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SHORT COMMUNICATIONS AND CASE REPORTS

Erythropoietin and radiotherapy in lung cancer patients

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Summary

Purpose: *To evaluate the effectiveness of recombinant human erythropoietin (rhEPO) in relation to low hemoglobin (Hb) level, overall tumor response rates, and rhEPO adverse events in patients with lung cancer undergoing radiotherapy (RT).*

Patients and methods: *Thirteen consecutive patients were included. All of them had measurable tumor before RT. 150 IU/kg of rhEPO-α or -β were administered 3 times per week, 7-10 days before RT. The target Hb value was 13 g/dl. Tumor response was assessed 6 weeks after completion of RT.*

Results: *Response to rhEPO was seen 62% (n=8) of the patients. Weekly mean Hb increment was 0.69 g/dl (range 0.42-1). The mean Hb value during RT was 13.2 g/dl (range 9-14.7) in responding patients, and 10.7 g/dl (range 9.7-11.8) in non-responding patients (p=0.005). Overall response rates to RT were significantly higher in responding than in non-responding patients (p=0.034).*

Conclusion: *rhEPO increased Hb levels in lung cancer patients undergoing RT. However, safety, and more importantly, indications need further clarifications.*

Key words: hemoglobin, lung cancer, radiotherapy, rhEPO

Introduction

Anemia in patients with cancer is considered to lessen the efficacy of RT by increasing the tumor hypoxia. Anemia associated with malignancy could be corrected by rhEPO which stimulates the proliferation of red blood progenitor cells [1,2].

Optimal oxygen pressure in the tumor was accepted in patients with an Hb value of 12-14 g/dl [3]. Moreover, transfusion is reserved for patients whose Hb level below 10 g/dl [4,5]. Furthermore, more than one blood transfusion should be performed during RT because of the Hb level reached by transfusion is maintained for approximately 15 days [6].

The objectives of this study were to evaluate the effectiveness of rhEPO in relation to low Hb level, toxicities or adverse events associated with rhEPO and overall tumor response in lung cancer patients undergoing RT.

Patients and methods

Thirteen consecutive patients treated with RT for lung carcinoma who also received rhEPO for anemia (Hb 10-13 g/dl) between January 2000 and April 2001 were included in this study. All of them had measurable tumor before RT. Complete blood count was performed weekly for each patient before and during RT.

150 IU/kg of rhEPO-α or -β were administered 3 times per week, 7-10 days before RT until the Hb level reached 13 g/dl during RT. If Hb target values exceeded 13 g/dl, rhEPO was withdrawn. All of the patients were given iron supplements along with rhEPO.

RT delivered to the primary tumor and areas of known nodal disease was 66 Gy for non-small cell lung carcinoma (NSCLC) and 56 Gy for small-cell lung carcinoma (SCLC).

Acute toxicities were scored using the RTOG tox-

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icity criteria. Tumor response was assessed according WHO methodology by CT scans.

Statistical methods

Two-tailed x^2 test was used for comparative analysis between categorical variables. Fisher's exact test was used to compare the relationship between the different parameters.

Results

Patient characteristics are shown in Table 1. Table 2 shows rhEPO results. Hb values increased in 8 (62%) patients. The weekly mean Hb increment was 0.69 g/dl (0.42-1). No Hb level more than 14.7 g/dl was recorded during RT.

Table 1. Patient and disease and characteristics

Characteristic	*n (%)*
Age (years), median (range)	60 (38-69)
Histopathology	
NSCLC	8 (61)
SCLC	5 (39)
Stage	
NSCLC	
IIIA	3 (22)
IIIB	5 (39)
SCLC	
Limited disease	5 (39)
Neoadjuvant ChT	
Yes	10 (77)
No	3 (23)
Weight loss ≥10%	
Yes	4 (31)
No	9 (69)
Smoking	
Yes	12 (92)
No	1 (8)

NSCLC: non-small cell lung carcinoma, SCLC: small cell lung carcinoma, ChT: chemotherapy

rhEPO was administered for 2-8 weeks (median 4 during RT). After Hb reached 13 g/dl rhEPO was stopped and Hb level of ≥ 13 g/dl was maintained for an additional 2-5 weeks (median 4). The mean Hb value during RT was 13.2 g/dl (range 9-14.7) in responding patients and 10.7 g/dl (range 9.7-11.8) in non responding patients (p=0.005).

