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Letter to the editor

Epoetin receptor status may alter the outcomes in head and neck cancers treated with radiotherapy and darbepoetin-α

To the Editor

We read with great interest the Danish Head And Neck Cancer Group (DAHANCA) 10 study reported by Overgaard J et al. [1], and would like to congratulate the authors for their multi-institutional effort regarding the influence of the darbepoetin-α on clinical outcomes of patients with locally-advanced head and neck squamous cell carcinoma (LA-HNSCC) who underwent radiotherapy (RT). The investigators randomized 522 LA-HNSCC patients with pre-treatment hemoglobin (Hb) <14.0 g/dL to one of darbepoetin-α or observation arms during the planned accelerated fractionated RT. The primary objective of this collaborative effort was to assess the role of darbepoetin-α stimulated continuous increase in the effective Hb concentration and resultant oxygenation of the tumors during RT of HNSCC patients. The authors reported that the use of darbepoetin-α was associated with significantly poorer tumor control ($p = 0.0021$) and survival ($p = 0.030$) outcomes than their counterparts with no darbepoetin-α. This collaborative randomized phase 3 trial undoubtedly provides highly relevant Level I data on one of the most commonly debated issues of oncologic management of such patients. However, we have one critical concern to be addressed.

Both the epoetin (EPO) and darbepoetin demonstrate their actions mainly on the bone marrow progenitor cells pool in a similar fashion with the end goal to increase the quantity of red blood cells in the circulation and therefore to treat anemia [2]. Previous reports demonstrated that EPO receptor (Epo-R) has a highly variable expression on the HNC cells and the presence of Epo-R was shown to be associated with a detrimental effect of EPO administration [3–5]. Although the specific function of the EpoR is not fully understood, a postulated possible mechanism is that the growth factor recombinant EPO protects residual tumor cells from the radiation effects after its binding to EpoR by stimulating the cellular proliferation and angiogenesis [6]. In a study reported by Henke et al., the authors demonstrated that the 50 (32.5%) of 154 advanced HNSCC patients were EpoR negative [7]. Supporting the above mentioned postulate, the author reported that locoregional progression-free survival was substantially poorer only if EPO was administrated to patients with positive tumoral EpoR expression compared with placebo ($p < 0.01$), while administration of EPO increased the Hb levels it had no negative impact on the clinical outcomes. Furthermore, revealed from the survival graphic, locoregional disease-free survival status began to separate approximately at 18–20 months after treatment which retained and became more profound favoring the EPO group over the none-EPO at 5 years, which suggests a beneficial role for EPO administration in EpoR negative HNSCCs. Therefore, if available, such kind of analyses and presentation of the outcomes in 522 patients may prove more valuable in reaching more conclusive results about the impact of the use of darbepoetin-α on clinical outcomes of LA-HNSCC patients.

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