

Mistletoe in Cancer

State of Evidence: Effectiveness and Safety

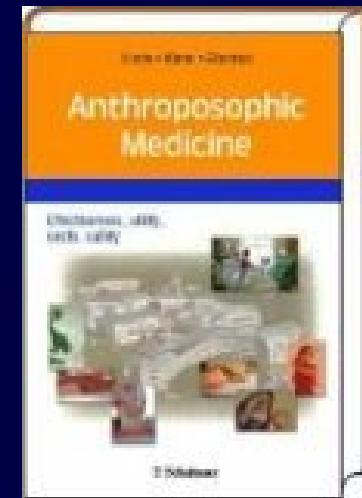
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Dr. med. Gunver S. Kienle
IFAEMM

Institute for Applied Epistemology and Medical Methodology
D-Freiburg i. Brsg., Bad Krozingen
gunver.kienle@ifaemm.de

State of evidence

- Health Technology Assessment Report
- On effectiveness, utility, costs and safety of Anthroposophic Medicine
- Commissioned, peer-reviewed, and approved by the Swiss Federal Social Insurance Office
- Complementary Medicine Evaluation Program (PEK)
- Kienle G. S., Kiene H, Albonico H: *Anthroposophic Medicine*. Schattauer, Stuttgart, New York 2006.



Research in Mistletoe Extracts *Viscum album* L.

1. Usage

2. Laboratory Research

3. Clinical Research

- Efficacy / Effectiveness
- Safety

Usage of Mistletoe in Cancer

- *Viscum album* L.: Highly investigated
- 40% of cancer patients in Europe use CAM
- Most frequently prescribed CAM-therapies in central Europe
- 25-60% of cancer patients in Germany, Austria, Switzerland
- Recommended by their doctor
- German doctors feel well informed
- Reimbursed by health insurance in many countries

Ann.Oncol. 2005, Onkologie 1998;21:144-9. Support Care Cancer 9, 267-274 (2001).
Swiss Med Wkly 133, 233-240 (2003).

Laboratory Research

(~ 1000 investigations)

- Highly cytotoxic
- Induction of apoptosis
(direct and indirect via FasL)
- DNA-stabilization
- Immunomodulation
- Antitumoral effective in animal models (n=130)
- Inhibition of angiogenesis

No simple conclusions can be drawn for
clinical application

Overview: Kienle GS: *Die Mistel in der Onkologie*. Stuttgart 2003. Büssing A: *Mistletoe. The Genus Viscum*. Amsterdam 2000. PubMed and other scientific databases

Cytotoxicity

- Highly cytotoxic compounds
- Mechanism:
 - Induction of apoptosis
 - Protein synthesis inhibition
 - Cell necrosis
- Effective in cancer cells resistant to other drugs (e.g. MDR+)
- Enhances cytotoxicity of other anticancer drugs
- Cytotoxicity similar to classical anticancer drugs

Toxicology 2002; 171: 187-199, Cancer Res 1999; 59: 2083-2090, Apoptosis 1996; 25-32. Cell Death and Differentiation 1998; 5: 231-240. Drug Res 2001; 51: 748-757

Overview: Kienle GS: Die Mistel in der Onkologie. Stuttgart 2003. Büssing A: Mistletoe. The Genus *Viscum*. Amsterdam 2000

Immunomodulation

→ Mistletoe extracts stimulate immune cells

(Natural killer cells, monocytes, dendritic cells, T- and B-lymphocytes, granulocytes, cytokines)

Mistletoe-activated macrophages and natural killer cells inhibit tumor growth and metastases in mice

→ Augmentation of immune response to other antigens (adjuvant)

→ Fever

Cancer Res 1990; 50: 3646-3651. Anticancer Res 1994; 953-962. Immunol Letters 1993; 38: 111-119.

Immunol Investigations 1993; 22:431-440, Immunol Investigations 1999;28:1-8 and 2000;29:219-231

Overview: Kienle GS: Die Mistel in der Onkologie. Stuttgart 2003.

