Articles

Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial

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Summary

Background Anaemia is associated with poor cancer control, particularly in patients undergoing radiotherapy. We investigated whether anaemia correction with epoetin β could improve outcome of curative radiotherapy among patients with head and neck cancer.

Methods We did a multicentre, double-blind, randomised, placebo-controlled trial in 351 patients (haemoglobin <120 g/L in women or <130 g/L in men) with carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Patients received curative radiotherapy at 60 Gy for completely (R0) and histologically incomplete (R1) resected disease, or 70 Gy for macroscopically incompletely resected (R2) advanced disease (T3, T4, or nodal involvement) or for primary definitive treatment. All patients were assigned to subcutaneous placebo (n=171) or epoetin β 300 IU/kg (n=180) three times weekly, from 10–14 days before and continuing throughout radiotherapy. The primary endpoint was locoregional progression-free survival. We assessed also time to locoregional progression and survival. Analysis was by intention to treat.

Findings 148 (82%) patients given epoetin β achieved haemoglobin concentrations higher than 140 g/L (women) or 150 g/L (men) compared with 26 (15%) given placebo. However, locoregional progression-free survival was poorer with epoetin β than with placebo (adjusted relative risk 1·62 [95% CI 1·22–2·14]; p=0·0008). For locoregional progression the relative risk was 1·69 (1·16–2·47, p=0·007) and for survival was 1·39 (1·05–1·84, p=0·02).

Interpretation Epoetin β corrects anaemia but does not improve cancer control or survival. Disease control might even be impaired. Patients receiving curative cancer treatment and given erythropoietin should be studied in carefully controlled trials.

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Introduction

The benefits of radiotherapy for patients with cancer diminish when anaemia is present.[1] Correction of anaemia has been suggested to reverse this haemoglobin effect,[2] thereby improving cancer control. Recombinant human erythropoietin can correct anaemia[3–5] and improve quality of life in anaemic patients with cancer.[6,7] Furthermore, preclinical data suggest that erythropoietin increases the radiosensitivity of tumours[8,9] and might improve the clinical efficacy of radiation[10] and chemotherapy.[11] However, the potential of erythropoietin to improve cancer outcomes has not been established. Therefore, we investigated whether epoetin β could improve cancer control and survival of patients irradiated for head and neck cancer.

Patients and methods

Patients

We enrolled patients between March, 1997, and April, 2001. Patients older than 18 years with histologically proven squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx who were scheduled to undergo definitive treatment with radiotherapy or postoperative radiotherapy for advanced disease (T3, T4, or nodal involvement) qualified for the study. Further eligibility criteria were haemoglobin concentration lower than 120 g/L for women or lower than 130 g/L for men, and a Karnofsky score of 60 or more. Exclusion criteria were treatment-refractory hypertension, thrombocytosis (>750×10^9/L), epilepsy, any other simultaneous malignant disease, treatment with any cytostatic drug within 3 months before the study, hypersensitivity to the preservative in the study medication, pregnancy or inadequate contraception, or participation in any other experimental protocol. The trial was approved by the ethics committees of the participating centres and done in accordance with the revised Declaration of Helsinki and good clinical practice guidelines. All patients provided written informed consent.

Methods

We did a double-blind, randomised, placebo-controlled trial. We stratified patients according to tumour resection status: stratum 1, postoperative radiation of complete (R0) resection; stratum 2, postoperative radiation of incompletely resected disease (R1 or R2); and stratum 3, primary definitive radiotherapy. Centres were supplied for each stratum with individually numbered but otherwise identical packages containing at random either placebo or active drug. For allocation to treatment groups, each new patient was assigned the next available medication package of the appropriate stratum (figure 1). The study code was kept sealed at the biometric department of the sponsor. Sealed envelopes with the code for individual patients were provided to the treating physicians and all were recollected unopened.

Placebo or epoetin β (300 IU/kg) were administered subcutaneously three times per week, with a minimum of 24 h between treatments. Additional 200 mg iron-III-saccharate (Haussmann, Switzerland) or 187·5 mg iron-III-gluconate (Nattermann, Köln, Germany) was administered intravenously once weekly if transferrin saturation was lower than 25%. Alternatively, oral iron could be given. Placebo or epoetin β were started 10–14 days before and continued throughout radiotherapy. Treatment was discontinued when target haemoglobin concentrations were achieved (≥140 g/L in women or ≥150 g/L in men) or when haemoglobin increased by more than 20 g/L within 1 week; it was resumed if the haemoglobin concentrations fell to lower than the target concentration.

