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[Intervention Protocol]

Mistletoe extracts for cancer treatment

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of mistletoe extracts (*Viscum album*, European mistletoe) as antitumour treatment and for supportive/palliative care in adults with cancer. We will assess whether mistletoe extracts administered alone or in combination with tumour-specific therapies prolong progression free-intervals (PFI) and/or overall survival (OS); enhance tumour response; alleviate treatment-related adverse effects from conventional cancer treatment e.g. chemo- or radiotherapy; improve patient-reported outcomes including health-related QOL; and whether mistletoe extracts produce adverse effects.

BACKGROUND

This is a protocol for the update of an earlier Cochrane Review entitled *Mistletoe therapy in oncology* published in 2008 (Horneber 2008). We will update this Cochrane Review following the methods outlined in Higgins 2019 and MECIR 2021.

Description of the condition

Cancer remains one of the major health challenges worldwide. According to the GLOBOCAN estimates, 19.3 million new cases of cancer and almost 10 million deaths from cancer occurred in 2020 (Sung 2021; WHO 2020). About half of people with cancer turn to complementary and alternative medicine (CAM) (Horneber 2012; Keene 2019) in the hope of prolonging survival, improve the tolerability of cancer treatments, or enhance quality of life. One such CAM modality is mistletoe (*Viscum album* L), which is particularly popular in Europe as a complementary treatment in cancer care.

Description of the intervention

Commercially available mistletoe extracts are prepared from the hemiparasitic plant *Viscum album* L. or European mistletoe. Mistletoe grows on several types of trees, and the extracts derived from it contain numerous ingredients (see below) in varying concentrations depending on the species of the host tree, the time of year harvested, and the pharmaceutical process used to prepare the extracts (Becker 2000; Rostock 2020). Mistletoe preparations are often named according to the host tree e.g. P = pinus, pine tree; M = malus, apple tree, Qu =Quercus, oak tree, and each have different variations. The applicable parts are berries, leaf and stem.

The treatment for people with cancer using extracts from mistletoe was first introduced around 1920 by the Austrian philosopher Rudolf Steiner (1861 to 1925) as part of a holistic and human-centred therapeutic approach within anthroposophically-extended medicine (Heusser 2014). In anthroposophically-extended medicine, mistletoe constitutes the central component of a broader treatment regimen; outside the context of anthroposophic care it is used as a single herbal treatment agent. In practice, mistletoe extracts are applied both in adjuvant and in palliative treatment situations, mainly complementing conventional tumour therapy. There are two different approaches to the production and clinical application of mistletoe preparations (Kienle 2003); Rostock 2020.

- Mistletoe preparations produced according to pharmaceutical guidelines from anthroposophical medicine (including abnobaVISCUM, Helixor, Iscador, Iscucin): it is assumed that the overall pharmacological and therapeutic effects do not derive from a single component but from several compounds acting together, additively or synergistically. With this approach, the dosages of the mistletoe preparations are usually ascending, depending on the individual's general condition, the extent of the local reaction at the place of injection, and the regulation of body temperature. Some physicians also adjust the dosage, depending on certain immunological parameters. The preparations are applied by subcutaneous injection, two to three times a week. Radiation fields and inflamed areas of the skin as well as body regions with existing lymphoedema are avoided as sites for injection.
- Phytotherapeutic mistletoe preparation: the preparation (e.g. Lektinol) is standardised for a defined content of mistletoe lectin and it is applied subcutaneously in a fixed dosage twice a week.

Furthermore, preclinical trials have shown cytotoxic effects experimentally with direct contact between mistletoe extract and cancer cells. This would correlate with intratumoural, intrapleural as well as intravesical application for clinical usage. Data from phase I/II trials and a safety registry are available (Cho 2016; Huber 2017; Rose 2015; Steele 2015); however, these forms of application, as well as mistletoe infusions, are beyond regulatory drug approval.

Initial studies of the intravesical instillation of mistletoe extract to prevent the recurrence of superficial bladder cancer have shown effects comparable to those of usually employed therapies (mitomycin or BCG) (Elsaesser-Beile 2005; Rose 2015). Based on these data a multi-centre German-wide phase III trial is currently being conducted (Rexer 2016).

Adverse events of mistletoe are generally considered to be mild to moderate and transient. (Steele 2014; Steele 2015; ; Rostock 2020). Local reactions at the injection site and raised temperature are relatively common, while serious adverse events appear to be rare. (Rostock 2020; Steele 2015) In very rare cases, local or general allergic reactions including anaphylaxis have been reported, especially at high doses after rapid dose increase (Casetti 2021).

