REVIEW ARTICLE

Drug Safety 2002; 25 (7): 525-535
0114-5916/02/0007-0525/$25.00/0

Management Options for Cancer Therapy-Related Anaemia

Tim J. Littlewood

Department of Haematology, John Radcliffe Hospital, Oxford, United Kingdom

Contents

Abstract

Anaemia is common in patients with haematological malignancy, occurring in the majority of patients with malignant disease who are treated with chemotherapy. Most patients will have their anaemia attributed to the cytokine-mediated anaemia of chronic disease. Many of these patients with anaemia will be symptomatic with fatigue, which is the single most important symptom reported. Data from many studies indicate that treatment of patients with anaemia with recombinant human erythropoietin (rHuEpo) will increase their haemoglobin level, decrease transfusion need and also improve their quality of life. Recent clinical and experimental work suggest that improving the haemoglobin level may improve the patients' prognosis but this finding needs to be confirmed.

Treatment of anaemia with rHuEpo in patients with cancer may produce many benefits. Unfortunately, rHuEpo is effective in only around 60% of patients, is slow acting and is expensive. These drawbacks have restricted its use in many healthcare systems. However, a failure to treat anaemia may have important adverse effects for the patient both in terms of their quality of life and, just possibly, in terms of their life expectancy.

Anaemia is a well recognised complication of cancer and cancer treatment. The frequency of anaemia in patients with cancer varies according to tumour type and treatment. For example, in patients with myeloma around 50% will have a haemoglobin level of <10.5 g/dl at presentation and most of the remainder will develop anaemia during their initial chemotherapy.[1] Successful control of the myeloma will usually help to improve the haemoglobin level but anaemia will recur with disease progression. For patients with lymphoma, anaemia (haemoglobin level <12.0 g/dl) is present in around 40% at diagnosis and this figure increases towards 70% after 4 to 6 cycles of chemotherapy.[2]

In a retrospective survey of 2719 patients with solid tumours being treated with chemotherapy, 38% had an haemoglobin level <11.0 g/dl during the course of treatment, and 33% of the patients required at least one blood transfusion.[3] Anaemia will continue to be a significant problem in overall patient management as new and more cytotoxic generations of chemotherapeutic agents are employed.[4]

1. Causes of Anaemia

Anaemia is common in patients with malignant disease. Most commonly the anaemia will be attributed to the anaemia of chronic disease, to tumour infiltration of the bone marrow and, sometimes, to concomitant renal failure.[5] Treatment with chemotherapeutic agents, which cause myelosuppression and can also reduce erythropoietin production, will contribute to the anaemia experienced by these patients. The levels of the principal cytokines implicated in the anaemia of chronic disease (interleukin-1, tumour necrosis factor-α and interferon-γ) are elevated in patients with cancer and these cytokines inhibit erythropoiesis both directly and indirectly by inhibiting erythropoietin production in the kidney.

Miller et al.[6] demonstrated the relative decrease in erythropoietin production which occurs in patients with malignant disease by contrasting serum erythropoietin levels in patients with iron deficiency anaemia with the levels in patients with a variety of cancerous illnesses. They showed that for any haemoglobin level, serum erythropoietin levels were lower in patients with cancer than for patients with iron deficiency. Although the patients studied had solid tumours, the same relative erythropoietin deficiency has been demonstrated in approximately 75% of patients with haematological malignancies such as chronic lymphocytic leukaemia (CLL), lymphoma and myeloma.[7]

2. Symptoms of Anaemia

Anaemia results in important symptoms for the patient. Common symptoms include fatigue, breathlessness, swollen feet, chest pain and loss of mental acuity. Fatigue is a significant problem for patients with malignant disease and one which is underestimated by physicians.[8,9] Fatigue may be caused by physiological or psychological factors and anaemia is just one of the possible physiological explanations. In a survey on fatigue it was found that about 75% of patients with cancer experienced fatigue during their treatment and that just under one half of these reported that the fatigue had an important negative impact on their daily activities.[9] Patients and their oncologists have a differing perception as to whether pain or fatigue has the larger impact on quality of life. It could be that the importance of fatigue is underestimated in the belief that it is caused by the disease or its treatment and that there is no effective treatment.