Standard or three-dimensional planning techniques were allowed for radiotherapy. Whichever planning technique a centre used for the first study patient had to be used for all subsequent study patients. The radiation volume included the tumour (or tumour bed) with a 2–3 cm safety margin and the regional lymph-node areas. 6 mega electron volt linear accelerators were used and standard dose and fractionation protocols (five fractions of 2·0 Gy per week or five fractions of 1·8 Gy per week) followed. We prescribed 60 Gy (allowable range 56–64 Gy) to regions for R0 or R1 resected disease, and 70 Gy (allowable range 66–74 Gy) for macroscopically incompletely resected tumour (R2) or primary definitive treatment. The spinal cord was shielded after 30–36 Gy.

Patients were seen for first follow-up 6 weeks after completion of radiotherapy, and thereafter every 3 months to assess locoregional tumour control and survival. Radiotherapy quality was ascertained by an independent radiation oncologist, who was not involved with the study and who was unaware of treatment group. Resection status, tumour stage, treatment volume, safety margins, total dose applied, and overall treatment time were verified from source documents. Patients were classified as protocol correct when treated according to protocol, and as minor violation when the treatment volume did not include the safety margin or when the total dose was 2·0 Gy higher or lower than the allowed dose range. All other protocol deviations were classified as major violations.

The primary endpoint of the study was locoregional progression-free survival, defined as the time to locoregional tumour progression or death, whichever came first. We also assessed time to locoregional tumour progression and survival. Tumour progression was assumed when tumour size increased by more than 25%. We measured changes in haematological values (haemoglobin concentration, platelet and leucocyte counts, serum iron, transferrin, and ferritin) weekly during the treatment phase. In addition, we recorded adverse events and serious adverse events.

Statistical analysis

The study followed a sequential design and two interim analyses were planned, preserving a nominal p=0·048 for the final analysis. Study power was set at 80% to detect a 32% risk reduction for locoregional progression-free survival at 220 events. The primary analysis was done by intention to treat. We also analysed a radiotherapy-correct population, including patients who received radiation (dose, fraction, and treatment time) according to protocol and presented on at least one follow-up visit (this population differed from the protocol-correct population analysed in the radiotherapy quality assessment programme) and a per-protocol population. The per-protocol population included all radiotherapy-correct patients, except those who received less than 80% of their scheduled study medication administrations.

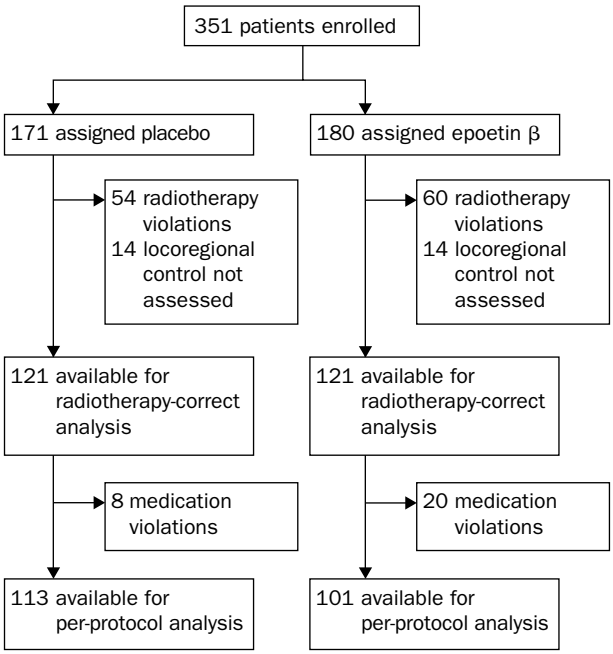

Figure 1: **Trial profile**

We assessed locoregional progression-free survival in the intention-to-treat population with Cox's proportional hazards model,[12] for which stratum and American Joint Cancer Committee stage were cofactors. Differences were tested with the two-sided Wald χ^2 test. In addition, we calculated Kaplan-Meier estimates,[13] hazard ratios or relative risk with 95% CI, two-sided logrank statistics, and did an unadjusted Cox's regression analysis. In all defined populations we assessed locoregional progression-free survival, locoregional progression, and survival. Haematological changes were assessed descriptively. We summarised the frequency of most severe adverse events by body system, excluding pre-existing adverse events at baseline. Cancer-related, non-cancer-related, and potentially drug-related adverse events were summarised separately.

