

Review

Mistletoe Preparation Iscador: Are there Methodological Concerns with Respect to Controlled Clinical Trials?*

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In Europe many cancer patients use complementary therapies, particularly mistletoe. Only a few controlled clinical trials have been performed with the mistletoe preparation Iscador as a complementary treatment for cancer, many of them with medium to low quality due to methodological shortcomings. Reasons for some quality concerns, particularly discontinuation of treatment and/or participation and premature termination are analyzed. Analysis is based on controlled clinical trials dealing with Iscador. Data stem from the archive of published and ongoing research of the «Verein für Krebsforschung» (Society for Cancer Research) in Arlesheim, Switzerland. Controlled clinical studies with cancer patients that were started after 01.01.1990 or were not completed by then have been evaluated. Fifty-six controlled studies are documented, 24 of them randomized and 32 non-randomized. Nine of the randomized studies were done by matched-pair design, the others by conventional parallel group design; six of the last were terminated prematurely primarily for slow recruitment due to patient preferences and compliance of physicians. Patient and physician preference seem to be important factors limiting recruitment for randomized trials and hence implementation. This adds to the overall unwillingness of participation by patients with serious diseases. A well-balanced mix of designs using different research methods and outcomes is suggested combined with analyses, in countries where mistletoe therapy in general or Iscador in particular is unknown or not available.

Keywords: cancer – patient recruitment – preference

Background

In Europe, a substantial portion of patients suffering from cancer use complementary therapies. However, evidence of these treatments regarding efficacy on disease progression and survival is discussed controversially (1). Amongst complementary therapies against cancer, aqueous extracts of European mistletoe (*Viscum album* L.), developed on the basis of anthroposophical medicine, are the most frequently used medications,

particularly in German speaking countries (2,3). In recent systematic reviews (4–6) the authors concluded that in spite of the longstanding and widespread use of mistletoe preparations, only few controlled clinical trials have been performed; the quality of many older studies is generally medium to low due to methodological shortcomings, the more recent ones tend to be better.

Objective

Reasons for some specific quality issues, particularly discontinuation of treatment and/or participation and premature termination of recent controlled clinical studies with cancer patients using the mistletoe preparation Iscador as a complementary treatment are analyzed. Consequences for future research are suggested.

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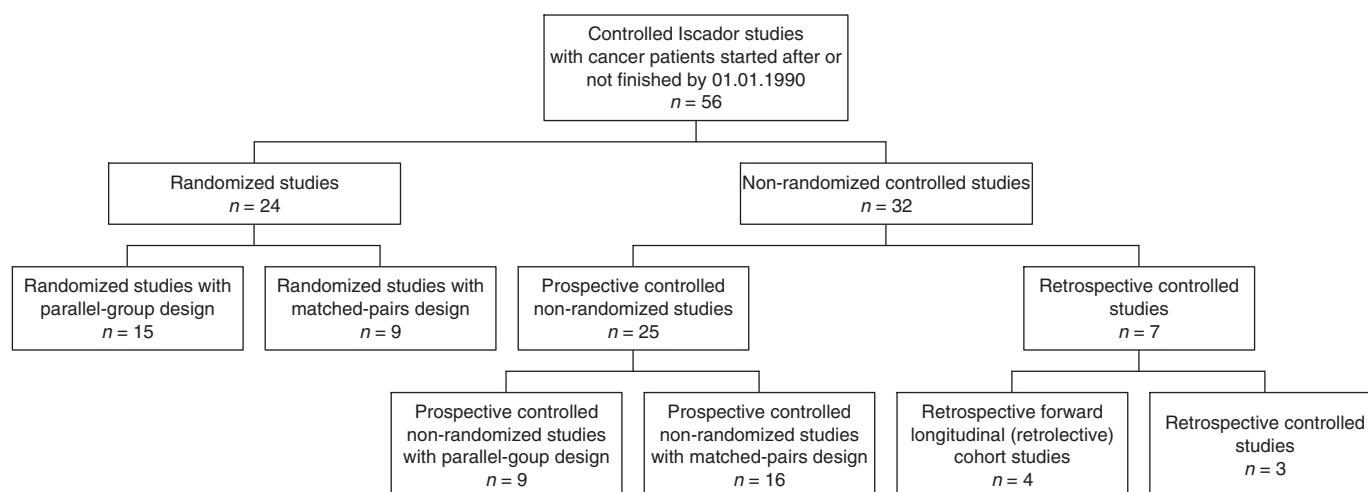


Figure 1. Controlled clinical studies for cancer patients with the mistletoe preparation Iscador; started after or not finished by 01.01.1990.

Patients and Methods

Unfulfilled quality criteria in published research reveal some of the difficulties that mistletoe might encounter but are in some cases not specific for mistletoe. However, looking for concerns intrinsic to research with the mistletoe preparation Iscador, additional information can be gained from difficulties with ongoing research and from reasons for discontinuation. The following analysis is based on controlled clinical studies dealing with the mistletoe preparation Iscador (see subsequently). All data stem from the archive of published and ongoing research of the «Verein für Krebsforschung» (Society for Cancer Research) in Arlesheim, Switzerland. In order to concentrate the analysis on newer research, only controlled clinical studies with cancer patients that were started after 01.01.1990 or were not completed by then have been evaluated, including non-finished and non-published ones (7,8). The control group always received conventional cancer therapy (adjuvant or palliative) and the treatment group additionally Iscador. Within this time frame, 56 controlled studies are documented, 24 of them randomized and 32 non-randomized (Figure 1). Subgroups of these will be discussed separately.

For the discussion of research with other mistletoe products than Iscador and concerning other quality issues, see e.g. (3,4,6,9). References also give a detailed quality assessment of controlled clinical studies with mistletoe preparations (4,6,9).

Mistletoe Characteristics

Mistletoe extracts for cancer therapy were first used in 1918 by Ita Wegman on the basis of anthroposophy (10). Pharmacological and toxicological properties of mistletoe extracts are documented by various publications on immunological and anti-cancer effects *in vitro* and *in vivo* [overviews in (3,11–14)]. Iscador is a fermented

aqueous extract of European mistletoe (*Viscum album* L.) that is treated by a special mechanical process of anthroposophical pharmaceuticals to increase efficacy (15). There are different doses and sorts of Iscador depending on the host tree, and various application schemes (12,16). Iscador is generally administered subcutaneously two to three times a week. For information concerning the specific therapy regimes, one has to consult the original studies.

Systemic adverse reactions are very rare (3,17–20) and mild to moderate in almost all cases (i.e. CTC/WHO grade 1–2) with spontaneous recovery within one week (21,22). No irreversible events or deaths were reported. This means that there exists no real risk in using mistletoe, which is an important condition for planning and implementing mistletoe studies even if the clinical effects are still discussed controversially (1). However, local reactions at the injection site are frequent with spontaneous recovery after some hours or days. These effects are expected and typical for mistletoe preparations, especially Iscador: in consequence, the dose is adjusted according to the size of the local reaction. This makes it difficult to design a pharmacologically and medically inert placebo showing similar reactions (23). Given this situation, blinding of patients and physicians is nearly impossible. In case a placebo with a similar set of reactions is used, the placebo might not be a true placebo (showing no specific effects) any more and thus results of the treatment comparison might be at least questionable.

