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REVIEW – CLINICAL ONCOLOGY

Mistletoe in oncological treatment: a systematic review

Part 2: quality of life and toxicity of cancer treatment

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Abstract

Purpose One important goal of any cancer therapy is to improve or maintain quality of life. In this context, mistletoe treatment is discussed to be highly controversial. The aim of this systematic review is to give an extensive overview about the current state of evidence concerning mistletoe therapy of oncologic patients regarding quality of life and side effects of cancer treatments.

Methods In September and October 2017, Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, CINAHL and "Science Citation Index Expanded" (Web of Science) were systematically searched.

Results The search strategy identified 3647 articles and 28 publications with 2639 patients were finally included in this review. Mistletoe was used in bladder cancer, breast cancer, other gynecological cancers (cervical cancer, corpus uteri cancer, and ovarian cancer), colorectal cancer, other gastrointestinal cancer (gastric cancer and pancreatic cancer), glioma, head and neck cancer, lung cancer, melanoma and osteosarcoma. In nearly all studies, mistletoe was added to a conventional therapy. Regarding quality of life, 17 publications reported results. Studies with better methodological quality show less or no effects on quality of life.

Conclusions With respect to quality of life or reduction of treatment-associated side effects, a thorough review of the literature does not provide any indication to prescribe mistletoe to patients with cancer.

Keywords Mistletoe · Cancer · Complementary and alternative medicine (CAM) · Patient-relevant outcomes

Background

Incidence and prevalence of cancer are increasing (Bray et al. 2018). The most important goal of cancer therapy is to achieve cure whenever possible. Another important goal is to improve or maintain quality of life (Khan et al. 2005).

Quality of life is the subjective perception of a person about their place in life in relation to the culture and the value systems in which they live and in relation to their goals, expectations, standards and concerns and is influenced by physical and mental health, degree of independence, social contacts, personal goals and relationship to environment (WHO 1996).

Once cancer occurs, restrictions arise in almost every area of life. Cancer is associated with disease-related or therapy-related cognitive, physical or functional impairments. In addition, therapy or stigmatization can create social and financial burdens (Deutschinoff et al. 2005). Therefore, cancer has a huge impact on quality of life.

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To become active, to support therapy and to improve the quality of life, more and more patients are using complementary and alternative medicine (CAM) for a variety of reasons. Reasons are mostly to strengthen body and immune system or to do something for oneself (Huebner et al. 2014). From a global perspective, usage of CAM has risen from about 25% since the 1970s to at least 50% since 2000 (Horneber et al. 2012).

This is highly relevant as the co-administration of conventional therapy and CAM may lead to potential direct and indirect health damages (Stub et al. 2016). While indirect risks are related to the treatment context, e.g., delaying or even dispensing an effective conventional therapy, direct risks are caused by the treatment itself. They consist of adverse effects such as intoxication or allergic reactions. Furthermore, direct risks may be interactions with conventional cancer treatment.

One of the most common methods is therapy with mistletoe (*Viscum album*). Mistletoe treatment of cancer patients was already examined in several systematic reviews and is discussed to be controversial in science. Some authors suggest a clear benefit of mistletoe treatment regarding quality of life (Melzer et al. 2009; Kienle and kiene 2007, 2010; Kienle et al. 2009; Bussing et al. 2012), other authors concluded that mistletoe treatment has no benefit for cancer patients (Ernst et al. 2003) or that results regarding efficacy concerning survival and toxicity reduction were insufficient (Horneber et al. 2008; Lange-Lindberg et al. 2006). However, their results provide the first support that mistletoe could improve quality of life (Horneber et al. 2008). Yet, all authors of systematic reviews and meta-analysis were relatively aware about the great heterogeneity and the more or less insufficient methodological quality of clinical mistletoe research to that date. As even the newest one of these reviews was published several years ago, a systematic summary also including recent literature regarding mistletoe is lacking.

Objectives

The aim of this systematic review is to give an extensive overview about the current state of clinical research concerning mistletoe therapy of oncologic patients. Important outcomes considered in this context were efficacy of mistletoe treatment regarding survival, quality of life and safety.

Results are presented in two publications. Part 1 (submitted to *J Cancer Res Clin Oncol*) presents all data of the systematic search on survival data as well as on safety under mistletoe therapy. Part 2 (this publication) presents all data on quality of life and on impact on toxicity of cancer treatment under mistletoe therapy.

Methods

In September and October 2017, the following databases were systematically searched: Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, CINAHL and "Science Citation Index Expanded" (Web of Science). For each database, a complex search strategy was developed consisting a combination of MeshTerms/keywords and text words regarding cancer and mistletoe. No search string was restricted by filter of study type to make sure that no randomized controlled trial would be missed.

The exact search strategy for each database is listed in Table 1.

Only articles published in English or German and published after 1994 were considered. Regarding study type, only randomized controlled studies were included in this review. All other inclusion and exclusion criteria are listed in Table 2 based on a PICO-Schema. Study selection was made in three steps. First, titles and abstracts of all studies were screened by two independent reviewers (MF and JH) regarding their relevance for this review. Reasons for rejecting studies at this stadium were irrelevant topics, other study types than randomized controlled studies and preclinical studies. Second, full texts from all remaining studies were screened and again it was decided if they matched with inclusion criteria. In the last step, studies were excluded if they were double publications or reported no patient-relevant outcome.

