Author's response to reviews

Title: Survival of cancer patients treated with mistletoe extract (Iscador): a systematic literature review

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Author's response to reviews:

Dear Sir.

Thanks a lot for the critical (and encouraging) comments of the reviewers which were helpful to improve the manuscript. Here are the comments to the reviewers and changes within the manuscript in detail:

Thanks a lot for Udo Schumacher´s comments which are appreciated. It is difficult to ignore the papers of R. Grossarth-Maticek, because this would be a selection bias too. At least we have already analysed the impact of these papers (see page 12): “…and matched-pair studies gave significantly better results than others (ratio of HRs: 0.33; CI: 0.17 to 0.65, p=0.0012)“. These studies were exclusively his studies – be we avoided to blame him with speculations about the validity of the data. Moreover, we added on page 11: “The extent to which study-level variables were associated with log HRs was investigated by fitting multivariable meta-regression models. The following variables were considered: standard error of log HR, tumor localization (breast, stomach, lung, colon, ovary, corpus, skin yes/no), randomization (yes/no), matched-pair comparison (yes/no) - due to the fact that all matched-pair studies were from the same source.” = papers of Grossarth-Maticek, a fact which can easily be noticed by the readership. But we stated this fact very clearly at page 18: “In particular the pooled effect estimates are mainly driven by the study type (i.e., matched-pair design).”

To make it clear: The Hiscia provided financial support of our chair to run the review, and we had to pay the statistician, get the original manuscripts, analysed the data etc. – But as an univnesity we were completely free to interpret the data – and to write the manuscript – according to a strict scientific rationale. Moreover, the Hiscia is primarily a research organisation, albeit they earn their money with the Iscador product. – We would like to ask the editor for an advise!

According to Grossarth-Maticek´s comments we have specified the databases which were used (see yellow highlights in materials and Methods). We have stated:
“We searched several databases such as PubMed/Medline, the Excerpta Medica Database (EMBASE), the Cochrane Library, database of DIMDI (Deutsches Institut für Medizinische Dokumentation und Information) and CAMbase for clinical studies focusing on survival of cancer patients using Iscador extracts. Separate search terms were “Iscador” and “study”, “mistletoe” and “study”, and “Viscum” and “study”. Finally we asked several experts for gray literature not listed in the above mentioned databases, checked the reference lists of relevant articles and authors, and contacted the manufacturer of mistletoe preparation. The complete search was performed between February and April 2008.

Moreover, we have described more precisely the methodological quality checklist used for the analysis (pages 7-8):

“Two review authors independently assessed trials for inclusion in the review. They took part in the extraction of data and assessment of study quality and clinical relevance. Disagreements were resolved by consensus. We graded the methodological quality of the studies by the following checklist (rater assessment): Adequate description of the study design (retrospective, prospective, retrolective, multicenter study etc.), subject assembly process (randomization, matched pairs, etc.), comparability of groups, description of drop outs, allocation concealment (analysis of concealed treatment allocation was difficult because most studies did not provide sufficient data to judge – either there were no statements or information are at least unclear), description of the intervention (dosage and duration of VA-E application), description of statistical analysis, external validity (representative patients, relevant therapeutic concepts, generalization of results). However, we did not explicitly refer to rating scores such as the JADAD, because blinding of VA-E application is difficult and, due to ethical reasons, rejected by several medical doctors. Thus, 2 out of 5 criteria of the JADAD score were not applicable for these studies; nevertheless, randomization as a criterion was assessed, also dropouts. (…)

The reviewers asked for methodological quality of the studies. As can be seen in the primary Table and the description, none of the studies was blinded, just some randomised etc. We added some additional information on the studies enrolled for statistical analysis (Table 2), i.e., blinding, multi-center recruitment, description of drop-outs. Thus the reader may draw his own conclusion that the quality of the studies is limited. With respect to the results, we have added: “The studies included in this meta-analysis were of moderate or even poor quality, as indicated by randomization, matched pair building, blinding, multicenter, description of dropouts etc. (Table 1).

The reviewer asked what actively controlled trials were. These “active controls” were analysed separately from “passive” placebo trials, and involve interferon alpha2b or interferon gamma, Bacillus Calmette-Guérin (BCG), Vitamin B complex, or radiation. This information was added (page 9/10).

Grossarth-Maticek recommended to inform the reader about the Moose guidelines. This information was added (see page 8).
The reviewer asked to specify the term “outcomes”. We have added (page 9): *Outcome(s): Survival (median survival, overall survival, 3-, 5- or 10-year survival etc.)*

Grossarth-Maticek recommended to discuss our findings compared to other actual systematic reviews on mistletoe. However, this discussion can already be found on pages 14-17. If one reads the already mentioned statements of the other researchers, one has to conclude that our findings are in line with the other findings – but we calculated hazard ratios, and were able to indicate a publication bias.

Reviewer 3 correctly indicated that our abstract was somewhat confusing with respect to the hazard ratios. We have stated in the methods of the abstract: “Outcome data were extracted as they were given in the publication, and expressed as hazard ratios (HR), their logarithm, and the respective standard errors using standard formulas.”

The reviewer argued that the selection process was confusing and recommended a flow of included studies. This is indeed a good idea! We thus added a figure depicting the study selection process (new figure 1) and specified (page 11): “As depicted in Figure 1, eight studies citing the same results twice in different papers were excluded, four studies were excluded because of the usage of two different mistletoe extracts (Helixor and/or Iscador) which were not shown separately. Five studies used alternative or placebo controls (these data were presented independently), and 35 studies investigated effects of Isacdor versus no extra treatment (with 41 extracted strata).

The plots in figure 2 represent individual results of the 41 strata. This was added in the respective figure legend.

In hope that our comments to the reviewers were appropriate and that the manuscript has improved in quality, we would like to re-submit the revised version for publication. If there any open questions, do not hesitate to contact me.

With best wishes (in behalf)

Yours

Prof. Dr. Arndt Büßing