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Original article

DAHANCA 10 – Effect of darbepoetin alfa and radiotherapy in the treatment of squamous cell carcinoma of the head and neck. A multicenter, open-label, randomized, phase 3 trial by the Danish head and neck cancer group

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ABSTRACT

Purpose: To evaluate if correction of low hemoglobin (Hb) levels by means of darbepoetin alfa improves the outcomes of radiotherapy in patients with squamous cell carcinoma of the head and neck (HNSCC).
Patients and methods: Patients eligible for primary radiotherapy and who had Hb values below 14.0 g/dl were randomized to receive accelerated fractionated radiotherapy with or without darbepoetin alfa. Patients also received the hypoxic radiosensitizer nimorazole. Darbepoetin alfa was given weekly during radiotherapy or until the Hb value exceeded 15.5 g/dl.
Results: Following a planned interim analysis which showed inferiority of the experimental treatment the trial was stopped after inclusion of 522 patients (of a planned intake of 600). Of these, 513 were eligible for analysis (254 patients treated with darbepoetin alfa and 259 patients in the control group). Overall, the patients were distributed according to the stratification parameters (gender, T and N staging, tumor site). Treatment with darbepoetin alfa increased the Hb level to the planned value in 81% of the patients. The compliance was good without excess serious adverse events.
Results: The results showed a poorer outcome with a 5-year cumulative loco-regional failure rate of 47% vs. 34%, Hazard Ratio (HR): 1.53 [1.16–2.02], for the darbepoetin alfa vs. control arm, respectively. This was also seen for the endpoints of event-free survival (HR: 1.36 [1.09–1.69]), disease-specific death (HR: 1.43 [1.08–1.90]), and overall survival (HR: 1.30 [1.02–1.64]). There was no enhanced risk of cardiovascular events observed in the experimental arm or any significant differences in acute or late radiation related morbidity. All univariate analyses were confirmed in a multivariate setting.
Conclusion: Correction of the Hb level with darbepoetin alfa during radiotherapy of patients with HNSCC resulted in a significantly poorer tumor control and survival.
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There is abundant evidence for the prognostic importance of the hemoglobin (Hb) concentration for the outcome of radiotherapy (RT) of squamous cell carcinoma of the head and neck cancer (HNSCC) [1–5]. Thus, patients with low Hb in general have a poor local regional tumor control and survival. This has especially been linked with tumor hypoxia, and there is a strong evidence that hypoxia in HNSCC is associated with poor outcome of RT [6–8]. Both experimental and clinical studies have shown that a rapid increase in the Hb concentration by transfusion might result in an increase in tumor oxygenation, although only temporary [1,9,10].

HNSCC is characterized by a high degree of hypoxia [7,11,12], and attempts to overcome this has been addressed using different kinds of hypoxic modification (e.g. normo- or hyperbaric oxygen, hypoxic cell radiosensitizers) and both the experience from the DAHANCA 2 and DAHANCA 5 studies [13,14] as well as a meta-analysis has shown that such modifications of hypoxia result in significantly better local control and survival [7,8,15]. Furthermore,

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studies have shown that especially the amount of oxygen being brought forward to the tumors by the blood is of importance for the curative result. This supports the observation that patients who smoke in connection with RT have a poor loco-regional control, probably due to less oxygen supply to the tumors [16,17].

On this basis trials have been performed in which patients with low Hb values were randomized to +/− transfusion prior to RT. A sub-randomization of the DAHANCA 5 trial unfortunately showed that transfusion did not significantly improve the treatment outcome [18]. However, in this trial transfusions were given several days prior to RT. In such case tumors probably adapted to the increasing Hb level by responding with an increased growth of oxygenated tumor cells, which in principle resulted in creating more better-oxygenated tumor cells, but the hypoxic fraction was maintained [1,19]. This is supported by observations [4] that tumors of the same volume are more resistant if they have a lower Hb concentration, suggesting that in such tumors the level of hypoxic cells is higher. These results are in agreement with a well-argued hypothesis by Hirst [10], suggesting that it is not the Hb concentration in itself, which is important. Rather, it may be that a better tumor oxygenation is achieved as a result of a gradual increase in the Hb concentration occurring concurrently with RT induced tumor regression.

Contrary to transfusion, human recombinant erythropoiesis stimulating agents (ESA) is capable of producing a gradual increase in Hb concentration in patients with HNSCC during a course of RT [20–22]. Darbepoetin alfa has a biological effect and toxicity profile comparable to recombinant human erythropoietin, with the exception that it is more slowly released and can be administrated less frequently without losing clinical efficiency [23]. The drug appears to be safe and well tolerated [23,24].