Results

The search revealed 3647 hits. After removing duplicates, 2006 studies remained. From these, 111 articles were selected to complete review and 33 RCTs of these studies were considered as relevant. Finally, 28 publications were included in this review (see Fig. 1). In some of these publications, data from one study were described [first study and follow-up (Troger et al. 2013, 2014a), different outcomes reported per publication (Lenartz et al. 1996, 2000; Steuer-Vogt et al. 2001, 2006)]. In one case, four publications described one set of patients from a study with three arms. Two publications reported the results of one treatment arm, respectively, versus the control group (Troger et al. 2009, 2014b) and the remaining two publications were follow-up studies of the former (Troger et al. 2012, 2016). Moreover, there were two publications reporting two different datasets of patients (with and without metastasis) in one article (Grossarth-Maticek and Ziegler 2007b, 2008). Accordingly, the included 28 publications reported data

Table 1 Search strategies for each database

Database	Search strategy (2017/26/09–2017/10/11)
Medline/Embase via Ovid	1 mistletoe$.mp. or exp Mistletoe/ or viscum album.mp. or exp Viscum album/ or ("ABNOBAViscum" or "Lektinol" or "Plenosol" or "Isorel" or "Iscucin" or "Iscador" or "Iscar" or "Helixor" or "Eurixor" or "Vysorel").mp. 2 exp neoplasms/ or neoplasm$.mp. or cancer$.mp. or tumo?r$.mp. or malignan$.mp. or oncolog$.mp. or carcinom$.mp. or leuk?emia.mp. or lymphoma.mp. or sarcom$.mp. 3 1 and 2 4 limit 3 to english or limit 3 to german
CENTRAL	#1 [mh mistletoe] or mistletoe? or "Viscum album" or "Viscum" or "ABNOBAViscum" or "Lektinol" or "Plenosol" or "Isorel" or "Iscucin" or "Iscador" or "Iscar" or "Helixor" or "Eurixor" or "Vysorel" #2 [mh neoplasms] or neoplasm* or cancer? or tum*r? or malignan* or oncolog* or carcinom* or leuk*mia or "lymphoma" or sarcoma? #3 #1 and #2
CINAHL	S1 (MH "Mistletoe" OR TX Mistletoe OR TX "Viscum album" OR TX "Viscum" OR TX "ABNOBAViscum" OR TX "Lektinol" OR TX "Plenosol" OR TX "Isorel" OR TX "Iscucin" OR TX "Iscador" OR TX "Iscar" OR TX "Helixor" OR TX "Eurixor" OR TX "Vysorel") S2 (MH "Neoplasms+" OR TX neoplasm* OR TX cancer OR TX tumo#r OR TX malignan* OR TX oncolog* OR TX carcinom* OR TX leuk#emia OR TX lymphoma OR TX sarcoma) S3 (LA German OR LA English) S4 S1 AND S2 AND S3
PsycINFO	S1 (TX Mistletoe OR TX "Viscum album" OR TX "Viscum" OR TX "ABNOBAViscum" OR TX "Lektinol" OR TX "Plenosol" OR TX "Isorel" OR TX "Iscucin" OR TX "Iscador" OR TX "Iscar" OR TX "Helixor" OR TX "Eurixor" OR TX "Vysorel") S2 ((DE "Neoplasms" OR DE "Benign Neoplasms" OR DE "Breast Neoplasms" OR DE "Endocrine Neoplasms" OR DE "Leukemias" OR DE "Melanoma" OR DE "Metastasis" OR DE "Nervous System Neoplasms" OR DE "Terminal Cancer") OR (TX neoplasm* OR TX cancer OR TX tumo#r OR TX malignan* OR DE "oncology" OR TX oncolog* OR TX carcinom* OR TX leuk#emia OR TX lymphoma OR TX sarcoma)) S3 (LA German OR LA English) S4 S1 AND S2 AND S3
Science Citation Index Expanded (Web of Science)	#1 (TS = Mistletoe* OR TS = "Viscum album" OR TS = Viscum OR TS = "ABNOBAViscum" OR TS = "Lektinol" OR TS ="Plenosol" OR TS = "Isorel" OR TS = "Iscucin" OR TS = "Iscador" OR TS = "Iscar" OR TS = "Helixor" OR TS = "Eurixor" OR TS = "Vysorel") #2 (TS = neoplasm* OR TS = cancer OR TS = cancers OR TS = > tumo$r OR TS = tumo$rs OR TS = malignan* OR TS = oncolog* OR TS = carcinom* OR TS = leuk$emia OR TS = lymphoma OR TS = sarcoma OR TS = sarcomas) #3 #1 AND #2

Table 2 Inclusion and exclusion criteria

PICO	Inclusion criteria	Exclusion criteria
Patient	Cancer patients (all entities and stages) Adult patients (age > 18)	Patients with precancerous conditions or carcinoma in situ Primary prevention Preclinical studies
Intervention	Every intervention with mistletoe extract No restrictions regarding mistletoe extract, dose, mode of application	
Comparison	All possible control groups (active control, placebo, standard/guideline/usual care, wait list)	
Outcome	Mortality (overall survival) Morbidity (progression/disease-free interval, tumor response) Patient-reported outcomes (i.e., quality of life or other important psychological outcomes) Toxicity and adverse events (CTCAE)	Only laboratory parameters
Others	Language: German and English Full publication Studies published since 1995	Gray literature (conference articles, abstracts, letters, ongoing studies, unpublished literature…)

from 24 different studies. Detailed characterization of the studies is shown in part 1 of this review. Furthermore, a table with characteristics of included studies can be found as a supplementary material (Table S1) of this publication.