Multivariate Cox's regression analyses adjusted for different baseline characteristics were done for epoetin-β effect. Furthermore, we analysed the primary endpoint in different subgroups, such as radiotherapy stratum, tumour location, and baseline haemoglobin concentration.

Role of the funding source

The study sponsor was actively involved in the study design, data collection, and organisation of study conduct, did the statistical analysis, and participated in interpretation of results and drafting and final approval of the report.

Results

We enrolled 351 patients in 23 centres in Austria, France, Germany, and Switzerland. The last patient entered the study in April, 2001. At that time the sponsor decided to omit the scheduled second interim analysis because the statistical penalty was deemed to be too high and changes in overall conduct of the study were not expected. The data were unmasked at the end of November, 2002, analyses finished in April, 2003, and results were presented to the investigators in July, 2003. Authors consented to the final draft of the manuscript in August, 2003. All randomised patients were included in the

	Placebo (n=171)	Epoetin β (n=180)
Characteristics		
Male sex	145 (85%)	158 (88%)
White patients	171 (100%)	179 (99%)
Median (range) age (years)	57 (36–87)	58 (35–81)
Median (range) weight (kg)	65·5 (40–113)	67 (42–115)
Current smoker	91 (53%)	118 (66%)
Median (range) haemoglobin concentration (g/L)	118 (6·9–14·6)	117 (8·5–14·4)
Median (range) serum erythropoietin concentration (U/L)	11 (3·3–168·1)	11 (11–446·2)
Relapse at entry	13 (8%)	18 (10%)
Tumour location		
Oral cavity	36 (21%)	43 (24%)
Oropharynx	74 (43%)	72 (40%)
Hypopharynx	43 (25%)	40 (22%)
Larynx	39 (23%)	41 (23%)
AJCC stage		
I	2 (1%)	2 (1%)
II	0	6 (3%)
III	46 (27%)	37 (21%)
IV	123 (72%)	135 (75%)
Treatment stratum		
1	94 (55%)	102 (57%)
2	38 (22%)	39 (22%)
3	39 (23%)	39 (22%)
Resection status		
R0	94 (71%)	102 (72%)
R1	33 (25%)	33 (23%)
R2	5 (4%)	6 (4%)

AJCC=American Joint Cancer Committee. Values n (%) unless marked otherwise.

Table 1: **Baseline characterstics**

intention-to-treat population. 18 patients withdrew or were excluded. 242 patients were analysed in the radiotherapy-correct and 214 in the per-protocol populations (figure 1). The characteristics of the patients in the intention-to-treat population were similar in the two treatment groups at baseline, with the exception of a higher proportion in the epoetin-β group of smokers and of patients with relapsed cancer (table 1).

A mean of 63·1 Gy (SD 9·7, range 0–74) was administered to placebo patients in 43·3 days (9·1, 0–57) and 62 Gy (10·8, 0–74) to epoetin-β patients in 42·5 days (9·6, 0–56). Radiotherapy quality assessment was done for 333 patients. Of these, 243 (73%) patients had correctly classified resection status and tumour-node-metastases status, and were treated according to protocol. There were 23 (14%) minor and 13 (8%) major protocol treatment violations in the placebo group and 25 (15%) and 17 (10%), respectively, in the epoetin-β group.

Mean haemoglobin concentrations increased with epoetin-β treatment for up to 6 weeks and stayed stable thereafter. Mean values after 4 weeks of treatment were 124 g/L (SD 13) for placebo and 148 g/L (18) for epoetin-β patients. After 9 weeks, the values were 129 g/L (19) or 154 g/L (17). 148 (82%) epoetin-β patients achieved haemoglobin target values during radiotherapy compared with 26 (15%) placebo patients.

208 (59%) patients of the 351 intention-to-treat population experienced locoregional tumour progression or died during follow-up—92 in the placebo and 116 in the epoetin-β group. 79 and 64 patients, respectively, were censored. The stage-adjusted and stratum-adjusted relative risk for locoregional progression-free survival was 1·62 for epoetin β (95% CI 1·22–2·14, p=0·0008; table 2), and the corresponding Kaplan-Meier estimate showed a median locoregional progression-free survival of 745 days for placebo compared with 406 days for epoetin β (p=0·04, figure 2). In the radiotherapy-correct population, locoregional tumour progression or death occurred in 66 placebo and 72 epoetin-β patients. The adjusted relative risk for locoregional progression-free survival was 1·42 (95% CI 1·01– 2·01, p=0·04; table 2) and the Kaplan-Meier estimate for time to progression slightly, but not significantly, favoured placebo (795 *vs* 551 days, p=0·41). In the per-protocol population, 63 placebo and 58 epoetin-β patients experienced locoregional tumour progression or death, with an adjusted relative risk for locoregional progression-free survival of 1·35 (95% CI 0·94–1·95, p=0·11; table 2). The Kaplan-Meier estimate was 748 days for placebo compared with 605 days for epoetin β (p=0·8).

