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Effects of anemia correction with epoetin beta in patients receiving radiochemotherapy for advanced cervical cancer

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Abstract. Strauss H-G, Haensgen G, Dunst J, Hayward CRW, Burger H-U, Scherhag A, Koelbl H. (On behalf of the March investigators and coordinators) Effects of anemia correction with epoetin beta in patients receiving radiochemotherapy for advanced cervical cancer. *Int J Gynecol Cancer* 2008;**18:**515–524.

Patients with cervical cancer frequently suffer from anemia. This two-stage, adaptive-design study investigated the effect of anemia correction with epoetin beta on treatment outcomes. Patients with stage IIB–IVA cervical cancer received radiochemotherapy (RCT) and were randomized to epoetin 150 IU/kg three times weekly ($n = 34$) or standard care (control; $n = 40$) for up to 12 weeks. Primary end point for stage 1 aimed to establish a correlation between anemia correction and treatment failure (no complete response or relapsing within 6 months after RCT initiation) as a proof of concept before moving into stage 2. Secondary end points included progression/relapse-free survival, overall survival, response to RCT, hemoglobin (Hb) response, and safety. Median baseline Hb was 11.4 and 11.6 g/dL in epoetin and control groups, respectively. At treatment end point, median Hb increased by 1.3 g/dL with epoetin, but decreased by 0.7 g/dL in the control group ($P < 0.0001$). No significant correlation between Hb increase and treatment failure was demonstrated. There were no significant differences between epoetin and control groups in progression/relapse-free survival (29.4% vs 32.5% patients with events; $P = 0.96$), overall survival (23.5% vs 12.5% patients with events; $P = 0.22$) or overall complete response (53% vs 58%; $P = 0.86$). Adverse events were well matched between groups. This study shows that epoetin beta rapidly, effectively, and safely increases Hb levels in patients with cervical cancer receiving RCT. No positive correlation of Hb increase and improvement in clinical outcomes could be demonstrated.

KEYWORDS: cervical cancer, epoetin beta, hemoglobin, radiochemotherapy.

Patients with advanced cervical cancer are often found to have anemia. This may be a consequence of bleeding caused by the tumor or because of aggressive anticancer treatment. Patients with advanced cervical cancer are likely to benefit from concurrent radiochemotherapy (RCT)[1], with cisplatin and radiotherapy (RT) being the most commonly used agents[2]. Anticancer therapies impact upon patients' hemoglobin (Hb) levels, with a higher proportion of patients receiving chemotherapy or RCT having anemia than those not receiving cancer treatments[3]. Moreover, decreases in Hb have been shown to be significantly greater in patients receiving RCT than those receiving RT alone[3,4].

Erythropoietin therapies have demonstrated the ability to improve Hb levels, therefore improving quality of life and reducing the need for blood transfusions in patients with solid tumors or lymphoid malignancies[5–10]. In patients specifically with cervical

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cancer receiving RCT, epoetin has shown efficacy in improving Hb[11,12].

Anemia is a negative prognostic factor in many cancers[13,14]. In patients with cervical cancer treated with RT or RCT, anemia has a negative impact on local control, disease-free survival, and overall survival[15,16]. Studies have suggested that maintaining optimal Hb levels during treatment may therefore help with control of the tumor[17–19].

The primary objective of this study was to investigate whether in patients with cervical cancer the effectiveness and outcome of RCT (RT plus cisplatin) could be positively influenced by treatment with epoetin. This objective was to be addressed in a two-stage, adaptive-design study, the first stage of which was designed to provide a proof of concept before moving into the second stage. The second stage was intended to investigate whether the survival of anemic patients with cervical cancer following RCT could be positively influenced by treatment with epoetin beta. The design of the second stage was to be adapted or rejected depending on the outcome of the first stage of the trial. The purpose of this paper is to report the findings of the first stage of this study.

