in the abstract publications [31;33] with too little information.

Study Results

Main study results are shown in Table 3 - Table 6. On *survival* (Table 3): Out of 17 controlled trials, eight (5 of 10 RCTs) had statistically significant positive results [44;51;53;54;56-59], eight (4 of 10 RCTs) positive trends [42;43;49;50;52;55;66], one RCT no effect [60].

On *disease-free interval* and *recurrence* (Table 4): Out of two RCTs, one had a negative trend [60], one no effect [49].

On *remission of tumour and malignant effusion* (Table 4): Out of four controlled trials (3 RCTs, 1 N-RCT), one N-RCT reported a statistically significant positive effect [43], one RCT a positive trend [66], one no effect [42]; one trial on malignant pleural effusion found significantly higher remissions with mistletoe than with doxycyclin [32]. Of 12 cohort studies (Table 6), five reported remission of solid tumours or of FL in 22-62% of patients, three reported remission of malignant effusion in 70-88% of patients, one an increase of interval between two successive paracenteses after mistletoe instillation, one reported remission of CIN in 68% of patients, and two reported stable and progressive disease, but no tumour remission. Time to remission (CR) of solid tumours was 4-6 months in two trials [63;64]. Concurrent conventional cytoreductive therapy was explicitly given in only two cohort studies, one with substantial [33] and one with no tumour remission [65].

On *QoL* and *coping* (Table 5): Out of five RCTs, three found a statistically significant benefit [59;61;66], one RCT did not report the results [60;67]. (Six further trials investigated QoL related to chemotherapy

Table 3. Controlled Trials on Mistletoe Treatment in Cancer: Survival (RCTs and N-RCTs each ordered by decreasing quality. See Table 1 and Table 2).

Author, Year	Site	Stage	Intervention (evaluable patients)	Survival Outcomes					
				Mean (Months) partly censured	Median (Months)	Hazard ratio	5-year survival	Others	P or CI
Randomized controlled trials									
Grossarth 2001 [59]	Breast	IIIA-IIIB	• Iscador (17) • None (17)	• 57.5 • 28.9	• 75 • 28				P=0.02
Dold 1991 [66]	Lung	All stages	• Iscador U or Qu, c.Hg. (114) • Placebo (vitamin B) (113) • Polyerga (110)		• 9.1 • 7.6 • 9.0				• n.s. (p=0.24) • n.s. (p=0.13)
Grossarth 2001 [59]	Breast, lung, colon, rectum, stomach	All stages	• Iscador (39) • None (39)	• 42 • 29	• 30 • 29				P=0.04
Kleeberg 2004 [60;67]	Melanoma	High risk primary (≥3MM) or LN+	• Surgery, Iscador M (102) • Surgery, IFN-α (240) • Surgery, IFN-γ (244) • Surgery (244/102)			• 1.21 • 0.96 • 0.87			• n.s. (CI: 0.84-1.75) • n.s. (CI: 0.76-1.21) • n.s. (CI: 0.69-1.10)
Salzer 1991 [49]	Lung	I-IV	• Surgery, Iscador (87) • Surgery (96)		• 33 • 31				n.s.
Douwes 1986 [42]	Colon, rectum	Advanced	• 5FU/FA, Helixor (20) • 5FU/FA, Ney Tumorin (20) • 5FU/FA (20)	Responder | non-Respon. • 27 | 12 • 24 | 12 • 14 | 5					not shown
Gutsch 1988 [51]	Breast	T1-3, N0-3, M0	• Surgery, radiation[I], Helixor (192) • Surgery, radiation[I] , CMF (177) • Surgery, radiation[I] (274)		n.a.[II]		• 69.1% • 67.7% • 59.7%		• P=0.048 • (P=0.025)
Salzer 1979, 1983 [56-58]	Stomach	II-III	• Surgery, Iscador (62) • Surgery (75)	Lymph node + | − • 25 | 55 • 18 | 45	LN + | − • 22 | n.a.[II] • 11 | 40				LN + | − P<0.05 | n.s.
Cazacu [44]	Colon, rectum	Dukes C or D	• Surgery, 5-FU, Isorel A (29) • Surgery, 5-FU (21) • Surgery (14)	Dukes D • 17 • 7 • 15	Dukes C • 25 • 18 • 17				P<0.05 (for D and C)
Salzer 1987 [55]	Lung	I (II)	• Surgery, Iscador (12) • Surgery (14)		• 117 • 34.5				not shown

Table 3. (continued)