How the intervention might work

There has been a significant amount of preclinical research on the proposed mechanisms of effect of mistletoe in cancer care. This evidence has been collated from *in vitro*, *in vivo* and *ex vivo* research across both animal and human studies. Whilst no definitive pathway has been determined, the studies indicate that a range of mistletoe preparations and extracts can influence both general immunomodulatory and antitumour activity within the body (Szurpnicka 2020).

In terms of supportive immunomodulatory activity, which could influence the quality of life for people with cancer, research has indicated that mistletoe preparations can increase the maturation and activation of dendritic cells, whose main function is to present antigens, as well as counter-act tumour-induced immunosuppression of dendritic cells (Elluru 2008; Kim 2014). These activated human dendritic cells have also been shown to stimulate CD4 +T cells CD8+T cells, as evidenced by increased secretion of Tumour necrosis factor- α (TNF-α) and Interferon- γ (IFN γ). TNFα has pleiotropic effects on normal and malignant cells, especially in combination with IFNα (Hajto 1990; Steinborn 2017). There is both experimental and clinical evidence to show that immune cell recruitment plays a pivotal role in cancer recognition and eradication.

Further research in healthy human participants shows that mistletoe treatment induces granulocyte-macrophage colony-stimulating factor (GM-CSF) and Interleukin-5 (IL-5) production by peripheral blood mononuclear cells, which in turn increases blood granulocyte and eosinophil counts, supporting defence against infections(Huber 2005; Huber 2011). In a further human cancer patient study, mistletoe lectin treatment was shown to increase T

helper lymphocytes (CD4+) and the CD4+/CD8+ ratio (Semiglasov 2004).

The main anticancer compounds isolated from Viscum species are lectins and viscotoxins, phenolic compounds, triterpene acids and non-polar compounds (Szurpnicka 2020). It has been reported that complete mistletoe extract is more potent at inhibiting tumour cells than isolated compounds (Felenda 2019), and there may be synergistic action between different groups of mistletoe compounds.

In terms of anti-tumour activity, several studies show in cultured human and mice cells, and cell lines that mistletoe extracts increase the activity of natural killer (NK) cells, which contain enzymes capable of killing tumour cells (Hajto 1986; Kim 2018; Schink 2007; Tabiasco 2002). Mistletoe lectins have been shown to enhance the cellular and humoral immune response in mice (Yoon 2001), and whole mistletoe extract has shown similar effects in a case series of four people with cancer (Gardin 2009).

The effect of mistletoe in the inhibition of cancer cell proliferation was initially proposed to be due to its lectin and viscotoxin content. This is predominately based on *in vitro* studies with a variety of human cancer cell lines, including melanoma, breast carcinoma, bladder carcinoma and sarcoma cells (Thies 2005; Eggenschwiler 2007; Felenda 2019). However, further research has shown that phenolic, triterpene and non-polar compounds of mistletoe preparations can also inhibit cancer cell proliferation, although some of the evidence is in animal *ex vivo* and *in vivo* studies (Delebinski 2015; Melo 2018; Ćebović 2008). In terms of specific antitumour activity, there is evidence from studies showing induction of apoptosis in mice, and mice and human cancer cell lines (Han 2015; Mishra 2018; Park 2012; Ćebović 2008), as well as inhibition of angiogenesis with mistletoe lectins in human cancer cell lines (Elluru 2009; Park 2001).

Why it is important to do this review

Immunotherapy is playing an increasingly important role in cancer care. With extracts from the plant European mistletoe (*Viscum album* L) possessing immunomodulatory properties, further investigation of this herbal extract is timely. Mistletoe is widely used in oncology in European countries, in particular German-speaking countries. About 40% to 50% of people with cancer worldwide use complementary medicine in addition to conventional therapies (Keene 2019; Horneber 2012). Within the framework of the Competence Net Complementary Medicine in Oncology ("Kompetenznetz Komplementärmedizin in der Onkologie, KOKON") funded by the German Cancer Aid, an evaluation of therapeutic consultations of nearly 2000 people with cancer and their relatives identified mistletoe as the by far most frequently requested form of complementary treatment (Witt 2017). Within the entire German-speaking area, interest in mistletoe therapy is notably high, especially from the patient's point of view. In Switzerland, mistletoe extracts prescribed by medical doctors are covered by statutory health insurance. In Germany, statutory health insurance covers mistletoe extracts prescribed by medical doctors in palliative care; in cases of poor tolerance of antitumour therapy, it is possible to request reimbursement for these costs during adjuvant therapy (https://www.mistel-therapie.de/informationen-fuer-patientinnen/kostenerstattung). In many other countries mistletoe extracts are used for therapeutic measures with data available form not only from German-speaking countries, but also from China, Egypt, Italy, Serbia, Bulgaria, Ukraine, Russia and USA.

