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CLINICAL INVESTIGATION **Lung**

IMPROVEMENT IN PERFORMANCE STATUS AFTER ERYTHROPOIETIN TREATMENT IN LUNG CANCER PATIENTS UNDERGOING CONCURRENT CHEMORADIOTHERAPY

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Purpose: A prospective Phase II trial was carried out to evaluate the effectiveness of erythropoietin in improving or maintaining performance status as determined by the Karnofsky performance status (KPS) score and hemoglobin (Hb) levels in lung cancer patients treated with concurrent chemoradiation (CH-RT).

Methods and Materials: A total of 51 patients with lung cancer (11 with small-cell, limited stage and 40 with non–small-cell disease, 17 with Stage IIIA and 23 with Stage IIIB), who underwent three different concurrent CH-RT protocols were enrolled. Baseline Hb and KPS values were recorded, as were the nadir Hb and KPS values before concurrent CH-RT. The final Hb and KPS values were recorded the last week of concurrent CH-RT. An Hb level of ≤11 g/dL before concurrent CH-RT was required before receiving erythropoietin. Prognostic factors for KPS improvement and survival were assessed by univariate and multivariate studies.

Results: Of the 51 patients, 47 (92.3%) were men (mean age 63.6 years, range 40–75). The median baseline KPS score was 80, and the mean baseline Hb was 12.2 ± 1.76 g/dL (range 9–16.9). The mean nadir and final Hb value was 9.98 ± 0.67 g/dL (range 8.6–11) and 11.33 ± 1.59 g/dL (range 6.9–14.4), respectively. A significant increase was seen in the Hb and KPS score ($p < 0.05$) in the final measurements. Differences were found between the final and nadir Hb in the predictive value for differences in performance status ($p = 0.001$). On univariate study, pathologic findings ($p = 0.0234$), weight loss ($p = 0.0049$), baseline Hb ($p = 0.0057$), and final Hb improvement ($p = 0.0237$) were prognostic factors for survival. Nadir Hb ($p = 0.027$), final Hb improvement ($p = 0.0069$), pathologic findings ($p = 0.0006$), and weight loss ($p = 0.0001$) had significant prognostic value for survival in multivariate analysis.

Conclusion: In this study, erythropoietin appears to have a significant, beneficial impact on the KPS and Hb of patients undergoing concurrent CH-RT. © 2003 Elsevier Science Inc.

Lung cancer, Erythropoietin, Chemoradiation, Karnofsky performance status score, Anemia.

INTRODUCTION

Malignant diseases and associated cancer treatment typically impair the functional status of patients. Previous studies have proposed a link between functional status and anemia (1). Anemia occurring during cancer may be the result of several causes: chronic disease, chemotherapy (CH), radiotherapy (RT), blood loss, direct bone marrow infiltration by tumor, and decreased erythropoietin response. In a retrospective cohort study, 18% of the cancer patients receiving CH required transfusions. Of all the patients with solid tumors, transfusion for anemia was most frequently observed in those with lung cancer (34%) (2).

Transfusion for the treatment of these symptoms often carries significant risks. An estimated 20% probability exists for some associated adverse effect to occur, including fever, chills, rash, urticaria, and exposure to hepatitis (3). Immunosuppression associated with blood transfusion can also occur (4) and has been attributed to a worsening of survival in patients with various malignancies who have received blood products compared with the survival of nontransfused patients with similar histopathologic conditions and similar cancer stage (5). The administration of recombinant human erythropoietin (r-HuEPO) may be used to increase hemoglobin (Hb) levels, as well as to treat anemia symptoms, without the limitations and risks inherent in blood transfusion.

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Preliminary analysis of this study, of 27 patients, presented during American Society for Clinical Oncology Meeting, May 1999, Atlanta, GA.

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The likelihood of tumor control in some cancers treated with RT is associated with low Hb levels during treatment. In patients with head-and-neck tumors, the predictive value of Hb for survival has been demonstrated, but the reasons for a possible effect on locoregional control are not clear. The combination of r-HuEPO and oral iron supplementation has been shown to increase Hb levels significantly in cancer patients during the course of RT, and this may improve the effectiveness of RT and local control. It is not yet fully understood whether anemia is a characteristic of aggressive disease or whether low Hb values impair the effect of RT because of a reduced oxygen effect. The latter concept is supported by the observation that locoregional tumor relapse rates increase in anemic patients and, that after correction of the anemia, local tumor control and survival can be improved (6).