Author, Year	Site	Stage	Intervention (evaluable patients)	Survival Outcomes					
				Mean (Months) partly censured	Median (Months)	Hazard ratio	5-year survival	Others	P or CI
Non-randomized controlled trials									
Grossarth 2001 [59]	Breast, lung, colon, rectum, stomach	All stages	• Iscador (396) • None (396)	• 50.8 • 36.6	• 44 • 32				P<0.001
Salzer 1978 [53]	Lung	I-III	• Surgery, Iscador (37) • Surgery (40)		• 63 • 10			6-year survival • 38% • 15%	P<0.01
Douwes [43]	Colon, rectum	Advanced	• 5FU/FA, Helixor (19) • 5FU/FA (20)		• 26 • 14				n.s. (P=0.063)
Schuppli 1990 [52]	Melanoma	Not specified	• Surgery, Iscador P c. Hg (84) • Surgery, BCG (114)		n.a.[II]		• ~86% • ~72%		not shown
Salzer 1987 [55]	Breast	I-III	• Surgery, Iscador, (76) • Surgery, radiation, hormone (79)					Alive 1985 (after 11-14 years) • 29% • 24%	not shown
Fellmer 1966 [54]	Cervix	I-III	• Radiation, Iscador (81) • Radiation (709)				• 83% • 69%		P=0.05
Majewski 1963 [50]	Genital	All stages	• Surgery[I], radiation[I], Iscador (155) • Surgery[I], radiation[I] (not shown)					Disease-specific survival partly improved	not shown

CMF: Cyclophosphamid, Methotrexat, 5FU; 5FU: 5-Fluorouracil; FA: Folic acid; P (p-value), CI (95%-confidence interval): Statistical significance of difference between mistletoe (or other verum) and control group; n.s.: not statistically significant; [I] Co-intervention (i.e. radiation) applied to part of the group; [II] n.a.: not applicable since more than 50% alive at study termination; "•"-outcomes relate to corresponding "•"-treatment group.

Table 4. Controlled Trials on Mistletoe Treatment in Cancer: Tumour Behaviour or Pleurodesis (RCTs and N-RCTs each ordered by decreasing quality. See Table 1 and Table 2)

Author, Year	Site	Stage	Intervention (evaluable patients)	Tumour or pleural effusion			
				Remission	Disease-free interval, Hazard ratio	Recurrence	P or CI
Randomized controlled trials							
				Complete resp. | overall regression[I]			
Dold 1991 [66]	Lung	All stages	• Iscador U or Qu, c.Hg. (114) • Placebo (vitamin B) (113) • Polyerga (110)	• 4% | 26% • 3% | 20% • 2% | 19%			• n.s. (p=0.1) • (n.s. p=0.5)
Kleeberg 2004 [60;67]	Melanoma	High risk primary (≥3MM) or LN+	• Surgery, Iscador M (102) • Surgery, IFN-α (240) • Surgery, IFN-γ (244) • Surgery (244/102)		• 1.32 • 1.04 • 0.96		• n.s. (0.93-1.87) • (n.s. 0.84-1.30) • (n.s. 0.77-1.2)
Salzer 1991 [49]	Lung	I-IV	• Surgery, Iscador (87) • Surgery (96)			• 50% • 55%	n.s.
				Complete resp. | partial response			
Douwes 1986 [42]	Colon, rectum	Advanced	• 5FU/FA, Helixor (20) • 5FU/FA, Ney Tumorin (20) • 5FU/FA (20)	• 15% | 35% • 15% | 25% • 15% | 30%			not shown
				Complete resp. | partial response[III]			
Kim 1999 [32]	Pleural effusion[II]	Advanced	• Helixor (11) • Doxycyclin, Meperidin, Lidocain (15)	• 81% | 9% • 40% | 26%			P<0.05
Non-randomized controlled trials							
				Complete | partial | minimal resp.			
Douwes 1988 [43]	Colon, rectum	Advanced	• 5FU/FA, Helixor (19) • 5FU/FA (20)	16% | 37% | 26% 0% | 30% | 20%			"significant", p-value not shown

5FU: 5-Fluorouracil; FA: Folic acid; P (p-value), CI (95%-confidence interval): Statistical significance of difference between mistletoe (or other verum) and control group; n.s.: not statistically significant; [I]Not corresponding to WHO-definition of tumour response; [II]plural effusion indicates treatment site; [III]side effects in Helixor and doxocyclin group: pain in 6 and 14, fever in 3 and 6, burning sensation in 0 and 5 patients, respectively; difference statistically significant (p<0.05).
"•"-outcomes relate to corresponding "•"-treatment group.

and radiation – see below.) Of eight cohort trials, five reported improved, one reported decreasing QoL, and two reported symptomatic relief (reduction of nausea, vomiting, fatigue, diarrhoea, constipation, dyspnoea, and symptoms of ascites).