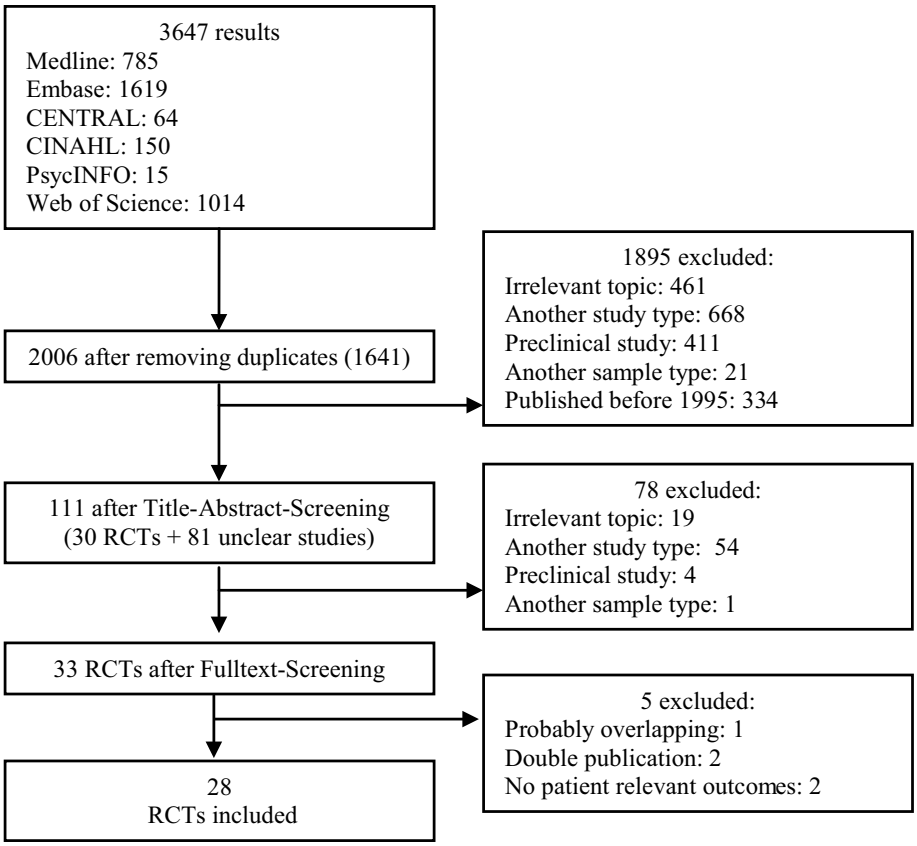

Fig. 1 Consort diagram

The following main patient-relevant endpoints were reported (see Table S1): overall survival (OS, 14 studies, $n = 1054$), morbidity (progression- or disease-free survival PFS/DFS, tumor response, 10 studies, $n = 1091$), quality of life (QoL, 17 studies, $n = 2167$) and toxicity of main intervention (11 studies, $n = 1409$). Apart from that, two studies with 68 various cancer patients in sum examined the efficacy of mistletoe as palliative treatment for malignant pleural effusion (El-Kolaly et al. 2016; Gaafar et al. 2014).

Efficacy of mistletoe treatment

Quality of life

From all included studies, 17 reported results regarding QoL. Of these, six did not examine QoL by widespread validated instruments but used a self-developed questionnaire regarding psychosomatic self-regulation as indicator of QoL (Grossarth-Maticek et al. 1995).

Overall, there is a big heterogeneity concerning the way of assessing QoL, the observation period (range 3 months to 3 years) and the methodological quality of this research (see Table 3). Following multidimensional and unidimensional questionnaires were used:

General quality of life:

- European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) (Aaronson et al. 1993): seven studies (Bar-Sela et al. 2013; Kim et al. 2012; Longhi et al. 2014; Semiglasov et al. 2004; Steuer-Vogt et al. 2006; Troger et al. 2009, 2012, 2013, 2014a, b, 2016); additional gastric cancer module (QLQ-STO22): one study (Kim et al. 2012), additional lung cancer module (QLQ-LC13); one study (Bar-Sela et al. 2013)
- Functional Assessment of Cancer Therapy-General (FACT-G) (Cella et al. 1993): two studies (Heiny and Albrecht 1997; Semiglazov et al. 2006)
- Global Life Quality (GLQ-8) (Coates et al. 1990) and Spitzer Quality of Life Uniscale (Spitzer et al. 1981): two studies (Semiglasov et al. 2004; Semiglazov et al. 2006)
- Functional Living Index-Cancer (FLIC) (Schipper et al. 1984); Karnofsky Performance Index (KPI) (Karnofsky and Burchenal 1949) and Traditional Chinese Medicine Index (TCM): one study (Piao et al. 2004)
- Spitzer Quality of Life Index (Spitzer et al. 1981): one study (Lenartz et al. 1996).