Randomized Iscador Studies with Parallel-group Design

From 15 randomized Iscador studies with parallel-group design (Table 1) six had to be terminated prematurely (No. 3, 4, 6–9). In five cases (No. 3, 6–9) the most important reason was slow recruitment, due to

Table 1. Randomized mistletoe studies with Iscador in parallel-group design

Study No.	Indication	Outcome parameter	Patients (planned)	Status	Reasons for termination
1	Non-small-cell lung cancer	Overall survival	86 Iscador/97 control	Start 1981, published 1991 (34)	–
2	Melanoma	Disease-free-interval, overall survival	2 × 102	Start 1988, published 2004 (35)	–
3	Advanced cancer	QoL (QLQ-C30, SELT, HADS)	(3 × 40)	Start 1995, terminated 1998	Slow recruitment (patient preferences, language barriers, logistical problems, refusal of participation in trial), drop-outs because of death (36)
4	Colon cancer, stage III	Disease-free survival, global QoL	(3 × 150)	Start 1996, terminated 1996	After study start: negative expert opinion from DKG (Deutsche Krebsgesellschaft) concerning insufficient data for mistletoe which lead to termination
5	Breast cancer	QoL (Spitzer)	20 Iscador/10 control	Start 1997, published 1999 (37)	–
6	Throat, nose and ear cancer	Side effects of radiation therapy (immune system, DNA, infections)	(2 × 20)	Start 1997, terminated 1999	Slow recruitment (suboptimal motivation and compliance of physicians, compliance of patients)
7	Breast cancer	Immunological side effects of radiation therapy after operation, QoL	(2 × 60)	Start 1997, terminated 2005	Slow recruitment (patient preferences, refusal), many drop-outs (compliance/motivation of physicians), shut down of radiation department
8	Bladder cancer	Safety of pre-operative Iscador instillation, anti-tumor effects, QoL	(2 × 13)	Start 1999, terminated 2003	Slow recruitment (patient preferences, refusal), suboptimal motivation and compliance of physicians
9	Small-cell lung cancer	QoL (QLQ-C30), disease-free interval, overall survival	(2 × 47)	Start 2000, terminated 2001	very slow recruitment
10	Colorectal cancer	Natural killer cell activity during peri-operative Iscador infusion	2 × 21	Recruitment 2002–2004, published 2007 (38)	–
11	Non-small-cell lung cancer	Overall survival, progression-free interval, QoL (QLQ-C30), immunological parameters, safety	(2 × 25)	Recruitment 2004–2007	–
12	Breast cancer	QoL, cortisol level, immunological parameters	2 × 24	Recruitment 2005–2006, published 2004/5 (39,40)	–
13	Breast cancer	QoL (QLQ-C30), fatigue, neutropenia, immunological parameters	(3 × 30)	Recruitment 2005–2006	–
14	Colon cancer with metastases	QoL (QLQ-C30), ECOG, tolerability, overall survival	(2 × 25)	Start 2005	–
15	Spindle-cell bone-sarcoma	Post-relapse disease-free survival, QoL (QLQ-C30)	(2 × 18)	Start 2007	–

Table 2. Example: recruitment and randomization in mistletoe studies (39)

<i>N</i>	Characteristics	Exclusion	Reasons for exclusion
1922	Breast operation from May 1999 to August 2001 in Heidelberg university hospital	518	Only biopsy, benign tumor
1404	Diagnosis breast cancer	883	Inclusion criteria not fulfilled or exclusion criteria fulfilled: no primary breast cancer (316), other stage (105), pre-operative chemotherapy (72), age (63), other missing inclusion criteria (73), other exclusion criteria (254)
521	Post-operative check of inclusion and exclusion criteria with clinical registry	367	Refusal of trial in general (184), logistics (74), <i>mistletoe preferred</i> (51), no histology (42), participation in other study (13), refusal of chemotherapy (3)
154	Patient interview: all inclusion and exclusion criteria OK	80	No chemotherapy (55) or other chemotherapy (inclusion criteria) (19), other reasons (6)
74	Study group	45	Prefers to determine the therapy (22), <i>prefers mistletoe</i> (14), prefers no injections (4), other (5)
29	Willing to be randomized		

insufficient compliance on the physicians' side (preference for other ongoing studies: i.e. recruitment for trials with conventional drugs if available; no equipoise in view of mistletoe treatment with Iscador; lack of methodological education for performing clinical trials) and on the patients' side [refusal of participation in trial, therapy preferences, in favor of Iscador; see also (23)]. However, trial participation generally has many hurdles and is particularly bad with patients having therapy preferences (24–29). The situation concerning recruitment and compliance in randomized studies is even more complicated in the context of complementary oncology compared to conventional oncology (3,30–33).

Obviously, these difficulties were also encountered in completed studies. For instance, in a large trial in Germany during the eighties, the investigators had to revise the power calculation twice to reduce sample size, but still needed more than 9 years for patient recruitment (41). Another study needed considerably more time for completion than anticipated (35,42). In addition, for both cases showing no significant effect of Iscador on tumor progression or survival, one can argue that they suffered from a false-negative bias (3,4,6). Given these experiences, an empirical study was conducted to evaluate the willingness of patients to participate in a randomized clinical mistletoe trial (39). The results are shown in Table 2 and present a whole bundle of reasons why particular patients were not able to enter the trial. Among these, preference of mistletoe is the only mistletoe-specific reason for not participating. The refusal of trials in general as well as the wish to determine the therapy itself is prominent as well.

Randomized Matched-pair Studies with Iscador

The concept of randomized matched-pair studies is rather unusual in cancer research. The recruitment and

randomization of patients for this kind of trial is executed pair-wise: From a successively filled pool of cancer patients not treated by any kind of mistletoe or therapy stimulating the immune system, pairs according to pre-specified prognostic factors are built and then randomized separately. Details of the randomization process (43) were executed according to pre-specified rules, in accordance with the suggestions of the CONSORT statement (44,45).

Randomization and Concealed Allocation

Two slips of paper with names of the two matched partners were put into a hat by the primary investigator, and a masked assistant drew one of the slips. It was determined that the patient selected first was asked if he or she would be willing to ask the attending doctor for a complementary therapy using Iscador. Thus, intervention did not consist of giving a therapy with Iscador, but of making a suggestion for an Iscador therapy.

Implementation

The patient recruitment happened strictly according to the matching rules without interference from investigators. The random allocation result was implemented by the primary investigator non-involved in the random selection process.