On *reduction of side effects of surgery, chemotherapy and radiation and related improvement of QoL* (Table 5): Of seven controlled trials, two RCTs and two N-RCTs showed a statistically significant positive effect [35;39;45;48], one RCT found improved QoL and prevention of lymphopenia, however, without computing statistical significance of the difference between the two comparison groups [47]; one small pilot RCT reported mixed results (no effect on QoL, a significant reduction of suppression of activated CD56+/CD69+/CD45+NK-cells, no effect on other immune cells) [46]; one RCT mentioned fewer side effects of 5-FU and a positive effect on QoL without giving details [44]. Furthermore, one of these trials reported that with additional mistletoe therapy the dosage of Cisplatin and Holoxan could be increased because of less intensive side effects. [35]

Tolerability was generally good. One case of urticaria and angioedema was described [45]. Otherwise, no major side effects or toxicity were reported. Minor dose-dependent and spontaneously subsiding symptoms included reactions at the injection site (swelling, induration, erythema, pruritus, local pain) and mild flu-like symptoms or fever. After intrapleural instillation mistletoe extract induced significantly fewer side effects than doxycyclin ([32], see Table 5)

Discussion

Mistletoe therapy, especially AM preparations, is widely used to treat cancer patients in Central Europe. Most of the clinical trials report a benefit for survival, QoL, side-effects of toxic conventional therapies, or tumour remissions. Quality of the trials varies substantially; however, even most of the better-conducted and published trials show a beneficial effect. In detail:

Survival benefit (see Table 3) was assessed by most of the controlled trials. Half of them found a significant positive result; the other half did not reach or did not calculate significance or found no benefit, while none found a disadvantage. All of these trials received some amount of critique [29]: Among the best trials with significant positive effects (by Grossarth-Maticek et al. [59]) were two RCTs embedded in a large cohort study that were small and had an epidemiological rather than a clinical trial design (for more details see [29]). This methodological approach is not well established, unfamiliar to most clinical researchers, and therefore raised concern [7;68]. Other trial publications mentioned major difficulties in patient recruitment or protocol violations [51;56-58], or had small and unequally distributed groups of patients [44]. Several trials had non-randomized designs, some of them carefully controlling for confounders. (Whether carefully conducted N-RCTs can be sufficient to yield valid results, is still the subject of controversial discussion. [69-71]) Survival benefit was usually reported under long treatment duration (several years) while the only trial with no benefit had a short treatment duration (months, with the maximum of one year only completed by 40% of the patients; for more details see [29]). Dependency of survival benefit on length of mistletoe therapy was reported in one of the trials. [59] (This was also mentioned by two recent retrolective pharmaco-epidemiological cohort studies of mistletoe in breast cancer and melanoma. [72;73]) Furthermore, variability of results might be explained by differences in design, methodology and quality of the studies as well as differences in cancer sites and stages investigated. Whether possible survival benefit also depends on the type of mistletoe preparation, host tree, or dosage, cannot be seen in the reviewed trials; they often lacked detailed information and homogeneity for reliable inter-study comparison. These issues need further clarification.

Tumour remission (see Table 4) was investigated by three controlled trials. Two of them [42;43], an RCT and an N-RCT, adding mistletoe to chemotherapy and finding higher remission rates, lacked sufficient quality and transparency in design and presentation. One three-arm study [66], conducted by the German Cancer Research Centre, investigating sole mistletoe treatment, found surprisingly high tumour remission rates in all groups, even with placebo alone (20%). However, as the diagnosis was advanced lung cancer, the spontaneous remission rate of 20% seems unlikely [74], suggesting insufficient documentation or undocumented additional therapy. (Unnoticed co-intervention that contaminates results might be an underestimated and widely neglected hazard for the validity of clinical trials; for instance up to 90% of patients enrolled in conventional cancer trials also use CAM therapies [75].) Disease-free interval was investigated in one trial [60], which, however, may have been influenced by detection bias [29]. Overall, questions of tumour behaviour remain unclear in these controlled trials.