Materials and methods

Study design

The present study was conducted as an open, randomized, two-arm, parallel-group, two-stage, adaptive study. The primary objective of the first stage of the study was to investigate if there was a correlation between anemia correction with epoetin beta and treatment failure in women with cervical cancer receiving RCT. In this context, treatment failure was defined as either no complete remission of tumor or complete remission and tumor recurrence within 6 months from initiation of RCT. After the first stage had been analyzed and the primary objective was met, the study protocol outlined a continuation of the study to a second stage where a further 450 patients were to be enrolled to investigate the potential impact of anemia correction with epoetin on survival.

The study was conducted in accordance with the Declaration of Helsinki and the principles of good clinical practice. The study protocol was approved by the responsible independent ethics committee of each collaborating center. All patients gave their written informed consent for participation in this study.

Study population

Major inclusion criteria were: age greater than or equal to 18 years; a histologically confirmed diagnosis of cervical cancer; FIGO stage IIB–IVA (except chorion carcinoma and neuroendocrine small-cell carcinoma); Hb levels between 9 and 13 g/dL at screening; a World Health Organization performance status of 0–2; and a life expectancy of at least 3 months. Other inclusion criteria were: adequate bone marrow function (platelets $>100 \times 10^9$/L and leukocytes $>3.0 \times 10^9$/L); adequate liver function (transaminases and/or alkaline phosphatases no greater than 2.5 $\times$ upper normal limit; bilirubin no greater than 1.5 $\times$ normal limit); adequate renal function (calculated creatinine clearance >60 mL/min); and no previous systemic antineoplastic therapy or RT for cervical cancer, except previous single brachytherapy fraction of the protocol-prescribed RT course as clinically indicated.

Major exclusion criteria were: patients with distant metastasis (M1 disease); positive para-aortic lymph nodes; chronic heart failure (NYHA [New York Heart Association] ≥ 2); uncontrolled arterial hypertension (systolic blood pressure ≥ 170 mm Hg, diastolic blood pressure ≥ 100 mm Hg); known history of deep vein thrombosis (DVT); thrombocytosis; known hemoglobinopathies; vitamin B12 and/or folic acid deficiency; hemolytic anemia; bleeding requiring transfusion within 3 months before planned start of study treatment; acute infection; transferrin saturation less than 20%; known presence of other neoplasias within the last 5 years; pregnancy or lactation; exposure to epoetins within 3 months; and contraindications against cisplatin therapy.

Study procedures

Eligible patients were centrally randomized to the epoetin arm or the control arm of the study. Those randomized to epoetin treatment were entered into a 2-week, preRCT-treatment period where they received epoetin beta (NeoRecormon; F. Hoffmann-La Roche Ltd., Basel, Switzerland) 450 IU/kg in three divided doses (corresponding to approximately 30,000 IU/week assuming an average body weight of 70 kg), which was self-administered by a pen device (RecoPen; F. Hoffmann-La Roche Ltd.). Epoetin beta was given for the duration of RCT. The 2-week epoetin beta pretreatment period was to ensure that anemic patients had acceptable Hb levels at the start of RCT. However, immediate initiation of RCT was permitted for medical reasons in patients randomized to the epoetin beta arm. In case of an insufficient Hb response (increase in Hb of <0.5 g/dL after 4 weeks of epoetin beta, or requirement of transfusion in the fourth week of epoetin beta treatment), the dose could be doubled to 900 IU/kg per week (corresponding to approximately 60,000 IU/week assuming an average

body weight of 70 kg). The administration of study drug was interrupted if Hb exceeded 15 g/dL and was to be resumed at 50% of previous dose until a Hb of less than or equal to 14 g/dL was reached. Similarly, dose reductions of 50% were implemented if Hb increased by greater than 2 g/dL in 4 weeks. Blood transfusions were given according to physicians' decision if Hb levels were less than 8.5 g/dL and were to be avoided in patients with a Hb of greater than 8.5 g/dL. Enrolled patients with a transferrin saturation of less than 20% were recommended to receive intravenous (IV) iron supplementation with a dose of 100 mg Fe^{3+} (preferably iron saccharate, if not available iron gluconate) per week. If contraindicated or not available, daily oral iron supplementation at a dose of 200–300 mg Fe^{3+} could be used alternatively. Patients in the control arm received RCT as soon as possible after randomization and received anemia treatment according to standard center practice.

