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*DAHTA@DIMDI*
*Waisenhausgasse 36-38a*
*D-50676 Köln*

*Tel.: +49 221 4724-525*
*Fax +49 221 4724-444*
*dahta@dimdi.de*
*www.dimdi.de*

# Mistletoe treatments for minimising side effects of anticancer chemotherapy

**Lange-Lindberg AM, Velasco Garrido M, Busse R**

## Background

More than 200000 persons died in 2002 in Germany as a consequence of cancer diseases. Cancer (ICD-9: 140-208, ICD-10: C00-C97) accounted for 28 % of all male deaths and for 22 % of all female deaths. Cancer treatment consists on surgery, radiotherapy and chemotherapy. During chemotherapy patients may experience a wide variety of toxic effects (including life-threatening toxicity) which require treatment. The type and the intensity of chemotherapy toxicity are one of the limiting factors in cancer treatment. Toxic effects are also one of the factors affecting health related quality of life (HRQOL) during chemotherapy.
Mistletoe extracts belong to the group of so called „unconventional methods“ and are used in Germany as complementary cancer treatments. It has been postulated that the addition of mistletoe to chemotherapeutical regimes could help diminish chemotherapy-induced toxicity and enhance treatment tolerability. The German drug index (“Rote Liste”) classifies mistletoe extracts into the group of cytostatic drugs, subgroup of phyto-cytostatics. The index includes six brand-names with a total of 20 mistletoe preparations differing in concentration or tree from where the mistletoe was harvested. These drugs are to be sold in pharmacies; however they belong to the group of OTC. In the ambulant sector mistletoe was the cytostatic drug most sold in the year 2003 with more than 18 million DDD.
The German social health insurance covers the prescription of ML I standardized mistletoe extracts when those are prescribed as complementary palliative cancer treatments with the aim of improving quality of life. However the costs of mistletoe are covered in the context of anthroposophical or homeopathical treatment without regard of treatment aim.
The German Agency for Health Technology Assessment commissioned a report on the effectiveness of mistletoe for the reduction of the toxicity of chemotherapy.

## Research questions

- Does the addition of mistletoe to chemotherapeutical regimes reduce their toxicity?
- Does the addition of mistletoe to chemotherapeutical regimes contribute to improve quality of life?
- Has the addition of mistletoe to chemotherapeutical regimes any effects on survival?
- Has the addition of mistletoe to chemotherapeutical regimes any effects on tumor-remission?

## Methods

We conducted a systematic literature search in following databases: The Cochrane Library, DIMDI Superbase und Dissertation Abstracts. We included systematic reviews and randomized controlled trials. Appraisal of literature was done by two authors independently. Checklists were used to guide

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literature appraisal. The Jadad-Score was used to score quality of RCT. Evidence was summarized in tables and in narrative form.

## Results and Discussion

The literature search yielded 437 potentially relevant papers. A total of 94 papers was retrieved. Of them, 48 were potentially relevant for answering the research questions and 46 for background information. In this report we summarize the results from three systematic reviews, five published RCT and two unpublished RCT. A protocol of an ongoing systematic review from the Cochrane Collaboration was also identified.
The information gathered from the systematic reviews was insufficient to answer the research questions. The relevant studies identified and synthetised in these reviews were appraised and extracted again. In addition, a set of recently published RCT was identified and included in these report.
A total of 722 patients has been included in the five published RCT. Cancer localisation were: colon, breast, lung and ovary. In addition 101 patients have been included in two unpublished RCT, including breast, lung, ovarian and ENT cancer. Mistletoe therapy was heterogeneous, including following preparates in various therapeutic regimes and doses: Helixor®, Isorel®, Lektinol® and Eurixor®.
The design and reporting quality of RCT was also heterogeneous. None of the RCT reported to have concealed allocation. In two RCT blinding was initially done but discovered by a large number of patients or assessors during study period.
None of the RCT defined frequency or severity of chemotherapy associated toxic effects as its primary outcome. Some of the RCT reported, however, rates of toxic effects or parameters related to treatment toxicity. The results are inconsistent among the RCT ranging from no effect on to positive effects (i.e. reduction) on chemotherapy toxicity. RCT with treatment toxicity as primary outcome are needed to answer the question of whether the addition of Mistletoe to chemotherapy schemes can help reducing the treatment toxicity.
HRQOL was the primary outcome in four RCT. The addition of mistletoe to chemotherapy showed to have a positive effect on HRQOL of women treated for breast cancer.
The results of our work are limited by the fact, that no contact was made to authors in order to complete missing data from original publications.

## Conclusions

The available evidence does not allow giving a conclusive answer to the question of whether the addition of mistletoe to chemotherapeutical regimes can reduce the toxicity of the latter. RCT are needed in which the primary outcome is treatment toxicity. Both rates and severity of chemotherapy related toxic effects, but also need of supportive therapies (such as antiemetics, antibiotics, blood products) could be measured in RCT studying this question.
The existing evidence is insufficient to recommend for or against the addition of mistletoe to conventional chemotherapy in oncologic patients with the purpose of reducing treatment toxicity.
The addition of standardised mistletoe extract to chemotherapeutical regimes in the treatment of women with breast cancer can lead to improvements in HRQOL. However, further research is needed including more patients with other cancer types.
The available evidence is insufficient to evaluate the effects of the addition

of mistletoe to chemotherapy on tumor-remission.
The coverage of standardised mistletoe preparations by the German social health insurance in the context of conventional cancer treatment (i. e. as complementary), as stated in the so called “OTC exception list” is limited to palliative treatment of cancer (a clear definition of „palliative“ is however not provided in the directive). In the appendices of the directive is stated, that there is enough evidence for this indication (however without referring to specific sources). In the light of the results from RCT summarised in this report, the competent self-governing bodies should evaluate the need to restrict the coverage of mistletoe in cancer to women with breast cancer receiving adjuvant therapy.