More reliable information on tumour remission is delivered by the cohort studies (see Table 6). Seven of these cohort studies were on solid tumours or on FL, four of them reporting substantial remission with no simultaneous conventional cytoreductive therapy (inoperable HCC, breast cancer pre-treated with chemotherapy, intracranial malignant tumour, FL). In a trial on pancreatic carcinoma, the intratumoural, endoscopic, ultrasound-guided, fine-needle injection of Helixor was combined with Gemcitabine treatment, and achieved tumour remission in 58% of patients, exceeding remission rates known with chemotherapy alone [33]. Notably, all four trials that documented remissions in solid tumours [31;33;63;64], other than the two trials with no remission [62;65], deviated from the common low escalating dosage and used high mistletoe doses from the beginning, and (in three studies) only once per week (due to chronobiological considerations; H. Werner, personal communication). Single-arm cohort studies, including phase II trials, that have no control group, need – besides careful outcome assessment and comprehensive documentation of all major covariables with potential influence on the tumour – an appraisal of spontaneous remissions. [76;77] Spontaneous remissions are common in a few tumour sites (e.g. CIN, renal cancer, melanoma, and

Table 5. Controlled Trials on Mistletoe Treatment in Cancer: Reduction of side effects of chemotherapy, radiation or surgery; QoL (RCTs and N-RCTs each ordered by decreasing quality. See Table 1 and Table 2).

Author, year	Site	Stage	Intervention (evaluable patients)	Reduction of side effects of chemotherapy or radiation		QoL (*during chemotherapy, radiation)			
				Outcome	P or CI	Measurement scale and outcome			P or CI
Randomized controlled trials									
				Chemotherapy-related adverse events		*Increase in FLIC-score	* Increase in TCM-score	*KPI increase in % of patients	
Piao 2004 [45]	Breast, ovary, lung (NSCLC)	T1-4, N0-3, M0-1	• Chemotherapy[I], Helixor A (115) • Chemotherapy[I], Lentinan (109)	• 28 • 77	not shown	• ↑ 9 • ↑ 4.7 (p=0.014)	• ↑ -1 • 0 (p=0.0007)	• 50 % • 32 % (p=0.002)	P=0.014 P=0.0007 P=0.002
Auerbach 2005 [46]	Breast	T1-2, N0-1, M0	• CMF, radiation, Helixor A (11) • CMF, radiation, placebo (9)	CMF-induced NK-cell decrease ↓ SCE-increase ↓ other immune markers: no difference	p=0.005 n.s.	*EORTC QLQ-C30	No difference, data not shown		not shown
Grossarth 2001 [59]	Breast	IIIA-IIIB	• Iscador (17) • None (17)			Self-regulation questionnaire (score 1-6)	• 2.92 → 3.7 • 2.87 → 2.99		P=0.13
Dold [66]	Lung	All stages	• Iscador U or Qu, c.Hg. (114) • Placebo (vitamin B) (113) • Polyerga (110)			Patients subjectively improved	• 59% • 45% • 43%		• P=0.018 • (P=0.4)
Lange 1985 [35]	Lung, head and neck, ovary	Inoperable	• Radiation, cisplatin, holoxan, Helixor (23) • Radiation, cisplatin, holoxan (21)	Nausea ↓ (p=0.005), vomiting ↓ (p=0,08), depression of myelopoiesis ↓ (leucocytes p= 0,003)	p=0.005, p=0.08, p=0.003	*KPI	• 67% → 76% (p=0.0008[II]) • 70% → 74% (p=0,12[II])		not shown
Borrelli 2001 [61]	Breast	IV	• Iscador spezial (20) • Placebo (10)			Spitzer score questionnaire	• ~ 5 → 7.2 • ~ 5.2 → 4.8		P<0,05
Grossarth 2001 [59]	Breast, lung, colon, rectum, stomach	All stages	• Iscador (39) • None (39)			Self-regulation questionnaire (score 1-6)	• 3.41 → 3.87 • 3.85 → 3.62		P=0,02
Kleeberg 2004 [60;67]	Melanoma	High risk primary (≥3MM) or LN+	• Surgery, Iscador M (102) • Surgery, IFN-α (240) • Surgery, IFN-γ (244) • Surgery (244/102)			"Quality of life evaluation"	Result not shown		not shown
				5-FU side effects (% of patients)	not shown	*"Quality of life"	"Improvement"; data not shown		not shown
Cazacu 2003 [44]	Colon, rectum	Dukes C or D	• Surgery, 5-FU, Isorel A (29) • Surgery, 5-FU (21) • Surgery (14)	• 0% • 19%					
						*KPI		*Score of Anxiety	
Enesel 2005 [47]	Gastro-intestinal	II-III	• Surgery, Isorel A (40) • Surgery (30)	Prevention of Surgery-induced lymphocyte reduction	not shown	• ↑ 22% (p<0.01[II]) • ↓ 13% (p<0.05[II])		• ↓ 2,9 (p<0.01[II]) • ↑ 1.5 (p<0.01[II])	not shown

Table 5 (continued).