Psychosomatic self-regulation:

Table 3 Effect of mistletoe treatment regarding quality of life of cancer patients

Study	Quality of life measurement points/intervals	Quality of life results
Breast cancer		
Grossarth-Maticek and Ziegler (2006a)	2/52 weeks	A: $n = 38$, B: $n = 38$ Psychosomatic self-regulation (1 = low to 6 = high): median of paired differences [95% CI], Wilcoxon paired sample test, p value 0.35 [0.05, 0.60], $p = 0.034$
Grossarth-Maticek and Ziegler (2006b)	2/12 weeks	A: $n = 17$, B: $n = 17$ Psychosomatic self-regulation (1 = low to 6 = high): median of paired differences [95% CI] 0.90 [0.0, 1.75]
Semiglasov et al. (2004)	2/baseline, week 15	A: $n = 66$ (low dose), B: $n = 65$ (medium dose), C: $n = 64$ (high dose), D: $n = 66$ (placebo) Changes in mean (SD) GLQ-8[d]: (negative values improvement of QoL) A: 16.6 (142.5), B: −37.3 (122.9), C: −9.2 (132.1), D: 23.5 (117.3) Spitzer uniscale: (negative values improvement of QoL) A: −2.6 (29.1), B: −3.7 (29.9), C: −19.0 (28.9), D: −4.1 (30.0), $p = 0.0035$ Exploratory pair-wise comparisons: A versus D: two-sided $p = 0.7063$, B versus D: two-sided $p = 0.007$, C versus D: two-sided $p = 0.4003$ EORTC QLQ-C30[a]: "no relevant differences" (only reported in text); data not shown
Semiglazov et al. (2006)	3/baseline (T0), week 15 (T1) and 2 months after CTX (T2)	T0-T1: A: $n = 169$, B: $n = 168$ T0-T2: A: $n = 103$, B: $n = 104$ Changes in mean (SD) FACT-G[b] (positive values improvement of QoL) *Between baseline and week 15* Total score: A: 4.40 (11.28), B: −5.11 (11.77), $p < 0.0001$; physical: A: 2.03 (5.07), B: −2.33 (5.10), $p < 0.0001$; emotional: A: 1.43 (4.11), B: −1.17 (4.36), $p < 0.0001$; functional: A: 0.94 (4.15), B: −1.61 (4.66), $p < 0.0001$ *Between baseline and 2 months of follow-up* Physical: A: 4.75 (5.57), B: 1.20 (4.45), $p < 0.0001$; emotional: A; 1.78 (4.67), B: −0.44 (3.83), $p < 0.0001$; functional: A: 2.02 (4.60), B: −0.42 (5.07), $p < 0.0001$ GLQ-8[d]: changes in mean (SD) (negative values improvement of QoL) *Baseline and week 15* A: −28.9 (154.6); B: 94.8 (141.1); $p < 0.0001$ Subscale GLQ-5: A: −42.9 (125.0), B: 60.3 (94.0), $p < 0.0001$ Subscale GLQ-3: A: 13.9 (52.4), B: 34.5 (57.0), $p = 0.0007$ *Baseline and month 2 after CTX* A: −70.7 (166.3), B: 34.2 (116.8), $p < 0.0001$ Subscale GLQ-5: A: −62.8 (133.1); B: 26.5 (81.9); $p < 0.0001$ Subscale GLQ-3: A: −7.9 (51.8), B: 7.6 (45.2), $p = 0.0040$ Spitzer uniscale (negative values improvement of QoL) *Baseline and week 15* A: −12.2 (30.7), B: 10.8 (26.1), $p < 0.0001$ *Baseline and month 2 after CTX* A: −16.3 (30.6), B: 2.7 (22.9), $p < 0.0001$

Table 3 (continued)

Study	Quality of life measurement points/intervals	Quality of life results
Troger et al. (2009, 2012, 2014b, 2016)	7/month 0, 1, 2, 3, 6, 9 and 12	Troger et al. 2009 A: $n = 30$, B: $n = 31$ EORTC QLQ-C30[a]: mean group difference over time [95% CI] *Global health status*: ns *Functioning*: role: 14.09 [9.02, 19.16], $p < 0.001$; emotional: 6.35 [2.15, 10.54], $p = 0.001$; social: 7.74 [3.37, 12.12], $p < 0.001$; physical: 3.56 [0.61, 6.51], $p = 0.014$; cognitive: ns *Symptoms*: pain: − 12.47 [− 16.85, − 8.08], $p < 0.001$; appetite loss: − 6.64 [− 12.28, − 1.01], $p = 0.017$; diarrhea: − 6.11 [− 9.47, − 2.75], $p < 0.001$; insomnia: − 8.25 [− 13.42, − 3.09], $p = 0.001$; nausea/vomiting: − 7.58 [12.25, − 2.91], $p = 0.001$; fatigue: − 4.92 [− 8.78, − 1.05], $p = 0.009$; dyspnea: − 3.70 [− 6.79, − 0.60], $p = 0.015$; financial problems: − 8.94 [− 14.21, − 3.67], $p < 0.001$; constipation: ns Troger et al. 2014b A: $n = 32$, B: $n = 29$ EORTC QLQ-C30[a]: mean group difference over time (SD) *Global health status*: ns *Functioning*: role: 10.5 (0.6), $p < 0.001$, emotional: 6.9 (0.5), $p < 0.001$, social: 6.2 (0.4), $p < 0.05$, cognitive: 4.8 (0.3), $p < 0.01$, physical: ns *Symptoms*: pain: − 10.81 (− 0.66), $p < 0.001$, appetite loss: − 8.3 (− 0.41), $p < 0.001$, diarrhea: − 7.05 (− 0.56), $p < 0.001$, insomnia: − 6.01 (− 0.34), $p < 0.05$, nausea/vomiting: − 5.77 (− 0.35), $p < 0.001$, constipation: − 4.03 (− 0.22), $p < 0.05$, fatigue, dyspnoea: ns, financial problems: ns
Colorectal cancer		
Heiny and Albrecht (1997)	8/every 6 weeks until week 42	A: $n = 13$, B: $n = 13$ Spitzer (mean) Week − 1: A:8, B: 8; week 1: A: 6, B: 7; week 12: A: 6, B: 5; week 24: A: 8, B: 5
Glioma		
Lenartz et al. (1996)	4/1 week before OP, post OP week 1, 12 and 24	A: $n = 13$, B: $n = 13$ Spitzer (mean) Week − 1: A:8, B: 8; week 1: A: 6, B: 7; week 12: A: 6, B: 5; week 24: A: 8, B: 5
Head and neck cancer		
Steuer-Vogt et al. (2001, 2006)	17/during week 0 and week 156 (8x after mistletoe treatment)	A: $n = 200$, B: $n = 199$ EORTC QLQ-C30[a] (mean group difference over time) *Global health status*: ns *Functioning*: ns *Symptoms*: ns
Lung cancer		
Bar-Sela et al. (2013)	2/day 1 CTX, day 1 third CTX cycle	A: $n = 27$, B: $n = 28$ EORTC QLQ-C30[a]: ns (only reported in text, data not shown) QLQ-LC13: mean (SD) Peripheral neuropathy: A: 1.2 (23.5), B: 22.6 (37.5), $p = 0.03$; others: ns