Consent

The acceptance of participation in this kind of study is one-sided, i.e. only the patient being suggested a therapy with Iscador was informed about this process. The other patient as well as the respective attending physician was left uninformed. Thus, this is a special case of the single randomized consent design of Zelen (46–48). That research was planned and started in the early 70s, where ethical committees did not yet exist; or there was

Table 3. Randomized mistletoe studies with Iscador in matched-pair design; outcome is in all cases overall survival and psychosomatic self-regulation

Study centers	Indication	Pairs of Patients				Status
		Recruited	Therapy declined or not received	Drop-out or lost	Final	
Fifteen in Germany	Breast cancer without recurrences or metastases	59	19	2	38	Published 2006 (49)
Fifteen in Germany	Breast cancer with lymphatic metastases	17	0	0	17	Published 2001 (50,51)
Eight in Germany	Cancer of the cervix with metastases	19	0	0	19	Published 2007 (52)
Eight in Germany	Cancer of the uterus body without metastases	38	7	1	30	Publication in preparation
Eight in Germany	Cancer of the uterus body with metastases	26	0	0	26	Publication in preparation
Eight in Germany	Cancer of the ovaries without metastases	25	4	0	21	Publication in preparation
Eight in Germany	Cancer of the ovaries with metastases	24	4	0	20	Publication in preparation
Fifteen in Germany	Several solid cancers	49	9	1	39	Published 2001 (50)
Eight in Germany	Melanoma	22	0	0	22	Publication in preparation

at least no mandatory requirement to have a study approved by them; however, one does not know their reaction on such a study proposal.

Exclusion of Pairs

If for any reason, a single patient had to be excluded, the whole matched-pair including this patient was excluded. The following criteria were applied to exclude patient pairs: (i) if the allocated suggestion for Iscador therapy has not been taken up either by the patient or the attending physician; (ii) if the control partner decided to start Iscador therapy or any other treatment modulating the immune system; (iii) if for one of the partners a certified non-tumor-related accident or suicide occurred; (iv) if after the matching process any patient refused to participate further for any reason, or if any partner dropped out for any other reason than death or if a patient could not be found any more in the follow-up process.

The statistical analysis of randomized clinical trials according to the principle of intention-to-treat (53,54) has two aspects which need to be differentiated: first to preserve the statistical balance of the baseline factors in the two therapy groups and second to present an adequate picture of the real life situation, where non-compliance and drop-out occur and might be associated with the therapy and the outcome. However, a sufficiently complete picture of the whole situation is only given if the intention-to-treat analysis estimating the effect of assignment to therapy (use-effectiveness) is complemented with an estimated effect of actually administered therapy (method-effectiveness—not to be confused with a simple per-protocol—or as-treated analysis) (55,56).

With respect to randomized matched-pair studies, the procedure of *exclusion of pairs* guarantees that randomization is not undermined by excluding patients. In other words, internal validity is not at issue since the structural comparability is preserved by pair-wise selection and exclusion. This covers the first aspect of an intention-to-treat analysis. However, by this exclusion process, not all randomized pairs are included in the analysis and hence there exists a kind of underreporting bias which does not interfere with the randomization but with the completeness of the analyzed data sets. A masking process was not applicable to the intervention of the randomized matched-pair studies, since it consisted not of a therapy as such but of a suggestion to perform a therapy with Iscador towards the randomly selected patient. In addition, neither the outcome assessors were masked nor the statisticians.

Nine studies of this kind have been executed (Table 3), four of which have been published (49,50,52,57–59) and the rest await final analysis and publication. Most of these took a very long time to execute (more than 10 years) and there have been some patients who declined participation or did not receive Iscador therapy (Table 3).

Concerns with Randomized Clinical Trials using Iscador

According to the aforementioned results reported, recruitment for a conventional randomized controlled clinical trial (RCT) is difficult for several reasons: physician or patient preferences either in favor of or against mistletoe therapies, preferred co-interventions, patient and physician compliance and drop-outs. The long tradition of using mistletoe preparations in German speaking countries has the consequence that mistletoe in general and Iscador in particular is well known among

cancer patients searching for complementary treatments. Thus, many informed patients explicitly want to use mistletoe extracts and therefore cannot be randomized.

Apart from this situation there are major general concerns using randomization and blinding in trials within complementary medicine (33). With respect to quality, blinding is nearly impossible in mistletoe studies: it was shown that at least in the long run most physicians and patients lose their blindness (23,60). However, also in chemotherapy trials, blinding is rare (61). In addition, any kind of standardized therapy as used in conventional randomized clinical trials is not representative of a population using the mistletoe preparation Iscador as a cancer treatment.

Randomized matched-pair studies have the drawback of not being well accepted by conventional trial experts and methodologists because of the unusual design. And, they share some of the limitations of RCTs in general which make recruitment and implementation difficult: physician or patient preferences in favor of or against complementary treatments, patient preferences, refusal to trial in general, compliance, drop-outs, rigid inclusion and exclusion criteria. Furthermore, a fairly big pool of cancer patients is required to recruit enough matching pairs. Not all quality issues concerning randomized mistletoe research can be mentioned here. Some authors (3,4,6) discuss other limits, particularly false-negative bias stemming from other kinds of biases.

Prospective Non-randomized Controlled Iscador Studies

Prospective non-randomized controlled studies are advantageous for including representative samples of patients and doing research on those receiving actual Iscador treatments, i.e. performing prospective data measurement. However, since they should consider all known possible prognostic factors and confounders, they tend to be expensive and, if the effect is not strong, unreliable due to selection bias (62,63). Table 4 shows the nine controlled prospective non-randomized studies in parallel-group design with Iscador that were recently finished or are still ongoing. According to the quality assessments of some of these in (4,6), they vary in quality. Compared to other types of cohort research (21,22) few patients are included, but compared to the randomized trials, the situation is acceptable. Note that none of them was discontinued.

The main work in realizing cohort studies should focus on the design and implementation phase. That is the place where random as well as systematic errors (bias) can be minimized, particularly by specifying adequate inclusion and exclusion criteria, and where adequate measures against selection bias (the biggest challenge for non-randomized designs), performance bias, detection

bias and attrition bias (80,81) can be provided. In a systematic way, this has only been regarded in the four parallel-group studies: No. II, V, VI, VII and, to some extent, in study VIII with matched-pairs. The report on random and systematic error prevention is insufficient within the others (82), as is the statistical analysis.

Prospective Non-randomized Matched-pair Studies with Iscador

There are 16 prospective non-randomized matched-pairs studies with Iscador for different solid cancers, eleven published (50,52,57–59); the remaining still await analysis and publication.

Pair-wise matching is one of the strongest measures against selection bias in non-randomized cohort research. Within these, not only tumor-specific prognostic factors are considered, but also the year of diagnosis: for matching pairs, difference between the years of initial diagnosis is at most 3 years. This allows patient recruitment in pairs over a long period of time (and hence long periods of follow-up) without risking the danger of significantly different prognostic or therapeutic procedures due to medical progress. In other words: there is no danger of stage migration (83).

If for any reason a single patient was excluded, in any case the whole matched-pair including this patient was excluded. These pairs have neither been followed up nor used for other purposes in any other Iscador research. This process does not explicitly favor one of the two therapy groups. In most cases, the excluded patient pairs did not exceed 10% of those recruited. No study was prematurely terminated due to lack of patients. However, the recruitment period in most cases exceeded 10 years.

