CORRESPONDENCE

Quality of Life of Patients With Advanced Pancreatic Cancer During Treatment With Mistletoe: A Randomized Controlled Trial

by Dr. rer. nat. Wilfried Tröger, Prof. Dr. med. Danijel Galun, Dr. rer. nat. Marcus Reif, Dipl.-Math. Agnes Schumann, Dr. med. Nikola Stanković, Prof. Dr. med. Miroslav Milićević in issue 29–30/2014

Many Questions Left Open

In a single-center study conducted in Serbia, 220 patients with advanced pancreatic cancer were randomized into two arms: best supportive care (BSC) and mistletoe treatment. A significant survival improvement from 2.7 months to 4.8 months was found and published elsewhere. Now quality-of-life data are presented (1). Here again, mistletoe appears to be superior to BSC. The following questions arise:

- Why was no placebo-control performed? Other mistletoe studies show that even a double-blind design with placebo control is possible (2).
- The method of randomization raises the question whether a violation of allocation concealment may have occurred.
- Is an intent-to-treat analysis available?
- Only in 43 of the 220 patients, histological confirmation was performed. What steps were taken to ensure that no patients with benign or other histologies were included?
- Prior treatments and aftercare were not reported separately.
- *Table 4* shows that patients treated with mistletoe had more frequent physician contacts. Thus these patients may have received better palliative care which can extend the lives of patients (3).
- What was the composition of the tumor board?
- Which imaging data are available for each of the two cohorts?
- How was determined that palliative chemotherapy, which can extend survival and quality of life of patients, could not be given?
- The QoL analysis is based on the so-called missing-at-random assumption. Whether patients attend physician appointments is likely to depend on their symptoms (quality of life) at those times. This cast fundamental doubt on the reliability of the QoL analysis.
- Of concern: "The decision of the CCS consultation service was considered final".

Various studies found quality of life improvements along with mistletoe treatment, for example (2). The molecular causes are manifold and include increased endorphin levels which perhaps could also be achieved with other treatments (4).

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Prof. Neubauer is Head of the Committee on Cancer Therapy of the German Cancer Aid.

Positive Scientific Approach

In my primary care practice, mistletoe treatment has been used as a second-line therapy in the management of various cancers for almost 30 years; prior to that for 30 years in my father's practice. In recent years, I have administered mistletoe in some cases in consultation with the treating oncologist in parallel to chemotherapies. The impact on the quality of life was at times astonishing compared with patients without mistletoe treatment; especially the use of analgesics in relation to the respective tumor stage was significantly lower—an observation frequently confirmed by skeptical hospital colleagues when these patients stayed on their wards.

I have provided this therapy over many years on a purely pragmatic basis, without scientific support, according to the manufacturer's (Weleda) recommendations using various Iscador mixtures, more recently also Cefalektin. Since I never felt comfortable with the anthroposophical explanation of the mechanism of action, I am very pleased to see that mistletoe treatment did so well in this study based on scientific criteria (1), even though apparently the mechanism of action still remains unclear.

In this context, I would like to mention a very interesting article: "Bacteria against Tumors [Bakterien gegen Tumoren]" published in *Spektrum der Wissenschaft* July 2014, pp. 30 ff, describing the "discovery" of mistletoe lectin as a so-called PRR ligand.

Conclusion: Empirically well-established treatments should not be refused a priori, just because sometimes the explanations for their effects are abstruse. Continued

research is necessary until eventually scientifically acceptable proof of their efficacy can be established.

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Mistletoe Treatment as Homeopathic Magic

Since time immemorial, the mistletoe branch has been held in superstitious veneration across Europe. Plinius mentioned that the druids considered nothing else to be as holy as the mistletoe and the tree on which it grows, provided it is an oak tree. The druids called the mistletoe the cure-all. In today's Celtic language of the Bretagne, Wales, Ireland, and Scotland, the expression cure-all still is synonym with mistletoe (1).