In one patient the Hb value dropped below 13 g/dl 2 weeks later, so readministration of rhEPO started. However, that patient was unable to reach the target level again.

In another patient Hb values did not reach the target value; that patient was shown to have obstructive pneumonia unresponsive to antibiotic treatment.

At the end of the 3rd month visit after RT completion bone metastasis developed in 3 patients (1 with NSCLC, 2 with SCLC), whereas at the 8th week after RT completion brain metastasis developed in 1 patient with SCLC.

Tumor progression was not seen in the radiation portal at the 6th week after RT completion. Complete response to RT was seen only in 1 (8%) patient in the non-responsive group compared with 5 (39%) patients in the responsive group (p=0.043). Overall response rates were significantly higher in responsive patients than in non-responsive ones (55 vs. 16%; p=0.034). Pre-RT Hb levels had no impact on tumor response (p=0.2).

rhEPO response was found in 5 of 8 (63%) patients with NSCLC and in 3 of 5 (60%) patients with SCLC. Moreover, response rates to rhEPO were similar between the 2 histological subtypes (p=0.6; Table 3).

Four (31%) patients experienced weight loss more than 10% of total body weight before diagnosis, Hb values did not reach 13 g/dl and early distant metastasis occurred in all of them. There was statistically significant inverse relation between weight loss and rhEPO response (p=0.007; Table 3).

All of the rhEPO-related adverse events were of grade 1. Hypertension in one (8%) patient and skin irritation at the injection site in another one (8%) were observed. Thromboembolic events did not occur.

Table 2. Results of rhEPO administration

		p-value
Mean (range) Hb level at the beginning of RT (g/dl)	9.9 (9-11.2)	
Mean (range) weekly Hb increment (g/dl)	0.69 (0.42-1)	
Mean (range) Hb value during RT (g/dl)		
Non responsive patients	10.7 (9.7-11.8)	0.05
Responsive patients	13.2 (9-14.7)	
Mean (range) Hb level at the 5th week during RT (g/dl)		
Non responsive patients	11.1 (10.2-12)	0.01
Responsive patients	13.4 (12.6-13.9)	

Hb: hemoglobin, RT: radiotherapy

Table 3. Relationship between rhEPO response and other factors

Patients (n=13)	*Non-reponsive patients n (%)*	*Responsive patients n (%)*	*p-value*
Histopathology			
NSCLC	3 (23)	5 (39)	0.6
SCLC	2 (15)	3 (23)	
Weight loss ≥10%			
Yes	4 (31)	0	0.007
No	0	9 (69)	

NSCLC: non-small cell lung carcinoma, SCLC: small cell lung carcinoma

Discussion

This study showed that the use of rhEPO increased Hb level during RT. In addition, Hb level was maintained more than 13 g/dl in responsive patients during RT. Moreover, we found a significant relationship between rhEPO response and tumor response. Safety evaluations confirmed that rhEPO was well tolerated in patients receiving RT.

There was no significant relation between pre-RT Hb levels and response rates to RT in our study. Our results are in concordance with previous reports [7]. Moreover, overall response rate to RT significantly increased in rhEPO-responsive patients whom mean Hb level was 13.2 g/d during RT (p=0.034).

In our study not all patients responded equally well to rhEPO. Response to rhEPO is affected by disease and treatment factors [8-10]. In our study, one patient who did not respond to rhEPO treatment experienced obstructive pneumonia during RT, so this rhEPO failure might be related to the infection in this patient. Moreover, distant metastases were observed shortly after RT completion in 4 patients with rhEPO failure. In all patients who experienced weight loss, early distant metastases were observed in the current study. In addition, our results showed that weight loss significantly decreased rhEPO response (p=0.007).

In conclusion, treatment with rhEPO increases Hb levels and reduces transfusional needs in patients with lung cancer undergoing RT. However, the effectiveness, indications, and issues regarding safety of rhEPO need to be investigated in future studies with larger numbers of cancer patients.

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