Table 3 (continued)

Study	Quality of life measurement points/intervals	Quality of life results
Melanoma		
Grossarth-Maticek and Ziegler (2007a)	2/12 months	A: $n = 22$, B: $n = 22$ Psychosomatic self-regulation (1 = low to 6 = high): median of paired differences [95% CI] 0.55 [0.15–0.85], $p = 0.048$
Osteosarcoma		
Longhi et al. (2014)		A: $n = 9$, B: $n = 11$ EORTC QLQ-C30[a]: mean [95% CI] *Global health status*: A: 11.17 [2.62; 19.72], $p = 0.013$; B: 3.51 [−3.51; 10.54], $p = 0.301$ *Functioning*: physical: A: 7.30 [0.15; 14.44], $p = 0.046$;, B: −2.45 [−8.93; 4.03], $p = 0.430$, emotional: A: −5.98 [−10.58; −1.37], $p = 0.014$; B: −2.48 [−9.84; 4.87], $p = 0.481$, social: A: 11.76 [4.64; 18.88], $p = 0.003$;, B: 11.76 [4.64; 18.88], $p = 0.003$, role and cognitive: ns *Symptoms*, fatigue: Arm A: −9.85 [−16.31; −3.38], $p = 0.005$; Arm B: 1.13 [−5.72; 7.99], $p = 0.73$, pain: Arm A: −10.71 [−18.83; −2.60], $p = 0.012$; Arm B: 10.54 [4.64; 16.45], $p = 0.002$, dyspnoea: Arm A: −12.63 [−16.94; −8.32], $p < 0.0001$; Arm B: 5.82 [−1.04; 12.68], $p = 0.09$, insomnia: Arm A: −11.35 [−20.74; −1.96], $p = 0.020$, Arm B: 5.79 [−2.95; 14.53], $p = 0.177$, financial problems, Arm A: −11.46 [−16.21; −6.70], $p < 0.0001$, Arm B: −2.53 [−6.88; 1.83], $p = 0.234$, nausea/vomiting, appetite loss, constipation and diarrhea: ns
Other gastrointestinal cancers		
Gastric cancer		
Kim et al. (2012)		A: $n = 16$, B: $n = 16$ EORTC QLQ-C30[a] *Global health status:* $F = 7.7133$, $p < 0.01$ *Functioning*: ns *Symptoms*: ns QLQ-STO22[f] *Symptoms*: ns

- Psychosomatic self-regulation questionnaire (Grossarth-Maticek et al. 1995): six studies (Grossarth-Maticek and Ziegler 2006a, b, 2007a, b, c, 2008).

Regarding general QoL from 11 studies, 6 within 7 publications showed a significant benefit of mistletoe treatment in most of the examined items analyzing breast, colorectal and pancreatic cancer patients (Heiny and Albrecht 1997; Piao et al. 2004; Semiglasov et al. 2004; Semiglazov et al. 2006; Troger et al. 2009, 2014a, b). Furthermore, in two studies with glioma and osteosarcoma a stronger improvement of QoL was reported for the mistletoe group than for the control group. However, no statistical test could support this difference because of small sample size (Lenartz et al. 1996; Longhi et al. 2014). In the remaining studies, three analyze QoL by EORTC QLQ-C30 questionnaire. Two showed significant improvements in the mistletoe arm (Bar-Sela et al. (2013): peripheral neuropathy; Kim et al. (2012): global health status) and one showed no significant difference between mistletoe and control groups (Steuer-Vogt et al. 2006). The exact results regarding quality of life are listed in Table 3. Considering only studies with low risk of bias and, therefore, considering only one

Table 3 (continued)

