Pergamon

European Journal of Cancer, Vol. 33, No. 14, pp. 2428–2431, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(97)00264-5

Short Communication

Management of Chemotherapy-related Anaemia with Low-dose Recombinant Human Erythropoietin in Patients with Small Cell Lung Cancer

K. Zarogoulidis, A. Papagiannis, E. Ziogas, E. Fahantidou, G. Dermitzakis, D. Gioulekas and C. Vamvalis

Lung Tumour Research Section, Pulmonary Department, Aristotelion University of Thessaloniki, G. Papanicolaou General Hospital, GR 570 10 Thessaloniki, Greece

We examined the efficacy of low-dose erythropoietin in the management of chemotherapy-related anaemia in patients with small cell lung cancer (SCLC). We gave recombinant human erythropoietin A (rHuEPO) to 63 SCLC patients, 30 with limited disease (LD) and 33 with extensive disease (ED) who underwent chemotherapy with carboplatin, etoposide and ifosfamide and had previously received blood transfusions for chemotherapy-related anaemia. rHuEPO was given at a dose of 2000 IU subcutaneously three times per week for 2 weeks after every chemotherapy cycle, starting 48 h after the end of chemotherapy. Before the use of rHuEPO, all patients in both groups had to be transfused after a mean of 5.5 CT cycles. In 64 CT cycles following administration of rHuEPO, only 5/30 LD patients (17%) had to be transfused in six cycles (9%). In 88 cycles following the use of rHuEPO, 7/33 ED patients (21%) had to be transfused in 11 cycles (12.5%). Haemoglobin values in patients with ED (but not those with LD) were significantly improved after rHuEPO administration on both day 14 and day 28 after chemotherapy. No adverse effects were recorded. rHuEPO considerably decreased the degree of anaemia and the need for blood transfusion at doses markedly lower (25–30 IU/kg body weight) than those reported in the literature so far (150 IU/kg body weight), without toxicity. © **1997 Elsevier Science Ltd.**

Key words: erythropoietin, anaemia, chemotherapy, small cell lung cancer
Eur J Cancer, Vol. 33, No. 14, pp. 2428–2431, 1997

INTRODUCTION

ANAEMIA IS the most common haematological manifestation of cancer. It may be due to many factors such as blood loss, bone marrow infiltration by tumour, poor nutrition and cachexia, hypersplenism, and immune haemolysis, but in many cases no specific causative factor can be identified (anaemia of chronic disease). The problem of anaemia is compounded by the toxic effects of radiotherapy or chemotherapy, especially with high-dose, platinum-based regimens. The use of aggressive combination chemotherapy has yielded the best response rates and led to a significant improvement in the survival of patients with small cell lung cancer (SCLC) [1]. The development of treatment-related anaemia may delay the administration of chemotherapy, and this in turn may decrease the efficacy of treatment or necessitate frequent blood transfusions. It also probably contributes to the impaired quality of life of these patients who already face the many stresses of malignancy.

Erythropoietin (EPO) is a natural hormone that promotes the proliferation and maintains the viability of erythroid progenitor cells [2]. It was purified by Miyake [3] and its gene has been cloned. The commercial production of recombinant human erythropoietin (rHuEPO) led to the introduction of this substance in clinical practice. Naturally enough, rHuEPO was first used to manage the anaemia of chronic renal failure, and produced dose-dependent erythropoietic responses in doses of 15 IU/kg upwards per administration [4, 5]. These responses were associated with highly significant

Correspondence to K. Zarogoulidis.
Received 3 Feb. 1997; revised 9 May 1997; accepted 15 May 1997.
Presented in abstract form at the European Respiratory Society Congress in Stockholm, 7–11 September 1996.

improvements in the quality of life and functional status of the patients [6]. Following this success, Erslev in 1987 [7] predicted that in the future erythropoietin would probably be investigated as a possible treatment for almost all types of anaemia, and this prediction has been borne out in the last few years. So far rHuEPO has been used for the management of anaemia in rheumatoid arthritis [8], chronic disease [9], AIDS [10], cancer [11, 12] and inflammatory bowel disease [13], with varying degrees of success. In the studies reported in the literature rHuEPO has been given at doses ranging from 50 to 300 IU/kg body weight, producing a dose-dependent response [2]. Such treatment has a considerable cost, and this increases the financial burden of neoplastic disease.