Author, year	Site	Stage	Intervention (evaluable patients)	Reduction of side effects of chemotherapy or radiation		QoL (*during chemotherapy, radiation)	
				Outcome	P or CI	Measurement scale and outcome	P or CI
Non-randomized controlled trials							
Büssing 2004 [39]	Breast (suspected)		• Surgery, Iscador M spezial (47) • Surgery (51)	Prevention of surgery-associated inhibition of granulocyte function (PMA- and E.coli-stimulated oxidative burst)	P<0.0001, P<0.001		
Von Hagens 2005 [48]	Breast	I–II	• Surgery, CMF/EC, Iscador (33) • Surgery, CMF/EC (33)	CMF/EC-induced lymphocyte decrease ↓, platelet decrease ↓	n.s, p=0.01	* EORTC QLQ-C30, B 23	Reduced increase of nausea/vomiting, general side effects of CMF/EC p=0.02 p=0.02

QoL: Quality of life; KPI: Karnofsky Performance Index. SCE: Sister Chromatid Exchange; ↑: Increase; ↓: decrease. P (p-value): Statistical significance of difference between mistletoe (or other verum) and control group; n.s.: not statistically significant; CMF: Cyclophosphamid, Methotrexat, 5FU; 5FU: 5-Fluorouracil; FA: Folic acid;
[I] Chemotherapy: Breast Cancer: CAP, CAF; Ovarian cancer: CP, IcP; NSCLC: VP, MViP. Cyclophosphamid (C), Adriamycin (A), Cisplatin (P), 5-Fluorouracil (F), Vinorelbine (V), Mitomycin (M), Ifosfamid (I), Vindesine (Vi), Carboplatin (cP).
[II] statistical significance of pre-post-difference within each group;
"•"-outcomes relate to corresponding "•"-treatment group.

lymphomas) but are extremely rare in most common cancers. [78;79] Accordingly, among the cohort studies reviewed, spontaneous remissions might have occurred in CIN [34] or in FL [41].

Tumour remission under mistletoe therapy may depend on mode of application (local subcutaneous, intratumoural, intravenous, intrapleural), on chronobiological aspects (e.g. application once versus three times per week), and on dosage (slowly increasing versus high dosage from the beginning, as, for instance, antibodies against active ingredients are induced within weeks or months of treatment). These links are also suggested by anecdotal therapeutic reports, and are biologically plausible considering the substantial antitumoural, cytotoxic and pro-apoptotic VAE activity in vivo and in vitro that is partly inhibited by serum proteins and ML antibodies. [8;9] These issues should be investigated in more detail.

All seven trials investigating *reduction of side effects of toxic conventional treatments* (chemotherapy, radiation, surgery) (see Table 5) found a benefit. The methodologically best trial, an RCT conducted in China, investigated side effects of various chemotherapeutics and found significantly less adverse effects, better QoL and physical condition with mistletoe compared to the phytopharmacon Lentinan. [45] An unpublished German trial, small-sized but otherwise reasonably well-designed, showed fewer side effects of Cisplatin, Holoxan and radiotherapy with additional mistletoe therapy (less nausea and vomiting, better physical condition) and a positive effect on Holoxan and Cisplatin dosage (fewer dose reductions were necessary because of reduced side effects). [35] A small Austrian pilot trial reported no effect on QoL, less suppression of activated NK-cells and a trend towards less chromatin damage. This trial, well designed in many aspects, was severely underpowered for effect estimation, and the tested laboratory markers (SCE: Sister Chromatid Exchange, immune parameters) are more of experimental relevance than clinically well-established, and display high inter-individual variability. [46] The latter also applies to the N-RCT on surgery-associated inhibition of granulocyte function [39]; here, outcomes in two different hospitals (an AM hospital applying pre-operative mistletoe infusion, a COM hospital applying routine surgery only) were compared, matching for patient characteristics and length of surgery. Despite matching, residual differences of the two self-selected patient populations and settings (AM, COM) might also have affected the investigated immune function. [39] Biological plausibility of these side-effect reductions might lie in DNA-stabilizing properties of VAE [20-22]. These properties, however, seem not to attenuate the cytoreductive effects of radiotherapy and chemotherapy [35;42;43]; they were, rather, enhanced by VAE in vitro and in vivo. [9]

QoL (see Table 5) was investigated altogether in eleven controlled trials: Seven trials (one double blind [61]) found a benefit for mistletoe treatment, one reported a trend [59], one study (small, double-blind but unblinded by most patients [46]) found no difference, one did not present the results of an "improvement" [44]; one RCT cited "quality of life evaluation" in a pre-publication report [67] but did not mention it any

Table 6. Single-Arm Cohort Studies (e.g. Phase II Trials) on Mistletoe Treatment in Cancer (ordered chronologically).