Study	Quality of life measurement points/intervals	Quality of life results
Pancreatic cancer		
Troger et al. (2014b)	7/before each CTX cycle and at least 3 weeks after CTX (12 month)	A: $n = 96$, B: $n = 72$ EORTC QLQ-C30[a]: mean group difference over time [95% CI] *Global health status*: 26.1 [22.7; 29.6], $p < 0.001$ *Functioning*: role: 17.8 [11.9; 23.6], $p < 0.001$, emotional: 19.5 [13.6; 25.4], $p = 0.045$, social: 11.4 [4.72;18.16], $p = 0.506$, cognitive: 18.7 [11.8; 25.6], $p = 0.016$, physical: 22.3 [17.6; 27.1], $p < 0.001$ *Symptoms*: pain: −23.0 [−29.0; −17.0], $p <$ 0.001, appetite loss: −43.9, [−51.0; −36;7], $p = 0.031$, diarrhea: −4.5 [−7.3; −1.7], $p = 0.028$, insomnia: −37.2 [−45.8; −28.6], $p < 0.001$, nausea/vomitting: −10.9 [−16.0; −5.9], $p < 0.001$, constipation: −1.3 [−2.8; 0.1], $p = 0.121$, fatigue: −30.6 [−36.1; −25.0], $p < 0.001$, dyspnoea: −3.70 [−6.79, −0.60], $p = 0.015$, financial problems: −15.6 [−23.1; −8.2], $p = 0.626$
Other gynecological cancers		
Cervical cancer		
Grossarth-Maticek and Ziegler (2007b)		A: $n = 19$, B: $n = 19$ Psychosomatic self-regulation (1 = low to 6 = high): median of paired differences [95% CI] 0.70 [0.15–1.05], $p = 0.014$
Corpus uteri cancer		
Grossarth-Maticek and Ziegler (2008)		No metastases A: $n = 30$, B: $n = 30$ Psychosomatic self-regulation (1 = low to 6 = high): median of paired differences [95% CI] 0.40 [0.15, 0.70], $p = 0.0012$
Ovarian cancer		
Grossarth-Maticek and Ziegler (2007c)		A: $n = 21$, B: $n = 21$ Psychosomatic self-regulation (1 = low to 6 = high): median of paired differences [95% CI] 0.58 [0.30, 0.90], $p = 0.0002$
Various cancers		
Piao et al. (2004)		A: $n = 115$, B: $n = 108$ FLIC[c]: mean (SD): A: 9.0 (16.6), B: 4.7 (17.5), $p = 0.0141$ TCM[g]: mean (SD): A: −1.3 (2.4), B: −0.2 (2.3), $p = 0.0007$ KPI[e]: *n* (%): increase: A: 58 (50.4), B: 35 (32.4); stable: A: 53 (46.1), B: 61 (56.5); reduced: A: 4 (3.5), B: 12 (11.1), $p = 0.002$

CTX chemotherapy, *QoL* quality of life, *ns* no significant differences

[a]EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (Aaronson et al. 1993)

[b]FACT-G = Functional Assessment of Cancer Therapy-General (Cella et al. 1993)

[c]FLIC = Functional Living Index-Cancer (Schipper et al. 1984)

[d]GLQ-8 = Global Life Quality (Coates et al. 1990)

[e]KPI = Karnofsky Performance Index (Karnofsky and Burchenal 1949)

[f]QLQ-STO22 = Gastric cancer module, EORTC QLQ-C30 QLQ module under development—phase III

[g]TCM = Traditional Chinese Medicine Index

study, there could not be shown any effect of mistletoe treatment (Steuer-Vogt et al. 2006).

Concerning self-regulation (Table 3), most studies (breast cancer, gynecological cancer and melanoma patients) found significant benefits of Iscador® treatment over a period of 12 months (Grossarth-Maticek and Ziegler 2006a, 2007b, c, 2008). Only exception is the group of breast cancer patients without metastasis analyzed over 3 months by Grossarth-Maticek and Ziegler (2006b).

Pleural effusion

In two small studies, efficacy of mistletoe treatment regarding pleural effusion was examined. In a three-arm study, group differences between mistletoe ($n=15$), Vincristine ($n=15$) and povidone-iodine ($n=15$) pleurodesis were investigated. El-Kolaly et al. (2016) found a significant benefit of mistletoe ($n=11$, 73.3%) as well as povidone-iodine ($n=11$, 73.3%) compared to Vincristine ($n=8$, 53.3%) regarding the complete absence of pleural fluid re-accumulation after pleurodesis ($\chi^2=11.52$, $p=0.021$). In contrast, there was no significant difference concerning number of people with partial (mistletoe: $n=2$, 13.3%; Vincristine: $n=3$, 20%; povidone-iodine: $n=1$, 6.7%; $\chi^2=2$, $p=0.157$) or no (mistletoe: $n=2$, 13.3%; Vincristine: $n=4$, 26.7%; povidone-iodine: $n=3$, 20%; $\chi^2=3$, $p=0.223$) treatment success. Pleurodesis with mistletoe ($n=13$, dropout: $n=3$) in comparison to Bleomycin ($n=10$, dropout: $n=3$) was analyzed in a pilot study (Gaafar et al. 2014). In the mistletoe arm, treatment success was described in eight patients (61.5%) while two patients had no treatment success (15.4%). In contrast, in the Bleomycin arm only three patients responded to treatment (30%) and in four patients (40%) pleurodesis failed. However, maybe due to small sample size, this difference was not significant ($p=0.2138$, 95% CI [–0.1203, 0.6325]).

Toxicity of main intervention

Altogether, seven studies (25%) examined the effect of mistletoe treatment regarding side effects of chemotherapy and two studies (4%) regarding side effect of pleurodesis.

Chemotherapy Most of the studies found some positive effects of mistletoe treatment concerning toxicity of chemotherapy.

In the study by Bar-Sela et al. (2013) examining patients with lung cancer, the difference of toxicity of chemotherapy between the mistletoe and control groups was the primary outcome. The Iscador® and the control arm did not differ significantly regarding absolute number of grade 3–4 adverse events (Arm A: 48%; Arm B: 57%) and regarding number of hematologic toxicity (Arm A: 42%; Arm B: 49%). In contrast, in the Iscador® arm, significantly less patients showed non-hematologic adverse events (Arm A: 18%; Arm B: 41%, $p=0.04$), less patients needed to be hospitalized due to adverse events (Arm A: 24%; Arm B: 54%; $p=0.02$) and in less patients the doses of chemotherapies were reduced (Arm A: 13%, Arm B: 44%, $p=0.005$).