Büssing A: Mistletoe. The Genus *Viscum*. Amsterdam 2000

Experimental Animal Tumors

(~130 Investigations)

Most experiments:

- Survival benefit
- Inhibition of tumor growth and metastatic spread
- Tumor regression
- Increase of effect of chemotherapy or radiotherapy
- Haematopoietic recovery after chemo-/radiotherapy

Literature, e.g.: Antony S.: J Exp Clin Cancer Res 1997; 16:159-162. Antony S.: Immunol Invest 1999; 28:1-8. and 2000; 29:219-231. Burger A.M.: Proc AACR; 1999 40:399. Jurin M: Oncology 1993; 50: 393-398. Kuttan G : Tumori 1993; 74-76. Kuttan G: Carcinogenesis 1996; 17: 1107-1109. Rentea R: Lab Invest 1981; 44: 43-48. Zarkovic N.: Anti-Cancer Drugs 1997; 8:S17-S22. Braun JM: Anticanc Res 2002; 22:4187-4190. Pryme IF: Cancer detection and Prevention 2004; 28: 52-56. *Overview:* Kienle GS: Die Mistel in der Onkologie. Stuttgart 2003. Büssing A: Mistletoe. The Genus *Viscum*. Amsterdam 2000

Clinical Studies

AM-Mistletoe Therapy in Oncology

10 Systematic reviews/HTA-report

113 Clinical studies

- 21 randomised controlled trials
 - 14 non-randomised controlled trials
 - 13 prospective single-arm cohort studies
 - 4 pharmacoepidemiologic cohort studies
-
- 22 retrospective single-arm cohort studies
 - 39 retrospective controlled trials

Results

Controlled Clinical Trials (n=35)

	Positive			Negative	
	↗ Sign.	↗ Trend	Zero	↘ Trend	↘ Sign.
26 x Survival	13	12	1	-	-
5 x Disease-free Survival	3	-	1	1	-
4 x Remission	2	1	1	-	-
11 x QoL*	9	1	-	-	-
8 x QoL and tolerability of surgery, chemo-, radiotherapy	8	-	(1)	-	-

* One study (Kleeberg et al. 2004) did not report their QoL result

Results

Single-arm Cohort Studies (n=12)

Cancer of Intestine, pancreas, liver, breast, brain, kidney; lymphoma:

- Remission: 5 studies, in 22-62% of patients
- No remission: 2 studies

Cervical intraepithelial neoplasia:

- Remission: 1 study, in 68% of patients

Malignant pleural effusion, ascites:

- Remission 4 studies, in up to 88% of patients

QoL: improvement in 7 studies; impairment in 1 study

CAVE: remission does not mean cure!

Problems in Clinical Mistletoe-Studies

- Randomisation often not possible or fails
- Blinding only *pro forma*, unblinding
- Protocol deviation frequent
- Mistletoe application primarily in institutions (practices, centers, hospitals) with no infrastructure and special expertise for clinical research and *vice versa*
- Enrollment of appropriate number of patients within reasonable time

Results and Conclusions

Best evidence exists for

- Improvement of QoL and tolerability of cytotoxic therapies
- Survival benefit has been shown but not beyond critique
- Tumor remissions are shown in single-arm cohort studies that mainly investigate high dose or local application
- Many studies have methodological weakness
- Reasonably well-conducted studies indicate benefit

Problems with Iscador?

- More metastases ?
- Earlier death ?

What is the background ?

Melanoma Trial

Kleeberg, Eggermont, et al.: *Eur J Cancer*, 2004; 40: 390-402

Randomised trial compared Iscador vs. interferon vs. control

- 102 patients: Iscador M
- Overall survival: no effect,
Hazard-Ratio 1.2 (95% CI: 0.84-1.75), $p=0,031$;
- Disease-free survival: negative trend,
HR 1,3 (95% CI: 0.93-1.87), $p=0,12$
- Preliminary reports:
More brain metastases in Iscador patients ?
- No mention of brain metastases in final publication
More distant metastases, no statistical significance
(38,3 % vs. 33,4 %; pure chance?)
- Quality of life: No results reported

Metastases? Disease-free Survival?

Kleeberg, Eggermont, et al.: *Eur J Cancer*, 2004; 40: 390-402

Were groups comparable? Bias regarding diagnosis?