However, the opinion the medical community holds on the mistletoe's healing properties has changed dramatically. While druids believed that the mistletoe is capable of curing all illness, the physicians of more recent times are of the opinion that it cures no illness at all (2). The most valuable property of the mistletoe could be that it provides satisfactory protection against witchcraft. Rudolf Steiner (1861–1925) was the founder of the Anthroposophical Society, some mix of religion and philosophy which influenced anthroposophical hospitals, Waldorf kindergartens and schools, curative education facilities, and also bio-dynamic agriculture (Demeter). The anthroposophically extended medicine does not provide any dogmas dictating what an anthroposophical physician should and should not do. For a start, an anthroposophical physician is a physician with the same standard training in conventional medicine as any other doctor. The anthroposophical extension states that a human being is a unity comprising body, soul and spirit (3). However, although it has been used for several decades, there is still no proof that the treatment of cancer patients with mistletoe can prolong lives or reduces the tendency to develop metastatic disease. Because of the risk that the stimulation of the immune defense could also stimulate tumor growth, and because of potential adverse reactions (to the extent of life-threatening shock), both the American Cancer Society and the Swiss Society for Oncology (SGO) are opposed to mistletoe injections.

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Several Flaws

The study published here as an original article has already been published with a focus on survival data in the European Journal of Cancer in 2013 (1).

Both articles have several flaws. These include unclear inclusion criteria (histological confirmation of pancreatic cancer not required), inclusion of patients who refused chemotherapy and undefined best supportive care. In the first original publication it is stated that this therapy was adapted to the individual requirements in the medical center. Patients in the mistletoe treatment group were given the opportunity to choose to receive the mistletoe injections in the local health center and with this have contact with nurses and/or physicians significantly more often. Thus it cannot be ruled out—or rather it should be hoped—that the patients treated with mistletoe injections received a more intensive supportive therapy.

In the first publication it was stated that the patients in the mistletoe group experienced weight gain. So far, I am not aware of any other study results in the entire literature about mistletoe that are in line with this finding. Therefore it seems reasonable to assume that the better supportive therapy has led to a better nutritional status and consequently to a better overall survival. Thus, the conclusion from this study would be: A good supportive and palliative treatment offers a significant survival advantage to patients with pancreatic cancer.

The assumption that factors other than primary causal effect functions of the mistletoe play a role is also supported by the broad improvement of quality of life parameters, including financial problems. I am not aware of any mechanism of action by which mistletoe treatment could resolve financial hardships. However, good psychosocial support at the health center may help to improve a patient's financial situation.

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New Drug for the Treatment of Inoperable Pancreatic Cancer?

In Germany, pancreatic cancer is the malignancy with the lowest survival rates. Even though anti-tumor therapy with cytostatic and targeted agents helps to alleviate symptoms and improves the median time of survival to 7–11 months, there is still a significant unmet need for new and effective drugs (1).

Deutsches Ärzteblatt published the results of a quality-of-life analysis from a randomized clinical study investigating the use of a mistletoe product (Viscum album [L.]) in patients with inoperable pancreatic carcinoma. This single-center study was conducted in Belgrade (Serbia). In the mistletoe arm, median survival was significantly longer compared with the control arm (4.8 months versus 2.7 months) (2).

Unfortunately, this study had several methodological shortcomings. Of these, the most significant are as follows:

- Only 43 of the 220 patients had the diagnosis pancreatic carcinoma confirmed by histology. In 25 patients, the diagnosis was solely based on imaging findings.
- The study had no placebo control. Lack of blinding at randomization has a particularly strong influence in studies with subjective endpoints such as quality of life (3).
- The study conditions are not transferable to the setting in Germany. The patients in the control arm received no anti-tumor therapy. No interdisciplinary tumor board was involved.
- The study arms show significant imbalances with regard to the number of analyzable patients.

Apart from methodological aspects, the publication in the DÄ has a health political dimension. For some years now, scientific societies and the German Cancer Aid, among others, have undertaken significant efforts to integrate complementary and alternative treatment modalities into cancer patients' care (3). The publication of biased studies which are not transferable to the setting of care in Germany, sends out a signal in the wrong direction.

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Unsustainable Claims

Tröger and co-authors assume to have presented evidence proving that mistletoe treatment in patients with locally advanced or metastatic pancreatic carcinoma significantly improves quality of life compared with best supportive care (BSC). In the original publication (1) the authors claim that survival was significantly extended by this therapy. To publish the primary endpoint, survival, and the secondary endpoint, quality of life, separately (2), follows in the tradition of unnecessary multiple publications. Both statements are unsustainable because of the study's serious methodological shortcomings.