Despite the existence of elaborated therapeutic concepts, numerous interventional trials and systematic reviews with meta-analyses, as well as the experiences from a long and widespread use, there is longstanding debate about the efficacy of this treatment modality (Cordier 2004; Edler 2004; Ernst 2006), which has to date not been resolved. For example, in 2015 the publication of a randomised controlled trial (RCT) of mistletoe extracts in patients with advanced pancreatic cancer (Tröger 2014) triggered a vivid debate in the *Deutsches Ärzteblatt* (Tröger discussion 2015).

Subsequently, four systematic reviews have been published in 2019 and 2020, which have produced inconsistent, and in many aspects conflicting, results (Freuding 2019a; Freuding 2019b; Loef 2020; Ostermann 2020). The publication of the two systematic reviews by Freuding and colleagues received critical comments on their methods of assessing and interpreting trial results (Matthes 2019).

For healthcare professionals and people with cancer, this ongoing debate creates a high level of uncertainty. A comprehensive systematic review update using rigorous methods and addressing meaningful clinical questions is therefore needed to help resolving the ongoing debate.

OBJECTIVES

To assess the effects of mistletoe extracts (*Viscum album*, European mistletoe) as antitumour treatment and for supportive/palliative care in adults with cancer. We will assess whether mistletoe extracts administered alone or in combination with tumour-specific therapies prolong progression free-intervals (PFI) and/or overall survival (OS); enhance tumour response; alleviate treatment-related adverse effects from conventional cancer treatment e.g. chemo- or radiotherapy; improve patient-reported outcomes including health-related QOL; and whether mistletoe extracts produce adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include randomised controlled trials (RCTs). We will include studies reported as full-text. Observational studies, studies of a cohort or matched-pair design, retrospective/retrolective studies, and unpublished data will be excluded.

Types of participants

Adults (18 years and older) diagnosed with cancer without restriction to the type or stage of the disease.

Types of interventions

Mistletoe extracts; any dosage, any length of treatment, any route of administration. We will exclude trials assessing mistletoe as one of several active components in a combination preparation, where it is not possible to determine effects specific to mistletoe.

We will include the following comparisons.

- Mistletoe extracts versus placebo.

- Mistletoe extracts versus no intervention (e.g. wait-list controls).
- Mistletoe versus any active comparator (e.g. tumour-specific treatment, usual care).

Types of outcome measures

We will include studies reporting at least one outcome related to survival, tumour recurrence, patient-reported outcomes or adverse effects of conventional treatment (e.g. chemo-, radio- or immunotherapy).

Primary outcomes

Survival

- overall survival: survival until death from all causes.
- tumour objective response rate (ORR).
- progression-free interval: time interval until progression of disease, rate of recurrence.

Patient-reported outcomes

- health-related quality of life, including domains of physical, emotional, cognitive and social functioning; assessed by any generic or specific validated scales.
- improvement of treatment-related adverse effects from e.g. chemo- or radiotherapy.

We will exclude trials reporting only physiological measures (e.g. immune parameters etc.).

Secondary outcomes

Adverse outcomes of treatment with mistletoe extracts

- Adverse effects of mistletoe extracts and any other safety issues reported in the included studies.
- Other reported safety issues.

Search methods for identification of studies

Electronic searches

We will search the following databases using text and keywords (MeSH terms) relating to the concepts of mistletoe/*Viscum album*; cancer survival, cancer progression; quality of life.

- Cochrane Central Register of Controlled Trials (CENTRAL; year, Issue), in the Cochrane Library;
- MEDLINE via PubMed (November 2008 to date);
- Embase via Ovid (November 2008 to date);
- CINAHL via EBSCO (November 2008 to date);
- Science Citation Index (Web of Science: November 2008 to date).

The MEDLINE search strategy is presented in Appendix 1. For databases other than MEDLINE, we will adapt the search strategy accordingly.

Searches will be conducted for the period from the last search date of the existing Cochrane Review (Horneber 2008) to date and limited to RCTs. We will not impose any other restrictions.

Searching other resources

Unpublished and grey literature

We will search the following resources for ongoing trials and grey literature.