In the intention-to-treat population, locoregional tumour progression occurred in 49 placebo and 65 epoetin-β patients, with 122 and 115 censored observations, respectively. The adjusted relative risk for locoregional progression was 1·69 (95% CI 1·16–2·47, p=0·007; table 2). The univariate Kaplan-Meier estimate showed a difference in time to progression favouring placebo (median not reached *vs* 280 days, p=0·09). In the same population, 89 placebo and 109 epoetin-β patients died (82 and 71 censored). The adjusted relative risk of death was 1·39 for epoetin-β patients (95% CI 1·05–1·84, p=0·02; table 2). In the actuarial analysis, patients treated with placebo survived a median of 928 days compared with 605 days in the epoetin-β group (p=0·09).

According to stratum, locoregional tumour progression or death occurred in 41 placebo and 47 epoetin-β patients in radiotherapy stratum 1, and the Kaplan-Meier estimate for locoregional progression-free survival was 1152 and 1049 days, respectively (p=0·9, figure 2). By contrast, 16 placebo and 30 epoetin-β patients in stratum 2 experienced locoregional progression or died, and median locoregional progression-free survival was 1791 and 377 days, respectively (p=0·001, figure 2). Similarly, in stratum 3, 35 placebo and 39 epoetin-β patients had locoregional tumour progression or died, and the Kaplan-Meier analysis showed a favourable outcome for placebo (207 *vs* 141 days, p=0·006; figure 2).

Multivariate analysis, including treatment stratum, tumour stage, baseline smoking, and relapse status, tumour site, haemoglobin concentration, transferrin saturation, and days between start of drug administration and radiotherapy supported the finding that epoetin-β treatment is associated with unfavourable outcome (relative risk 1·26 [95% CI 0·93–1·7], p=0·13).

In univariate analysis, haemoglobin concentration at baseline correlated with locoregional progression-free survival (0·77 [0·69–0·87], p<0·0001). Time-adjusted haemoglobin concentrations (area under curve) during radiotherapy was also significant (0·85 [0·78–0·93], p=0·0002).

	Relative risk (95% CI)	p
Population and outcome		
Intention to treat		
Locoregional progression-free survival	1·62 (1·22–2·14)	0·0008
Locoregional progression	1·69 (1·16–2·47)	0·007
Survival	1·39 (1·05–1·84)	0·02
Radiotherapy correct		
Locoregional progression-free survival	1·42 (1·01–2·01)	0·04
Locoregional progression	1·38 (0·88–2·14)	0·15
Survival	1·22 (0·86–1·73)	0·26
Per protocol		
Locoregional progression-free survival	1·35 (0·94–1·95)	0·11
Locoregional progression	1·41 (0·87–2·27)	0·16
Survival	1·13 (0·78–1·64)	0·52

Cox's proportional hazards analyses adjusted for stratum and American Joint Committee on Cancer stage.