Over the last few years we have used rHuEPO at a lower dose schedule in the management of chemotherapy-related anaemia in patients with both SCLC and NSCLC. The results achieved in the latter tumour have been presented elsewhere [14]. In this paper we describe our experience with this regimen in SCLC.

PATIENTS AND METHODS

We examined retrospectively our records for patients with SCLC who had been given recombinant human erythropoietin A (Eprex, Janssen-Cilag Pharmaceutica) at some time during their chemotherapy. Each chemotherapy cycle consisted of carboplatin (equivalent to an area under the curve [AUC] of 7 mg/ml.min) on day 1, ifosfamide 3.5 mg/m^2 plus mesna on day 1 and etoposide 200 mg/m^2 given over days 1–3. This was repeated every 28 days for up to eight cycles, depending on patient response and tolerance.

Haemoglobin (Hb) values were obtained before the onset of chemotherapy (baseline) and on 14 (D14) and 28 days (D28) of each cycle. If the value of Hb was lower than 10 g/dl on day 28, blood transfusion was given along with the next cycle of chemotherapy, which was thus not delayed.

On day 28 patients whose Hb fell below 10 g/dl were given rHuEPO at a dose of 2000 IU subcutaneously three times per week for 2 weeks after every subsequent chemotherapy cycle, the first dose given 48 h after the end of chemotherapy.

Table 1. *Mean haemoglobin levels before and after treatment with rHuEPO*

	Limited disease HB (Mean ± S.D.; n=30)		Extensive disease HB (Mean ± S.D.; n = 33)	
	Pre-EPO	Post-EPO	Pre-EPO	Post-EPO
Baseline HB	12.48 ± 1.72	12.48 ± 1.72	12.37 ± 1.7	12.37 ± 1.7
Day 14	10.12 ± 0.82	10.86 ± 1.86	10.00 ± 0.75	11.27 ± 0.79
	NS		P < 0.001	
Day 28	10.25 ± 0.93	10.75 ± 0.70	10.32 ± 0.94	11.51 ± 0.85
	NS		P < 0.001	

For the purpose of this study we compared the D14 and D28 Hb values obtained before and after the use of rHuEPO, as well as the need for blood transfusion after the introduction of rHuEPO. Statistical comparisons were made by use of the unpaired t-test.

RESULTS

Between 1991 and 1995, we identified 63 SCLC patients (Table 1), all male, 30 with limited disease (LD; mean age ± S.D. 61.1 ± 7.4 years; no bone metastases) and 33 with extensive disease (ED; mean age ± S.D. 61.2 ± 6.4 years; 11 had bone metastases), who underwent chemotherapy in our department and had to receive blood transfusions and subsequently rHuEPO. Before the use of rHuEPO, all patients in both groups had to be transfused after a mean of 5.5 chemotherapy cycles. In 64 chemotherapy cycles after the introduction of rHuEPO, only 5/30 LD patients (17%) had to be transfused in six cycles (9%). In 88 cycles followed by the use of rHuEPO, 7/33 ED patients (21%) had to be transfused in 11 cycles (12.5%). Granulocyte colony stimulating factor (G-CSF) was also used after 17/64 cycles in LD and 28/88 cycles in ED patients for concomitant neutropenia.

The values of Hb at baseline, D14 and D28 for both groups before and after the use of rHuEPO are shown in Table 1 and Figure 1. There was a significant improvement after the introduction of EPO (P < 0.001).

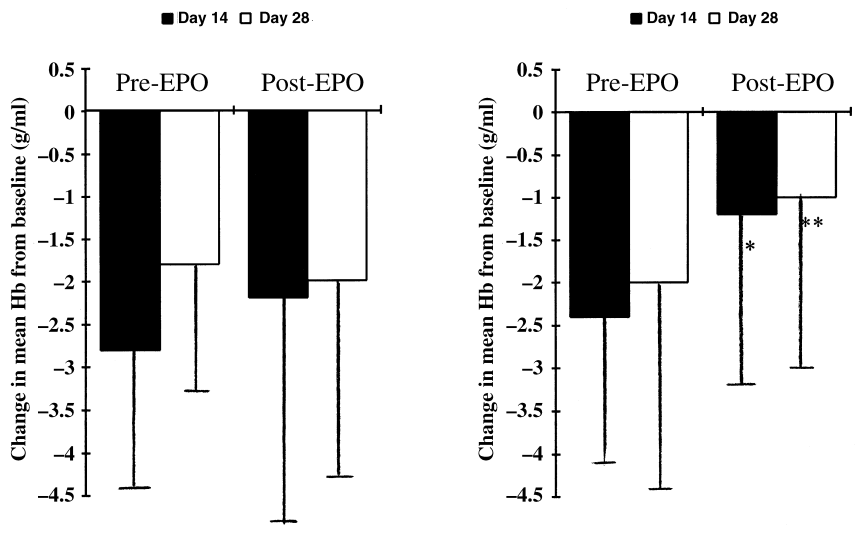

Figure 1. Haemoglobin values (mean ± S.D.) at baseline and after transfusion and rHuEPO.