Controlled Forward Longitudinal («retrolective») Cohorts using Iscador

Controlled retrospective forward longitudinal («retrolective») cohort analyses (84) include systematic searches of patient archival data in clinical registries according to specific criteria of inclusion and exclusion, guided by a protocol that adheres to the principles of good epidemiological practice (85,86). These are advantageous for being easy to implement for a long treatment period in a comparatively short data gathering period for a large sample. As such they give a picture of the real world effectiveness, since they do not require any additional selection process. The randomized selection of study centers from an available pool guarantees external validity. Their main disadvantage regards reliance on complete archival data, that is on a retrospective data collection (i.e. measurements and recordings of observations happened before study onset and for

Table 4. Prospective controlled non-randomized mistletoe studies with Iscador in parallel-group design

Study No.	Indication	Outcome parameter	Patients Iscador/Control	Status	Comments
I	Cancer, different locations	IL-6 in blood serum	99/28	Published 2000–04 (64–67)	Evaluation of different patient groups to measure the variations of the IL-6 level in blood serum under Iscador treatment compared to healthy controls
II	Advanced cancer of different locations	Socio-demographic and medical characteristics	221/280	Published 2002 (68)	Register study to evaluate patient characteristics
III	Several gynecological cancers	QoL	64/64	Published 2005 (69)	
IV	Several gynecological cancers	Side effects of chemotherapy, QoL	43/41	Published 2005 (70)	
V	Primary breast cancer without metastases	Immunological parameters, QoL, safety	33/33	Published 2005 (40)	Feasibility study to prepare a randomized mistletoe trial
VI	Breast cancer	Granulocyte function, QoL	53/52	Published 2004/05 (71–73)	Modulation of immune suppression due to operation with peri-operative i.v. infusion of Iscador, GCP quality standards
VII	Breast cancer	Immunological parameters, QoL, tolerability of chemotherapy, safety	(50/50)	Start of recruitment 2004, preliminary publication (74)	Modulation of immune suppression due to chemotherapy with i.v. infusion of Iscador before and after chemotherapy; slow recruitment; GCP quality standards
VIII	Breast cancer	Coping, QoL	60/60	Published 2001–06 (75–78)	Coping was measured using the Mental Adjustment to Cancer Scale (MAC), Iscador and control patients were matched
IX	Ear, nose and throat	Microcirculation, immunological parameters	10/10	Published 2005 (79)	Small study to evaluate systemic and local reactions at the injection site of Iscador treatment

(QoL, quality of life; GCP, good clinical practice)

different reasons). Therefore they are subject to selection bias: measurements and recordings of all known prognostic factors, possible confounders, and all wanted and unwanted events cannot be assured. Four relevant studies are available, two of which are finished and published (21,22) and the remaining two are still being analyzed and prepared for publication.

Retrospective Controlled Cohort Studies with *Iscador*

Three classical retrospective cohort studies have been performed since 1990 (87–89). They are easy to do and complement the overall picture concerning characteristics of the *Iscador* population.

Reflections and Consequences

Quality

There are avoidable problems of quality, such as transparency and completeness of reporting data. Other problems are more difficult to overcome; however, they are not specific to mistletoe and induce different kinds of biases (3,4,6): systematic differences in care provided apart from the mistletoe treatment (performance bias), dropouts, withdrawals and protocol deviations (attrition bias). If the outcome is survival or tumor progression, detection bias is not problematic. The situation for quality of life is more complicated necessitating the use of validated questionnaires.

Duration of clinical phase

Many mistletoe studies have a clinical phase of less than 12 months; one might argue, that this is insufficient to bring into action long-term effects of mistletoe therapy (81,84,90). More research on long-term applications of *Iscador* is needed to evaluate effectiveness as well as safety.

Designs

If one wants to compare parallel groups, continue to randomize even if difficult. However, as shown earlier, recruitment may be the utmost problem for randomized trials with the mistletoe preparation *Iscador*. Before rejecting randomization, one should search for alternative designs for randomized trials [i.e. comprehensive cohort design (91–93), and (94–96)]. Thus randomized matched-pair studies might take a long time, depending on availability of patients, but they seem to be an alternative that requires evaluation. A survey within an academic center in the USA showed that for conventional physicians working in such an institution the attitude

towards using complementary therapy methods may be strongly linked to the existence of randomized trials in favor of such a treatment (97). However, randomization does not solve all problems. If the number of recruited patients is small, they might not be representative. In addition, the use of randomization might severely undermine the representativeness (or the generalizability) of results, since patients who agree to randomization might be different from those who do not, especially in the context of complementary and alternative medicine, where strong preferences are more common (36,68,98).

One of the most important points in this respect is to use different designs that complement each other (99,100). This was the underlying reason for implementing randomized matched-pair studies together with non-randomized ones (50). Thus, well-designed non-randomized research is not just an excuse for not being able to do randomized trials, but an important contribution to the overall clinical picture of *Iscador* therapy. If randomization is not possible or can only be done in small groups, one can use in addition prospective controlled non-randomized studies (101,102) and adhere to high quality standards (63,80,82). Under some circumstances, results of prospective controlled non-randomized studies might be comparable to randomized for the same outcome and similar population characteristics (103–106). However, care is required to prevent overestimation (62,63,82). If resources and time frames are limited, they can be complemented by retrospective controlled («retrolective») cohort studies using archival data and guided by a protocol (84–86) and by classical retrospective controlled cohort studies. If all this does not work, a look for other sorts of designs is essential (107). Even prospective one-arm studies can be useful, if designed and evaluated properly (108,109).

Centers

It is essential to do research in countries or populations unaware of mistletoe, in general or *Iscador* in particular or where mistletoe is not readily available (as in Beograd or in the USA). The experience from Beograd (Table 1) shows: randomization is not a real problem; drop-outs are seldom, since patients are content having a chance to receive complementary therapy with *Iscador*; compliance is high, since patients follow closely the physician's instructions.

Outcome

Consider reduction of symptoms, side effects of conventional therapy (chemotherapy, radiotherapy) and quality of life in addition to survival and tumor behavior.

Preclinical Studies with Healthy Volunteers

It was pointed out in (110) that there are also few *in vivo* controlled studies with healthy volunteers concerning immunomodulating effects of the mistletoe preparation Iscador or lectin extracts of mistletoe; however, the reasons are unknown. The trial in (110) complements the already existing four trials (111–117). Such research could be important for design of further clinical trials investigating the immunological effects of mistletoe preparations.

Conclusion

Randomized mistletoe research has been notoriously difficult to perform, especially in German speaking countries where mistletoe preparations are readily available outside of clinical trials. Patient and physician preference in favor of or against complementary therapy with mistletoe seem to be the most important factors limiting implementation of such trials with Iscador. This adds to the overall unwillingness of participation in trials for patients with serious diseases. Hence a well balanced mix of designs using different research methods and different outcomes is suggested, combined with research in countries, where mistletoe in general or Iscador in particular are unknown or unavailable.