All patients were scheduled to receive RT over a 6-week period (to a maximum duration of 50 days) plus concomitant chemotherapy with cisplatin (intravenously once per week at a dose of 40 mg/m^2) starting on day 1 of the RT. Total duration of cisplatin therapy was also 6 weeks. RT was provided as external beam RT 45.0–50.4 Gy in daily doses of 1.8 Gy, plus brachytherapy to a total dose at point A of 75 Gy (70–80 Gy) with high–dose rate brachytherapy or 80 Gy (75–85 Gy) with low–dose rate brachytherapy.

Efficacy assessments

The primary study end point in stage 1 was the number of treatment failures—defined as patients with no complete response or relapsing within 6 months after initiation of RCT—in correlation with the Hb change from baseline to study end. Secondary end points were progression/relapse-free survival, overall survival, and overall response rates to epoetin beta therapy and RCT. All end points were compared between the two study groups.

Safety assessments

For the safety assessments, data on adverse events, laboratory parameters, and vital signs were collected at each study visit. Adverse or serious adverse events could also be reported throughout the study, independently from the scheduled study visits. Adverse events and changes in laboratory parameters were graded according to the National Cancer Institute Common Toxicity Criteria.

Statistical analysis

The analysis of the primary end point in stage 1 and all other study end points followed the intention-to-treat principle. The effect of Hb change from baseline (primary variable) on treatment failure (defined as patients with no complete response or relapsing within 6 months after initiation of RCT) was analyzed using a logistical regression analysis (two-sided test at $\alpha = 5\%$ with change from baseline in Hb as main factor in the model). A proof of concept for the first stage of the study was to be accepted if a positive correlation between the change in Hb levels from baseline to the end of the treatment period, and treatment failure (ie, patients with no complete response or relapsing within 6 months after initiation of RCT) could be established, and no important safety concerns were raised in an initial group of approximately 80 patients.

Progression/relapse-free survival and overall survival were analyzed by log-rank testing and Cox regression analysis. Multivariate analysis was performed using a stepwise Cox regression procedure. The overall response was analyzed using the Chi-squared test with Schouten correction and 95% Clopper-Pearson confidence intervals (CIs). Change from baseline in Hb at the end of the treatment period was tested in an analysis of covariance model, with Hb at baseline as covariate. Hb change from baseline was assessed at week 4 and at the end of the treatment period.

All randomized patients were included in the intention-to-treat population and all efficacy results are provided for this population. The safety population comprised of all patients who received at least one dose of the trial medication with RCT and/or epoetin in the epoetin beta group and at least one dose of RCT in the control group.

Results

Baseline characteristics, patient disposition, and RCT

A total of 74 patients were randomized into the study between 15 October, 2001 and 7 July, 2003 from 20 participating institutions in Europe, Turkey, and Thailand and were included in the intention-to-treat population. Three patients were excluded from the safety analysis population (one from the treatment arm and two from the control arm), as they did not receive study treatment.

A total of 12 patients (16%) were withdrawn prematurely from the study (ie, before completion of the

full follow-up period), eight in the epoetin arm and four in the control arm. Most early withdrawals occurred after completion of the study treatment period. There were no withdrawals because of adverse events in either study group. Reasons for withdrawal were death (two patients in the epoetin arm for reasons not related to study medication), refusal of further treatment (one patient in each study arm), failure to return for treatment (two patients in the epoetin arm), inclusion criteria not being met or exclusion criteria being fulfilled (three patients in the epoetin arm and one patient in the control arm), RCT not given according to protocol (one patient in the control arm), and other organizational reasons (one patient in the control arm).

There were no major differences between groups in baseline demographics (Table 1). The overall follow-up time was similar for the two groups: median follow-up for overall survival was 482 (interquartile range 447–617) days in the epoetin beta group and 466 (interquartile range 446–513) days in the control group.

The median time between randomization and start of RT was 15 days in the epoetin beta arm and 5.5 days in the control arm (Table 2). Indeed, only nine patients (28%) in the epoetin beta group received RCT within 7 days of randomization, whereas 25 patients (66%) in the control group received RCT within 7 days. Moreover, 20 patients (62.5%) in the epoetin group received RCT greater than 13 days after randomization and only 4 patients in the control group received RCT greater than 13 days after randomization.

