Challenges of anemia correction during radiotherapy and chemoradiation

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The effect of radiotherapy depends on optimal tumour oxygenation, as tumour hypoxia impairs the production of radiation-induced cytotoxic free radicals resulting in less tumour cell kill. The range of haemoglobin levels optimal for tumour oxygenation is 12–14 g/dl in women and 13–15 g/dl in men. It appears reasonable to elevate the haemoglobin level in anaemic cancer patients into this optimal range. This may be achieved with red blood cell transfusions (RBCT) or erythropoiesis stimulating agents (ESAs). However, RBCT have had negligible or even negative effect on patient outcome, possibly because RBCT induce immunosuppression or result in haemoglobin levels too high for optimal tumour oxygenation. Several randomized trials have demonstrated that patients irradiated for head-and-neck cancer had worse outcomes with ESAs than the control group. However, in the majority of these trials, over-treatment with ESAs resulted in haemoglobin levels above the optimal range. Tumour oxygenation is impaired by inappropriately high haemoglobin levels due to increased blood viscosity and decreased tumour cell perfusion. This concept is supported by the findings of prospective studies in cervix cancer and esophageal cancer patients. In these studies the ESA administration was withheld at a haemoglobin level of 14 g/dl resulting in a positive effect of ESAs on treatment outcome. In summary, the effect of RBCT and particularly of ESAs during radiotherapy remains unclear. Further randomized trials are required. Until such trials are available, one should follow the ASCO and ESMO guidelines that are very conservative regarding the administration of ESAs during radiotherapy and chemoradiation.

Keywords: Anaemia correction, chemoradiation, erythropoiesis stimulating agents, radiotherapy, red blood cell transfusions

Introduction

Controversy exists regarding the benefit of anaemia correction during radiotherapy or chemoradiation of solid tumours.

The correction of anaemia can be achieved with red blood cell transfusions (RBCT) or erythropoiesis stimulating agents (ESAs). ESAs were demonstrated to be effective in improving fatigue and quality of life in patients with chemotherapy-induced anaemia over 15 years ago [1]. However, a recent meta-analysis including individual data from 13,933 cancer patients who participated in 53 randomized trials suggested that the use of ESAs was negatively associated with survival [2]. Similar results were found in another meta-analysis of 1,397 patients from five randomized trials of radiotherapy for head-and-neck cancer [3].

The limitation of both meta-analyses was the fact that the haemoglobin levels were pushed quite high by administration of ESAs in a considerable proportion of patients. This is particularly important in regards to the effectiveness of radiotherapy depending on optimal tumour oxygenation. According to radiobiological studies, tumour hypoxia impairs the production of radiation-induced cytotoxic free radicals leading to less DNA damage and tumour cell kill. Tumour oxygenation can be impaired by both anaemia and inappropriately high haemoglobin levels. High haemoglobin levels lead to increased blood viscosity and decreased perfusion of the tumour cells [4]. In addition, high haemoglobin levels predispose to pathologic clot formation. Haemoglobin levels must be 12–14 g/dl in women and 13–15 g/dl in men to achieve optimal tumour oxygenation and the best results from radiotherapy [5]. These data have been confirmed in a retrospective study of 108 oesophageal cancer patients, where haemoglobin levels during radiotherapy of 12–14 g/dl resulted in better 2-year loco-regional control than levels <12 g/dl or >14 g/dl (58% vs. 19% and 44%, $p < 0.001$) [6]. In another retrospective study of 181 patients with non-small cell lung cancer, haemoglobin levels during radiotherapy of <12 g/dl were associated with significantly lower 2-year loco-regional control (29 vs. 41%, $p = 0.004$) and 2-year overall survival rates (41 vs. 58%, $p = 0.013$) when compared to haemoglobin levels during radiotherapy of ≥ 12 g/dl [7].

Considering the radiobiological data regarding optimal tumour oxygenation, it appears reasonable to take a closer look at the studies investigating the administration of RBCT or ESAs in cancer patients treated with radiotherapy or chemoradiation.