The efficacy of r-HuEPO in increasing Hb levels and reducing transfusion rates in these patients has been documented in other clinical trials evaluating the use of r-HuEPO in patients who received no CH, noncisplatin CH, or cisplatin-containing CH (7). The initial research reported a weekly increase in Hb of between 0.4 and 0.7 g/dL in patients who received RT and were treated with r-HuEPO at doses of 450–1000 UI/kg weekly (8). However, the impact of r-HuEPO in CH-RT is less known. In addition, increased Hb or hematocrit levels caused by r-HuEPO treatment have been associated with improved quality of life (QOL) (9), but have been in discordance with performance status assessments (8). The functional status of the patient at diagnosis or on imitation of treatment is a major determinant of outcome. This finding has been confirmed repeatedly in a broad spectrum of tumor types. The underlying basis for the dependence of outcome on functional status is probably that a patient's ability to carry out daily activities is often related to the tumor burden. In addition to the value of performance status as a prognostic indicator, longitudinal estimates of performance status as therapy progresses are valuable indicators of the net effect of the disease and its treatment on the patient (10). The Karnofsky performance status (KPS) scale, a scale commonly used to measure the performance status of individual patients, ranges from 100 (normal; no complaints; no evidence of disease), 90 (able to carry out normal activities; minor signs or symptoms of disease), to 10 (moribund; fatal processes progressing rapidly) and 0 (dead) (11).

In general, the level of anemia relates to the dose and cisplatin combinations. In our experience, nearly 50% of patients (unpublished data) with either small-cell or non–small-cell lung cancer present with anemia after neoadjuvant CH. We therefore carried out a prospective study on the effectiveness of r-HuEPO in improving or maintaining performance status according to the KPS score, which is a good indicator of functional status and only partially of QOL (12), and Hb levels in patients with lung cancer treated with concurrent CH-RT after neoadjuvant CH. Finally, we also studied prognostic factors for survival.

Table 1. Patient characteristics

Characteristic	Value
Gender (*n*)	
Male	47 (92.3)
Female	4 (7.7)
Average age (y)	63.6 (range 40–75)
Stage (*n*)	
Limited small-cell	11 (21.57)
III A non–small-cell	17 (33.34)
III B non–small-cell	23 (45.09)
Weight loss (*n*)	
0%	30 (58.8)
≤5%	14 (27.5)
>5%	7 (13.7)

Numbers in parentheses are percentages, unless noted otherwise.

METHODS AND MATERIALS

A total of 51 patients with lung cancer (11 with small-cell, limited stage and 40 with non–small-cell lung cancer, 17 with Stage IIIA and 23 with Stage IIIB; Table 1) of a total of 90 patients treated between September 1996 and September 2000 with CH-RT protocols were enrolled in this prospective protocol at our hospital. Stage IIIA and IIIB disease was clinical and pathologically established by mediastinoscopy before treatment. A baseline KPS (B-KPS) of ≥70% was required to begin primary CH.

After primary CH with cisplatin, an Hb level ≤11 g/dL was required to receive r-HuEPO (150 IU/kg s.c., three times weekly), with oral iron supplements (600 mg/d), for a maximum of 8 weeks. If the increase in Hb levels was <1 g/dL after 4 weeks of therapy, the r-HuEPO dose was increased to 300 IU/kg three times weekly. Patients with Hb levels >14 g/dL did not receive additional r-HuEPO treatment until Hb levels <12 g/dL occurred. Thus, the only two inclusion criteria were to be receiving a protocol of neoadjuvant CH with cisplatin plus concurrent CH-RT and to have Hb values ≤11 g/dL (according to the Catalonian Erythropoietin Committee law restrictions) before CH-RT.

The baseline Hb (B-Hb) and B-KPS values were recorded. Nadir Hb (N-Hb) (considering N-Hb as the level of Hb necessary to give r-HuEPO after neoadjuvant CH) and nadir KPS (N-KPS) were determined after primary CH and at least 1 week before beginning concurrent CH-RT. Finally, the final KPS (F-KPS) and final Hb (F-Hb) were determined in the last week of concurrent CH-RT.

Treatment of non–small-cell lung cancer (Stage IIIB) consisted of two cycles of i.v. cisplatin 100 mg/m^2 on Day 1 (every 28 days) and gemcitabine 1000 mg/m^2 on Days 1, 8, and 15, followed by two cycles of cisplatin 100 mg/m^2 on Day 1 and Navelbine 30 mg/m^2 i.v. on Days 1 and 8, plus modified accelerated-hyperfractionated RT, concomitant boost (1.8 Gy plus 0.88 Gy × 23 days, total 61.64 Gy in 5 weeks) (13) and two more cycles of cisplatin plus gemcitabine.

