Eur J Cancer, Vol. 29A, No. 10, p. 1499, 1993.
Printed in Great Britain
0964–1947/93 $6.00 + 0.00

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Increased Blood Cell Destruction During Vigorous Regeneration of Bone Marrow after Intensive Chemotherapy for Non-Hodgkin Lymphoma

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WE HAVE reported a new high dose regimen for the treatment of non-Hodgkin lymphoma (NHL), CAMBO-VIP[1], consisting of four myelosuppressive drugs (doxorubicin, cyclophosphamide, etoposide and ifosfamide) and four non-myelosuppressive drugs (vincristine, methotrexate with leucovorin rescue, bleomycin, and prednisolone), administered during alternate weeks for a total period of 12 weeks. We obtained a high response rate and prolonged disease-free survival with this regimen. The treatment was well tolerated: myelosuppression was severe but transient and caused no serious infectious complications.

However, we noticed transient elevation of serum lactate dehydrgenase (LDH) level in some patients at or shortly after the completion of CAMBO-VIP treatment. 18 of 36 patients who were treated with this regimen showed LDH level over 1.5 times normal values, and 6 of them displayed over 3-fold normal values. LDH elevation was not associated with liver function abnormality as demonstrated by elevation of transaminases or total bilirubin. All of these patients were in complete or partial response with no evidence of tumour progression. Therefore, some other factors must be considered as the cause of LDH elevation. Klimo *et al.*[2] reported similar elevation of serum LDH of unknown aetiology after completion of MACOP-B treatment for NHL. Elevation of serum LDH in our patients consisted of increase in isozymes LDH_1 and LDH_2. Interestingly, serum haptoglobin was undetectable in all 6 patients who were examined at the time of LDH elevation. Reticulocytosis and leukoerythroblastosis in peripheral blood were also observed in all of these 6 and other patients. In one particular patient, as many as 166 erythroblasts per 100 white blood cells were counted. These abnormalities, including LDH elevation, returned to normal relatively rapidly, usually within 2–3 weeks.

These abnormalities suggest transient excessive blood cell destruction which might be associated with vigorous recovery of haemopoiesis following chemotherapy-induced myelosuppression. Haemopoiesis may become temporarily defective as a result of rapid cell proliferation, to such an extent that a proportion of newly formed cells are prematurely destroyed in the bone marrow or soon after they appear in the peripheral blood. Granulocyte or granulocyte–macrophage colony stimulating factors may augment these abnormalities, when they are used to expedite the recovery of bone marrow function following chemotherapy-induced suppression.

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Received 30 Oct. 1992; accepted 23 Dec. 1992

Eur J Cancer, Vol. 29A, No. 10, pp. 1499–1500, 1993.
Printed in Great Britain
0964–1947/93 $6.00 + 0.00

Erythropoietin Treatment of Anaemia Associated with Lymphoproliferative Disorders

Stefano Molica

A DECREASED ERYTHROPOIETIN (EPO) response to anaemia has been reported in cancer patients and in those receiving cytotoxic chemotherapy [1]. This finding suggests that anaemia in cancer patients is, at least partially, due to a relative deficiency of EPO and that therapy of anaemia with recombinant human EPO (rHuEPO) may be appropriate in such patients [2–4].

To investigate this a prospective phase II study of rHuEPO has been carried out in 11 patients with haemoglobin levels < 9 g/dl (median 7.5 g/dl; range 6.7–8.8) who were being followed-up for lymphoproliferative disorders. The patient cohort included 3 chronic lymphocytic leukaemia (CLL) and 8 multiple myloma (MM) cases. There were eight males and three females. The average age was 63.3 years (S.D. 11). Clinical and haematological details are summarised in Table 1.

rHuEPO (Eprex, Cilag) was administered three times a week by subcutaneous route on an outpatient basis at an initial dose of 50 U/kg body weight. The aim of treatment was a haemoglobin level of 10 g/dl without transfusion and this was defined as a complete response (CR). If CR was not achieved within 4 weeks, the rHuEPO dose was increased to 75,100 and 150 U/kg body weight at 4-week intervals. If there was no response within 16 weeks, rHuEPO treatment was discontinued.

rHuEPO was given simultaneously to alpha interferon in 2 MM patients. All CLL patients were receiving concomitant therapy with an alkylating agent (chlorambucil or cyclophosphamide) associated with low doses of steroids. For the remaining 6 MM patients treatment consisted of alternating courses of alkeran plus prednisone in 4 cases, cyclophosphamide plus high doses of dexametasone in 1 patient, and polychemotherapic regimen (DAV/CD/CED) in 1, respectively.

7 out of 11 patients (5 MM, 2 CLL) responded to rHuEPO therapy maintaining haemoglobin levels above 10 g/dl without transfusions. The median dose of rHuEPO requiring anaemia correction was 75 U/kg body weight (range 50–100). In responding MM patients, no correlation was found between the amount of serum M component and the simultaneous determination of haemoglobin levels ($r = -0.10$). This supports

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Revised 19 Jan. 1993; accepted 16 Feb. 1993.