Author, Year	Treatment[I]					Site[II]	Result[III]					n[IV]	Quality Criteria Fulfilled[V]					
	Preparation	Injection site	Dosage	Escalating dosage	Duration		CR	PR	NC	PD	QoL		L	M	N	O	P	Q
Solid tumours or lymphoma																		
Kuehn 2005 [41]	Iscador P (M, Qu occasionally)	sc	0.01-30mg	Yes	mean 24 months	Follicular lymphoma	17 % [IIIa]	25 % [IIIa]	–	38 %		24	(+)	(+)	+	+o [IIIa]	(+)	+
Matthes 2005 [33]	Helixor M	it[Ia]	300-1000 mg	Yes	repeatedly	Pancreas	8%	50%	33 %	8 %	↗	12	(-)	(+)	(+)	-o	(+)	+
Bar-Sela 2004 [62]	Abnobaviscum Qu	sc	3 x 0,15-15 mg/w	Yes	med. 14 w	Colon, Rectum	0	0	84%	16%	↗[IIIb]	25	+	+	+	(+)	+	+
Mabed 2004 [64]	Viscum fraxini	sc	1 x 30 mg/w	No	med. 17 w	HCC	13%	9%	(39%)[IIIc]	39%		23	+	+	+	(-)	+	+
Mahfouz 1999 [63]	Viscum fraxini	sc or it	1 x 45 mg/w	No	18-136 w	Breast	8%	54%	35%	4%	↗	26	(+)	(+)	+	(+)	+	+
Mahfouz 1998 [31]	Abnobaviscum Fr	sc	1 x 45 mg/w	No	17 w	Breast, Brain	27%	27%	27%	20%	↗	15	-	(-)	(+)	-	-	(+)
Kjaer 1989 [65]	Iscador Qu or M, c.Cu	sc	Varying	Yes	med. 13/47 w	Kidney	0	0	14%	86%	↓	14	+	(+)	+	+o	(+)	+
CIN																		
Portalupi 1995 [34]	Iscador M	sc	2 x 1 ng MLI /kg bw/w	No	16 w	CIN I-III	41%	27%	27%	5%		27	+	+	+	+	+	(+)
Malignant effusion																		
Bar Sela 2006 [100]	Iscador M	ipe	10 mg	No	repeatedly	Ascites	Increase of interval between two successive paracenteses from 7 to 12 days, p=0.001[IIId]				↗[IIIe]	23	(+)	(+)	+	(+)	+	+
Werner 1999 [101]	Abnobaviscum Fr	ip	1 x 75 mg/w	No	3-8 w	Pleural effus.	88%				↗	32	+	+	+	-	(+)	(+)
Stumpf 1994 [40]	Helixor A, M or P	ip	100-1000 mg each	Yes	repeatedly	Pleural effus.	61%	11%	22%			18	+	+	+	(+)	+	+
Friedrichson 1985 [36]	Helixor	ipe	100-1000 mg each	Yes	repeatedly	Ascites	70%				↗	12	(+)	(-)	+	-	(-)	+

[I] sc: subcutaneous, it: intratumoural, ip: intrapleural, ipe: intraperitoneal; w: week, med.: median. [Ia] Endoscopic ultrasound-guided fine-needle injection.

[II] HCC: hepatocellular carcinoma, CIN: cervical intraepithelial neoplasia, effus.: effusion (malignant). Stage: advanced, except CIN; plural effusion and ascites indicates treatment site.

[III] CR: complete, PR: partial remission, NC: no change, PD: progredient disease, QoL: quality of life, ↗: improved, ↓ impaired; [IIIa] responses under mistletoe monotherapy, without concomitant oncologic cytoreductive therapies; [IIIb] symptomatic relief (40% of patients); [IIIc] undetermined response due to early death; [IIId] median values, comparable abdominal circumference and symptom score or drained fluid before or during each paracentesis, respectively; [IIIe]Trend improvement in symptom score, especially abdominal pain, abdominal pressure, and waking up at night due to shortness of breath.

[IV] n: Number of participants.