Patients with preoperative Stage IIIA disease received

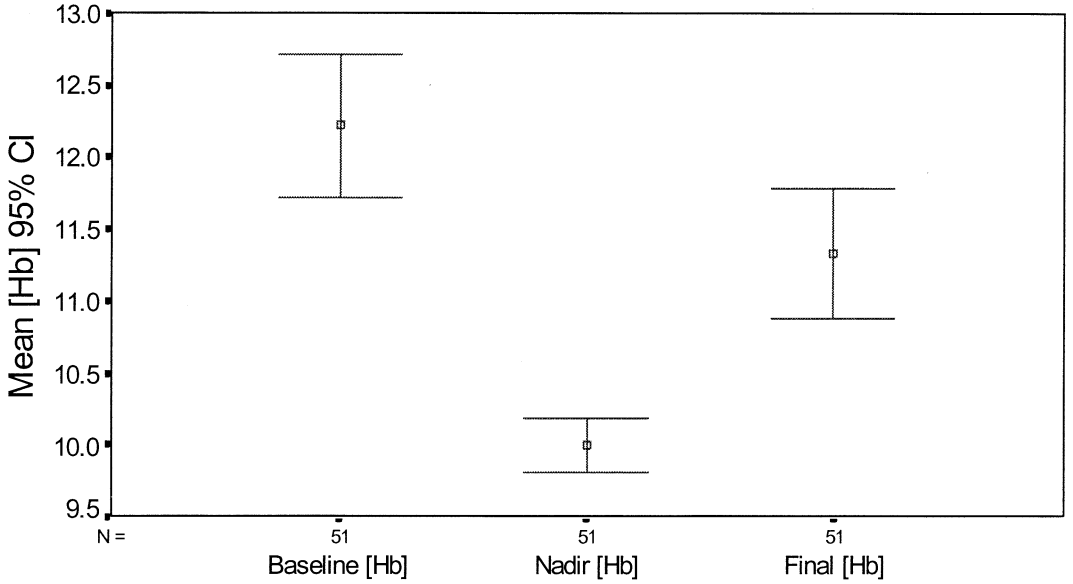


Fig. 1. Mean Hb distribution with 95% CI in Hb groups (baseline, nadir, final).

two cycles of cisplatin 80 mg/m^2 i.v., VP-16 100 mg/m^2 i.v. on Days 1, 2, 3 and ifosfamide 3 g i.v. on Day 1. RT was administered concurrently with the second cycle with the same schedule as for Stage IIIB, but for only 15 days (1.8 plus 0.88 Gy $\times$ 15 days, total dose 40.2 Gy in 3 weeks). Four to 6 weeks after the last day of RT, the patient was evaluated for thoracic surgery. In these patients, the F-Hb and F-KPS were determined in the last week of concurrent CH-RT before thoracic surgery. Four Stage IIIA patients received the Stage IIIB protocol because of medical or surgical limitations.

We administered a modification of the scheme of Turrisi *et al.* (14) in the protocol of small-cell lung cancer, with six cycles of cisplatin 90 mg/m^2 i.v. on Day 1 and VP-16 120 mg/m^2, and concurrent with the third cycle of accelerated-hyperfractionated RT (1.5 Gy b.i.d. $\times$ 15 days, total dose 45 Gy in 3 weeks).

Statistical analysis

Differences between the means were tested by the Student *t* test and analysis of variance with the multiple range Scheffé test, and a significance level of 0.05 was used to compare differences between pairs of groups (15). The nonparametric Friedman test was used to compare differences with a noncontinuous variable (KPS). Multivariate logistic regression analysis (16) was used to assess the impact on KPS and Hb improvement between the nadir and final measurements with possible prognostic variables. For this purpose, the differences for KPS and Hb were codified as categorical variables. Univariate analysis was calculated using the Kaplan-Meier method (17) to determine the prognostic features for overall survival; *p* values indicating the significance of differences by group were calculated with the Mantel-Hanzel log–rank test (18). Multivariate analysis was performed with the Cox model (19) for prognostic variables of survival.

RESULTS

Fifty-one patients with lung cancer were eligible for analysis, 47 were men (92.3%; mean age 63.6 years, range 40–75). Descriptive variables are summarized in Table 1. Fifteen patients had a B-Hb level of $\leq$11 g/dL and did not receive r-HuEPO before neoadjuvant or primary CH because of local public health care restrictions.

The median B-KPS score was 80, and 68.7% of the patients had a reduction in KPS from baseline to nadir (with a decrease of 10, 20, and 30 points in 51%, 15.7%, and 2%, respectively), previous to concurrent CH-RT, although treatment was not interrupted because of this.

A comparison of the N-KPS and F-KPS, with a mean period between both determinations of approximately 4 weeks, showed an improvement in 26 patients (51%; 19 improved by 10%, 5 by 20%, and 2 by 30%). The values remained the same in 17 patients (33.3%). In 8 patients (15.7%) the F-KPS decreased (from 70 to 60 in 4; from 80 to 70 in 3; and from 90 to 80 in 1).

The mean B-Hb was 12.2 g/dL for all patients. The decrease in Hb after CH (N-Hb) was significant (Fig. 1), with a mean of 9.99 (Table 2). After r-HuEPO administration and CH-RT treatment, the mean F-Hb was 11.33 g/dL, and only 12 patients had an Hb level $<$11 g/dL.

For the 15 patients classified as having low Hb, the mean B-Hb was 10.34 g/dL and was 13 g/dL for the other 36 patients. Although a decrease at N-Hb and Hb recovery after CH-RT with r-HuEPO, the mean differences in these patients showed only a trend toward significance ($p = 0.08$). For patients with higher B-Hb levels, the mean B-Hb, N-Hb, and F-Hb were significantly different (Table 2).