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Red blood cell transfusions (RBCT)

In 1995, Kelleher et al. suggested that worsening of tumour oxygenation due to anaemia could partially be reversed by administration of ESAs and RBCT in rats [8]. However, this effect was observed only for small tumours. In tumours ≥ 1.4 ml, anaemia correction did not significantly improve tumour oxygenation. In a retrospective analysis of 204 patients irradiated for cervix cancer, the response to RBCT was disappointing [9]. Non-responders to RBCT had poor outcomes in terms of disease-free survival, pelvic control, and metastases-free survival. In another retrospective series of 605 patients irradiated for cervix cancer, RBCT were positively associated with treatment outcomes on univariate but not on multivariate analysis [10]. RBCT were negatively associated with survival in a series of 130 patients irradiated for cervix cancer (RR: 2.2; $p < 0.001$) [11]. It is possible that the haemoglobin levels in patients receiving RBCT were increased beyond the range considered optimal for tumour oxygenation. Unfortunately, the proportions of haemoglobin levels during radiotherapy of >14 g/dl in women and >15 g/dl in men were not stated. A recently published randomized study from Denmark investigated RBCT in 414 patients with squamous cell carcinoma of the head-and-neck (SCCHN) [12]. Pre-radiotherapy haemoglobin levels of <13 g/dl in women and <14.5 g/dl in men were defined as “low”. RBCT was given to achieve haemoglobin levels in the “high” level range. Patients of the “high” level group had significantly better loco-regional control (LRC), disease-specific survival (DSS), and overall survival (OS) than patients with “low” pre-radiotherapy haemoglobin levels. In the “low” level group, RBCT had no significant benefit on LRC (HR 0.99; $p = 0.9$), DSS (HR 1.07; $p = 0.8$), and OS (HR: 1.10; $p = 0.6$). Again, it is possible that the haemoglobin levels in the patients receiving RBCT were higher than the optimal range for tumour oxygenation. The unsatisfying results after RBCT may also be explained by the fact that RBCT can cause immunosuppression [13]. Because RBCT showed no benefit or a negative impact on outcome after radiotherapy, radiation oncologists have been looking for alternative options to correct anaemia and improve tumour oxygenation during radiotherapy. This led to studies investigating the potential benefit of ESAs.

Erythropoietin stimulating agents (ESAs)

Currently, radiation oncologists are hesitant to use ESAs with radiotherapy, as several randomized trials have demonstrated no benefit or even a negative effect with respect to treatment outcomes. In 2003, the ENHANCE study was published that investigated the impact of epoetin beta in 351 patients irradiated for SCCHN [14]. Loco-regional control (RR: 1.69, $p = 0.007$) and survival (RR: 1.39, $p = 0.02$) were significantly better in the placebo group than in the epoetin beta group. However, this study was criticized because the study groups were not balanced for relevant prognostic factors and because about one-third of patients were not treated per protocol. Furthermore, 82% of the patients in the epoetin beta groups had haemoglobin levels greater than the optimal range for tumour oxygenation in comparison to only 15% of patients in the placebo group. Taking into account the importance of optimal tumour oxygenation for the effectiveness of

radiotherapy, it is no surprise that the placebo group did better than the (over-treated) epoetin beta group.

In 2007, the Radiation Therapy Oncology Group 99-03 trial evaluated the role of weekly erythropoietin in 141 evaluable patients receiving concurrent chemoradiation and/or accelerated radiotherapy for SCCHN [15]. The 3-year loco-regional failure rates were 44% in the erythropoietin group and 36% in the control group ($p = 0.56$). The 3-year overall survival rates were 56% and 57%, respectively.

The final results of a randomized trial from Denmark (DAHANCA 10) were presented in 2009 [16]. The impact of darbepoetin alfa on treatment outcomes was investigated in 522 patients irradiated for SCCHN. The 5-year loco-regional control rates were 59% in the darbepoetin group and 68% in the control group, respectively (RR: 1.47, $p = 0.04$). The 5-year disease-free survival rates were 37% and 47%, respectively (RR: 1.32, $p = 0.02$), and the 5-year overall survival rates were 37% and 47%, respectively (RR: 1.20, $p = 0.16$). The target haemoglobin range in the DAHANCA 10 was 14–15.5 g/dl, which was like in the ENHANCE study and beyond the optimal range for tumour oxygenation. Therefore, the prognosis of the patients in the control group was likely to be better than in the darbepoetin group due to over-treatment with darbepoetin.

In 2009, a randomized trial from the United Kingdom including 301 patients irradiated for SCCHN was published [17]. In contrast to the previous studies, an on-and-off strategy was used to avoid over-treatment with epoetin alfa. If the haemoglobin level became >15 g/dl, epoetin alfa was withheld until the haemoglobin level was <14.5 g/dl and restarted at 50% of the previous dose. Taking into account the optimal range for tumour oxygenation, the haemoglobin levels still were too high. According to that trial, the 5-year local disease-free survival rates were 41% in the epoetin alfa group and 44% in the control group, respectively ($p = 0.79$), and the 5-year overall survival rates were 49% and 50%, respectively ($p = 0.82$).