Brain metastases:

- Highly frequent and unnoticed in melanoma.
- Relative contra indication for Iscador
- Might necessitate brain CT or NMR in Iscador group especially if doctors are unexperienced with Iscador (1 patient recruited in 4 years per centre on average)

Therefore:

- Relatively more CT scans in Iscador patients?
- Leads to seemingly more distant metastases and impaired disease-free survival, just because more diagnostic screening is done

(No general screening of brain by CT or NMR in study protocol)

Were groups comparable? Maybe not:

Kleeberg, Eggermont, et al.: *Eur J Cancer*, 2004; 40: 390-402

Conclusion:

- Mistletoe patients should have received more diagnostic searches for brain metastases because Iscador is counter indicated for brain metastases
 - Control patients do not need more diagnostic searches
 - In Iscador patients therefore more brain metastases should have been detected
 - In control patients the same number of metastases may have been present, but not diagnosed because there was no reason for diagnostic searches
- Detection Bias, a systematic mistake

Overall Survival?

Kleeberg, Eggermont, et al.: *Eur J Cancer*, 2004; 40: 390-402

Survival curves can be explained by
pure chance alone (p=0,3)

Iscador group negatively biased regarding females

Speculating within these borders of pure chance:

- A few patients died early, within the first half year.
- After that everything was comparable and parallel (speaks **against** a negative Iscador effect)
- We do not know what happened regarding these early died patients:

Questions that were never answered

Kleeberg, Eggermont, et al.: *Eur J Cancer*, 2004; 40: 390-402

- ? Chance effect ($p=0,3$)?
- ? Detection bias? And then, what happened to these patients?
- ? Did they receive Iscador at all?
(60% of patients stopped Iscador early or never received it)
- Study authors never provided any data to clear these important points
- There is nothing available except a meager study report

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Augustin et al. 2005

Arzneimittel-Forschung/Drug Res. 55(1):38-49

- Prof. Dr. Matthias Augustin,
University of Freiburg/Hamburg, Dermatology
- **Safety and efficacy** of long-term mistletoe application
in melanoma stage II/III
- Multicenter, comparative, epidemiological cohort study
- 35 centers (D, CH), 686 consecutive unselected
patients
- Most patients from **University of Freiburg**,
uniform documentation
- **Iscador P** (83%), median 30 months

Augustin et al. 2005

Arzneimittel-Forschung/Drug Res. 55(1):38-49

Results:

- Brain metastases not increased, not earlier
- Less brain, lung and mediastinum metastases
(HR brain metastases: 0.33; 95% CI: 0.13-0.86)
- Tumor-related survival longer
HR 0.41 (95% CI: 0.23-0.71)
- Overall survival, disease-free survival and brain-metastases-free survival significantly longer
- Much better results with Iscador P than Iscador M
- Better results with longer treatment

Are Improvements in Quality of Life Placebo Effects?

Semiglasov 2006: *Anticancer Research* 2006; 26:1519-1530

Randomised controlled trial

352 breast cancer patients, CMF-chemotherapy:

- Mistletoe extract (Lektinol, n=176)
- Placebo (n=176)

Patients and physicians **blinded**

Result:

Significant improvement in quality of life:

Physical, emotional and functional well-being;
fatigue, nausea/vomiting, appetite,
feeling depressed

Safety

What has been investigated:

1. Toxicology
2. Clinical studies
3. Special safety studies
4. Case reports
5. Survey at drug agencies
6. Special safety investigations

Safety

- In 27 years 15 case reports of adverse effects (50.000 patients treated per year in Germany)
- Toxicology: safe, no toxic effects
- Occasional allergic reactions
- Besides, no major side effects or toxicity
- Minor dose-dependent, spontaneously subsiding symptoms:
 - Local: swelling, erythema, pruritus, local pain
 - Mild flu-like symptoms or fever

➔ Mistletoe treatment is safe

Stein, G. M. and P. A. Berg, *Adverse effects during therapy with mistletoe extracts*.p.195-208, and Stein, G. M., *Toxicology of mistletoe and their components*. In: Mistletoe. The Genus Viscum. (Ed. A. Büssing) pp. 183-194, Hardwood Academic Publishers, Amsterdam 2000.

Kienle, G. S., et al. *Anthroposophic Medicine*. Schattauer, Stuttgart, New York 2006.

**Thank you very much for your
attention!**

www.mistel-therapie.de