An increase in F-Hb occurred at the end of CH-RT in both the overall group of patients and the group of 15 patients with low B-Hb. In the global group, the mean increase in F-Hb was 1.33 g/dL (95% confidence interval

Table 2. KPS and Hb levels by evolution and comparison tests

	Baseline	Nadir	Final	Test/significance
KPS				
60	—	6 (11.8)	4 (7.8)	Nonparametric Friedman test
70	6 (11.8)	24 (47.1)	9 (17.6)	$\chi^2 = 38.22$
80	29 (56.9)	20 (39.2)	29 (56.9)	$p < 0.0001$
90	16 (31.4)	1 (2)	9 (17.6)	
Median	80	70	80	
Entire group ($n = 51$)				
Hb (g/dL)				
Mean ± SD	12.2 ± 1.76	9.99 ± 0.67	11.33 ± 1.59	ANOVA
Range	9–16.9	8.6–11	6.9–14.4	F = 31.38
95% CI	11.72–12.72	9.81–10.19	10.88–11.78	$p < 0.0001$
	(s)	(r)	(s)	Scheffé test with significance level
	(s)		(r)	$p < 0.05$
Low Hb group (B-Hb ≤11 g/dL, $n = 15$)				
Hb (g/dL)				
Mean ± SD	10.34 ± 0.69	9.87 ± 0.73	11.02 ± 2.18	ANOVA
Range	9–11	8.9–11	6.9–14.2	F = 2.62
95% CI	9.96–10.72	9.46–10.27	9.81–12.22	$p = 0$
				Scheffé test with significance level
				$p < 0.05$
High Hb group (B-Hb >11g/dL; $n = 36$)				
Hb (g/dL)				
Mean ± SD	13 ± 1.44	10.05 ± 0.65	11.46 ± 1.30	ANOVA
Range	11.1–16.9	8.6–11	9–14.4	F = 56.08
95% CI	12.5–13.49	9.83–10.27	11.02–11.9	$p < 0.0001$
	(s)	(r)	(s)	Scheffé test with significance level
	(s)		(r)	$p < 0.05$

Abbreviations: KPS = karnofsky performance status; Hb = hemoglobin; ANOVA = analysis of variance; CI - confidence interval; (s) = significant difference between pairs of groups; (r) = reference variable.

[CI] 0.87–1.8), with a previous decrease of 2.22 g/dL (95% CI 1.75–2.7) from B-Hb to N-Hb (Fig. 1). This increase was produced at approximately 4 weeks, which was the mean time between the N-Hb and F-Hb (mean increase 0.3325 g/dL weekly).

For patients with a high B-Hb, the mean reduction to the N-Hb was 2.95 (95% CI 2.47–3.44) and the mean F-Hb improvement was 1.41 (95% CI 0.94–1.88). In the group of 15 patients with a lower B-Hb, the improvement was less pronounced (1.15 g/dL; Fig. 2), and no differences were found between the means ($p = 0.08$).

Eight patients had a decrease in F-KPS, with a mean F-Hb of 9.43 ± 1.53 g/dL (range 6.9–11.4). In the remaining patients, in whom the F-KPS was maintained or increased, the mean F-Hb level was 11.68 ± 1.35 g/dL (range 9–14.4). The Student *t* mean comparison test showed statistically significant differences ($p < 0.001$; Fig. 3).

The F-Hb improvement was found to have predictive value for improvement in KPS (Table 3), when the differences between F-KPS and N-KPS were classified as decreased (8 patients) vs. equal or improved (43 patients). The F-Hb improvement increased the probability of KPS improvement by a factor of 4.71 (range 1.86–11.89). CH protocols, B-Hb, B-KPS, and weight loss were not predictive of Hb improvement.

In univariate analysis for survival, pathologic findings, weight loss, B-Hb, and F-Hb improvement were prognostic factors of survival. Stage, CH protocols, N-Hb, and F-KPS improvement showed only a trend toward significance (Table 4). Four variables showed a prognostic effect on multivariate analysis (Table 5).

As shown in Tables 4 and 5, patients with small-cell lung cancer had a greater survival at 1 and 2 years, increasing the survival probability by 2.3-fold.

Patients without weight loss had a better survival probability (Fig. 4), an effect that was maintained on multivariate analysis. Weight loss at diagnosis reduced survival by a factor of 0.4521.