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References

- Cassileth BR, Deng G. Complementary and alternative therapies for cancer. *Oncologist* 2004;9:80–9.
- Moschen R, Kemmler G, Schweigkofler H, Holzner B, Dünser M, Richter R, et al. Use of alternative/complementary therapy in breast cancer patients – a psychological perspective. *Support Care Cancer* 2001;9:267–74.
- Kienle GS, Kiene H. *Die Mistel in der Onkologie: Fakten und konzeptionelle Grundlagen*. Stuttgart: Schattauer, 2004.
- Kienle GS, Berrino R, Büssing A, Portalupi E, Rosenzweig S, Kiene H. Mistletoe in cancer: a systematic review on controlled clinical trials. *Eur J Med Res* 2003;8:109–19.
- Kienle GS, Kiene H. Klinische Studien zur Misteltherapie der Krebserkrankung – Eine Übersicht. *Erfahrungsheilkunde* 2004;53:193–209.
- Kienle GS, Kiene H. Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts. *Eur J Med Res* 2007;12:1–17.
- Ziegler R. *Klinische Versuche und Beobachtungsstudien seit 1990 mit Mistelextrakten, insbesondere Iscador*. Internes Dokument. Arlesheim: Vereins für Krebsforschung, 2006.
- Urech K, Ziegler R. *Documentation of Published Clinical Trials and Observational Studies with Iscador*. Arlesheim: Verein für Krebsforschung (www.hiscia.ch/forschung/klink/dokumentation.htm); June 2006.
- U.S. National Institutes of Health, National Cancer Institute: Mistletoe extracts (PDQ) (<http://www.cancer.gov/cancerinfo/pdq/cam/mistletoe>).
- Daems WF. Ita Wegman und das erste Mistelpräparat Iscar zur Krebsbehandlung. In: Leroi R (ed). *Misteltherapie - Eine Antwort auf die Herausforderung Krebs: Die Pioniertat Rudolf Steiners und Ita Wegmans*. Stuttgart: Freies Geistesleben, 1987, 35–44.
- Büssing A. Biological and pharmacological properties of *Viscum album* L. In: Büssing A (ed). *Mistletoe: The Genus *Viscum**. Amsterdam: Harwood Academic Publisher, 2000, 123–82.
- Büssing A. Mistel (*Viscum album*) – anthroposophischer und phytotherapeutischer Ansatz. In: Münstedt K (ed). *Ratgeber Unkonventionelle Methoden*. Landsberg: Ecomed, 2003, 184–99.
- Büssing A, Schietzel D, Schietzel M, Schink M, Stein GM. Keine Stimulation in-vitro-kultivierter Tumorzellen durch Mistellektin. *Dtsch Z Onkol* 2004;36:33–70.
- Büssing A. Pharmakologische Wirkungen von Mistelextrakten. In: Fintelmann V (ed). *Onkologie auf anthroposophischer Grundlage*. Stuttgart: Mayer (1. Lieferung), 2002, Section 3.2.4.1.
- Flückiger H, Baumgartner S. Auswirkungen des Iscador-Maschinenprozesses auf Mistelextrakte in botanischen Untersuchungssystemen. *Mercurstab* 2003;56:114–21.
- Matthiessen PF, Tröger W. Die Misteltherapie des Krebses. In: Wrba H (ed). *Kombinierte Tumortherapie - Grundlagen, Möglichkeiten und Grenzen adjuvanter Methoden*. Stuttgart: Hippokrates, 1995, 271–90.
- Stein GM, Berg PA. Adverse effects during therapy with mistletoe extracts. In: Büssing A (ed). *Mistletoe - The Genus *Viscum**. Amsterdam: Harwood Academic Publishers, 2000, 195–208.
- Saller R, Kramer S, Iten F, Melzer J. Unerwünschte Wirkungen der Misteltherapie bei Tumorpatienten - Eine systematische Übersicht. In: Scheer R, Bauer R, Becker H, Fintelmann V, Kemper FH, Schilcher H (eds). *Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung*. Essen: KVC Verlag, 2005, 367–403.
- Saller R, Reichling J, Melzer J. Die Misteltherapie. Erwünschte und unerwünschte Wirkungen in der wissenschaftlichen Diskussion - Teil 1. *PraxisMagazin* 2005;21:6–14.
- Saller R, Reichling J, Melzer J. Die Misteltherapie. Erwünschte und unerwünschte Wirkungen in der wissenschaftlichen Diskussion - Teil 2. *PraxisMagazin* 2005;22:6–17.
- Bock PR, Friedel WE, Hanisch J, Karasmann M, Schneider B. Wirksamkeit und Sicherheit der komplementären Langzeitbehandlung mit einem standardisierten Extrakt aus Europäischer Mistel (*Viscum album* L.) zusätzlich zur konventionellen adjuvanten onkologischen Therapie bei primärem, nicht metastasiertem Mammakarzinom. Ergebnisse einer multizentrischen, komparativen, retrolektiven, epidemiologischen Kohortenstudie in Deutschland und der Schweiz. *Arzneim/Drug Res* 2004;54:456–66.
- Augustin M, Bock PR, Hanisch J, Karasmann M, Schneider B. Safety and efficacy of the long-term adjuvant treatment of primary intermediate – to high-risk malignant melanoma (UICC/AJCC stage II and III) with a standardized fermented European mistletoe (*Viscum album* L.) extract: results from a multicenter, comparative, epidemiological cohort study in Germany and Switzerland. *Arzneim/Drug Res* 2005;55:38–49.
- Rostock M, Huber R. Randomized and double blind studies - demands and reality as demonstrated by two examples of mistletoe research. *Forsch Komplementarmed* 2004;11 (Suppl 1): 18–22.
- Prescott RJ, Gillespie WJ, Counsell CE, Grant AM, Ross S, Russell IT, et al. Factors that limit the quality, number and progress of randomised controlled trials. In: Black N, Brazier J, Fitzpatrick R, Reeves BC (eds). *Health Services Research Methods: A Guide to Best Practice*. London: BMJ Books, 1998, 86–97.
- Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, et al. Factors that limit the quality, number and progress of randomised controlled trials. *Health Technol Assess* 1999;3:1–134.
- Ross S, Grant AM, Counsell CE, Gillespie WJ, Russell IT, Prescott RJ. Barriers to participation in randomised controlled trials: a systematic review. *J Clin Epidemiol* 1999;52:1143–56.