Without blinding, it is not possible to make a valid statement with regard to quality of life and the chosen method of randomization using sealed envelopes does not meet the requirements of good study practice.

The study was terminated early after enrolment of approximately half of the intended number of patients. The authors do not mention that early termination may lead to significant overestimation of treatment effects, especially in small studies (3). The therapy standard at the time of the study was not adequately reported. Best supportive care is here a commonly used "euphemism" for doing without sensible disease-modifying therapies.

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More Questions Left Open Than Answered

The authors conducted the mistletoe trial in Belgrade (Serbia), because Serbian physicians and patients have a "complete lack of any expectation of success from mistletoe treatment", since in Serbia "mistletoe extracts are unknown and unavailable". Besides that it is unlikely that academic oncologists are not aware of the international literature, including complementary and alternative methods, the sponsors from Freiburg were obliged to inform the Serbian physicians involved in the trial about the mistletoe discussion.

To declare a single-center study with 220 patients—of whom only 168 were analyzable— as a phase III study disregards all requirements of the GCP/ICH guidelines for valid studies. In addition, early termination of a study may result in an overestimation of a drug's efficacy.

Patients were randomized to receive either mistletoe treatment or no mistletoe treatment. The authors deliberately decided to do without blinding, because local skin reactions and mild increases in temperature are considered to be signs of optimum dosing.

Since the authors chose, in line with the anthroposophical approach, the product Iscador® Qu (where Qu stands for Quercus, i.e. oak mistletoe extract), it would have been appropriate to choose a blinded design and use a less effective or ineffective mistletoe product derived from apple, pine or elm trees to substantiate the preferences for oak mistletoes.

Conclusion: Once again a mistletoe study that leaves more questions open than it answers. However, the manufacturer of Iscador® Qu, Weleda AG (Arlesheim, Switzerland), has reason to be content for in the near future Serbia will become a new market for their products. Since by then, Serbian physicians and patients will have developed certain expectations towards mistletoe treatment, the necessary multi-center blinded treatment trial can no longer be expected to be conducted in this country.

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The author declares that no conflict of interest exists.

In Reply:

We appreciate the opportunity to reply to the points criticized. In the following, we will address each point individually and name the authors of the matching correspondence items in brackets.

1. Blinding, double publication (Hübner, Neubauer, Meyer, Schmacke, Wörmann): 1. Overall Survival (OS) was the primary endpoint (1). For this, FDA guidelines do not require blinding (2) since no placebo effect is expected and an observer bias with regard to the time of death is not possible. The quality-of-life results published in *Deutsches Ärzteblatt* are consistent with the OS treatment effects (1). In the context of OS studies, it is common to provide secondary publications of quality-of-life data collected under non-blinded conditions (3, 4).

2. Phase III declaration, single-center design, concealment of randomization (Meyer, Neubauer, Schmacke): Phase III characteristics are to plan the number of cases and to conduct a confirmatory analysis according to the guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; multi-center design is not a requirement in the good clinical practice (GCP) guidelines. Selection/performance bias is unlikely: The patients who participated in the study came from all oncology centers in Serbia and received no study-specific intervention after admission to the treatment. The randomization procedure is in line with CONSORT ("Enclosing assignments in sequentially numbered, opaque, sealed envelopes can be a good allocation concealment mechanism") (5).

3. Termination of the study/overestimation of the treatment effect (Schmacke, Meyer): Since confirmatory significance levels for the OS superiority of the mistletoe group (α-level = 0.0042) were achieved, the group-sequential interim analysis allowed a protocol-compliant termination by the IDMC (Prof. Volker Diehl, Dr. Patrick Mansky, Prof. Ulrich Mansmann). An overestimation of the treatment effect is unlikely as the observed survival advantage is in line with those found in earlier studies (6).

4. No biopsy (Hübner, Neubauer, Wörmann): The current recommendations of the *International Study Group of Pancreatic Surgery* only require a biopsy proof of the diagnosis in cases in which the result is

relevant to the management of the patient (7). Many patients in this study had unambiguous intraoperative or repeatedly progressive CT scan findings; consequently, a biopsy was often not required.