None of our patients had to stop rHuEPO because of drug intolerance or technical difficulties. There were no reports of untoward reactions and none of the recorded side-effects of rHuEPO, such as hypertension and thrombocythaemia, were observed. Most patients experienced mild to moderate influenza-like symptoms (fever, myalgias, malaise), which were prevented when oral paracetamol was taken 30 min before injections.

DISCUSSION

In this study we observed a significant improvement in Hb values both on day 14 and day 28 after the introduction of rHuEPO in patients with extensive SCLC. This beneficial effect of rHuEPO was not seen in patients with limited disease. Endogenous EPO levels vary widely in different subjects, and cancer patients seem to have markedly depressed EPO production. Also, the response rate in published studies has been quite broad, ranging from 32% to 85% [2]. As we did not assay EPO in our population, we can only speculate that this factor may have been responsible for the lack of response. However, in both groups there was a considerable decrease in the need for blood transfusion.

Other factors that might be involved in the anaemia would be iron deficiency and bone marrow infiltration. Iron studies were not routinely done in our patients, but the red cell indices (mean corpuscular volume and haemoglobin concentration) were mostly normal. None of our patients used iron supplements. Again, bone marrow aspiration was not part of our routine screening procedure, although bone metastases were detected before chemotherapy in 11 of the patients with extensive disease. However, it has been documented that tumour type, bone marrow involvement or previous chemo- or radiotherapy do not significantly influence patients' response to EPO [2].

One might argue that the appearance of significant anaemia after a median of 5.5 cycles would have very little impact in the administration of further chemotherapy if patients were to receive only six cycles of treatment. At the time of the study all patients were planned to receive eight cycles of chemotherapy followed by irradiation of the primary site and prophylactic cranial irradiation in the responders. There are data showing that progression-free interval in SCLC patients is improved in those receiving more cycles of chemotherapy [15]. A large proportion of the patients attending our department have extensive disease, and we elect to give eight cycles as standard treatment if there is no other contraindication. There have also been reports of improved quality of life and performance status in patients who responded to EPO [2], and this concurs with the observations in chronic renal failure [6]. As we did not assess these parameters in our patients, we can only speculate that responding patients had an improved quality of life with increased Hb levels.

Transfusion practice varies in oncological centres, and some authorities might consider a haemoglobin level of 10 g/dl quite adequate for chemotherapy purposes. Our experience suggested a more favourable course when patients were transfused at a higher Hb level. The decision to transfuse each individual patient was made after consideration of factors such as distance from the treatment centre and the nearest facility where patients could have their scheduled blood tests, as well as their social circumstances and previous state of health. We did not encounter any patients with religious objections to blood transfusion, for whom rHuEPO might represent a useful and acceptable alternative.

None of the adverse effects recorded in the literature were observed or reported by our patients. This may be related to the lower dose of rHuEPO we used. In particular, there was no occurrence of thrombotic episodes, nor was there a difference in platelet counts before and after the introduction of rHuEPO. In anaemic patients dependent on dialysis, rHuEPO has been found to promote proliferation of both multipotent and myeloid progenitor cells [16, 17]. However, no significant changes in white cell or platelet count were observed as a consequence of EPO therapy in cancer patients [2]. In fact, an rHuEPO-related increase in the platelet count might even be beneficial, as thrombocytopenia is also a common problem in such patients, and its management can be more difficult than that of anaemia.

A significant finding in this study was the efficacy of rHuEPO at dose levels much lower than those so far reported in the literature. On average, the dose we used corresponded to 25–30 IU/kg body weight, while in the studies previously published doses of 50–300 IU/kg body weight have been used [2], producing a dose-dependent response. For purely practical reasons we used a fixed dose of 2000 IU per injection, rather than a body weight based regimen. This lower dose regimen may have considerable cost implications as well as be responsible for the absence of troublesome side-effects from our patients. Ludwig [12] used a dose of 300 IU/kg body weight in cancer patients who did not respond to 150 IU/kg of rHuEPO after 6 weeks of treatment, and the higher dose produced additional responses. We did give a dose of 10 000 IU of rHuEPO per injection to some of the initial non-responders, but we do not have sufficient data to draw any conclusions.