27. Ellis PM. Attitudes towards and participation in randomised clinical trials in oncology: a review of the literature. *Ann Oncol* 2000;11:939–45.
28. King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, et al. Conceptual framework and systematic review of the effects of participants' and professionals preferences in randomised controlled trials. *Health Technol Assess* 2005;9:1–186.
29. Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Brauholtz DA, Edwards SJL, et al. Lay public's understanding of equipoise and randomisation in randomised clinical trials. *Health Technol Assess* 2005;9:1–192.
30. Abel U. Spezielle Forschungsprobleme, Teil 1: Warum gibt es in der unkonventionellen Medizin so wenige aussagekräftige Studien? In: Bühring M, Kemper FH (eds). *Naturheilverfahren und Unkonventionelle Medizinische Richtungen, Sektion 01: Allgemeiner Teil*. Vol. 01.08, Teil 1. Heidelberg: Springer, 1998, 1–8.
31. Abel U. Grundlagen der Biometrie. In: Beuth J (ed). *Grundlagen der Komplementärökologie*. Stuttgart: Hippokrates, 2002, 45–62.
32. Hüry C, Heusser P, Bernhard J, Castiglione M, Cerny T. Verbessern nicht-konventionelle Zusatztherapien die Lebensqualität von Krebspatienten? – Eine methodenkritische Literaturübersicht. *Schweiz Med Wochenschr* 1994;124 (Suppl 62): 55–63.
33. Heusser P. Probleme von Studiendesigns mit Randomisation, Verblindung und Placebogabe. *Forsch Komplementarmed* 1999;6:89–102.
34. Salzer G, Danmayr E, Wutzlhofer F, Frey S. Adjuvante Iscador-Behandlung operierter nicht kleinzelliger Bronchuskarzinome. Ergebnisse einer randomisierten Studie. *Dtsch Z Onkol* 1991;23:93–98.
35. Kleeberg U, Suciú S, Bröcker EB, Ruiter DJ, Chartier C, Liénard D, et al. Final results of the EORTC 18871/DKG 80-1 randomised phase III trial: rIFN- α 2b versus rIFN- γ versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness > 3 mm) or regional lymph node metastasis. *Europ J Cancer* 2004;40:390–402.
36. Von Rohr E, Pampallona S, Van Wegberg B, Hüry C, Bernhard J, Heusser P, et al. Experiences in the realisation of a research project on anthroposophical medicine in patients with advanced cancer. *Schweiz Med Wochenschr* 2000;130:1173–84.
37. Borrelli E. Valutazione della qualità di vita in pazienti affette da adenocarcinoma mammario sottoposte a terapia con *Viscum album*. *Med Biol* 1999;27–30.
38. Schink M, Tröger W, Dabidian A, Goyert A, Scheuerecker H, Meyer J, et al. Mistletoe extract reduces the surgical suppression of natural killer cell activity in cancer patients. A randomized phase III trial. *Forsch Komplementarmed* 2007;17:9–17.
39. Gerhard I, Abel U, Loewe-Mesch A, Huppmann S, Kuehn JJ. Problematik randomisierter Studien in der Komplementärmedizin dargestellt am Beispiel der Misteltherapie bei Patientinnen mit Mammakarzinom. *Forsch Komplementarmed* 2004;11:150–57.
40. Von Hagens C, Loewe-Mesch A, Kuehn JJ, Abel U, Gerhard I. Prospektive kontrollierte nicht randomisierte Machbarkeits-Studie zu einer postoperativen simultanen Mistel-/Chemotherapie bei Patientinnen mit Mammakarzinom - Ergebnisse zu Rekrutier- und Randomisierbarkeit, Immunparametern, Lebensqualität und Verträglichkeit. In: Scheer R, Bauer R, Becker H, Fintelmann V, Kemper FH, Schilcher H (eds). *Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung*. Essen: KVC Verlag, 2005, 567–78.
41. Dold U, Edler L, Mäurer CM, Müller-Wening D, Sakellariou B, Trendelenburg F, et al. *Krebszusatztherapie beim fortgeschrittenen nicht-kleinzelligen Bronchialkarzinom - Multizentrische kontrollierte Studie zur Prüfung der Wirksamkeit von Iscador und Polyerga*. Stuttgart: Thieme, 1991.
42. Eggermont AM, Kleeberg U, Ruiter DJ, Suciú S. European organization for research and treatment of cancer melanoma group trial experience with more than 2000 patients, evaluating adjuvant treatment with low or intermediate doses of interferon alpha-2b. In: Perry MC (ed). *Educational Book, 37th Annual Meeting*. Alexandria VA: American Society of Clinical Oncology, 2001, 88–93.
43. Grossarth-Maticek R, Ziegler R. Randomisierte Kohortenstudien im Matched-Pair-Design zur Misteltherapie (Iscador) bei gynäkologischen Karzinomen. In: Scheer R, Bauer R, Becker H, Fintelmann V, Kemper FH, Schilcher H (eds). *Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung*. Essen: KVC Verlag, 2005, 611–23.
44. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *J Am Med Assoc* 2001;285:1987–91.
45. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663–94.
46. Zelen M. A new design for randomized clinical trials. *N Engl J Med* 1979;300:1242–45.
47. Zelen M. Randomized consent designs for clinical trials: an update. *Stat Med* 1990;9:645–56.
48. Altman DG, Whitehead J, Parmar MK, Stenning SP, Fayers PM, Machin DM. Randomised consent design in cancer clinical trials. *Eur J Cancer* 1995;31A:1934–44.
49. Grossarth-Maticek R, Ziegler R. Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador). *Forsch Komplementarmed* 2006;13:285–92.
50. Grossarth-Maticek R, Kiene H, Baumgartner S, Ziegler R. Use of Iscador, an extract of European mistletoe (*Viscum album*), in cancer treatment: prospective nonrandomized and randomized matched-pairs studies nested within a cohort study. *Altern Ther Health Med* 2001;7:57–78.
51. Grossarth-Maticek R, Ziegler R. Randomised and non-randomised prospective controlled cohort studies in matched pair design for the long-term therapy of breast cancer patients with a mistletoe preparation (Iscador): a re-analysis. *Europ J Med Res* 2006;11:485–95.
52. Grossarth-Maticek R, Ziegler R. Prospective controlled cohort studies on long-term therapy of cervical cancer patients with a mistletoe preparation (Iscador). *Forsch Komplementarmed* 2007;14:140–47.
53. Montori VM, Guyatt GH. Intention-to-treat principle. *Can Med Assoc J* 2001;165:1339–41.
54. Windeler J. Das Intention-to-treat-Prinzip in klinischen Arzneimittelprüfungen. *Arzneimitteltherapie* 1993;11:103–11.
55. Sheiner LB, Rubin DB. Intention-to-treat analysis and the goals of clinical trials. *Clin Pharmacol Ther* 1995;57:6–15.
56. Sheiner LB. Is intent-to-treat analysis always (ever) enough? *Br J Clin Pharmacol* 2002;54:203–11.
57. Grossarth-Maticek R, Kiene H, Baumgartner S, Ziegler R. Addendum to Iscador article. *Altern Ther Health Med* 2001;7:26.
58. Grossarth-Maticek R, Kiene H, Baumgartner S, Ziegler R. Verlängerung der Überlebenszeit von Krebspatienten unter Misteltherapie (Iscador) - Ergebnisse einer epidemiologischen Langzeitstudie. *Schweiz Z Ganzheitsmed* 2001;13:217–25.
59. Grossarth-Maticek R, Kiene H, Baumgartner S, Ziegler R. Synergieeffekte von Selbstregulation und Misteltherapie (Iscador) auf die Überlebenszeit bei Krebspatienten - Ergebnisse einer epidemiologischen Langzeitstudie, Teil II. *Schweiz Z Ganzheitsmed* 2004;16:81–9.
60. Auerbach L, Dostal V, Václavík-Fleck I, Kubista E, Rosenberger A, Rieger S, et al. Signifikant höherer Anteil aktivierter NK-Zellen durch additive Misteltherapie bei chemotherapierten Mamma-Ca-Patientinnen in einer prospektiv-randomisierten doppelblinden Studie. In: Scheer R, Bauer R, Becker H, Fintelmann V, Kemper FH, Schilcher H (eds). *Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung*. Essen: KVC, 2005, 543–54.
61. Nygren P, Glimelius B. The Swedish council on technology assessment in health care (SBU) report on cancer chemotherapy - project objectives, the working process, key definitions and general aspects of cancer trial methodology and interpretation. *Acta Oncol* 2001;40:155–65.
62. Deeks JJ, Dinnes J, D'Amico R, Sowden A, Sakarovich C, Song F, et al. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7:1–173.
63. Reeves BC. Reasons for caution when evaluating health care interventions using non-randomised study designs. *Forsch Komplementarmed* 2004;11 (Suppl 1): 40–5.
64. Kovacs E. Serum levels of IL-12 and the production of IFN- γ , IL-2 and IL-4 by peripheral blood mononuclear

