Journal of Cancer Research and Clinical Oncology (2019) 145:2405–2407
https://doi.org/10.1007/s00432-019-02926-y

LETTER TO THE EDITOR

Letter to the editors of the *Journal of Cancer Research and Clinical Oncology*

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Received: 20 March 2019 / Accepted: 22 April 2019 / Published online: 21 May 2019

Dear Editor,

Cancer patients frequently use extracts from European mistletoe (*Viscum album* L.) as a complementary treatment (Zänker and Kaveri 2015). Freuding et al. aimed at reviewing the effects of mistletoe extracts in cancer therapy on overall survival and safety and giving an overview about current research (Freuding et al. 2019). Risk of bias was declared to have been assessed by means of the Cochrane Risk of Bias Tool (Higgins et al. 2017). The authors conclude that "*most studies did not show any effect of mistletoe on survival*", and that "*with respect to survival, a thorough review of the literature does not provide any indication to prescribe mistletoe to patients with cancer.*" We argue in the following that both these statements of Freuding et al. are not supported by their own analysis.

In their analysis, 14 out of the 26 reviewed publications reported on survival time. Mistletoe extracts numerically prolonged survival in 11 of these 14 studies (79%), with five studies (36%) demonstrating statistically significant prolongation of survival.

Freuding et al. did not perform a meta-analysis in their review. The Cochrane Handbook for Systematic Reviews of Interventions states that *"Potential advantages of meta-analyses include an increase in power, an improvement in precision, the ability to answer questions not posed by individual studies, and the opportunity to settle controversies arising from conflicting claims"* (Deeks et al. 2017). Given the fact that 5 out of 14 studies yielded significant survival benefits and further 6 out of the 14 studies showed a favorable trend, a meta-analysis seems indicated to increase power to detect any real differences in survival. The meta-analysis conducted by Ostermann et al. in 2009 on the effects of fermented mistletoe extracts correspondingly came to the conclusion *"A random effect meta-analysis estimated the overall hazard ratio at HR = 0.59 (CI 0.53 to 0.66, p < 0.0001)"*. As a scientific community we should be committed to avoiding communication of false-positive as well as false-negative results. Therefore, the statement that "*most studies did not show any effect of mistletoe on survival*" seems not justified to us, in view of the available data.

Furthermore, risk of bias assessment is largely faulty and was only insufficiently conducted according to the declared methods (Cochrane Risk of Bias Tool (Higgins et al. 2017)). In the following, we refer mainly to Table 3 of the publication and the corresponding parts of the text.

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Regarding selection bias ("random sequence generation (RSQ)" and "allocation concealment (AC)" in columns 2 and 3 of Table 3), a 'high risk of bias' was attributed to all studies of Grossarth-Maticek et al. However, in all these studies the procedure of randomization has been described by *"The principal investigator put two slips of paper (each with the name of one of the patients in the pair) in a hat, and a masked assistant selected one."* This method is explicitly listed also in the Cochrane handbook in Table 8.5.d (*"coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, …")* as one criterion for an assessment of low risk of RSQ bias. Equivalently, AC can also be assigned only as low risk of bias because each single randomization was part of the enlisting process of a new patient and could therefore not be known beforehand. Thus, following the Cochrane Risk of Bias Tool, the publications of Grossarth-Maticek et al. show a low risk of selection bias. Table 3 should be corrected accordingly.

In terms of attrition bias, Freuding et al. attribute a high risk to a study on pancreatic cancer (Tröger et al. 2013) in Table 4, despite the fact that all patients were included in the analysis of OS. There were only few events of early study termination (2 and 5 of a total of 220 randomized patients in the mistletoe and control group, respectively). Withdrawn patients were included in the analysis as censored cases in accordance with a proper analysis of survival times and with the Cochrane handbook *(Chapter 9, Section 9.2.6).* Therefore, a low risk of attrition bias should be stated. Table 4 should be corrected accordingly.

Freuding et al. report on other risks of bias:

1. *"Further, in three studies less patients were included than was calculated in power analysis (Bar-Sela et al. 2013; Longhi et al. 2014; Troger et al. 2013). In these studies, there is a risk that no significant results were detected in spite of groups differing in reality"*. This statement may be true for the study of Bar-Sela et al. but not for Longhi et al. 2014 and Tröger et al. 2013, since significant results were achieved in both trials.
2. "*Apart from that, in 14 studies either no power analysis was conducted or it was not reported.*" We see no basis for a risk of bias due to a missing power calculation. This is confirmed by the Cochrane Handbook stating that *"review authors should focus on the mechanisms that lead to bias rather than descriptors of studies that reflect only quality"* (Higgins et al. 2017).
3. A multiple testing problem is attributed to the publication on pancreatic cancer (Tröger et al. 2013) in Table 4. Obviously, this is caused by misunderstanding the sequential study design. Overall survival was the only primary endpoint to be evaluated by a pre-planned testing procedure of three tests to be done with sample sizes of 50%, 75% and 100% of the total patient number, respectively. This statistical approach of group-sequential testing using properly adjusted stage-wise error levels holds the overall alpha error level and is accepted without reservation by regulatory bodies (E9 Statistical Principles for Clinical Trials 1998). Since the first interim analysis of this study already revealed a statistically significant difference, no reference to further group-sequential alpha level boundaries had to be done. So, a single test on a single primary parameter was performed, annihilating any multiple testing problem. Table 4 should be corrected accordingly.
4. "*In some studies, there was an unclear therapeutic setting."* The authors pretend that the best supportive care that was administered in a pancreatic cancer trial (Tröger et al. 2013) in both mistletoe and control group *"was not described at all"*. This is wrong, since it has been reported: *"During the trial, all patients received best supportive care (BSC), which was delivered by the trial physicians. The nature of BSC was determined in the trial center; it consisted of the symptomatic treatment of pain, nausea, vomiting, and dyspepsia and was individually adapted at each of the patient's visits (in Months 1, 2, 3, 6, 9, and 12)"* (Tröger et al. 2014). Thus the text of the review should be corrected.
5. *"Finally, it is seen as a risk of bias that there are many studies which, respectively, were written by the same group of authors or several studies even refer, respectively, to a one cohort of patients. There is a high probability that results of different studies from the same group of authors are not independently of each other"*. The Cochrane Handbook does not list multiple studies from the same group of authors as a possible source of bias. We suggest that the text of the review should be corrected accordingly.

Finally, we conclude that the review of Freuding et al. does to a relevant extent not fulfill the criteria for a systematic literature review and therefore should be thoroughly corrected or withdrawn by the authors.

Acknowledgements H. Matthes is a member of the guideline committee for integrative oncology. F. Schad received research grants from Abnoba, Helixor and Hiscia and R. Huber has been working in a scientific advisory board for Abnoba and received research grants from Abnoba, Helixor and Hiscia.

Compliance with ethical standards

Conflict of interest The authors R.-D. Hofheinz, G. Bar-Sela, D. Galun, D. Martin, J. Langhorst and P.F. Matthiessen declare that they have no conflict of interest.

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