Patients with low B-Hb had a median survival of 11.41 months, and only 49% remained alive 1 year after treatment. Those with high B-Hb had a median survival of 19.8 months

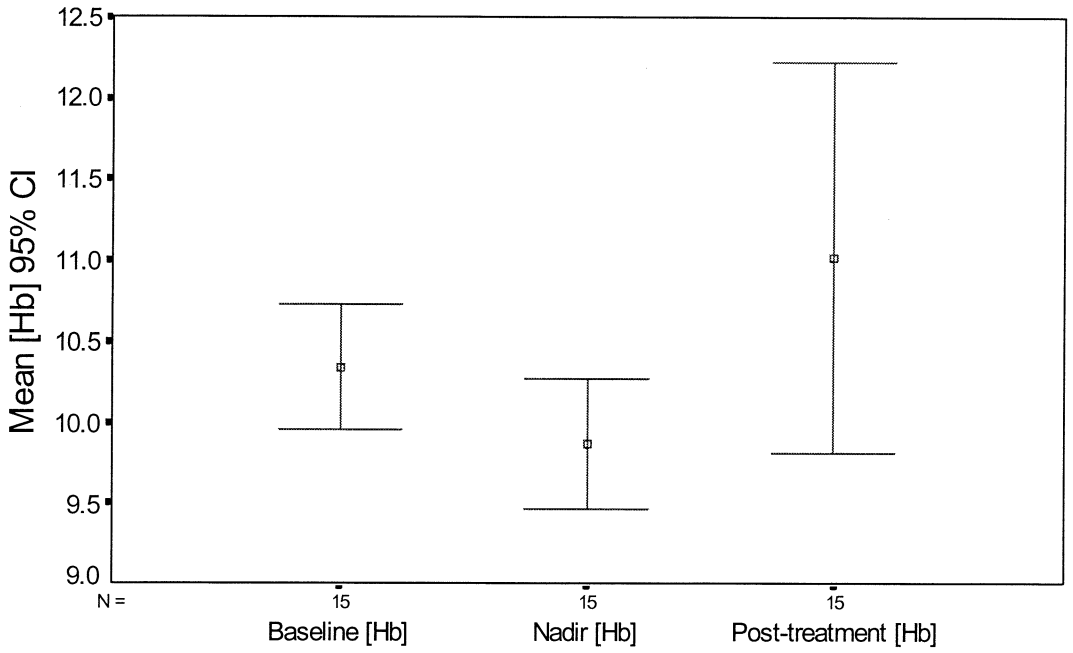


Fig. 2. Mean Hb distribution with 95% CI in Hb groups (baseline, nadir, final) for the low B-Hb group (≤11 g/dL).

with an 80% survival rate at 1 year. The differences were statistically significant (Fig. 5), although no effect was seen for this variable on multivariate analysis.

Patients with low and high N-Hb levels had a median survival and 1-year survival rate of 14.4 months and 63.33% and 19.8 months and 76.08%, respectively (Fig. 6). Multivariate analysis showed that higher N-Hb improved the survival probability 1.53-fold (Table 5).

Univariate analysis showed that F-Hb improvement was a prognostic feature for survival ($p < 0.0237$; Fig. 7). This effect was maintained on multivariate analysis (Table 5 increasing the survival probability by twofold.

DISCUSSION

Previous prospective placebo-controlled and non–placebo-controlled studies have shown that the administration of r-HuEPO to patients who have received cytotoxic CH is associated with improvement in QOL measurements (20, 21) while preventing anemia and reducing transfusion requirements (22). The positive influence of r-HuEPO on transfusion requirements has also been studied in patients receiving preoperative CH-RT for rectal cancer (23). That study was an open-label, Phase I and II, nonrandomized, two-center trial. All the patients received 50.4 Gy RT with

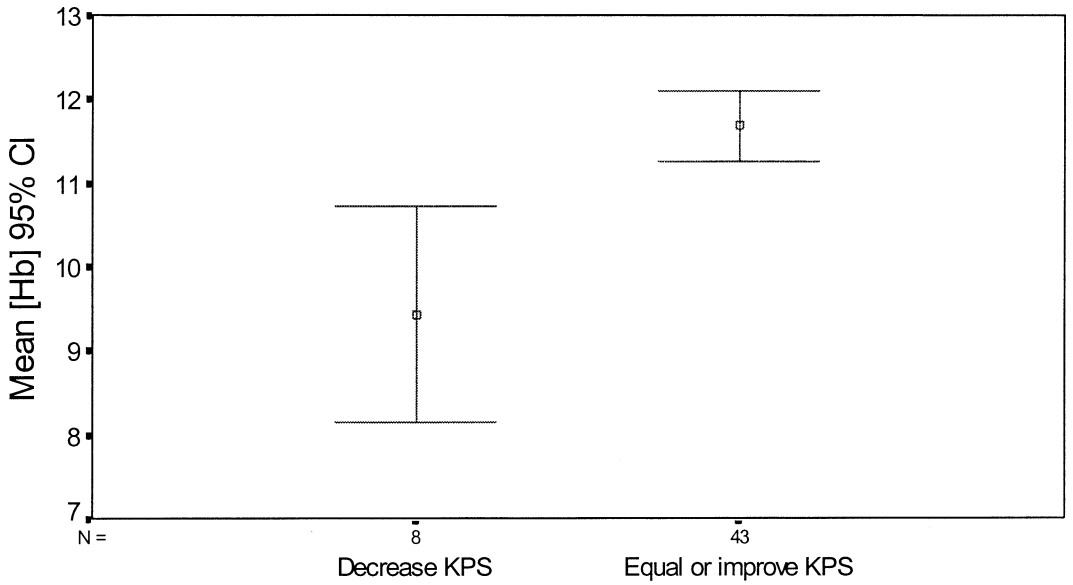


Fig. 3. Mean Hb distribution with 95% CI in F-KPS groups (decreased vs. equal or improved performance status).

