Eur J Cancer, Vol. 29A, Suppl. 2, pp. S13-S14, 1993
Printed in Great Britain

0964-1947/93 $6.00+0.00

Erythropoietin for the Prevention of Anaemia in Neoplastic Patients Treated with Cisplatin

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INTRODUCTION

ANAEMIA IS a common cause of morbidity in cancer patients [1]. The lack of the normal feedback mechanism that stimulates the erythropoietic response to anaemia is one of the most interesting mechanisms implicated in the genesis of anaemia in these patients. Miller *et al.* [2] have demonstrated a significantly lower serum erythropoietin level in anaemic cancer patients compared to iron-deficient anaemic patients with equivalent haemoglobin values. This characteristically low erythropoietin response to anaemia in cancer patients reflects the lack of a linear relationship between erythropoietin and haemoglobin levels in neoplastic disease. In iron deficiency or haemolytic anaemia, on the other hand, lower haemoglobin levels are directly related to higher erythropoietin levels [2].

The mildly blunted erythropoiesis found in cancer patients worsens with chemotherapy. Although the haematological toxicity of antineoplastic agents is usually more pronounced in white than in red blood cells, the nephrotoxic agent cisplatin exerts an especially toxic effect on erythropoiesis. Cisplatin-associated anaemia is generally normochromic, normocytic, with an inappropriately low reticulocyte count and a low erythropoietin response to anaemia [3,4]. Various trials have shown a greater than 2 g/dl haemoglobin drop in 9 to 40% of patients receiving a standard dose of cisplatin [5]. Although there is currently no sure relationship between cisplatin dosage and anaemia severity, cumulative dose and haemoglobin level seem to be related [6].

The present study, which is ongoing, is being conducted to establish whether or not the use of exogenous erythropoietin (r-HuEPO) in cancer patients can prevent cisplatin-induced iatrogenic anaemia, and thereby improve this agent's therapeutic index.

PATIENTS AND METHODS

Patients with advanced tumours, no history of chemo- or radiotherapy treatment, candidates for a chemotherapy regimen that included cisplatin, with good bone marrow function (i.e. haemoglobin ≥10 g/dl), and good cardiac and renal functions were eligible to enter the trial. To date, 57 patients have entered the study (Table 1). There are 31 men and 26 women, with a median age of 56 years (range 21 to 74 years). One-half of this patient group have ovarian or non-small cell lung cancer (NSCLC).

Patients, stratified for chemotherapy regimen, are randomised to receive either r-HuEPO at a dose of 150 U/kg subcutaneously along with protoferrin 40 mg orally, both administered three times weekly, or protoferrin alone at the same dosage and schedule. [The human erythropoietin used in this study was obtained by DNA technology using a Chinese hamster ovary cell expression system provided by Cilag, and manufactured in a buffered saline solution containing 10 000 U/ml erythropoietin (epoietin alpha) in 2.5 mg/ml human serum albumin for each 1 ml of solution.] Anaemia prevention treatment continues for 12 weeks, while the chemotherapy regimen involving cisplatin lasts for a maximum of 6 months.

The following parameters are monitored every 2 weeks: haemoglobin, haematocrit, RBC, WBC, reticulocyte count, and platelet count. Fe, ferritin, haptoglobin, erythropoietin, creatinine, creatinine clearance, serum protein and serum albumin are assessed at baseline, then again at 4-week intervals during the 12 weeks of r-HuEPO therapy.

Table 1. Patient characteristics

Evaluable	Total enrollment n=57	Currently n=38
Male/Female	31/26	17/21
Age (years)		
Median	56	54
Range	21–74	21–74
ECOG performance status		
Median	0	0
Range	0–2	0–2
Cancer		
Ovarian	16	16
Non-small cell lung (NSCLC)	13	7
Small cell lung (SCLC)	8	6
Head and neck	5	—
Testis	4	4
Gastric	4	3
Uterine	3	—
Sarcoma	2	1
Bladder	2	1

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Revised 1 Mar. 1993; accepted 17 Mar 1993.