- ClinicalTrials.gov (http://www.clinicaltrials.gov)
- International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

Handsearching

We will handsearch the citation lists of included studies and previous systematic reviews.

To identify further reports of RCTs, we will contact institutions and individuals with expertise in cancer treatment with mistletoe preparations including the German Anthroposophic Doctors Association (Gesellschaft Anthroposophischer Ärzte in Deutschland) as well as manufacturers of mistletoe extracts including Iscador AG, HELIXOR Heilmittel GmbH, ABNOBA GmbH, Wala Arzneimittel and Madaus/Meda Pharma.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to Endnote and remove duplicates. Two review authors will examine the remaining references independently. We will exclude those studies that clearly do not meet the inclusion criteria, and obtain copies of the full-text of potentially relevant references. Independently, two review authors will assess the eligibility of the retrieved reports/publications. We will resolve any disagreement through discussion or, if required, we will consult a third person. We will identify and exclude duplicate reports and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table. In case of missing information, we will contact the trial authors.

Data extraction and management

Independently, two review authors will extract study characteristics and outcome data from included studies on to a piloted data collection form. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person. One review author will transfer data into the Review Manager file (Review Manager 2020). We will double-check that data have been entered correctly by comparing the data presented in the systematic review with the study reports. A second review author will 'spot-check' the accuracy of the study characteristics against the trial report.

For included studies, we will extract the following data.

- Publication details: authors, year of publication, country, language, journal citation
- Study design and setting
- Study population: inclusion/exclusion criteria, diagnosis, patient characteristics, total numbers enrolled/randomised, number of participants allocated to each intervention group,

number analysed for each outcome, and the missing participants.
- Details of intervention: name, doses, regimen, duration, co-intervention
- Comparison name, doses, regimen, duration, co-intervention
- Duration of follow-up
- Outcome measures: primary and secondary
- Results: we will extract the number of participants allocated to each intervention group, the total number analysed for each outcome, and the missing participants [see also below]
- Risk of bias in each study [see below]
- Notes: funding for trial, and notable conflicts of interest of trial authors

Results will be extracted as follows.

- For time to event data (survival and disease progression), we will extract hazard ratios (HR) with 95% confidence intervals (CIs), their logarithms and respective standard errors (SEs). If these are not available, we will attempt to estimate the log (HR) and its SE using the method of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events) we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR) and 95% CI.
- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation (SD) of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its SE.

We will note the time points at which outcomes were collected and reported.

In case of missing information, we will contact the trial authors.

Assessment of risk of bias in included studies

We will assess and report on the methodological risk of bias of included studies in accordance with the Cochrane Handbook (Higgins 2019), which recommends the explicit reporting of the following individual elements for RCTs; individual risk of bias items are listed in Appendix 2.

1. Selection bias: random sequence generation and allocation concealment
2. Performance bias: blinding of participants and personnel (i.e. treatment providers)
3. Detection bias: blinding of outcome assessment
4. Attrition bias: incomplete outcome data
5. Reporting bias: selective reporting of outcomes
6. Other possible sources of bias

Two review authors will apply the risk of bias tool independently and resolve differences by discussion or by appeal to a third review author. We will judge each item as being at high, low or unclear risk of bias as set out in the criteria provided by Higgins 2019, and provide a quote from the study report or a statement as justification for the judgement for each item in the risk of bias table or both. We will summarise results in both a risk of bias graph and a risk of bias summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table.

Measures of treatment effect

We will use the following measures of the effect of treatment.

- For time-to-event data, we will use the hazard ratio (HR) with CI and SE.
- For dichotomous outcomes, we will analyse data based on the number of events and the number of participants assessed in the intervention and comparison groups. We will use these to calculate the risk ratio (RR) and 95% CI.
- For continuous outcomes, we will analyse data based on the mean, standard deviation (SD) and number of participants assessed for both the intervention and comparison groups to calculate mean difference (MD) between treatment arms with a 95% CI. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method in Review Manager 5 (Review Manager 2020).

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants, outcomes and the underlying clinical question are similar enough in at least three studies for pooling to make sense.

Unit of analysis issues

The unit of analysis is the individual participant and trials will be analysed accordingly.

We will give special consideration to RCTs where individual participants undergo more than one intervention (e.g. in a cross-over trial) or RCTs with multiple treatment arms.

Dealing with missing data

We will attempt to contact study authors to obtain missing data (participant, outcome, or summary data). For participant data, we will, where possible, conduct analysis on an intention-to-treat basis; otherwise data will be analysed as reported. We will report on the levels of loss to follow-up and critically appraise this as a source of potential bias.