The DAHANCA guidelines prescribe the use of accelerated fractionation as developed in the DAHANCA 6 and 7 trials [25,26], and the use of the hypoxic radiosensitizer nimorazole, following the results of the DAHANCA 5 study [14]. However, the prognostic relationship between low Hb values and poor outcome is independent of treatment with hypoxic modification, since it yields a benefit at all Hb levels, but with persistence of the Hb related difference in outcome [13,14,17,18]. On this basis the current trial was designed to explore the benefit of darbepoetin alfa in patients who were also given hypoxic modification with nimorazole.

Although not proven, it is intuitive that there might be a causal relationship between the Hb concentration, tumor oxygenation and response to RT. Thus, there is a rationale for improving outcome of RT by increasing the Hb level in patients with low Hb concentration receiving curative RT for HNSCC. This hypothesis has also been addressed in at least 3 other randomized trials which investigated the role of ESA in curative radiotherapy of HNSCC [27–31].

The aim of the present study was to evaluate the role of a darbepoetin alfa stimulated continuous increase in the effective Hb concentration and consequently the oxygenation of the tumors during primary RT for HNSCC. Since the therapy implies an increase in Hb it was limited to patients who had a low Hb value. The study was performed as open randomized trial.

Patients and methods

Protocol design and patient eligibility

The study was activated in July 2002. The patients should be candidates for primary curative radiotherapy and, with the exception of the disease in question, not be in a state or condition which could be expected to influence the compliance to RT or affect the assessment of the treatment. The criteria for eligibility were: untreated (including prior neck dissection), histopathologically proven invasive squamous cell carcinoma of the larynx, oropharynx, hypopharynx, or oral cavity (Stage I–IV, except stage I glottic tumors) and no evidence of distant metastases; WHO performance score 0–2; age 18 years or older; adequate hepatic, renal and neurological function; no hypertension (diastolic blood pressure > 100 mm Hg) refractory to treatment; no symptomatic cardiovascular disease or deep vein thrombosis; and no currently ongoing treatment with ESA. The Hb value, measured within 10 days before randomization, should be <14.5 g/dl for men, and <13.5 g/dl for women.

Patients were stratified according to gender, tumor localization (larynx vs. pharynx vs. oral cavity), tumor classification (T1-2 vs. T3-4; nodal classification (N0 vs. N1-3), and institution. They were randomly assigned to RT alone or to RT with darbepoetin alfa.

The study was conducted according to the Helsinki Declaration II and approved by the relevant ethics committees.

Treatment

Radiotherapy was initiated within 3 weeks of randomization and applied according to the DAHANCA 2002 guidelines [32]. Patients were treated with accelerated fractionation with 6 weekly fractions of 2 Gy as previously described [25,26,33]. Patients were given 1 fraction per day, Monday through Friday with the sixth fraction given either during the weekend or as an additional fraction on one of the weekdays, but allowing at least a 6-h interfraction interval. Macroscopically involved tumor area with a margin of 1 cm was given a minimum dose of 66–68 Gy (2 Gy per fraction, 6 fractions per week). The total dose depended on the tumor size, with primary tumors or nodes larger than 4 cm receiving a minimum dose of 68 Gy. Uninvolved nodal areas were treated with 50 Gy, and no elective neck dissection was allowed.

Darbepoetin alfa (Aranesp®) was administered subcutaneously in a dose of 150 μg, irrespective of the gender and body weight. The first dose was given 7–15 days prior to the first day of RT and was continued with weekly intervals until completion of RT, or until the Hb concentration exceeded 15.5 g/dl, or in case of severe drug related side effects. Hb values were monitored at registration and before each weekly injection. If Hb values were between 14.0 g/dl and 15.5 g/dl for men or 13.5 g/dl and 15.0 g/dl for women, the dose of darbepoetin alfa was reduced to 75 μg. If Hb values exceeded 15.5 g/dl for men or 15.0 g/dl for women, the drug was withheld. If Hb values were decreasing after administration of 4 times 150 μg darbepoetin alfa, the weekly dose was increased to 300 μg per week. Se-ferritin was monitored weekly. If Se-ferritin decreased below 200 μg/l the patients were given oral iron supplement in a daily dose of 200 mg until the end of the radiotherapy. If oral administration was difficult, equivalent intravenous iron was used.

Nimorazole was administered in doses of 1,2 g/m^2 body surface in connection with the first 30 radiation treatments. Total dose was planned to be approximately 36 g/m^2 and not allowed to exceed 40 g/m^2 or a total of 75 g. The drug was given 90 min prior to each radiation treatment as described elsewhere [34].

Evaluation and statistical considerations

Patients were followed for at least 5 years or until death except 1 patient who emigrated. Only patients with recurrence or severe morbidity related problems were subjected to longer follow-up than 5 years. In case of residual tumor, recurrence, or progression of the disease, salvage surgery or palliative treatment were performed depending on the condition of the individual patient, symptoms, and previous treatment.

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