Thirty-one of the 34 patients (91%) in the treatment arm and 36 of the 40 patients (90%) in the control arm received brachytherapy during the study. Cumulative doses of brachytherapy are shown in Table 2. In addition, 91% of epoetin-treated patients and 95% of control patients received external beam RT (Table 2). There were no differences in the mean number of RT fractions received by either group (Table 2) or the actual vs the planned doses of external beam RT (epoetin beta group: -0.2 ± 1 Gy; control group 0.3 ± 2.9 Gy).

Likewise, there was no difference between the treatment arms in terms of the mean cumulative dose and median duration of cisplatin therapy received during the study (Table 2). Almost all patients (33/34) randomized to the epoetin arm received at least one dose of epoetin beta and 31/34 patients received epoetin beta for at least 6 weeks. The median weekly dose of epoetin beta ranged from 31,500 IU at weeks 9 and 13 to 45,000 IU at week 11. Overall, the median duration of epoetin beta treatment was 63 days (range: 3–98 days). Concomitant iron treatment was received by 27 patients (79%) in the epoetin group. Of these, 15 received IV iron and 12 received oral iron supplementation. In addition, iron treatment was received by 22 patients (55%) in the control group, with 12 patients receiving IV iron and 10 patients receiving oral iron supplementation.

Table 1. Baseline demographics for patients with cervical cancer receiving RCT (intention-to-treat population)

	Epoetin beta ($n = 34$)	Control ($n = 40$)	*P*-value
Age, years			
Mean	48.8	49.2	0.957
SD	10.2	12.8	
Weight, kg			
Mean	70.1	71.0	0.931
SD	15.2	18.0	
Height, cm			
Mean	160.0	160.0	0.970
SD	6.3	7.5	
Tumor stage (FIGO definition), *n* (%)			
IB	1 (2.9)	0	—
IIB	17 (50.0)	23 (57.5)	0.593
IIIB	14 (41.2)	14 (35.0)	0.665
IVA	2 (5.9)	2 (5.0)	0.945
IVB	0	1 (2.5)	—
WHO PS, *n* (%)			
0	21 (61.8)	27 (67.5)	0.689
1	13 (38.2)	12 (30.0)	0.529
2	0	1 (2.5)	—
Hb at baseline, g/dL			
Median	11.4	11.6	0.371
IQR	10.8–12.0	10.9–12.4	
Hb before RCT, g/dL			
Median	11.8	11.7	0.633
IQR	10.6–13.1	10.9–12.4	

SD, standard deviation; WHO PS, World Health Organization performance status; IQR, interquartile range.

Efficacy of epoetin beta—Hb response and reduction in transfusions

By week 4 after initiation of RCT, median Hb had increased by 1.1 g/dL from baseline in the epoetin group, but decreased by 0.6 g/dL in the control group (Fig. 1). Improvements in the epoetin group were maintained to the end of the treatment period (median change in Hb between last value and baseline was 1.3 g/dL). Equally, decreases in the control arm were also maintained throughout the study (change in Hb between last value and baseline was –0.7 g/dL). An analysis of covariance showing a difference in least square means (adjusting for baseline Hb) indicated that the change in Hb from baseline was highly significant between the groups ($P < 0.0001$). More patients in the treatment group achieved target Hb levels of 13 g/dL than those in the control group (71% vs 25%).

Table 2. RCT received during the study

	Epoetin beta ($n = 34$)	Control ($n = 40$)
Median (range) time between randomization and start of RT,[a] days	15 (1–25)	5.5 (−1–27)
Received brachytherapy	31 (91)	36 (90)
Mean ± SD cumulative dose of HDR	29.2 ± 4.9 ($n = 21$)	24.2 ± 6.3 ($n = 22$)
Mean ± SD cumulative dose of LDR	28.4 ± 12.2 ($n = 10$)	30.1 ± 9.2 ($n = 14$)
Received external beam RT	31 (91)	38 (95)
Mean ± SD actual dose	49.2 ± 4.8	50.0 ± 5.2
Mean ± SD number of RT fractions received	27 ± 2	28 ± 3
Mean ± SD cumulative dose of cisplatin,[a] mg	345.5 ± 82.2	344.5 ± 63.0
Median (range) duration of cisplatin treatment,[a] days	36 (14–50)	36 (28–73)

SD, standard deviation; HDR, high dose rate; LDR, low dose rate.
[a]Data available for 32 patients in the epoetin group and 38 patients in the control group who received RCT during the study.