Furthermore, anaemia is a poor prognostic factor at diagnosis for many tumours (e.g. myeloma, non-Hodgkin's lymphoma, CLL and non-small-cell lung cancer) and some recent data has suggested that treatment of the anaemia can improve the patients life expectancy.[10,11]

3. Treatment of Anaemia by Blood Transfusion

The possible treatments for the anaemia are to do nothing, to transfuse with red cells or to treat with recombinant human erythropoietin (rHuEpo). The majority of anaemic cancer patients do not get treated,[3] probably because symptoms of fatigue

and lethargy are attributed to the underlying malignancy and/or treatment.

Blood transfusion is the most commonly used approach to treat anaemia in patients receiving chemotherapy. The haemoglobin level at which a transfusion will be suggested varies considerably.[3] Some doctors will recommend transfusion when the haemoglobin level falls below 10.0 g/dl; others believe that transfusion should be withheld until the haemoglobin level is less than 8.0 g/dl. Blood transfusion is costly, is a finite resource, is inconvenient for the patient, usually has to be given in a hospital environment with the associated resource implications and is, of course, not completely safe. However, for the large majority of patients it is an effective way of safely increasing their haemoglobin level and making them feel better. The beneficial effects usually last for 2 to 4 weeks at which point another blood transfusion may be needed.

rHuEpo is an alternative, albeit expensive, treatment option for anaemia in patients with haematological malignancy. A standard treatment dose of 150 IU/kg three times per week will cost approximately £1000/month. There are substantial data detailing its use in patients with both haematological and solid tumours and in patients receiving chemotherapy (either platinum or non-platinum containing) and in patients being treated with radiotherapy. There are less extensive data in patients with myelodysplasia.

Clinical trials have been conducted using both epoetin alfa and epoetin beta. These two preparations appear to have identical pharmacological action and efficacy and will not be distinguished during the rest of this article.

This review covers the benefits and shortcomings of treatment with rHuEpo in these situations. rHuEpo is not commonly used in patients with acute leukaemia probably because serum erythropoietin levels tend to be high and because the intensive myelotoxic chemotherapy regimens mitigate against a treatment response.

4. Clinical Studies Using Recombinant Human Erythropoietin (rHuEpo)

In 1990, Ludwig et al.[12] published the first report on rHuEpo treatment of 13 anaemic patients with advanced myeloma. The treatment regimen of rHuEpo was 150 IU/kg by subcutaneous injection three times per week. The median baseline haemoglobin level was 10.2 g/dl and 11 (85%) of the patients responded to treatment with a haemoglobin level increase of >2.0 g/dl. The time to response ranged from 3 to 20 weeks with a median of 5 weeks. In this pilot study, in addition to the beneficial impact on the haemoglobin level, there was no evidence that rHuEpo treatment caused any worsening of the myeloma. As a result of this important initial study several randomised trials were conducted to establish the effectiveness of rHuEpo in anaemic patients with CLL, non-Hodgkin's lymphoma and myeloma. The questions being asked were:

- Does treatment with rHuEpo cause an important rise in the haemoglobin levels in patients who are anaemic?
- Does the treatment reduce the blood transfusion requirements for these patients?
- What is the correct dose of rHuEpo?
- And, lastly, is the treatment well tolerated?

A summary of the results from three randomised trials is shown in table I.[13-15] Although there were minor differences in the entry criteria, all the studies required that patients be anaemic at entry with a haemoglobin level of less than 10.0 g/dl (<11.0 g/dl in the studies by Cazzola et al.[13] and Dammaco et al.[15]). Response was defined as an increase in haemoglobin level of >2.0 g/dl above baseline independently of blood transfusion. This was achieved in between 58 to 61% of patients in the treatment arms and 7 to 24% in the placebo arms. These differences were statistically significant. The proportion of patients requiring transfusion dropped by around 50% in the treatment compared with the placebo arms. Two of these studies randomised patients to different dosages of rHuEpo and were able to confirm that a

Table I. Clinical studies of recombinant human erythropoietin in patients with myeloma and lymphoma

Trial	Year	No. of patients	Treatment response (%)	Control response (%)
Cazzola et al.[13]	1995	146	61	7
Osterborg et al.[14]	1996	121	60	24
Dammaco et al.[15]a	2001	145	58	9

a Only patients with myeloma were investigated in this study.

starting dose of or equivalent to 150 IU/kg subcutaneously three times per week produced a superior response to a lower starting dose. This starting dose has been the most commonly used in clinical trials and clinical practice. Doubling the dose to 300 IU/kg in non-responders after 4 weeks produces a response in a further quarter of patients. Patients who have not responded with a haemoglobin level increase of >1.0 g/dl after a total of 8 weeks of rHuEpo treatment should probably have this medication stopped. Many patients who do respond to rHuEpo can be maintained on a relatively low dose such as 10 000IU once per week.