Furthermore, in the study by Cazacu et al., four patients with colorectal cancer in the control group (19%) versus no patient in the Isorel® group reported digestive and/or hematological toxicity due to chemotherapy (p value unknown). Analogously, Heiny and Albrecht (1997) investigated chemotherapy-related adverse events in colorectal cancer patients. Considering non-hematologic toxicity, significantly less patients from the mistletoe group reported grade 3 mucositis (A: 25.8%, B: 17.9%; $p=0.321$) and the duration of CMS score ≥ 6 in days was significantly shorter in the mistletoe group compared to the control group [A: mean (SD) = 16.6 (1.8), B: mean (SD) = 12.2 (2.7), $p=0.033$]. On the other hand, concerning hematologic toxicity, leucopenia was the only significant one (A: 38.7%, B: 32.1%, $p=0.001$). In another study, patients in the mistletoe group had 28 adverse events due to chemotherapy while in control group there were 77 events. A p value or significance test was not reported (Piao et al. 2004). In the study of Semiglasov et al. (2004), patients reported white cell and reticuloendothelial system disorders (placebo: 20%, low dose (10 ng mistletoe): 22.4%, medium dose (30 ng mistletoe): 16.4%, high dose (70 ng mistletoe): 20.6%), gastrointestinal side effects (placebo: 8.6%, low and medium doses, respectively: 9.0%, high dose: 14.6%), resistance mechanism disorders (placebo: 5.7%, low dose: 6.0%, medium dose: 7.8%, high dose: 8.8%) and red blood cell disorders (placebo: 5.7%, low and medium doses, respectively: 3.0%, high dose: 11.8%) (p values not reported).

In contrast, Kim et al. (2012) found almost no significant differences between study arms (number of weeks to onset of moderate adverse events: AbnobaVISCUM: 92, control: 96) with the exception of number of weeks with diarrhea (AbnobaVISCUM: 6.7%, Control: 50%, $p=0.014$).

Finally, in Semiglazov et al. (2006), in the mistletoe group, 82 patients suffered from adverse events in contrast to placebo group where only 63 reported side effects. However, these numbers of patients included both chemotherapy- and mistletoe-related side effects. The authors only reported that of a total of 288 adverse events from both groups, 253 are probably related to chemotherapy. Considering several adverse events separated, in most of the cases there were no significant differences regarding number of suffering patients between the groups. The only exception was "General disorders and administration site conditions". In this case, in the mistletoe group, 56 persons reported this adverse event versus only 27 persons in placebo group ($p=0.0003$). Apart from that, the rates of granulocytopenia/leucopenia

were also examined (mistletoe: 9.9% ± 2.3%, placebo: 14.0% ± 2.7%, $p = 0.2595$).

Surgery In Longhi et al. (2014), during the trial occurred five serious adverse events whereas according to the authors three were due to hospitalization of patients for surgery (mistletoe: two, etoposide: one). The remaining two were cases of pneumonia (mistletoe: zero, etoposide: two) which were probably related to Etoposide.

Pleurodesis El-Kolaly et al. (2016) investigated complications of pleurodesis with mistletoe ($n = 15$), Vincristine ($n = 15$) and povidone-iodine ($n = 15$) treatment. They found no significant differences regarding number of patients with pain (mistletoe: $n = 8$, 53.33%; Vincristine: $n = 10$, 66.67%; povidone-iodine: $n = 4$, 26.67%, $\chi^2 = 1.6$, $p = 0.206$), fever (mistletoe: $n = 6$, 75%; Vincristine: $n = 7$, 46.67%; povidone-iodine: $n = 2$, 13.3%, $\chi^2 = 0.6$, $p = 0.439$), failed expansion (mistletoe: $n = 0$; Vincristine: $n = 0$; povidone-iodine: $n = 1$, 6.7%) and surgical emphysema (mistletoe: $n = 0$; Vincristine: $n = 0$; povidone-iodine: $n = 1$, 6.7%). Mean duration of indwelling chest tube was 5.6 days (SD = 1.35) in the mistletoe group, 6.47 days (SD = 1.19) in Vincristine group and 5.8 days (SD = 1.373) in povidone-iodine group ($F = 1.81$, $p = 0.176$).

In Gaafar et al. (2014), on the one hand, patients of the mistletoe group reported fever, chills, headache, malaise (all were grade 1) and in two cases allergic reaction (no hospitalization necessary, but patients discontinued study participation) and, on the other hand, patients of bleomycin group suffered from mild fever and chest pain (all were grade 1). The authors provided no information about exact numbers and significance tests.

Other outcomes

Troger et al. (2014a) investigated the development of body weight. Averaged over all follow-up visits (1, 2, 3, 6, 9 and 12 months after baseline), patients with pancreatic cancer in the mistletoe group gained 5.3% body weight compared to a loss of 3.2% in the control group ($p < 0.001$).