Table 3. Logistic regression results for final KPS and Hb improvement

Prognostic features	KPS improvement	Hb improvement
Pathologic finding	0.1148	0.7496
Stage	0.0978	0.6500
Chemotherapy protocols	0.6058	0.5734
Baseline Hb	0.7892	0.1980
Baseline KPS	0.4394	0.7303
Weight loss	0.2176	0.8174
Final Hb improvement	0.001	—

Abbreviations as in Table 2.
Data presented as the *p* value.

5-fluorouracil infusions. The patients diagnosed with rectal cancer received 250 U/kg of r-HuEPO s.c. three times weekly during preoperative CH-RT. Oral iron was given to patients receiving r-HuEPO. The patients who received both RT and CH were used as controls. No significant differences were noted between the groups with respect to age, gender, stage, or Hb level before therapy. Hb levels were significantly higher in the r-HuEPO treatment group during Weeks 1, 3, and 5. The transfusion requirements were significantly decreased in patients who received r-HuEPO (0.4 vs. 3.7 U).

Recently, the impact of r-HuEPO administration on the efficacy of preoperative CH-RT for squamous cell carcinoma of the oral cavity and oropharynx was evaluated (24). That study found that the Hb level is an independent prognostic factor for the response to neoadjuvant CH-RT and tumor control after neoadjuvant therapy and surgery for squamous cell carcinoma of the oral cavity and oropharynx.

Another retrospective study on cervical carcinoma patients undergoing CH-RT showed that the N-Hb is highly predictive for treatment response, but the Hb level at the time of presentation did not show this effect (25).

A number of randomized clinical trials and meta-analyses now support the conclusion that platinum-based CH improves survival, symptom control, and QOL compared with the best supportive care by itself in Stage IV lung cancer and that platinum-containing CH-RT programs result in longer survival compared with RT by itself in Stage III lung cancer patients (26–28).

Table 4. Univariate analysis for overall survival by the Kaplan-Meier method

		Overall survival (%)			
Prognostic features	*N*	1 y	2 y	*p*	Events (*n*)
Stage				0.0729	
IIIa	17	68.18 (5/9)	29.83 (9/3)		11
IIIb	23	65.22 (8/15)	21.74 (18/5)		19
Limited small cell	11	90 (1/9)	60 (3/4)		4
Pathologic type				0.0234	
Non–small-cell	40	66.25 (13/24)	23.99 (27/7)		30
Small-cell	11	90 (1/9)	60 (3/4)		4
Weight loss (%)				0.0049	
0	30	82.21 (5/22)	49.20 (12/9)		16
≤5	14	46.75 (7/6)	7.79 (12/1)		12
>5	7	71.43 (2/5)	14.29 (6/1)		6
B-KPS				0.1063	
70	6	50 (3/3)	—		6
80	29	74.19 (7/19)	33.34 (15/5)		15
90	16	7.5 (4/12)	41.25 (9/6)		13
B-Hb (g/dL)				0.0057	
≤11	15	49.09 (7/6)	—		11
>11	36	8.0 (7/27)	39.23 (19/11)		23
Chemotherapy protocol				0.0756	
IIIa	13	65.63 (4/7)	39.38 (6/3)		8
IIIb	27	66.67 (9/18)	20.2 (21/5)		22
Limited small-cell	11	9.0 (1/9)	6.0 (3/4)		4
N-Hb (g/dL)				0.0881	
<10	20	63.33 (7/12)	21.11 (15/4)		17
≥10	31	76.08 (8/20)	38.65 (15/7)		17
F-KPS improvement				0.0632	
None	8	37.50 (5/3)	25 (6/2)		6
Same	17	86.67 (2/13)	55.41 (6/6)		8
Increased	26	72.69 (7/17)	16.36 (18/3)		20
F-Hb improvement				0.0237	
None or same	8	1.5 (6/1)	1.5 (6/1)		6
Increased	43	80.86 (8/32)	33.82 (24/10)		28

Abbreviations: B = baseline; N = nadir; F = final; other abbreviations as in Table 2.
Data presented as the percentage with the number of events/patients at risk in parentheses, unless otherwise noted.

Table 5. Multivariate Cox analysis for overall survival

Prognostic feature	e^{beta}	Beta	Standard error	χ^2	p
Weight loss	0.4520	−0.7941	0.2088	15.0582	0.0001
Final Hb improvement	2.2042	0.7904	0.2681	7.2930	0.0069
Pathologic finding	2.3102	0.8373	0.2843	11.7101	0.0006
Nadir Hb	1.5297	0.4251	0.1932	4.8917	0.0270

Abbreviation: Hb = hemoglobin.