- cells (PBMC) in cancer patients treated with *Viscum album* extract. *Biomed Pharmacother* 2000;54:305–10.
65. Kovacs E. *Viscum album* und Interleukin-6 - Was ist daran? In: Scheer R, Bauer R, Becker H, Berg PA, Fintelmann V (eds). *Die Mistel in der Tumortherapie Grundlagenforschung und Klinik*. Essen: KVC Verlag, 2001, 315–25.
 66. Kovacs E, Kuehn JJ. Measurements of IL-6, soluble IL-6 receptor and soluble gp130 in sera of B-cell lymphoma patients. Does VISCUM ALBUM treatment affect these parameters? *Biomed Pharmacother* 2002;56:152–58.
 67. Kovacs E. Effects of *Viscum album* extract therapy in patients with cancer: relation with interleukin-6, soluble interleukin-6 receptor, and soluble gp130. *J Altern Complement Med* 2004;10:241–46.
 68. Pampallona S, Von Rohr E, Van Wegberg B, Bernhard J, Helwig S, Heusser P, et al. Socio-demographic and medical characteristics of advanced cancer patients using conventional or complementary medicine. *Onkologie* 2002;25:165–170.
 69. Toelg M, Reiss B, Antonu H. Chemotherapie mit begleitender Misteltherapie - Prospektive, nicht randomisierte, kontrollierte, offene Studie (AWB) zur Lebensqualität. *CO'MED* 2005;11:18–22.
 70. Toelg M, Antonu H, Reiss B, Ramos MH. Lebensqualität von Tumorpatientinnen unter begleitender Misteltherapie - Ergebnisse einer prospektiven, nicht randomisierten, kontrollierten, offenen Studie (AWB) mit Iscador M. *Schweiz Z Ganzheitsmed* 2005;17:294–99.
 71. Büssing A, Bischof M, Hatzmann W, Bartzsch F, Soto-Vera D, Fronk E-M, et al. Beeinflussung der Granulozytenfunktion durch einmalige perioperative Mistelextrakt-Infusion. *Dtsch Z Onkol* 2004;36:148–53.
 72. Büssing A, Bischof M, Hatzmann W, Bartzsch F, Soto Vera D, Fronk E-M, et al. Beeinflussung der Granulozytenfunktion durch eine perioperative Infusion eines fermentierten Mistelextraktes. In: Scheer R, Bauer R, Becker H, Fintelmann V, Kemper FH, Schilcher H (eds). *Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung*. Essen: KVC Verlag, 2005, 555–66.
 73. Büssing A, Bischof M, Hatzmann W, Bartsch F, Soto Vera D, Fronk E-M, et al. Prevention of surgery-induced suppression of granulocyte function by intravenous application of a fermented extract from *Viscum album* L. in breast cancer patients. *Anticancer Res* 2005;25:4753–58.
 74. Büssing A. Immune modulation using mistletoe (*Viscum album* L.) extracts Iscador. *Arzneim/Drug Res* 2006;56:508–15.
 75. Carlsson M, Arman M, Backman M, Hamrin E. Perceived quality of life and coping for Swedish women with breast cancer who choose complementary medicine. *Cancer Nurs* 2001;24:395–401.
 76. Carlsson M, Arman M, Backman M, Flatters U, Hatschek T, Hamrin E. Evaluation of quality of life/life satisfaction in women with breast cancer in complementary and conventional care. *Acta Oncol* 2004;43:27–34.
 77. Carlsson M, Arman M, Backman M, Hamrin E. Coping in women with breast cancer in complementary and conventional care over 5 years measured by the mental adjustment to cancer scale. *J Altern Complement Med* 2005;11:441–47.
 78. Carlsson M, Arman M, Backman M, Flatters U, Hatschek T, Hamrin E. A five-year follow-up of quality of life in women with breast cancer in anthroposophic and conventional care. *Evid Based Complement Alternat Med* 2006;3:523–31.
 79. Klopp R, Schmidt W, Werner E, Werner M, Niemer W, Beuth J. Influence of complementary *Viscum album* (Iscador) administration on microcirculation and immune system of ear, nose and throat carcinoma patients treated with radiation and chemotherapy. *Anticancer Res* 2005;25:601–10.
 80. Ziegler R. Elements of the therapeutic research structure. *Forsch Komplementarmed* 2004;11 (Suppl 1): 5–12.
 81. Ziegler R. Möglichkeiten und Grenzen klinischer Studien mit Iscador. *Mistilteinn* 2004;5:44–73.
 82. Reeves BC, Gaus W. Guidelines for reporting non-randomised studies. *Forsch Komplementarmed* 2004;11 (Suppl 1): 46–52.
 83. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985;312:1604–08.
 84. Ziegler R. Neue Studien zum Mammakarzinom und zum malignen Melanom mit dem Mistelpräparat Iscador. In: Streit E, Rist L (eds). *Ethik und Wissenschaft in der anthroposophischen Medizin*. Bern: Peter Lang, 2006, 95–114.
 85. Bock PR, Friedel WE, Hanisch J, Karasmann M, Schneider B. Retrospective, comparative, epidemiological cohort study with parallel groups design for evaluation of efficacy and safety of drugs with “well established use” - experience with the long-term treatment using the European mistletoe extract (*Viscum album* L.) in addition to conventional oncologic therapy in primary, non-metastatic breast carcinoma. *Forsch Komplementarmed* 2004;11 (Suppl 1): 23–29.
 86. Schneider B. Beobachtungsstudien zum Nachweis der Wirksamkeit von Arzneimitteln. *Dtsch Z integrative Onkol* 2004;2:22–7.
 87. Hellan J, Danmayr E, Hellan M. Stellenwert der Komplementärmedizin in der Behandlung onkologischer Patienten - dargestellt anhand des kolo-rektalen Karzinoms. *Dtsch Z Onkol* 1995;27:85–94.
 88. Schaefermeyer G, Schaefermeyer H. Treatment of pancreatic cancer with *Viscum album* (Iscador): a retrospective study of 292 patients 1986–1996. *Complement Ther Med* 1998;6:172–77.
 89. Stumpf C, Rieger S, Schietzel M. Retrospektive Untersuchung zur Therapie mit Mistelextrakten bei Mammakarzinom. *Dtsch Z Onkol* 2005;37:106–13.
 90. Ziegler R. Neuere klinische Studien mit Iscador zum Mammakarzinom und malignen Melanom. *Mistilteinn* 2004;5:74–99.
 91. Schumacher M, Davis CE. Combining randomized and nonrandomized patients in the statistical analysis of clinical trials. *Recent Results Cancer Res* 1988;111:130–37.
 92. Schmoor C, Olschewski M, Schuhmacher M. Randomized and non-randomized patients in clinical trials: experiences with comprehensive cohort studies. *Stat Med* 1996;15:263–71.
 93. Olschewski M, Schumacher M, Davis K. Analysis of randomized and non-randomized patients in clinical trials using the comprehensive cohort follow-up study design. *Control Clin Trials* 1992;13:226–39.
 94. Chow SC, Liu JP. *Design and Analysis of Clinical Trials: Concepts and Methodologies*. New York: John Wiley & Sons, 1998.
 95. Piantadosi S. *Clinical Trials: A Methodologic Perspective*. New York: John Wiley & Sons, 1997.
 96. Schumacher M, Schulgen G. *Methodik klinischer Studien*. Berlin-Heidelberg: Springer, 2002.
 97. Wahner-Roedler DL, Vincent A, Elkin PL, Loehrer LL, Cha SS, Bauer BA. Physicians' attitudes toward complementary and alternative medicine and their knowledge of specific therapies: a survey at an academic medical center. *Evid Based Complement Alternat Med* 2006;3:495–501.
 98. Von Rohr E, Pampallona S, Van Wegberg B, Cerny T, Hürny C, Bernhard J, et al. Attitudes and beliefs towards disease and treatment in patients with advanced cancer using anthroposophical medicine. *Onkologie* 2000;23:558–63.
 99. Walach H, Falkenberg T, Fønnebo V, Lewith G, Jonas WB. Circular instead of hierarchical: methodological principles for the evaluation of complex interventions. *BMC Med Res Methodol* 2006;6 (Suppl 29): 1–9.
 100. Heusser P. Kriterien zur Beurteilung des Nutzens von komplementärmedizinischen Methoden. *Forsch Komplementarmed* 2001;8:14–23.
 101. Rosenbaum PR. *Observational Studies*, 2nd edn. New York: Springer, 2002.
 102. Hulley SB, Cummings SR, Browner WS, Grady D, Hearst N, Newman TB. *Designing Clinical Research*. Philadelphia: Lippincott Williams & Wilkins, 2001.
 103. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000;342:1878–86.
 104. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000;342:1887–92.
 105. MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AM. A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies. *Health Technol Assess* 2000;4:1–145.