We can only speculate whether the results would be similar in cases of anaemia due to cancer alone and not to chemotherapy. Certainly the experience with rHuEPO in renal failure might be different as patients with non-functioning kidneys may have no endogenous EPO production. We did not estimate this production in our patients, who all had to have a normal serum creatinine level to be eligible for chemotherapy.

This study was a retrospective analysis of practice in our department, and its results obviously do not carry the weight of a randomised controlled trial. The use of rHuEPO in a fixed, low-dose regimen significantly improved chemotherapy-related anaemia in patients with extensive SCLC, and may be a useful alternative to blood transfusion. The choice of one or the other method will have to based not only on financial cost, but also on the availability of blood donors or the recombinant product, local facilities and patient circumstances and possibly personal beliefs or objections to blood transfusion. We believe that the use of rHuEPO in this context merits more detailed study.

1. Aisner J, Alberto P, Bitran J, *et al.* Role of chemotherapy in small cell lung cancer: A consensus report of the International Association for the Study of Lung Cancer workshop. *Cancer Treat Rep* 1983, **67**, 37–43.
2. Spivak JL. Recombinant human erythropoietin and the anemia of cancer. *Blood* 1994, **84**, 997–1004.
3. Miyake T, Kung CK, Goldwasser E. Purification of human erythropoietin. *J Biol Chem* 1977, **252**, 5558–5564.

4. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin: results of a Phase I and II clinical trial. *N Engl J Med* 1987, **316**, 73–78.
5. Winearls CG, Oliver DO, Pippard MJ, Reid C, Downing MR, Cotes PM. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* 1986, **2**, 1175–1178.
6. Amerling R, Levin NW. Erythropoietin update. *The Kidney* 1993, **26**, 1–7.
7. Erslev A. Erythropoietin coming of age. *N Engl J Med* 1987, **316**, 101–103.
8. Smith MA, Knight SM, Maddison PJ, Smith JG. Anaemia of chronic disease in rheumatoid arthritis: effect of the blunted response to erythropoietin and of interleukin-1 production by marrow macrophages. *Ann Rheum Dis* 1992, **51**, 753–757.
9. Henry DH. Changing patterns of care in the management of anemia. *Semin Oncol* 1992, **19** (Suppl. 8), 3–7.
10. Fischl M, Galpin JE, Levine JD, *et al.* Recombinant human erythropoietin for patients with AIDS treated with zidovudine. *N Engl J Med* 1990, **322**, 1488–1493.
11. Oster W, Hermann F, Gamm H, *et al.* Erythropoietin for the treatment of anaemia of malignancy associated with neoplastic bone marrow infiltration. *J Clin Oncol* 1990, **8**, 956–962.
12. Ludwig H, Fritz E, Leitgeb C, Pecherstorfer M, Samonigg H, Schuster J. Prediction of response to erythropoietin treatment in chronic anemia of cancer. *Blood* 1994, **84**, 1056–1063.
13. Schreiber S, Howaldt S, Schnoor M, *et al.* Recombinant erythropoietin for the treatment of anemia in inflammatory bowel disease. *N Engl J Med* 1996, **334**, 619–623.
14. Zarogoulidis K, Papagiannis A, Fahantidou E, Hatziapostolou P, Constantinidis TC. The role of erythropoietin in the management of chemotherapy-related anaemia in patients with non small cell lung cancer. *Proc 2nd Int Congress on Lung Cancer*, Crete, Sept. 9–13, 1996, 435–439.
15. Ihde DC, Pass HI, Glatstein EJ. Small cell lung cancer. In DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*, 4th edn. Lippincott, Philadelphia, 1994, 739.
16. Dessypris EN, Graber SE, Krantz SB, Stone WJ. Effects of recombinant erythropoietin on the concentration and cycling status of human marrow hematopoietic progenitor cells *in vivo*. *Blood* 1988, **72**, 2060–2062.
17. Stockenhuber F, Kurz RW, Geissler K, *et al.* Recombinant human erythropoietin activates a broad spectrum of progenitor cells. *Kidney Int* 1990, **37**, 150–156.