Twenty-five patients (73.5%) in the epoetin beta group and 28 (70%) in the control group remained transfusion free. The nine patients in the epoetin beta group with blood transfusions received a median of 3.3 (range: 0.9–6.4) units, and the 12 patients in the control arm received a median of 3.0 (range: 0.9–6.0) units (P = non-significant).

Primary analysis—correlation of anemia correction with treatment failures and survival

The primary analysis did not demonstrate a significant impact of Hb increase with epoetin beta on treatment failure (defined as no complete response or relapse after complete response at month 6). There were similar proportions of treatment failures in both study groups: 11 patients (32.4%) in the epoetin beta arm and 12 patients (30.0%) in the control arm met the respective criteria, that is, no correlation between treatment failure and change from baseline in Hb was observed ($P = 0.32$, logistic regression) (Table 3). Similarly, no correlation between the type of treatment (epoetin beta and control, respectively) and treatment failure was seen ($P = 0.62$, logistic regression). These results demonstrated that the study failed to meet the primary criterion at the end of stage 1 and an increase in Hb did not lead to a lower rate of treatment failures.

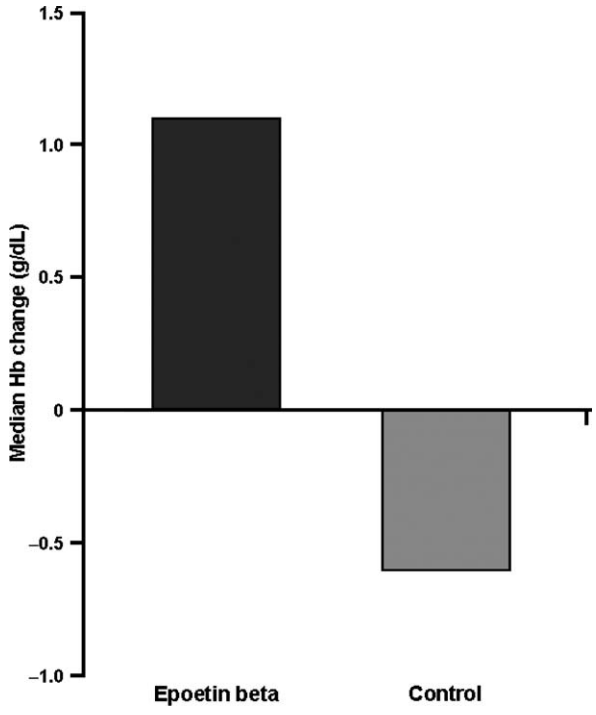

Figure 1. Median Hb change in patients with cervical cancer receiving RCT after 4 weeks of treatment compared with control.

There was no significant difference in the proportion of patients with complete response between the epoetin (18 patients [52.9%]) and control groups (23 patients [57.5%]; $P = 0.86$) (Table 3). Similar findings were observed for partial response, whereas more patients in the epoetin treatment group (20.6%) had progressive disease than the control group (7.5%; $P = 0.12$). There were no significant differences between epoetin and control groups for progression/relapse-free survival (10 events [29.4% of patients] vs 13 events [32.5% of patients], respectively [Table 3]; relative risk [RR] 0.98, 95% CI 0.43–2.23, $P = 0.96$). There were also no significant differences between treatments for overall survival (eight patients [23.5%] in the epoetin beta group and five patients [12.5%] in the control group died up to study end [Table 3]; RR 2.0, 95% CI 0.65–6.15, $P = 0.22$). In a stepwise multivariate analysis of overall survival, including FIGO stage at baseline, size of the primary lesion, need for transfusion and blood pressure as covariates, only FIGO stage was associated with an increased risk ($P = 0.001$).