Table 2: **Effect of epoetin-β treatment on study endpoints**

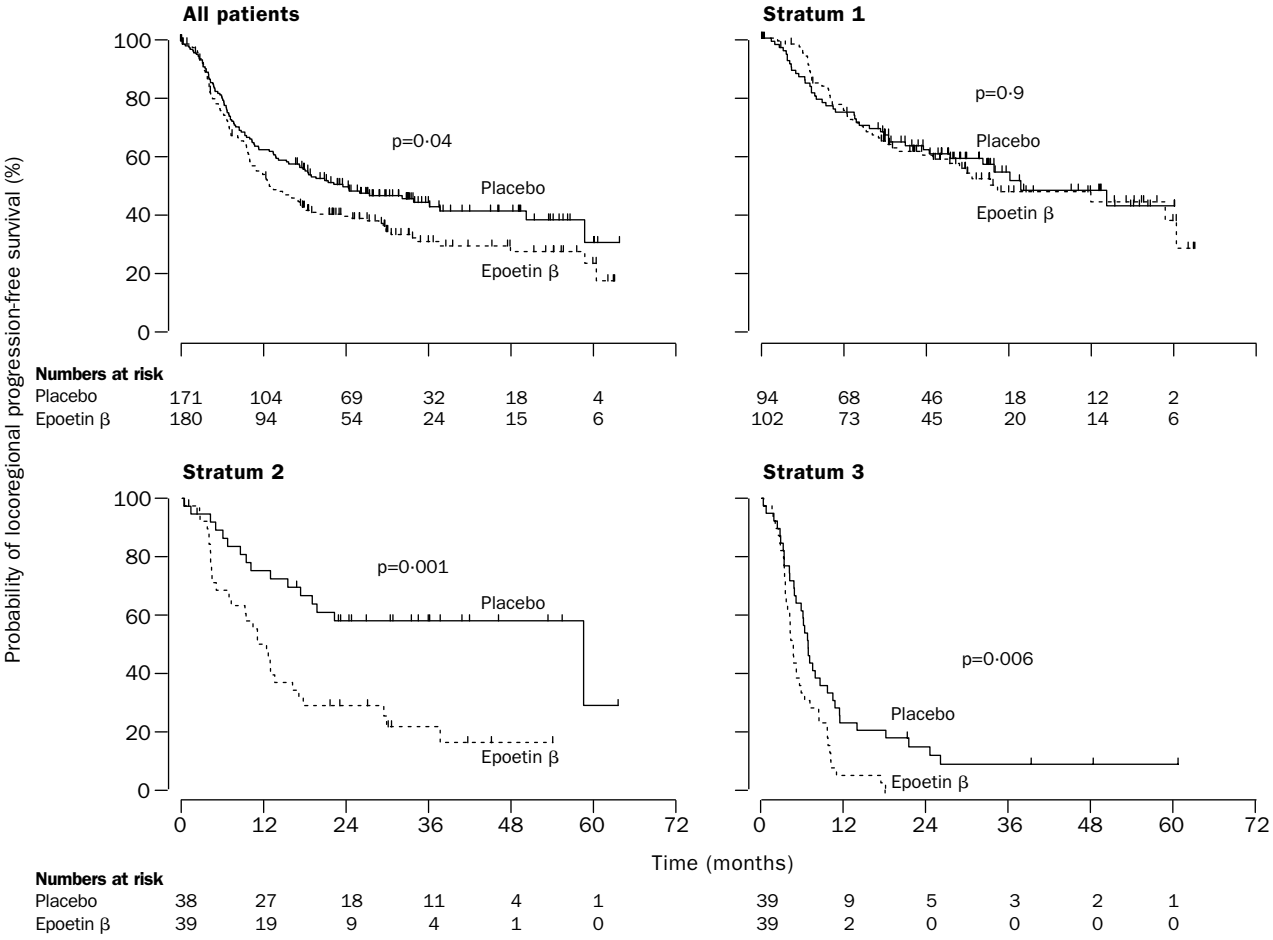

Figure 2: **Locoregional progression-free survival**
Ticks represent censored patients.

In subgroup analyses, epoetin β was related to a significant poor outcome only among patients younger than 60 years, in patients in whom haemoglobin at baseline was higher than 110 g/L, and among patients who had advanced disease or cancer of the hypopharynx. Notably, among patients with cancer of the hypopharynx, lower proportions of placebo-treated patients than epoetin-β patients had certain unfavourable baseline characteristcs (men 86 *vs* 90%; smoker 40 *vs* 55%; relapse at baseline 7 *vs* 15%; stage IV disease 70 *vs* 85%).

Cancer-related adverse events occurred in 78 (46%) placebo patients and in 92 (51%) epoetin-β patients, and local tumour progression was reported in 50 (29%) and 65 (36%), respectively. The rate of distant metastases was similar in the two groups (23% *vs* 25%). Non-cancer-related adverse events were documented in 111 (65%) placebo patients and 123 (68%) epoetin-β patients, and comprised general disorders (25% *vs* 30%), skin disorders (22% *vs* 24%), infections (20% *vs* 21%), disorders of the blood and lymphatic system (8% *vs* 13%), respiratory, thoracic, and mediastinal-system disorders (11% *vs* 6%), and vascular disorders (5% *vs* 11%). Vascular disorders were hypertension, haemorrhage, venous thrombosis and pulmonary embolism, and cerebrovascular disorders.

Overall, 89 (52%) patients in the placebo and 109 (61%) in the epoetin-β group died. 119 (34%) patients in the two treatment groups died from cancer. Mortality differed between groups for cardiac and general disorders: five placebo and ten epoetin-β patients died from cardiac disorders, and one placebo and nine epoetin-β patients from general disorders.