Assessment of heterogeneity

We will assess clinical heterogeneity by comparing and discussing variability in terms of participants, interventions, comparators and outcomes across studies. Where at least three studies are considered similar enough to allow pooling of data using meta-analysis, we will assess the degree of heterogeneity by visual inspection of forest plots, by estimation of the percentage heterogeneity (I^2 measurement) between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Chi^2) (Deeks 2001) and, if possible, by subgroup analyses. We will regard heterogeneity to be substantial if I^2 is greater than 30% and there is a low P value (< 0.10) in the Chi^2 test for heterogeneity.

If there is evidence of substantial clinical, methodological or statistical heterogeneity across included studies, we will not pool

results for meta-analysis but instead will use a narrative approach to our data synthesis. In this event we will investigate and report the possible clinical or methodological reasons for this level of heterogeneity.

Assessment of reporting biases

If we include 10 or more studies that investigate a particular outcome, we will examine funnel plots corresponding to meta-analysis of the outcome to assess the potential for small-study effects such as publication bias. We plan to assess funnel plot symmetry visually, and if asymmetry is suggested, we will perform exploratory analyses to investigate it.

Data synthesis

If a sufficient number of clinically similar studies (in terms of participants, settings, intervention, comparison and outcome measures) are available to ensure meaningful conclusions, and if statistical heterogeneity is low (I^2 < 30%) we will pool their results in meta-analyses using the fixed-effect model in Review Manager (Review Manager 2020). If there is variability in the study population, interventions and outcomes of included studies, or if statistical heterogeneity is substantial (I^2 > 30%) we will use the random-effects model with inverse variance for meta-analysis (DerSimonian 1986).

- For time-to-event data, we will pool hazard ratios (HRs) using the generic inverse variance facility in Review Manager 2020.
- For any dichotomous outcomes, we will calculate the risk ratio (RR) for each study.
- For continuous outcomes, we will pool standardised mean differences (SMD).

If we are unable to pool the data statistically using meta-analysis we will conduct a narrative synthesis of results following the Synthesis without Meta-Analysis (SWiM) guideline (Campbell 2020). We will present major outcomes and results according to intervention categories (survival, tumour regression and PRO quality of life). Depending on the retrieved research, we will explore the possibility of organising the data by cancer type or intervention type.

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses to assess differential effects according to:

- population: cancer type and/or disease stage;
- intervention: mistletoe preparation used (route of administration, different doses, frequency, duration of treatment).

We will consider these factors in the interpretation of any heterogeneity.

Sensitivity analysis

We will attempt to assess the robustness of data by conducting sensitivity analyses. We will consider excluding:

- studies at high risk of bias;
- cross-over studies;
- publication date of studies (i.e. older versus newer studies);
- studies for which missing data had to be retrieved from study authors.

Summary of findings and assessment of the certainty of the evidence

We will present the overall certainty of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity such as directness of results (Langendam 2013; Schünemann 2011); see Appendix 3 for the GRADE criteria. We created a summary of findings table 1 based on the methods described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2019) and using GRADE 2016. We will use the GRADE checklist and GRADE Working Group certainty of evidence definitions (Meader 2014). We will downgrade the evidence from 'high' certainty by one level for serious (or by two for very serious) concerns for each limitation.

- High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate-certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low-certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- Very low-certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

If meta-analysis is not possible, we will present results in a narrative summary of findings table format.Table 1

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ADDITIONAL TABLES

Table 1. Summary of findings

Title: Mistletoe extracts for cancer treatment

Patient or population: Adults (18 years and older) diagnosed with cancer without restriction to the type or stage of the disease

Settings: Outpatient

Intervention: Mistletoe

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	No of participants (studies)	Certainty of evidence (GRADE)	Comment
	Assumed risk	Corresponding risk				
Overall survival						
Progression-free interval						
Adverse events						
General quality of life						
Fatigue						
Pain						
Nausea and vomiting						

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the
assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; HR: hazard ratio; MD: mean difference; RR: risk ratio; OR: odds ratio

GRADE Working Group grades of evidence

Table 1. Summary of findings *(Continued)*

- ***High-certainty:****we are very confident that the true effect lies close to that of the estimate of the effect.*
- ***Moderate-certainty:****we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*
- ***Low-certainty:****our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.*
- ***Very low-certainty:****we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.*