Discussion

Efficacy of mistletoe treatment regarding quality of life

Quality of life was examined in most of the included studies. As in previous reviews (Bussing et al. 2012; Horneber et al. 2008; Kienle et al. 2009; Kienle and Kiene 2007, 2010; Lange-Lindberg et al. 2006; Melzer et al. 2009), in majority of these studies, positive effects of mistletoe treatment on quality of life were found (Grossarth-Maticek and Ziegler 2006a, 2007a, b, c, 2008; Heiny and Albrecht 1997; Lenartz et al. 1996; Longhi et al. 2009; Piao et al. 2004; Semiglasov et al. 2004; Semiglazov et al. 2006; Troger et al. 2012, 2014a, 2016). Only two studies found no difference between treatment and control groups at all (Grossarth-Maticek and Ziegler 2006b; Steuer-Vogt et al. 2006) and two studies found only one significant difference in favor of the mistletoe group (Bar-Sela et al. 2013; Kim et al. 2012).

Nevertheless, there are several reasons why these data are insufficient to confirm the statement that mistletoe treatment improves quality of life in cancer patients.

First of all, as quality of life is a subjective endpoint in all studies there was a high risk for performance and detection bias because of missing blinding. Neither a placebo effect nor an effect due to an increased attention on complaints in the treatment group can be excluded as an explanation in any of the positive studies. Additionally, there is a high risk of attrition bias in many studies because of higher dropout rates.

To that date, the impossibility for blinding because of the local skin reaction to mistletoe is an unsolved problem in studies on mistletoe. As the study by Troger et al. (2014a) shows, a decisive step in further study protocols would be to ensure that the control group gets exactly the same amount of attention and supportive care by professionals as the treatment group (Hübner 2015).

Moreover, the six publications by Grossarth Maticek and Ziegler who derived all the data from a huge cohort of different cancer patients add a large group of patients to the entire group of participants in mistletoe but the methodological quality of these studies is low. Moreover, five of these six studies report an improvement of psychosomatic self-regulation as indicator of quality of life instead of using a validated instrument and reporting on quality of life. Troger et al. (2012, 2016) published the data of a three-armed study with mistletoe from two different companies in two different papers each reporting on the comparison of one mistletoe preparation with the control group and no data on the direct comparison are provided.

Efficacy of mistletoe regarding pleural effusion

To that date, only two very small RCTs were published providing first evidence for the benefit of mistletoe in pleurodesis. In both studies, no significant differences between mistletoe and active control groups could be shown. With respect to the strong adverse events of the actually most often used reactants, mistletoe might be a promising alternative being better tolerable. More studies including larger groups of patients would be needed to support this first evidence.

Efficacy of mistletoe regarding toxicity of cancer treatment

Comparison of conventional intervention-induced adverse events between mistletoe and control groups was analyzed in less than half of all studies whereas in most of the studies, chemotherapy-related side effects were examined (Bar-Sela et al. 2013; Cazacu et al. 2003; Heiny and Albrecht 1997; Kim et al. 2012; Piao et al. 2004; Semiglasov et al. 2004). Most of these studies indicated at least some improvements of adverse events due to chemotherapy because of mistletoe treatment. However, as Lange-Lindberg et al. (2006) have already stated in their review, evidence regarding improvement of therapy-related side effects is low due to strong drawbacks in the methodological quality of the studies.

With the exception of Bar-Sela et al. (2013), no study examined toxicity of main intervention as primary outcome. Accordingly, the quality of reporting is very bad. Only in four of seven studies, significance tests or p values were reported (Bar-Sela et al. 2013; Heiny and Albrecht 1997; Kim et al. 2012). Furthermore, in studies without data on significance, adverse events were not specified and described in detail (Cazacu et al. 2003; Piao et al. 2004; Semiglasov et al. 2004).

In the remaining studies, results were very heterogeneous. In Bar-Sela et al. (2013), only grade 3 or 4 adverse events were investigated. In this study, patients of the mistletoe group showed less non-hematologic adverse events, needed less times to be hospitalized and needed less chemotherapy doses. Heiny and Albrecht (1997) reported significantly less cases of chemotherapy-induced grade 3 mucositis and a shorter duration of this adverse event in the mistletoe group than in the control group. However, this study has important methodological deficits. Finally, in the last study almost no significant differences occurred (Kim et al. 2012). Only diarrhea was more frequent in the control group than in the mistletoe group. Also, this result has a high probability to be biased. In this study, many single tests were conducted without controlling for multiple testing. This might very well explain this single significant result. Chance instead of real improvement would also explain that the diarrhea item of the quality of life questionnaire did not reach significance. Finally, in Semiglazov et al. (2006), almost no differences regarding adverse events were reported. Also, in this article, reporting of adverse events is of low quality. In part, the authors compared the whole number of adverse events and for other items they compared the number of people having experienced adverse event.

Limitations of this work

Several limitations of this systematic review have to be mentioned. First, we only included randomized controlled studies. Information from well-described case reports, case series and cohorts was not assessed systematically. Second, we focused on adults, omitting literature on children. Third, due to the heterogeneity of considered RCTs, no meta-analysis could be conducted, and no moderators of mistletoe treatment determined. Finally, this review focused on more recent mistletoe literature and excluded articles publicized earlier than 1995.

Conclusion

To date, no clear statement regarding the efficacy of mistletoe treatment can be derived from randomized controlled studies. Studies with better methodology show less or no effects on quality of life or side effects of cancer therapy. There are some arguments to assume that genuine side effects from mistletoe or interactions with conventional therapy may not be reported adequately in studies and not even noticed in regular cancer care. Accordingly, the benefit–risk assessment for mistletoe is difficult and no evidence-based indications can be stated today. Physicians should not prescribe mistletoe in case of leukemia, lymphoma or renal cancer and melanoma. Furthermore, interactions with cancer drugs should be avoided and more attention should be paid to reporting any possible interaction in scientific publications.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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