Adverse events were judged to be study-drug related in ten (6%) placebo and 15 (8%) epoetin-β treated patients. Six (4%) or 12 (7%) of the respective patients had disorders of the blood and the lymphatic system thought to be drug related. On review, brain-stem infarction, calf-vein thrombosis, and acute larynx oedema, in one patient each, were deemed potentially related to the study treatment. The larynx oedema was thought to be associated with intravenous iron. Further side-effects of iron treatment were not reported.

Discussion

Despite a reliable rise in haemoglobin concentrations, we saw no benefit for locoregional progression-free survival, locoregional progression, or survival. On the contrary, patients given placebo fared significantly better than those given epoetin β. A contribution of study design or conduct to this unexpected finding is unlikely. Centre performance, data collection, validation, and processing followed good clinical practice guidelines, and adherence to study-drug administration and to radiotherapy were ascertained. Furthermore, results of the intention-to-treat analysis were partly confirmed in the radiotherapy-correct population and in a separate analysis from the largest recruiting centre (data not shown).

Overall, patients' baseline characteristics were balanced and demographic data and tumour and treatment features of our patients compared well with most published reports,

as did prognostic factors.[14–17] Haemoglobin concentration at baseline and during radiotherapy significantly correlated with outcome. Thus, adequate patients were selected for this study, although we could not confirm a larger prognostic significance of haemoglobin concentrations towards the end of radiotherapy.[18]

Epoetin β affected various populations differently. This heterogeneity raises issues in the interpretation of the study results, and it is unclear whether the overall result is applicable to all patients undergoing radiotherapy for head and neck cancer. In particular, the subgroup of patients irradiated for manifest cancer (strata 2 and 3) fared worse when given epoetin β than when given placebo. Subgroup-specific differences of the haemoglobin effect[19] might explain this observation. Furthermore, epoetin β had a particular negative impact on outcome of patients with cancer of the hypopharynx, but imbalances of baseline characteristics of these patients might be the underlying cause.

Although baseline imbalances of particular subgroups might contribute to the negative impact of epoetin β on the outcomes in our patients, underlying biological phenomena are also a possibility. Originally, the haemoglobin effect was thought to directly alter cancer treatment, particularly radiotherapy. Low haemoglobin concentrations reduce tumour oxygenation,[20] amplify tumour hypoxia,[21] and might decrease, via the oxygen effect,[22] radiosensitivity.

Conversely, erythropoietin activates potent antiapoptotic pathways that promote erythropoiesis[23,24] and protect from damage in non-haemopoietic cells.[25,26] Furthermore, breast-cancer cells express erythropoietin receptors[27] that are functional,[28] and there is increasing evidence that tumour cells use the erythropoietin system for growth and angiogenesis.[29,30] Thus, antiapoptotic mechanisms activated by endogenous, anaemia-released erythropoietin could also explain the haemoglobin effect. This scenario clearly is not restricted to radiotherapy and may account for unfavourable clinical results in anaemic patients after surgery[31] or chemotherapy,[32] and eventually correspond with the observations of this study.

Most previous erythropoietin studies focused on quality of life in palliative cancer treatment.[33,34] Only two studies report improved survival on erythropoietin treatment.[10,35] One, however, is missing important baseline and treatment characteristics[35] and the other is constrained by a retrospective control group.[10] In another trial, impaired survival was reported when erythropoietin was given to patients treated for metastatic breast cancer, but conclusions are limited by pitfalls in the methods.[36] Our data describe decreased tumour control and survival rates in erythropoietin-treated radiotherapy patients. The study is well controlled and was designed to investigate cancer outcome. Thus, given our, and other, results the contribution of erythropoietin to curative cancer treatment is at present questionable.

Although epoetin β efficiently corrects anaemia among patients undergoing curative radiotherapy, it is not associated with improved cancer control or survival. On the contrary, erythropoietin might impair disease control when manifest cancer is irradiated. Future erythropoietin trials should thus carefully analyse cancer control and survival, and investigations on the underlying mechanism of the clinically relevant haemoglobin effect should be reinforced.

Contributors

All researchers contributed to the study design, implementation of the study, and collection of the data. U Burger analysed data and M Henke undertook plausibility testing. M Henke drafted the report. All researchers took part in the critical revision of the paper and approved the final version.

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Conflict of interest statement

M Henke, K D Haase, K T Beer, and H Frommhold have received consulting fees. B Schilcher has received travel expenses. U Burger and C Dougherty are employees at F Hoffmann-La Roche.

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