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Letter to the editor

Effect of ESA as a modifier of radiotherapy in curative intended treatment of squamous cell carcinoma of the head and neck (HNSCC)

We will like to thank Topkan and Yildirim [1] for their comments related to our descriptions of the outcome of the randomized phase 3 DAHANCA 10 trial: Effect of darbepoetin alfa and radiotherapy in treatment of squamous cell carcinomas of the head and neck [2].

Topkan and Yildirim concur with the DAHANCA 10 results as well as similar data in other head and neck cancer trials [3–5], evaluating Erythropoiesis-stimulating agents (ESA) as an adjuvant to curative radiotherapy. They do, however, point to the observation that there may be a relation between Erythropoietin receptor (EpoR) activity and response to radiotherapy. They do so, based on the previous paper by Henke et al. describing the ENHANCE trial [3] which was subsequent reanalyzed [6] in order to understand a similar outcome (as the DAHANCA 10 study) of an inferior tumor control. Although they observed a difference in outcome as a function of whether the tumor tissue expressed positive or negative EpoR activity, this may be associated with severe limitations [7–11]. We have briefly discussed this in our article and the explanation is probably more complex than described by Henke et al. [6].

Firstly, the methods used for the immunohistochemical estimation of EpoR activity have been subjected to criticism, as it may not specifically target the receptor, but also other targets such as a HSP70 protein [10,11]. Similarly, the majority of the patients in the Henke trial are treated with post-operative radiotherapy and do not have macroscopic tumor tissue at the time of radiotherapy. Thus they do not qualify for our hypothesis of the benefit of ESA, namely an increase of the hemoglobin level resulting in a consequently better tumor oxygenation in order to overcome hypoxia during radiotherapy [12].

The analysis by Henke et al [6] also suffers from an uneven distribution of patients in different strata, which favors a better result for the placebo group in the receptor positive cohort, and a poorer outcome in the EpoR negative group. Neither is the most prognostic factor for outcome of head and neck radiotherapy described. The study is so old that no correction or knowledge of the HPV/P16 status in the oropharyngeal carcinomas are analyzed [13].

Furthermore, the interpretation by Topkan and Yildirim of the survival curves in the EpoR negative group in the ENHANCE trial [6], is a rather liberal interpretation of statistical outcome. At 20 months, each group of patients only have 10 patients at risk (probably most of them given post-operative radiotherapy with no or only residual microscopic tumor left) and interpretation of such late responding data in a small number of patients is purely speculative and goes beyond the statistical conservatism, which is important to exercise by evaluating clinical trials.

We have considered to investigate the EpoR activity in the tumors in the DAHANCA 10 trial, but as indicated in our publication [2], it was not possible to do so in a way that ensures the necessary scientific stringency. Thus we, as most others studying these issues in HNSCC trials [2–5], are left with the overall response to the investigated hypothesis, namely that there is a general tendency that the use of ESA together with radiotherapy of HNSCC, is non-beneficial. Whether this is linked with a EpoR derived stimulation of tumor cell proliferation [7–9], still needs to be clarified, but until reliable and easy accessible methods are available, one should avoid too much unsubstantiated speculation.

The issue of ESA in HNSCC radiotherapy has been detailed investigated in clinical trials and three other randomized studies add to the results of the DAHANCA 10 study, and have shown mutually supportive evidence that this is a non-beneficial treatment (Fig. 1). These observations were in contradiction to the expected outcome, and illustrate very clearly the importance of conducting proper clinical trials to generate the needed evidence to foster progress in radiation oncology.

Thus, even the most obvious expected results (as in the case with ESA) may turn out to yield an unexpected negative outcome. The lessons from these studies are therefore, that progress must come from constantly generating evidence within the framework of clinical trials, an activity to which we all should contribute, in order to ensure a strong development of the scientific basis of radiation oncology. The trials addressing the use of ESA in curative radiotherapy is a prime example on how such clinical research shall be conducted. Also, when dealing with pharmacological agents, it is important that the PIs and the organization of the trials are independent and outside the control of the pharmaceutical industry, since the industry to a large intend has shown a very limited interest in securing analysis and publication of the "negative" data.

Conflict of interest

None declared.

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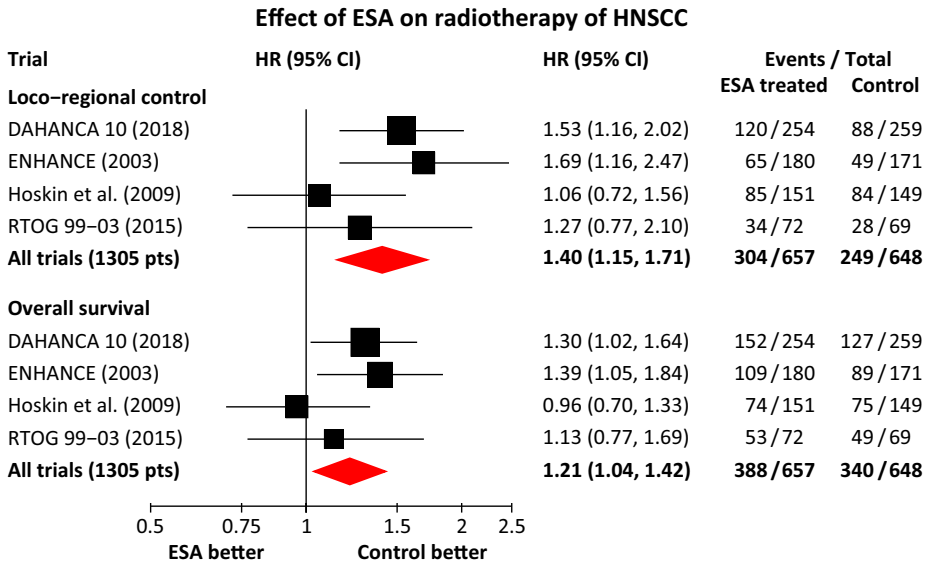

Fig. 1. Meta-analysis of randomized controlled clinical trials investigating the role of ESA as a modifier of radiation therapy in the curative treatment of HNSCC. The overview analysis demonstrates that such treatment results in a significantly inferior loco-regional tumor control and subsequent overall survival.

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