5. Statistical analysis, imbalances, distortions (Meyer, Neubauer, Wörmann): The current CONSORT statement 2010 differentiates the term "ITT": "We replaced mention of "intention to treat" analysis, a widely misused term, by a more explicit request for information about retaining participants in their original assigned groups." (8) Accordingly, the patient sub-groups with and without quality of live follow-up regarding QoL were compared (*Tables 1* and *2* of the DÄ publication). In addition, the relevant literature on the measurement of quality of life in dying patient populations (9–11) was taken into consideration, as after 3 months already half and at the final visit already 86% of patients had died: Sensitivity analyses with "worst/ last values" stratified by time of death were presented in the *e-Supplement*. According to Alshurafa (12), this is a valid analysis. A "last observation carried forward" (LOCF) analysis does not reveal any qualitative differences compared with the published group differences (mean, [95% confidence interval]): "Global quality of health" 24 (20 to 27); "physical function" 18 [13 to 22]; "role function" 14 [9 to 19]; "emotional function" 16 [11 to 21]; "cognitive function" 14 [8 to 20]; "fatigue" –26 [–31 to –21]; "nausea/vomiting" –11 [–16 to –7]; "pain" –20 [–25 to –14]; "insomnia" –31 [–39 to –24]; "appetite loss" –37 [–43 to –30]; body weight 6% [5 to 7] (all $p < 0.0001$ after Bonferroni correction). "Social function" 8 [3 to 14]; $p = 0.01$ showed in the original analyses a minor difference too and "dyspnoea" is not relevant to this disease. This LOCF analysis avoids imbalances; however, it distorts differences between means in a conservative direction and thus underestimates the true effect of the treatment.

6. Treatment standard, prior treatments/aftercare, best supportive care (BSC), (Hübner, Neubauer, Schmacke): The study arms are equivalent at baseline with regard to all studied sociodemographic and efficacy parameters; therefore, doubts relating to the successful randomization and consequently to the equal distribution of prior treatments are unfounded. Since the study was conducted as a centralized trial in Belgrade, it was possible to standardize the BSC options and offer them to all study patients.

7. Best palliative care (Hübner, Neubauer): Relative to survival time, the control patients, not the mistletoe patients, had more frequent contacts with the investigators. Patients with mistletoe treatment typically received only the initial mistletoe extract injections when they were admitted to the study center or the local health center; subsequently, the patients themselves or their relatives injected the mistletoe extract according to the instructions in the study protocol and documented each injection in the patient diaries.

8. Other mistletoe product for comparison (Meyer): The intention of this study was the *proof of concept* for mistletoe treatment versus BSC treatment alone.

*9. Composition of (no interdisciplinary tumor conference) und decisions (no palliative chemotherapy, no revision) of the tumor board (Neubauer, Wörmann): Pe*rmanent members of the CCS's tumor conference are pathologists, medical and gastrointestinal oncologists, radiologists, radiation therapists, and HBP surgeons; this composition fulfills the requirements for German oncology centers; its decision criteria were described in the DÄ publication.

10. Weight gain, financial situation (Hübner): Body weight stabilization or increase are frequently observed effects of mistletoe treatment and have been noted for several decades. In this trial, they were documented for the first time under standardized conditions. The mistletoe patients may have been more positive about their financial situation as the result of the reduced need for concomitant treatments.

11. Mistletoe treatment not known in Serbia (Meyer): Prior to the study, the investigators were informed about the mistletoe treatment; this did not change their neutral attitude towards mistletoe treatment.

12. Transferability to the German setting (Wörmann): In Germany, the proportion of patients who received no treatment other than BSC for various reasons is comparable in size (13). Therapies such as FOLFIRINOX are for patients in Germany just as little an option as for patients in Serbia.

13. Conflict of interest (Schmacke): It was made transparent that this study was financed by an interested party. With regard to the authors' conflict of interest, please refer to the following statement.

In our opinion, the criticism expressed in the correspondence items cannot diminish the validity of the results of this study (14).

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This trial was financially supported by the Swiss Cancer Research Association (Verein für Krebsforschung e. V. (VfK), Schweiz). The VfK receives license fees for the preparation of the active substance for the commercially available mistletoe drug Iscador from Weleda AG, the company that obtained approval for the drug. Weleda AG produced the trial drug as a separate lot and invoiced it to the VfK e.V. Wilfried Tröger, Marcus Reif, and Agnes Schumann are also involved in the conduct of other studies for the VfK.