Mistletoe in cancer: a systematic review on controlled clinical trials

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CRD summary
This well-conducted and reported review assessed the efficacy of mistletoe therapy for people with cancer. Twelve of the 23 included studies found a significant benefit from mistletoe therapy, seven showed positive trends, three found no effect, and one found a negative trend. The authors' conclusions are supported by the data they present, as is their call for further high-quality research.

Authors' objectives
To assess the efficacy of mistletoe therapy for people with cancer.

Searching
MEDLINE, Cancerlit, AMED, BIOSIS Previews, Conference Papers Index, the Cochrane Controlled Trials Register, Dissertation Abstracts, EMBASE, ExtraMED, MEDIKAT, the Science Citation Index, and the reference lists of identified studies, review articles and textbooks, were searched; the search terms were reported. Experts in the field and manufacturers were contacted for additional studies. There were no language restrictions. Unpublished studies were excluded.

Study selection
Study designs of evaluations included in the review
Published full reports or abstracts of fully completed prospective controlled clinical trials were eligible for inclusion, whether or not they were randomised.

Specific interventions included in the review
To be eligible for inclusion in the review, the studies had to include cancer treatment with a mistletoe preparation. Some of the included studies assessed mistletoe therapy administered concurrently with conventional treatment (chemotherapy, radiotherapy, corticosteroids), while others used mistletoe therapy following surgery or radiotherapy. Other studies used mistletoe as a primary treatment or as a direct comparator with other treatments. The included studies used the mistletoe preparations Iscador, Eurixor and Helixor. Most of the treatments involved intravenous administration of a substance extracted from fresh leafy mistletoe shoots and berries. Full details of the preparations used and the comparators were provided in tabular format. The doses were not reported.

Participants included in the review
To be eligible for inclusion, the studies had to focus on people with cancer of any type, including cervical intraepithelial neoplasia. The cancer sites in the studies included in the review were breast, lung, colon and rectum, melanoma, head and neck, stomach, kidney, bladder, glioma, gynaecological, and mixed sites. Details of disease stages were tabulated. The authors did not report details of the participants' age, gender, or other demographic or disease characteristics.

Outcomes assessed in the review
To be eligible for inclusion, the studies had to report overall or disease-free survival, remission, relapse, quality of life, or a reduction of adverse effects during cytoreductive therapy. These were the primary outcomes of the review. Studies that only measured toxicity, tolerability, or immunological parameters, were excluded.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection. Pre-specified inclusion criteria were used.

Assessment of study quality

Database of Abstracts of Reviews of Effects (DARE)
Produced by the Centre for Reviews and Dissemination
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Two authors independently performed a criteria-based analysis to assess methodological quality and the strength of the evidence. They used criteria adapted from the NHS Centre for Reviews and Dissemination's report and criteria for good methodology applied in a previous review (see Other Publications of Related Interest nos.1-2). Two further authors checked the assessment and any disagreements were resolved by discussion.

The criteria against which the studies were rated included: protection against selection bias (including randomisation); the minimisation of heterogeneity by pre-stratification or matching; protection against observer bias using blinding; protection against performance or treatment bias by standardisation and blinding; protection against measurement bias using standardised outcome assessment; protection against attrition bias with less than 10% lost patients, or by intention-to-treat analysis; relevant and well-described effect measurement, interventions, patient characteristics, disease characteristics, previous therapy, study design and results; and data quality assured by GCP-ICH guidelines including monitoring. A 4-point rating scale was used to score the articles on each dimension, and a summary score was calculated.

Data extraction
The data were extracted by one author and checked by a second. Data were extracted on the sample size, methodology, disease characteristics, interventions, attrition rate, outcomes and publication details.

Methods of synthesis
How were the studies combined?
The authors provided a narrative synthesis of the findings and they tabulated the main results. The data were not combined statistically because of heterogeneity in the study design, treatments, methodological quality and disease types.

How were differences between studies investigated?
The authors described differences between the studies and tabulated data on the study characteristics and main outcomes.

Results of the review
Twenty-three studies with at least 4,708 participants were included; the sample size of 2 studies was not reported. There were 16 randomised controlled trials (at least 2,502 participants), 2 quasi-randomised trials (at least 310 participants) and 5 non-randomised studies (1,896 participants).

The authors reported that study quality was generally below optimal and that there was significant heterogeneity between the studies.

Twelve of the 23 prospective controlled studies found a statistically significant benefit from mistletoe therapy in people with cancer, seven found a non-statistically significant benefit, three had no effect, and one found a non-statistically significant negative effect.

Survival: 8 studies found a statistically significant survival benefit from mistletoe therapy. A further eight reported positive but non-statistically significant survival benefits. Four studies found no effect on survival. One study reported a non-statistically significant trend towards improved disease-free survival, one study found no effect, and another study found that mistletoe had a non-statistically significant negative effect on disease-free survival. Two studies found that mistletoe had no effect on disease recurrence.

Remission: one study found that mistletoe statistically significantly improved tumour remission, 2 studies found non-statistically significant remission benefits, and 3 studies found no effect on remission.

Quality of life: 3 studies found that mistletoe statistically significantly improved quality of life. In addition, 3 studies found that mistletoe statistically significantly improved quality of life in relation to adverse effects during cyto-reductive therapy. One study found no effect on quality of life.
Adverse effects: the included studies did not report any major adverse effects. Mistletoe therapy was well tolerated. Minor adverse effects from mistletoe therapy included rubor, pruritus or induration at the injection site, and mild flu-like symptoms.

Authors' conclusions
Twelve of the 23 prospective controlled clinical studies found a significant benefit from mistletoe therapy for people with cancer, seven showed positive trends, three found no effect, and one found a negative trend. The authors suggested that further research is warranted given that the small number of well-controlled trials available indicate positive clinical outcomes.

CRD commentary
This review comprised a well-defined research question, clearly specified inclusion and exclusion criteria, and a comprehensive search strategy with no language restrictions. The only caveat with the search strategy is that publication bias may be evident. Experts in the field and manufacturers were approached for additional studies, but unpublished studies were not eligible for the review. The authors identified five unpublished studies but did not include data from these. They neither described the characteristics of these unpublished studies, nor provided a rationale for excluding unpublished material.

The authors clearly outlined the processes used to assess the validity of the studies and extract the data. Established guidelines were used to help assess the quality of the included studies. The authors acknowledged that many of the studies included in the review were not of optimal quality.

The authors summarised the data clearly in narrative and tabular formats, although further details of the characteristics of the participants may help readers to assess how well the findings could be generalised to local populations.

Given the broad scope of the included studies and differences in cancer sites, treatment types and comparators, and study quality, it appears appropriate that the authors have not pooled the data. However, it might have been useful if the tabulated results had been broken down according to whether mistletoe therapy was adjuvant or co-administered, or the results had been collated narratively by disease type. The authors' summary did not indicate whether there were any overall differences in the effects of mistletoe therapy according to whether it was administered as a treatment alone, as part of a multi-modal regimen, or to reduce adverse effects from other treatments.

Overall, this is a high-quality and well-reported review. The authors' conclusions are supported by the data they present, as is their call for further high-quality research on mistletoe therapy for people with cancer.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors suggested that further high-quality, well-controlled studies about the effects of mistletoe in people with cancer are needed. They stated that future studies should be designed to improve the methodological quality of the knowledge base, and to reflect how mistletoe therapy is used in practice, i.e. incorporated within multimodal complementary treatment with a focus on quality of life and symptom management.

Bibliographic details

PubMedID
12730032

Other publications of related interest

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.