For patients with good performance status and little cancer-related weight loss, there are both long-term and short-term survival advantages in receiving platinum-based CH and RT together, although these aggressive multimodality treatments may produce greater Grade 3 hematologic toxicity and esophagitis rates, affecting functional status. Investigators have sought to identify effective cytoprotection agents to avoid these complications. In this study, we attempted to do the same, although from a supportive level. Because anemia is a frequent complication in cancer treatment and is associated with a decreased QOL and impaired performance status and tissue oxygenation, critical for the efficacy of RT, we carried out a prospective study on the effectiveness of r-HuEPO to improve or maintain the KPS score and Hb level in patients with lung cancer treated with aggressive concurrent CH-RT protocols. The survival prognostic factors for lung cancer were also studied for this group of patients.

In our study, F-Hb improvement had a strong positive predictive value on F-KPS improvement, increasing the latter by a factor of 4.71 (range 1.86–11.89). We also found that F-Hb improvement, small cell histologic subtype, higher N-Hb, and the absence of weight loss at diagnosis were positive prognostic factors for survival on multivariate study; B-Hb only showed prognostic significance on univariate analysis.

Although B-KPS is considered a very important prognostic factor for survival in lung cancer patients, no effect was observed on survival in this study. This may be explained by the selection criteria for primary CH and the small percentage of patients with a KPS reduction <70% during treatment.

As far as we know, our study is the first in lung cancer patients to attempt to maintain KPS by control of anemia and thus improve CH-RT results by achieving treatment compliance, with a consequent effect on survival observed. Maintenance of nearly normal Hb levels during CH-RT improved KPS, and an improvement in survival was seen.

A meta-analysis determining whether anemia is an independent prognostic factor for survival in patients with cancer concluded that the relative risk of death increased by a factor of 1.9 (95% CI 1.10–1.29) in anemic patients with lung cancer (29).

Our results agree with the cited meta-analysis in that they also demonstrated the importance of N-Hb levels before radical treatment with CH-RT. However, in the case of B-Hb, our results only agree, in part, because, as previously noted, they lost significance on univariate analysis, probably because of the greater statistical weight of the other prognostic variables. In regard to N-Hb, our results also agree, showing a decreased survival in patients with low N-Hb, although low B-Hb did not have an impact when adjusted for other factors.

However, despite the heterogeneous, relatively small, group of patients, r-HuEPO intervention was of great benefit to these patients, because the improvement in F-Hb levels clearly improved the F-KPS, thereby confirming our initial hypothesis.

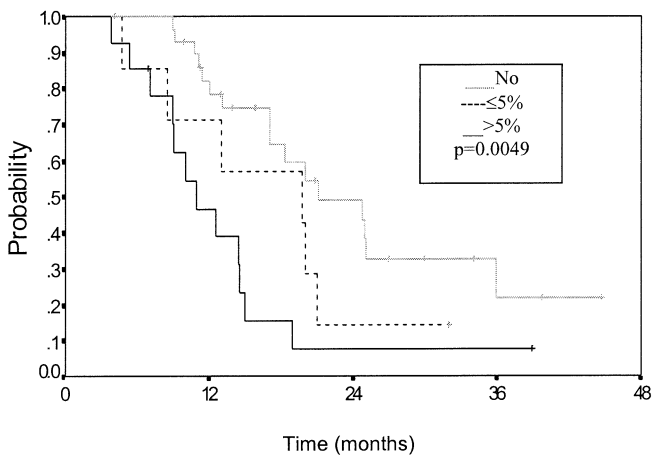


Fig. 4. Survival by weight loss (Kaplan-Meier method).

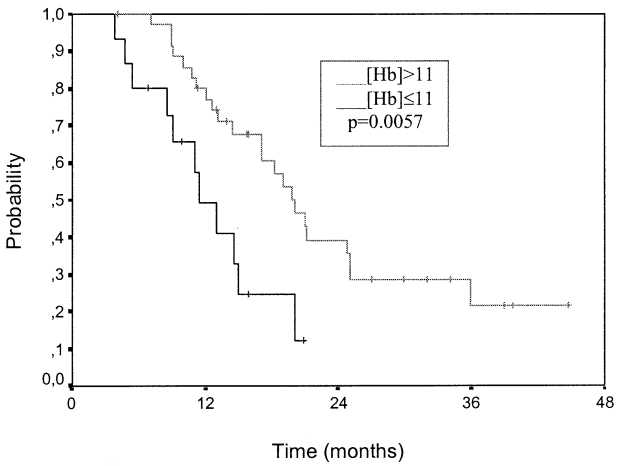


Fig. 5. Survival by B-Hb (Kaplan-Meier method).