Adverse events

Overall, treatment with epoetin beta was generally well tolerated. The proportion of patients reporting at least one adverse event was well matched between

Table 3. Clinical outcomes in response to RCT (intention-to-treat population)

	Epoetin beta ($n = 34$)	Control ($n = 40$)	*P*-value
Patients, *n* (%), meeting criteria for treatment failure	11 (32.4)	12 (30.0)	0.32
Patients, *n* (%), with:[a]			
Complete response	18 (52.9)	23 (57.5)	0.86
Partial response	4 (11.8)	6 (15)	0.83
Stable disease	0	3 (7.5)	—
Progressive disease	7 (20.6)	3 (7.5)	0.12
Progression/relapse-free survival, events (% patients)	10 (29.4)	13 (32.5)	0.96
Overall survival, deaths (% patients)	8 (23.5)	5 (12.5)	0.22

[a]Data on tumor response were missing for five patients in each group and are not included.

groups (epoetin arm, $n = 19$ [58%]; control arm, $n = 26$ [68%]). Most adverse events were mild to moderate in intensity. The most frequently reported adverse events are shown in Table 4, and were similar in the two groups.

Seven patients reported serious adverse events (epoetin arm: five patients [15%] reporting seven events; control arm: two patients [5%] reporting two events). The majority of serious adverse events were moderate in intensity. Only one serious adverse event was considered by the investigator to be related to study treatment: a DVT in a patient receiving epoetin beta. This patient had several other risk factors for thrombosis including hypertension, diabetes mellitus, and obesity. Only one other patient had an adverse event considered related to study treatment: an erythematous rash of moderate intensity in an epoetin beta–treated patient which resolved without sequelae.

Table 4. The most frequently reported adverse events during the study (occurring in ≥10% of patients in either group): safety population (patients receiving at least one dose of RCT and/or epoetin beta in the epoetin group and at least one dose of RCT in the control group)

Adverse event, *n* (%)	Epoetin beta ($n = 33$)	Control ($n = 38$)	*P*-value
Any adverse event	19 (58)	26 (68)	0.409
Diarrhea	9 (27)	10 (26)	0.973
Nausea	8 (24)	10 (26)	0.942
Leukopenia	7 (21)	13 (34)	0.278
Vomiting	7 (21)	7 (18)	0.877
Urinary tract infection	5 (15)	2 (5)	0.230
Fatigue	4 (12)	5 (13)	0.972
Neutropenia	4 (12)	5 (13)	0.972
Abdominal pain	4 (12)	3 (8)	0.684
Anemia	3 (9)	4 (11)	0.987
Hypokalemia	2 (6)	5 (13)	0.418
Constipation	2 (6)	4 (11)	0.637
Headache	1 (3)	4 (11)	0.313
Thrombocytopenia	1 (3)	4 (11)	0.313

Discussion

This study shows that epoetin beta in doses of approximately 30,000 IU/week rapidly, safely, and significantly increases Hb levels in women with cervical cancer who are receiving RT and cisplatin. However, no positive correlation between Hb increase and clinical outcomes, such as treatment failure (the primary study end point for stage 1, defined as patients with no complete response or relapsing within 6 months after initiation of RCT) or survival, could be established. Thus, the study did not meet the predefined criteria to proceed to its second stage and investigate the potential effects of anemia correction with epoetin beta on survival. The lack of correlation between Hb increase and clinical outcome may be explained by an overestimation of the potential treatment effects in the study design, resulting in a sample size too small to show any difference for the primary and secondary study end points investigated in the first stage of the study. Major correlations between treatment and outcome, especially of the size anticipated in the design for stage 2 (eg, a positive trend for a reduction in mortality), can be excluded; therefore, the study did not fulfill the criteria to proceed into the second stage for evaluation of the potential benefits of epoetin beta treatment on overall survival.

Various studies have confirmed that patients with anemia and cancer exhibit decreased tumor control and worse disease-free, relapse-free, and overall survival after anticancer therapy when compared with patients without anemia[13,14]. Although several mechanisms have been postulated for the worse prognosis of patients with anemia[13], anemia-related tumor hypoxia (occurring as a result of the reduced oxygen-carrying capacity of the blood and structural abnormalities within the tumor microvasculature which reduce perfusion) is likely to play the major role[20].