Table 2. Haemoglobin

	Initial values† Mean±S.D.	Final values† Mean±S.D.	Hb loss n	(%)	Mean±S.D.	Hb gain n	(%)	Mean±S.D.
r-HuEPO-treated (*n*=21)	12.2±1.38	13.1±2.58	5	(23.8)	2.86 g±0.85	16	(76.1)	2.10 g±1.41
Control (*n*=17)	12.7±2.06	11.2±2.35*	8	(47.0)	3.50 g±1.87	9	(52.9)	0.37 g±1.08

*P=0.02. †Expressed as g/dl.

RESULTS

At the present time, 38 patients (17 men and 21 women) were evaluable after having completed the treatment. They ranged in age from 21 to 74 years (median 54 years), with 60% of the patients having either ovarian (*n*=16) or NSCLC (*n*=7) cancer. This sample included 21 patients treated with r-HuEPO+iron and 17 patients treated with iron alone. Of the remaining 19 patients, 10 were still in the early phase of treatment, 8 had discontinued treatment due either to progressive disease (*n*=7) or intolerance (*n*=1), and 1 patient had refused chemotherapy.

Comparing initial and final haemoglobin levels (Table 2), the r-HuEPO-treated and control groups were statistically equivalent at the outset (with pretreatment values of 12.2 g/dl and 12.7 g/dl, respectively), but significantly different (P=0.02) at the end of therapy. Haemoglobin for the r-HuEPO-treated group rose an average of 0.9 g to 13.1 g/dl (S.D.±2.58). Haemoglobin for the control group fell an average of 1.5 g to 11.2 g/dl (S.D.±2.35). Separating each larger patient group into those who gained haemoglobin vs. those who lost haemoglobin during the 12 weeks (Table 2) shows that 76% of the r-HuEPO-treated group gained an average of 2.1 g, while 24% became anaemic with a 2.8 g haemoglobin loss. Among the untreated patients, 47% became anaemic with an average haemoglobin loss of 3.5 g, while the remaining 53% simply maintained their baseline level. The 16 responsive patients in the treated group exhibited a constant gain in haemoglobin over the 12 weeks, while those who became anaemic showed a steady decrease in haemoglobin after week 4 (Fig. 1).

Although the data are not fully complete, assessing initial and final serum erythropoietin levels indicates no effect of exogenous erythropoietin on this parameter (Table 3). From baseline to the end of the 12-week r-HuEPO therapy period, neither the treated (*n*=19) nor the control (*n*=13) group showed a statistically significant modification in serum erythropoietin level related to the increase or decrease in haemoglobin.

In terms of safety, no adverse experiences were observed. In particular, there was not a single episode of hypertension among the treated patients.

Table 3. Serum erythropoietin levels

	Initial value	Final value
r-HuEPO-treated (*n*=19)		
Mean	13.3 MU/ml	12.0 MU/ml
S.D.	±7.2	±5.1
Control (*n*=13)		
Mean	10.3 MU/ml	8.0 MU/ml
S.D.	±5.5	±3.2

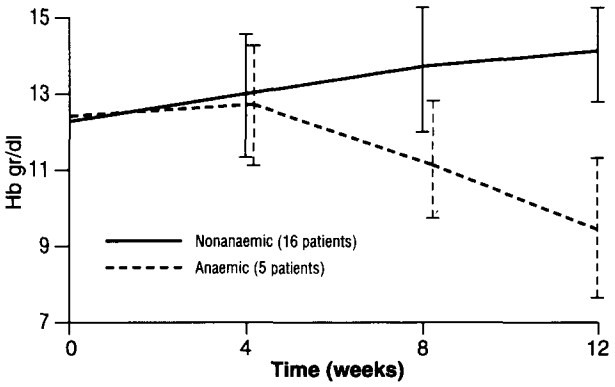

Fig. 1. Haemoglobin behaviour in r-HuEPO-treated patients.

CONCLUSIONS

Exogenous erythropoietin appears to have a beneficial effect in preventing anaemia in cisplatin-treated patients, as manifested by 76% of our evaluable patients in the r-HuEPO-treated group. Of the 5 treated patients who became anaemic, 3 had experienced a septic fever with severe leukopenia during the second cycle of chemotherapy. This event could have contributed to the lack of treatment efficacy. Perhaps a multivariate analysis will be able to identify the specific factors that will enable clinicians to predict a patient's response to r-HuEPO therapy in the context of cisplatin treatment.

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