In contrast to the four randomized trials of SCCHN, a recently published randomized trial of 257 patients receiving chemoradiation for cervix cancer showed a strong trend towards improved recurrence-free survival with the administration of epoetin alfa (HR: 0.66, $p = 0.06$) [18]. Overall survival was not significantly different (HR: 0.88, $p = 0.63$). A significant benefit of epoetin alfa regarding recurrence-free survival was observed for patients with stage IB-IIA disease (HR: 0.39, $p = 0.014$) and patients having a complete resection (HR: 0.55, $p = 0.039$). These results favouring epoetin alfa may be explained by the fact that in this trial, the epoetin alfa dose was reduced to 33% when the haemoglobin level reached 13 g/dl, and discontinued at 14 g/dl. A benefit on treatment outcome with epoetin alfa was also observed in a prospective observational study of 96 patients receiving chemoradiation for oesophageal cancer [19]. In that study, epoetin alfa was started at haemoglobin levels <13 g/dl and stopped at 14 g/dl. Due to this on-and-off strategy, 64% patients of the epoetin alfa group had the majority of weekly haemoglobin levels within the optimal range of 12–14 g/dl compared to only 17% in the control group.

The results of all the previously mentioned studies and meta-analyses regarding the administration of ESAs might have been influenced by tumour expression of erythropoietin and its receptor EPO-R. A retrospective analysis of patients

from the ENHANCE study suggested that tumour cell expression of EPO-R had a negative impact on treatment outcomes of patients receiving epoetin beta during radiotherapy [20]. Another retrospective study suggested that patients with low tumour expression of EPO-R and erythropoietin who received epoetin alfa during radiotherapy had better outcomes [21]. Furthermore, the results of the previously mentioned studies and meta-analyses might have been influenced by the patients' smoking habit, as smoking during radiotherapy has been shown to impair tumour oxygenation. This has been shown in particular for non-small cell lung cancer and head-and-neck cancer [7, 22–24]. In a retrospective study of 181 patients with non-small cell lung cancer, loco-regional control at 2 years was better in patients who did not smoke than in patients who did smoke during radiotherapy (58% *vs.* 41%, $p < 0.001$) [7]. In another retrospective study of 151 patients with non-small cell lung cancer, patients who had stopped smoking at the time of initial consultation (prior to surgery and postoperative radiotherapy) had a significantly better loco-regional control at 5 years (77% *vs.* 52%, $p = 0.002$) than patients who continued to smoke [22]. In the retrospective study of Kawakita et al. of 222 patients with cancer of the oral

cavity, non-smokers and light smokers (<30 pack years) had significantly better 5-year overall survival rates than moderate (31–59 pack years) and heavy smokers (≥ 60 pack years) [24]. The adjusted hazard ratios for moderate and heavy smokers versus light smokers were 2.44 (1.07–5.57, $p = 0.034$) and 2.66 (0.97–7.33, $p = 0.058$). The adjusted hazard ratio for non-smokers versus light smokers was 2.27 (0.84–6.15, $p = 0.11$).

ESAs have also been discussed in lymphoma patients, e.g. in patients receiving radiotherapy after autologous stem cell transplantation (ASCT). However, the data are very scarce. In 1998, Toren et al. reported grade 4 haematological toxicities requiring interruption of radiotherapy for more than one week in 11 of 93 patients (12%) who had received involved-field irradiation after ASCT [25]. Patients with malignant lymphoma were at a significantly higher risk of developing radiation-induced cytopenia than those patients with solid tumours (28% versus 5%, $p < 0.05$). Of the patients with a Non-Hodgkin's lymphoma, 8 of 14 (57%) patients who received the radiotherapy as planned and 6 of 7 (86%) patients who had a radiotherapy break of more than one week relapsed ($p < 0.05$). Thus, there may be a potential role for ESAs

Tab. 1: American Society of Clinical Oncology/American Society of Hematology clinical practice guideline for the use of ESAs. Dosing of ESAs in adults (modified according to [26])