Studies have shown that approximately 50% of locally advanced cervical cancers demonstrate hypoxic

regions and that patients with hypoxic tumors have significantly worse disease-free and overall survival than patients without hypoxia[21]. The poor outcome of patients with tumor hypoxia was found to be mainly associated with locoregional failures with and without distant metastasis[21]. Multivariate analysis subsequently confirmed that tumor hypoxia is a powerful prognostic indicator in cervical cancer[22]. Indeed, tumor hypoxia results in a more aggressive tumor phenotype with increased resistance to anticancer therapies[23]. In addition, studies suggest that sustained hypoxia may induce proteomic and genomic changes in the tumor; these changes result in a loss of apoptotic potential, possibly allowing tumor cells to overcome nutritive deficiencies or to escape from their hostile environment by invasion or metastasis[22,24].

Inhibition of apoptosis of colony-forming, unit-erythroid cells is one of the major roles of erythropoietin in inducing erythropoiesis, thereby allowing these bone marrow precursor cells to mature into functional red blood cells[25]. Recently, erythropoietin receptors (EPO-R) have been discovered in nonhematopoietic cells and a role of erythropoietin in protection against apoptosis following hypoxic injury in the central nervous system and the heart has been postulated[26]. However, studies have also demonstrated that EPO-R may be expressed by tumor cells and that administration of erythropoietin to patients expressing such receptors may induce tumor progression[27,28]. There are often design and methodology issues with respect to the specificity of the antibody commonly used to detect EPO-R and the functional relevance of the EPO-R on cancer cells[29,30], which complicate interpretation of such studies. There is clearly a need for further research in this area.

Because a relationship has been demonstrated between falling Hb levels, tumor hypoxia and reduced survival of patients with cancer, correction of Hb levels using an erythropoietin to improve tumor oxygenation might be expected to improve the prognosis of patients with cancer. The publication of two studies in patients with head and neck cancer[31] or breast cancer[32], however, triggered an ongoing discussion of the potential negative effects of erythropoietins in patients with cancer. Importantly, in this current context, the effects on survival and disease progression observed during the first stage of the current study have to be interpreted with caution because of the small number of fatal events observed (8 vs 5 deaths in the epoetin beta vs control groups, RR 2.0, 95% CI 0.65–6.15, $P = 0.22$) and disease progression/death (10 vs 13 events, respectively, RR 0.98, 95% CI 0.43–2.23, $P = 0.96$). Although obviously not reaching statistical significance, the sample size of stage 1 is also too small to exclude from these figures any potential negative effects of erythropoietin therapy, which for overall survival may slightly favor patients in the control group.

Nevertheless, no significant difference in overall survival has been described in a larger study ($n = 229$) by Blohmer *et al.*[12] in which patients with cervical cancer received RCT in combination with epoetin or standard control care. In contrast to the present study, patients in the epoetin group had significantly ($P < 0.05$) better relapse-free survival than those who received standard care. During the study, significantly fewer patients treated with epoetin than control had anemia (21% vs 47%, respectively; $P < 0.0001$) or required transfusions (12% vs 32%, respectively; $P = 0.0004$). However, there was no significant difference in overall survival between groups ($P = 0.20$) in this study at 229 weeks (16 vs 23 events, respectively).

Importantly, the findings of the present study contrast with those of a retrospective chart review reported by Temkin *et al.*[33] in which significantly shorter survival and disease-free survival were reported in patients with locally advanced cervical cancer receiving epoetin. However, in this study, outcomes were analyzed retrospectively, with only 18 patients receiving epoetin, and it is possible that the survival differences observed could at least partially reflect differences in chemotherapy regimens between epoetin-treated and nonepoetin-treated patients.