Table 1. Characteristics of patients included in the rHuEPO study

	MM	CLL
Number of patients	8	3
Mean age (years)	60.7	70.3
Sex (M/F)	5/3	3/—
Clinical stage		
III	*A,7	†C,3
III	*B,1	
Chemotherapy	6	3
Alpha interferon	2	—
Hb (g/dl), mean ± S.D.		
pre-rHuEPO	7.4 ± 0.4	8.1 ± 0.6
post-rHuEPO	10.6 ± 1.7	9.7 ± 2.0
Transfusion requirement	—	‡5.1 (U/month)
Neoplastic bone marrow infiltration, mean ± SD	26.1 ± 19.5	90 ± 8.1

*Durie and Salomon staging. †Binet staging. ‡Only one CLL patient was transfusion dependent.

the view that the improvement of anaemia is not due to a reduction of the tumour mass. In contrast to the findings in patients with end stage renal disease, no adverse reactions attributed to rHuEPO were observed.

An important aspect of rHuEPO therapy is an assessment of cost effectiveness. The cost of rHuEPO treatment is about $100 per 100 U/kg per week and the cost of a unit of RBC is about $200. Therapy with rHuEPO might be considered cost effective when utilised at a dose of 200 U/kg/week by abolishing transfusion requirements of four units of blood per month (1 unit/week). In the present study the mean of rHuEPO dosage utilised per week was 214 ± 54 U/kg/week. In 4 patients rHuEPO therapy has been effective at a weekly dosage lower than 200 U/kg.

Results of the present study provide further evidence for effective use of rHuEPO in the treatment of anaemia of malignancy due to bone marrow infiltration. The use of rHuEPO may provide an alternative to transfusions in this patient population. Phase III clinical trials should assess the impact of rHuEPO therapy on the course of lymphoproliferative disorders.

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4. Oster W, Herrmann F, Gamm H, *et al.* Erythropoietin for the treatment of anemia of malignancy associated with neoplastic bone marrow infiltration. *J Clin Oncol* 1990, **8**, 956–963.

Correction

Temozolomide: a New Oral Cytotoxic Chemotherapeutic Agent with Promising Activity Against Primary Brain Tumours, by S.M. O'Reilly *et al.*—Unfortunately, Fig. 1 of this paper was published in *The European Journal of Cancer* (Vol. 29A, No. 7, pp. 940–942) with part (b) missing. The correct version is reproduced below:

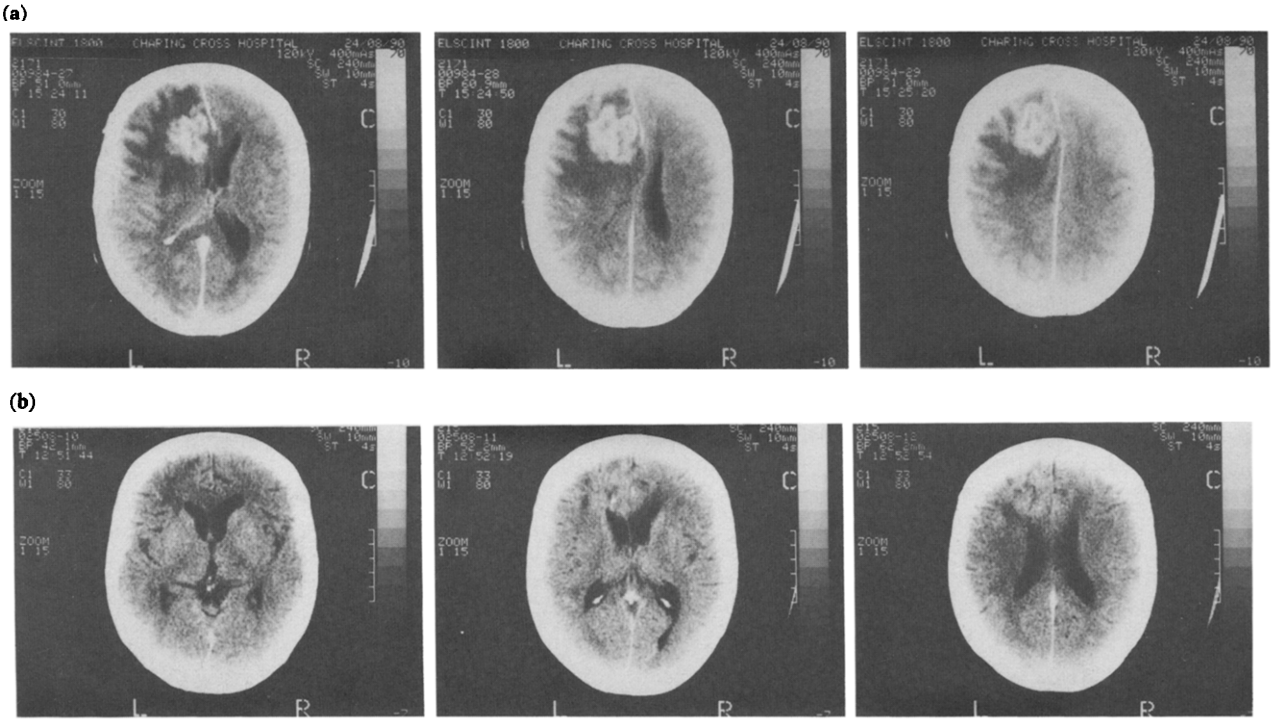

Fig. 1. Pretreatment CT scan (a) and CT scan after six courses of temozolomide (b) of a patient with a grade 4 glioma which had recurred after radiotherapy. The marked improvement in CT scan was accompanied by complete resolution of symptoms.