In an attempt to confirm these important findings two very large community based studies were conducted in the US.[16,17] Over 4000 patients were recruited into these trials. All the patients had cancer, were anaemic with a mean haemoglobin level of 9.2 g/dl in the first study by Glaspy et al.[16] and 9.3g/dl in the second study by Demetri et al.[17] and were treated in an open-label fashion with rHuEpo 150 IU/kg subcutaneously three times weekly for 4 months. Patients in these studies had both solid and haematological malignancies and were treated with a variety of cisplatin and non–cisplatin-containing chemotherapy regimens.

The mean increase in haemoglobin level in the study by Glaspy et al.[16] was 1.8 g/dl and 53.4% of patients responded with an increase in haemoglobin level of more than 2.0 g/dl. Sixty-one percent of patients responded in the study by Demetri et al.[17] In both of these trials transfusion need decreased by at least 50% from baseline to study completion. The results of these open-label studies and the randomised trials have confirmed that rHuEpo will cause a haemoglobin level increase in the majority of patients with cancer who are anaemic and that this increase will exceed 2.0 g/dl in around 50 to 60% of patients. They have also shown that transfusion need will decrease by approximately 50% in treated patients. A very similar study with virtually identical results has been reported by Gabrilove et al.[18] in which a once weekly injection of rHuEpo 40 000IU was used rather than a thrice weekly schedule.

A chart of a patient with an immunocytoma supported by blood transfusion and rHuEpo is shown in figure 1. No quality of life data are available for this patient but the abolition of transfusion need and the well sustained haemoglobin level whilst receiving rHuEpo are evident.

5. Quality of Life

The above studies[13-17] confirmed that treatment with rHuEpo is well tolerated, improves haemoglobin levels and reduces transfusion needs in patients with malignant diseases. Although this is useful to know it is also important to understand whether an increase in haemoglobin levels translates into an improved quality of life for the responding patients.

Quality of life was addressed by both the studies of Glaspy et al.[16] and Demetri et al.[17] Both investigators showed that quality of life improves with an increase in haemoglobin level and, very importantly, that the improvement in quality of life as a function of an increase in haemoglobin level seems to occur independently of tumour response. A further analysis of these data by Cleeland et al.[19] demonstrated a statistically significant, non-linear relationship between haemoglobin level and quality of life. rHuEpo-related increases in haemoglobin level were associated with quality of life improvements for the haemoglobin range of 8.0 to

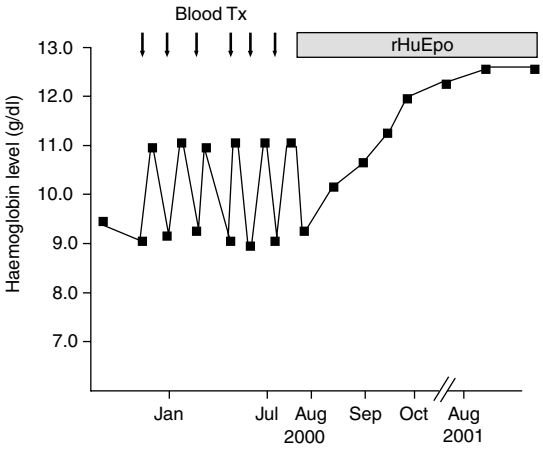

Fig. 1. The abolition of transfusion need by recombinant human erythropoietin (rHuEpo) in a patient with an immunocytoma. **Blood Tx** = blood transfusion.

14.0 g/dl. The largest quality of life improvement for each 1 g/dl increment in haemoglobin occurred when the haemoglobin increased from 11.0 to 12.0 g/dl.

A large, randomised, placebo-controlled, double-blind trail of rHuEpo in patients with either solid tumours or haematological malignancies[20] has confirmed that treatment with rHuEpo experience increased haemoglobin levels and reduced transfusion needs and that a significant improvement in quality of life occurs in the rHuEpo compared with the placebo-treated patients (figure 2). In this study, patients were treated with 150 IU/kg of study medication three times weekly by subcutaneous injection for 4 weeks. The dose was doubled after 4 weeks in nonresponders. Treatment was continued for 4 weeks after the last dose of chemotherapy and for a minimum of 12 weeks and a maximum of 28 weeks. In figure 3 the improvement in quality of life for one patient is shown.[15] This patient, who had myeloma, was started on rHuEpo when his haemoglobin was 9.0 g/dl. After 8 weeks of treatment the haemoglobin had increased to 13.5 g/dl and quality of life, as measured by a linear analogue scale had increased significantly. From this patient's perspective the improvement was noticeable in increased energy levels and an important improvement in the ability to perform day to day activities such as mow the lawn and walk his dog.