[V] L Well described patient characteristic and disease (diagnosis, stage, duration), prognostic factors
M Outcome parameter relevant and well described
N Well described intervention
O Concomitant therapies well described (o: concomitant conventional oncologic cytoreductive therapies in some of the patients)
P Outcome clearly described, temporal relationship between applied therapy and observed outcome precisely described
Q Selection of patients excluded

more in the final publication [60]. Since assessment of QoL might be influenced by patients' expectations, blinding is a relevant issue. However, due to local skin reaction (rubor, pruritus, induration) and mild flu- like symptoms, blinded subcutaneous mistletoe applications are usually unblinded by 80% - 100% of patients and physicians, as confirmed in two recent double-blind RCTs [46;80]. For this reason, the ethics committee for an RCT on non-anthroposophic mistletoe extracts [81] did not approve a double-blind design. When reliable blinding is questionable, a possibility is to apply active or pseudo-active control treatments that might generate similar expectations. This was done in the trial conducted in China when the control group received Lentinan, a polysaccharide cancer drug popular in China and Japan [45]; it was also done in a three-arm trial when two study groups received either vitamin B or Polyerga [66]. In both trials, QoL results in the mistletoe groups were rated significantly higher than in the control groups. – Besides, blinding of outcome assessment should be conducted whenever possible, or QoL assessment should be combined with other biological parameters that are less prone to subjectivity, as done in some of the mistletoe trials. Finally, the possibility of blinding of other application routes, like intravenous infusions, should be checked in future trials and done if possible.

Safety aspects: Mistletoe therapy was well tolerated in the reviewed trials. Impairment of QoL in one cohort study was due to progressive cancer disease. [65] Good tolerability was also shown in other investigations. [82] Currently, a phase I study at the NCCAM/NCI is investigating safety, toxicity and drug interactions between mistletoe extract and Gemcitabine. [83] A first interim report found good tolerability, with neither dose-limiting toxicity of the mistletoe extract nor any effects on the plasma concentration of gemcitabine. [84] Allergic reactions can occur, and a few case reports of anaphylactic reactions exist [82;85;86]. Recently, a list of serious side effects of mistletoe therapy was published [87;88] but turned out to be erroneous interpretations of reports not referring to mistletoe therapy (for details see [89] or [7]). Enhancement of brain metastases was discussed in preliminary reports [90;91] on the melanoma trial by Kleeberg et al. 2004 [60]. The data were not confirmed in the final publication [60], and may have resulted from detection bias [29;92]. Still, they gave rise to an elaborate GEP-conform, retrolective multi-centre study in Germany and Switzerland, conducted by the Dermatology Department of the University of Freiburg: in 686 consecutive patients (329 mistletoe, 357 controls) with melanoma stage II or III, treated in 35 randomly chosen centres, no tumour enhancement could be observed in mistletoe-treated patients, while incidence of brain metastases (multiple adjusted analysis), brain metastases-free survival, disease-free survival, and overall survival were all statistically significant in favour of the mistletoe group. [72] Regarding initial high-dose therapy, as reported in the Egyptian trials [31;63;64], safety aspects might have to be taken into account because high dosages might produce much stronger local reactions and flu-like symptoms. Furthermore, especially in Central Europe, prior mistletoe exposure through the widespread use of mixed herbal remedies or teas is possible and often not known to the patients; therefore adverse reactions to initial high mistletoe dosages are a theoretical possibility.

Strength and weakness of the review

The validity of this review largely depends on the primary trials. There are substantial weaknesses in several of the reviewed studies; however, some of the more recent ones, in particular, were reasonably well conducted. Strengths and weaknesses of most of the reviewed trials, such as potential performance bias, detection bias, attrition bias etc., have been described previously (see [29]) and are summarized and updated in Table 1, Table 2 and Table 6. Blinding of therapy was attempted in only two trials [46;61]; however, blinded application of mistletoe extracts is unblinded by most of the patients [46;80], which is why reliability of *pro forma* blinding might be questionable (see above).

In order to minimize publication bias, all unpublished trials were included and a comprehensive search was conducted, including personal contacts with approximately 150 experts in the field worldwide, most of them from Europe [6;7]. We consider it unlikely that important rigorous trials, especially RCTs, remained unnoticed, at least in Europe; however, we cannot exclude that we missed trials in distant, non-European countries, or small cohort studies unknown to our contacted experts and not listed in the screened databases. The two trials that were excluded because of validity concerns (see result section) reported results in favour of mistletoe treatment; therefore no positive bias is induced by these exclusions. One further N-RCT, a feasibility trial, not included in this review because it did not present quantifiable results, also reported results in favour of mistletoe therapy (fewer side effects and improved QoL in breast cancer patients undergoing chemotherapy with CMF or EC) [93]. Inclusion of different sorts of trials (RCT, N-RCT, cohort study) does not bias this review, since they are clearly indicated in Table 2 - Table 6 and explicitly identified in the text.