	Epoetin alfa	Darbepoetin alfa
Initial dose	150 IU/kg s.c. 3x/week (not initiated at Hb levels ≥ 10 g/dl)	40,000 IU s.c. 1x/week (not initiated at Hb levels ≥ 10 g/dl)
Dose increase	Increase dose to 300 IU/kg 3x/week if no reduction in transfusion requirements or Hb increase after 4 weeks	Increase dose to 60,000 IU 1x/week if no increase in Hb by ≥ 1 g/dl after 4 weeks (absence of RBCT)
Dose reduction	Decrease dose by 25% when Hb reaches a level needed to avoid transfusion or Hb increases >1 g/dl in 2 weeks	Decrease dose by 40% of previous dose when Hb reaches a level needed to avoid transfusion or Hb increases to >1 g/dl in 2 weeks
Dose withholding	If Hb exceeds a level needed to avoid transfusion; restart dose at 25% below previous dose when Hb approaches a level where transfusion may be required	If Hb exceeds a level needed to avoid transfusion; restart dose at 40% below previous dose when Hb approaches a level where transfusion may be required
Discontinue	Following completion of CT course or if no response after 8 weeks of therapy (measured by Hb levels or continuing need for transfusions)	Following completion of CT course or if no response after 8 weeks of therapy (measured by Hb levels or continuing need for transfusions)

Tab. 2: ESMO clinical practice guidelines for the use of ESAs. The EMEA labels the use of ESAs as follows [27]: – chemotherapy and haemoglobin level ≤ 10 g/dl: ESAs might be considered to increase haemoglobin to <2 g/dl or to avoid further decline of the haemoglobin level. – no chemotherapy: no indication for ESAs; there might be an increased risk of death when the target haemoglobin level is 12–14 g/dl. – curative treatment: ESAs should be used with caution.

Treatment recommendations according to label (EMEA) (modified according to [23])

	Epoetin alfa	Epoetin beta	Darbepoetin
Initial treatment	150 IU/kg s.c. 3x/week 450 IU/kg s.c. 1x/week	30,000 IU s.c. 1x/week	2.25 μ g/kg s.c. 1x/week 500 μ g (6.75 μ g/kg) s.c. every 3 weeks
Dose increase	300 IU/kg s.c. 3x/week	60,000 IU s.c. 1x/week	Not recommended
Dose reduction by 25–50%	If result achieved If Hb >12 g/dl If Hb rise >2 g/dl/4 weeks	If result achieved If Hb >12 g/dl If Hb rise >2 g/dl/4 weeks	If result achieved If Hb >12 g/dl If Hb rise >2 g/dl/4 weeks
Dose withholding	If Hb >13 g/dl until 12 g/dl	If Hb >13 g/dl until 12 g/dl	If Hb >13 g/dl until 12 g/dl

– In case of response, ESA administration should be discontinued 4 weeks after the end of chemotherapy.
– If the increase of the haemoglobin level is <1 g/dl after 8–9 weeks, patients may be considered as non-responders, and ESA administration should be discontinued.

and G-CSF in order to avoid cytopenia-induced radiotherapy breaks. However, the scarce data available do not allow serious conclusions regarding the use of ESAs in these patients.

Conclusions

It appears important to maintain the haemoglobin levels within the optimal range for tumour oxygenation (12–14 g/dl in women and 13–15 g/dl in men) to achieve the maximum effect of radiotherapy. The role of RBCT and in particular of ESAs for irradiated cancer patients treated remains unclear. Randomized trials using cautious strategies of ESA administration during radiotherapy and considering tumour expression of EPO-R and erythropoietin are required. Such trials should consider the ASCO guidelines (ESA adult dosing recommendations given in Table 1) and ESMO guidelines (treatment recommendations according to the European Medicines Agency EMA given in Table 2) [26, 27]. Both guidelines are extremely reserved regarding the use of ESAs in patients receiving radiotherapy. So are several meta-analyses [2, 28, 29]. The association between haemoglobin levels, tumour oxygenation, and effectiveness of radiotherapy remains complex and requires further investigation.

Take home message

It appears important to maintain the haemoglobin levels during radiotherapy within the optimal range for tumour oxygenation (12–14 g/dl in women and 13–15 g/dl in men) to achieve the best treatment outcome. The role of RBCT and ESAs remains unclear and needs to be clarified by randomized trials employing strategies that aim at maintenance of an optimal haemoglobin concentration. The ASCO and ESMO guidelines aid the clinician when considering correction of anaemia in the individual patient.

Conflict of interest

The authors declare that there is no conflict of interest.

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