106. Reeves BC, MacLehose RR, Harvey IM, Sheldon TA, Russell IT, Black AM. Comparison of effect sizes derived from randomised and non-randomised studies. In: Black N, Brazier J, Fitzpatrick R, Reeves BC (eds). *Health Services Research Methods: A Guide to Best Practice*. London: BMJ Books, 1998, 73–85.
107. Shadish WR, Cook TD, Campbell DT. *Experimental and Quasi-Experimental Designs for Generalized Causal Inference*. Boston: Houghton Mifflin, 2002.
108. Heusser P, Berger Braun S, Ziegler R, Bertschy M, Helwig S, Van Wegberg B, Cerny T. Palliative in-patient cancer treatment in an anthroposophic hospital: I. Treatment patterns and compliance with anthroposophic medicine. *Forsch Komplementarmed* 2006;13:94–100.
109. Heusser P, Berger Braun S, Bertschy M, Burkhard R, Ziegler R, Helwig S, et al. Palliative in-patient cancer treatment in an anthroposophic hospital: II. Quality of life during and after stationary treatment, and subjective treatment benefits. *Forsch Komplementarmed* 2006;13:156–66.
110. Hajto T, Hostanska K, Berki T, Palinkas L, Boldizsar F, Nemeth P. Oncopharmacological perspectives of a plant lectin (*Viscum album* Agglutinin-I): overview of recent results from in vitro experiments and in vivo animal models, and their possible relevance for clinical applications. *Evid Based Complement Alternat Med* 2005;2:59–67.
111. Klopp R. Immunmodulation mit Iscador. *Schweiz Z GanzheitsMed* 2001;13:290–91.
112. Wispler MJ, Kappler M, Soto Vera D, Reif M, Schnelle M, Zänker KS. Prospektive, randomisierte, kontrollierte Studie zur Aktivierung des Homings und des allgemeinen Aktivitätsniveaus von T-Lymphozyten durch subkutane Mistelextrakt-Injektionen bei gesunden männlichen Probanden. In: Scheer R, Bauer R, Becker H, Fintelmann V, Kemper FH, Schilcher H (eds). *Fortschritte in der Misteltherapie: Aktueller Stand der Forschung und klinische Anwendung*. Essen: KVC Verlag, 2005, 513–25.
113. Huber R, Klein R, Berg PA, Lütke R, Werner M. Effects of a lectin and viscotoxin rich mistletoe preparation on clinical and hematological parameters: a placebo controlled evaluation in healthy subjects. *J Altern Complement Med* 2002;8:857–66.
114. Klein R, Classen K, Berg PA, Lütke R, Werner M, Huber R. In vivo- induction of antibodies to mistletoe lectin-I and viscotoxin by exposure to aqueous mistletoe extracts: a randomised double- blinded placebo controlled phase I study in healthy individuals. *Eur J Med Res* 2002;7:1–9.
115. Huber R, Classen K, Werner M, Klein R. In-vitro-Immunreaktion gegen Lektin-reiche und Viscotoxin-reiche Mistel (*Viscum album* L.)-Extrakte Iscador nach Verabreichung an gesunde Probanden - Eine randomisierte doppelblinde Plazebo-kontrollierte Studie. *Arzneim/Drug Res* 2006;56:447–56.
116. Huber R, Rostock M, Goedl R, Lütke R, Urech K, Buck S, et al. Mistletoe treatment induces GM-CSF- and IL-5 production by PBMC and increases blood granulocyte- and eosinophil counts: a placebo-controlled randomized study in healthy subjects. *Eur J Med Res* 2005;10:411–18.
117. Huber R, Rostock M, Goedl R, Lütke R, Urech K, Klein R. Immunologic effects of mistletoe lectins: a placebo-controlled study in healthy subjects. *J Soc Integr Oncol* 2006;4:3–7.

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