For this review, blinded quality assessment was impossible, since most trials were previously known to the authors.

Clinical relevance and further research recommendations

All reported endpoints are clinically relevant. Some application and dosage modalities, especially in cohort studies, deviated from general recommendations.

In the reviewed trials, mistletoe therapy was mostly applied in non-AM and non-CAM settings. In AM settings, mistletoe therapy is usually part of a complex clinical approach that may include, besides COM remedies, further AM medicines, art and movement therapy, therapeutic massage and counselling for physical, mental, social and spiritual issues. [6;7;94] These multi-modal treatments claim to focus on the "whole" patient, trying to improve his or her inherent self-healing abilities. Comprehensive prospective trials on the whole system of AM cancer treatment were recently conducted by the Universities of Uppsala and Bern. The Swedish study compared QoL of breast cancer

patients in AM and COM settings. A prospective matched-pair design was chosen because an RCT was not feasible (funding from the Swedish Cancer Society and other sources did not cover expenses that would have included patients staying in an AM clinic). While AM patients had lower QoL-scores at study entrance, they significantly improved during AM therapy and, after one year, were superior compared to COM-treated patients, who showed no significant change of QoL. [95] The Swiss AM cancer study, a project by the Swiss National Science Foundation, consisted of three study modules including a three-armed randomized controlled trial investigating the benefit of additional AM or psychosocial treatment. This RCT had to be stopped as not enough patients at the Institute of Medical Oncology in Bern could be enrolled. [96]

Common difficulties with patient recruitment seem to be frequent in European mistletoe trials. [9] In a feasibility study by the University of Heidelberg, out of 1,922 patients receiving surgical treatment for breast cancer only 29 (1,5%) could have participated in an RCT. [97] Two larger RCTs that were finally brought to completion took eight and nine years of patient recruitment despite multi-centre designs and sample size re-calculation to reduce the required number of patients. [60;66] Reasons for hampered patient recruitment were multiple, e.g. not fulfilling inclusion criteria, preference or objection towards mistletoe treatment, general rejection of study participation or of randomized treatment allocation, participation in other studies, or logistical reasons. This issue has to be carefully considered in future trials.

Regarding the widespread use and the potential anti-tumour benefit of VAE, widely investigated especially in vitro and in animal models [8;9], clinical research should be further intensified and its quality further improved. This process would clearly benefit from public funding to enable more extensive and clinically detailed research. Future studies should take into account the methodological limitations and potential biases of the reviewed mistletoe trials (see also [29]). They should further explore the results of the cohort studies, and clarify the impact of different modalities of mistletoe applications (dosage, location, intervals, duration) on the outcome in different therapeutic situations. Furthermore, since a biomedical paradigm – viewing mind and body as separate – has been perceived as an additional violation by patients und may increase their suffering [98], multimodal systems (see above) should also be investigated and patients' perspectives evaluated in order to gain insights into ways of meeting their need of holistic, multimodal care. Appropriate research methods may include comparison trials of different complex treatment systems, high quality observational studies, or carefully performed qualitative research. [99] These complex approaches, however, require strong commitment by the research community, and often require more preparatory effort than conventional clinical trials. [99]

Conclusion

Quality of clinical trials on mistletoe therapy varies substantially, but has improved during recent years. With regard to quality of studies and consistency of results, the best evidence concerning efficacy of mistletoe therapy seems to exist for improvement of QoL and reduction of side effects of cytoreductive therapies (chemotherapy, radiation) – limited by the fact that the interventions are not blinded, and cannot be reliably blinded. Survival benefit is possible; conventional RCTs on this issue had varying results and best evidence relies mostly on small trials using epidemiological methodology unfamiliar to most scientists and less widely accepted [59;72;73]. In relation to tumour remission, the controlled trials are inconclusive; cohort studies describe tumour remissions mostly with high dosage and local application; they should be further explored. Tumour remission seems to depend on dosage and on mode of application. Mistletoe application seems safe except for rare allergic reactions.

As several reasonably well-conducted studies indicate beneficial effects, and results of preclinical research are promising, further properly designed trials should be encouraged to investigate clinical efficacy and its possible dependency on mode of application. Also, considering the widespread use of mistletoe among cancer patients as well as many patients' apparent need for complementary medicine and holistic care, research activities should be increased. Future controlled studies should take into account the methodological limitations and potential biases of these previous mistletoe trials.

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