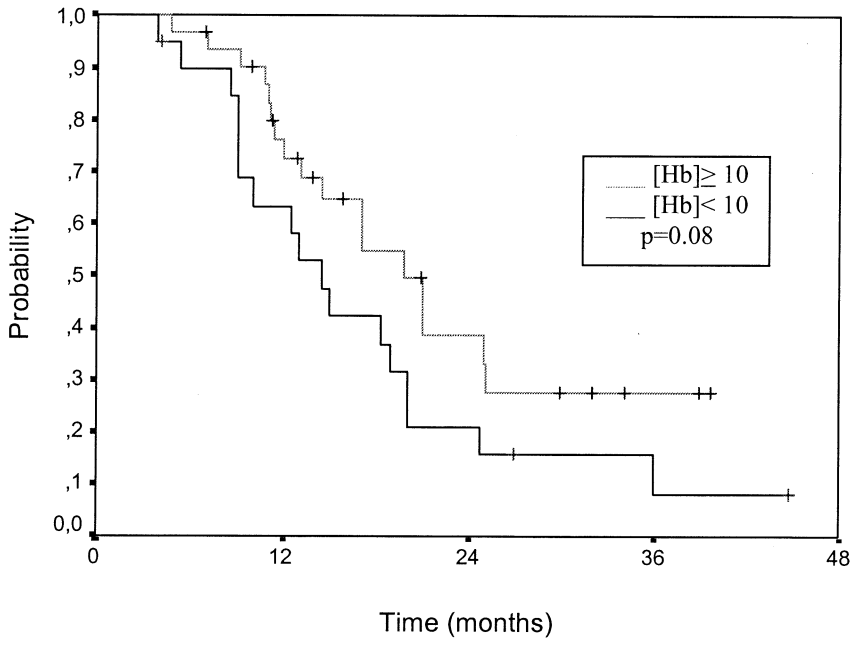


Fig. 6. Survival by N-Hb (Kaplan-Meier method).

We suggest that small-cell histologic subtype has a predictive prognostic factor for survival, probably secondary to the increase observed in patients with limited stage who are treated with early CH and hyperfractionated RT according to the schedule by Turrisi *et al.* (30) that we modified and adopted in 1994, with similar results in survival (unpublished data).

Because of public health care restrictions in Catalonia, r-HuEpo was initiated in patients with a low level of N-Hb, which may have been slightly disadvantageous to those with lower levels, because we have shown that a lower N-Hb correlates significantly with survival. To correct this, and after changes in these restrictions, we currently perform a more active intervention to maintain Hb levels within nonanemic levels in accordance with the World Health Organization anemia classification (31). The aim of future studies should be to assess the impact of this antianemic intervention on local control and survival in patients with N-Hb $\leq$11 g/dL vs. $>$11 g/dL. Moreover, an appropriate QOL scale (European Organization for Research and Treatment of Cancer, Functional Assessment of Cancer Therapy Anemia [FACT-L], Lung Cancer Symptoms Scale [LCSS]) should be added to KPS measurement to increase the knowledge of QOL construct, because the measurement of functional status is only one aspect of QOL.

Despite the limited number and heterogeneity of patients

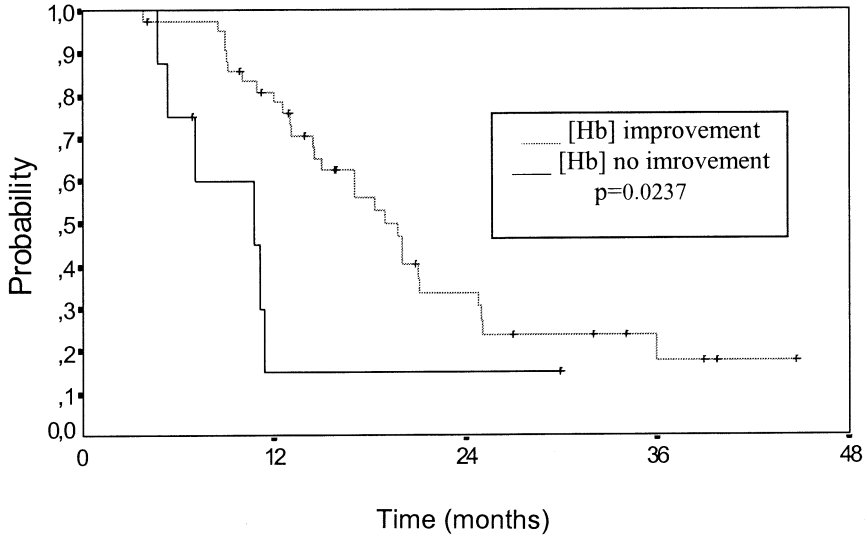


Fig. 7. Survival by Hb improvement (Kaplan-Meier method).

in our study (small-cell lung cancer and non–small-cell lung cancer), r-HuEPO administration appears to have had a significant, beneficial impact on the KPS score, Hb level, completion of radical treatment, and probably also on survival in patients with lung cancer receiving concurrent CH-RT after neoadjuvant CH. Our results justify additional randomized studies in this field comparing r-HuEPO administration in patients with different levels of Hb (mild anemia vs. maintenance of normal values according to World Health Organization), evaluating their impact, together with other known prognostic factors on survival.

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