Previous studies have investigated the benefit an improved Hb—before and during RCT—may have on treatment outcome in patients with solid tumors[17,34,35]. In patients with lung cancer treated with cisplatin and RT, those with a pretreatment Hb of greater than or equal to 11.6 g/dL had a superior 2-year survival rate to those with a pretreatment Hb below 11.6 g/dL (52.0% vs 15.5%, respectively; $P = 0.0075$)[34]. Furthermore, Dunst *et al.*[17] showed that Hb levels before and during RT are strong predictive factors for survival in patients with cervical cancer (FIGO stage IIB, IIIB, and IVA) and that a Hb of at least 11 g/dL should be maintained throughout RT. Patients with a pretreatment Hb greater than 13 g/dL had a better 3-year survival than those with Hb 11–13 g/dL or Hb less than 11 g/dL (79% vs 64% and 32%, respectively)[17]. These previous, encouraging findings could not, however, be confirmed by the current study, and potential benefits of treating anemic patients with erythropoietin prior to RCT needs further investigation. In general, the benefits of erythropoietin therapy in anemic patients with cancer are apparent;

epoetin beta has proven efficacy in both solid tumors and lymphoid malignancies for increasing Hb levels, improving quality of life and reducing need for transfusion in patients receiving chemotherapy[5–7,36–38].

As previous studies have suggested that pretreatment Hb level was an important predictive factor in patients undergoing RCT, patients randomized into the epoetin arm of this study underwent a 2-week, pretreatment period, during which they received epoetin beta to ensure acceptable Hb levels before initiation of RCT; however, RCT could be started sooner in the event of medical need. The difference in the time between randomization and initiation of RCT between the two study arms reflects this difference in treatment schedule. Indeed, 66% of control patients started RCT within 7 days of randomization, whereas a similar proportion of patients in the epoetin group (62.5%) started RCT more than 13 days after randomization. It is possible that the up to 2-week difference in initiation of RCT between the epoetin and control groups was disadvantageous to patients randomized to the epoetin beta arm. The study hypothesis was based on the assumption that these effects would be outweighed by the positive effects of epoetin beta on RCT treatment.

Epoetin was associated with a significant and sustained increase in Hb levels in the current study. In the epoetin arm, Hb levels increased from baseline by a median of 1.1 g/dL during the first 4 weeks of epoetin beta plus RCT and were maintained for the remainder of the treatment period. In contrast, Hb levels decreased in the control group by a median of 0.6 g/dL in the first 4 weeks of RCT and these reductions were also maintained for the remainder of the study. Despite the significant ($P < 0.0001$) difference in Hb levels between the epoetin beta and control groups, there was no apparent difference in the proportion of patients in the two study arms who received transfusions during the treatment period, with 73.5% of patients in the epoetin beta group and 70% of patients in the control group remaining transfusion free. One reason for the similar rates of transfusion between the two groups may have been the relatively high Hb levels at baseline. Although Hb levels decreased during the study in the control group, most patients in this group still maintained Hb levels above the transfusion trigger of 8.5 g/dL.

A recent meta-analysis has suggested that epoetins may be associated with a slightly increased risk of thromboembolic events (TEEs)[39]. However, in the current study there was only one case of DVT. Further analysis of epoetin beta data in a wider range of malignancies has shown that epoetin beta is associated with only modest increase in all TEEs (4% vs 6%, control vs epoetin beta groups, respectively) and, more importantly, is not associated with an increase in TEE-related mortality[40].

Conclusions

This study shows that epoetin beta rapidly, effectively, and safely increases Hb levels in patients with cervical cancer receiving RCT. Because no positive correlation of Hb increase and improvement in clinical outcomes such as a reduction in treatment failure could be demonstrated in stage 1 of this study, this study was not expanded to its second stage, which was designed to investigate the potential benefits of anemia correction on survival. Therefore, this study does not allow any definite conclusions to be drawn with respect to the positive or negative effects of epoetin therapy on survival or disease progression in patients with cervical cancer receiving RT.

Role of the sponsor

The trial was designed, implemented, and overseen by a scientific advisory committee (H.G.S., G.H., J.D., H.K., and Johannes Haerting) together with representatives of the sponsor F. Hoffmann-La Roche Ltd. The sponsor assisted in identification of participating centers and was responsible for monitoring of the centers, data collection, and data cleaning. The scientific advisory committee had access to all study data and was not restricted in the interpretation of the study results as presented in this manuscript.

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