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Mistletoe/
2. (mistel* or mistle* or viscum* or abnobaviscum or cefalektin or eurixor or helixor or iscador or iscucin or isorel or lektinol or plenosol* or vysorel or cefalektin or iscar or ABNOBAviscum or apotheker bauer's misteltinktur or isugran or viscysat).mp.
3. 1 or 2
4. exp Neoplasms/
5. (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma* or choriocarcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma* or oncolog*).mp.
6. 4 or 5
7. 3 and 6
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
10. randomized.ab.
11. placebo.ab.
12. drug therapy.fs.
13. randomly.ab.
14. trial.ab.
15. groups.ab.
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 7 and 16

key:

mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier
pt=publication type
ab=abstract
sh=subject heading
ti=title

Appendix 2. Risk of bias items

- Random sequence generation
  a. Low risk of bias, e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers
  b. High risk of bias, e.g. participants assigned to treatments on basis of date of birth, clinic identity-number or surname, or no attempt to randomise participants
  c. Unclear risk of bias, e.g. not reported, information not available
- Allocation concealment
  a. Low risk of bias, if the allocation sequence could not be foretold
  b. High risk of bias, if allocation sequence could be foretold by patients, investigators or treatment providers
  c. Unclear risk of bias, if allocation concealment was not reported

- Blinding of participants and personnel
  a. Low risk of bias if participants and personnel were adequately blinded
  b. High risk of bias if participants were not blinded to the intervention that the participant received
  c. Unclear risk of bias if this was not reported or unclear
- Blinding of outcomes assessors
  a. Low risk of bias if outcome assessors were adequately blinded
  b. High risk of bias if outcome assessors were not blinded to the intervention that the participant received
  c. Unclear risk of bias if this was not reported or unclear
- Incomplete outcome data: we will record the proportion of participants whose outcomes were not reported at the end of the study. We will code a satisfactory level of loss to follow-up for each outcome as:
  a. Low risk of bias, if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
  b. High risk of bias, if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms
  c. Unclear risk of bias if loss to follow-up was not reported
- Selective reporting of outcomes
  a. Low risk of bias, if review reports all outcomes specified in the protocol
  b. High risk of bias, if it is suspected that outcomes have been selectively reported
  c. Unclear risk of bias, if it is unclear whether outcomes had been selectively reported

Appendix 3. GRADE criteria

The GRADE system uses the following criteria to assign a certainty level to a body of evidence (Chapter 14, Higgins 2020).

- High: randomised trials; or double-upgraded observational studies.
- Moderate: downgraded randomised trials; or upgraded observational studies.
- Low: double-downgraded randomised trials; or observational studies.
- Very low: triple-downgraded randomised trials; or downgraded observational studies; or case series, case reports.

Factors that may decrease the certainty level of a body of evidence are:

1. limitations in the design and implementation of available studies suggesting high likelihood of bias;
2. indirectness of evidence (indirect population, intervention, control, outcomes);
3. unexplained heterogeneity, or inconsistency of results (including problems with subgroup analyses);
4. imprecision of results (wide confidence intervals);
5. high probability of publication bias.

Factors that may increase the certainty level of a body of evidence are:

1. large magnitude of effect;
2. all plausible confounding would reduce a demonstrated effect, or suggest a spurious effect when results show no effect;
3. dose-response gradient.

We will decrease the grade rating by one (- 1) or two (- 2), up to a maximum of - 3, to very low, if we identify:

- serious (- 1) or very serious (- 2) limitation to study quality;
- important inconsistency: some (- 1) or serious (- 2);
- some (- 1) or major (- 2) uncertainty about directness;
- imprecise or sparse data: some (- 1) or serious (- 2);
- high probability of reporting bias: some (- 1) or serious (-2).

CONTRIBUTIONS OF AUTHORS

MH and BW developed concept of the update protocol. BW, MR, AH and MH drafted the protocol. BW, MR, AH, GvA and MH reviewed the protocol.

DECLARATIONS OF INTEREST

Barbara Wider: none known
Markus Horneber: none known

Alyson Huntley: is Co- Principal Investigator on the Mistletoe And Breast cancer (MAB) study currently being conducted in the UK. This is a feasibility study (2019 to 20) and is in part funded by Iscador AG
Matthias Rostock: no personal conflict of interest. An ongoing continuous education on complementary medicine in oncology, which is in his responsibility, is sponsored by a mistletoe extract producing company
Gerd van Ackeren: none known

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  Salary of Barbara Wider

External sources

- None, Other

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NOTES

None.