6. Impact of Correcting Anaemia on Survival

There are a number of possible mechanisms by which a low haemoglobin concentration may impair survival:

- impairing tumour oxygenation,[21] thereby reducing the effectiveness of chemotherapy and radiotherapy;[22,23]
- indirect mechanisms resulting from a decrease in patients' QOL;
- decreasing the amount of treatment delivered to the patient possibly because of the above; and
- hypoxia induced changes within tumour cells which increase their malignant potential.[24]

The impact of correcting the anaemia on patient survival has been investigated in a number of randomised and non-randomised studies.

An Austrian study[11] evaluated the effectiveness of rHuEpo in treating anaemia in 191 patients with head and neck cancer who were undergoing chemotherapy with fluorouracil and mitomycin plus radiotherapy. Resection of the oral cavity tumour and bilateral neck dissection were carried out 5 weeks following completion of the neoadjuvant

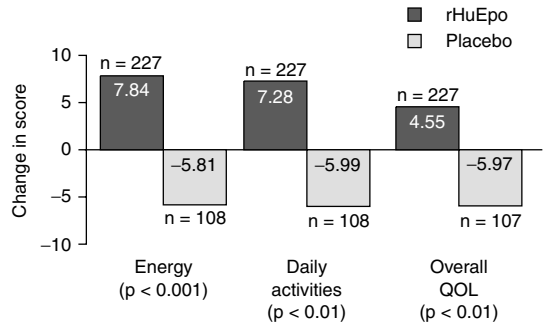

Fig. 2. The mean change in quality of life (QOL), comprising energy, ability to do daily activities and overall QOL, after treatment with recombinant human erythropoietin (rHuEpo) or placebo (reproduced from Littlewood et al.,[20] with permission from Lippincott Williams & Wilkins).

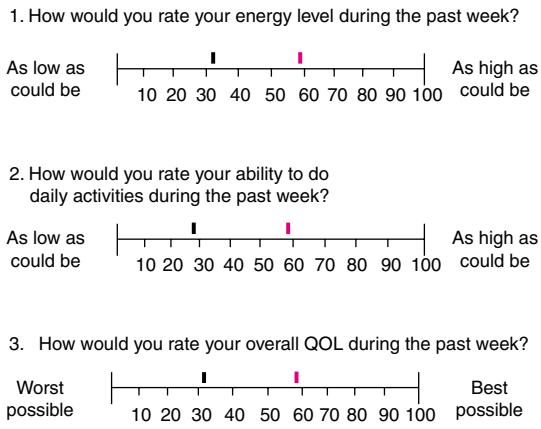

Fig. 3. The quality of life (QOL) [using the linear analogue scale] for a patient with myeloma with a pretreatment haemoglobin level of 9.0 g/dl (black) and in the same patient after the haemoglobin level had increased to 13.5 g/dl after 8 weeks' treatment with recombinant human erythropoietin 150 IU/kg three times weekly (blue).[15]

treatment. The results in the group treated with epoetin alfa were compared with those obtained in a group of patients who received the same anticancer regimen but were not treated with epoetin alfa. Results showed that treatment with epoetin alfa increased haemoglobin level and reduced transfusion requirements, and also significantly improved response rate ($p < 0.01$), local control ($p < 0.01$), and 2-year overall survival ($p < 0.001$).

A large, placebo-controlled, randomised, double-blind clinical trial of epoetin alfa was conducted in 375 patients with anaemia (baseline haemoglobin <10.5 g/dl, or >10.5 but <12.0 g/dl following a haemoglobin decrease of >1.5 g/dl in the previous month) who received nonplatinum chemotherapy for nonmyeloid haematological and solid malignancies.[20] The original objectives of this trial were to assess the effects of epoetin alfa on transfusion requirements, haemoglobin level, quality of life and safety. Before the study was unblinded, an additional objective was included to explore a possible relationship between increased haemoglobin level and survival. Patients were randomised to receive rHuEpo 150 to 300 IU/kg three times weekly for up to 24 weeks (n = 251), or placebo (n = 124). Median survival times were 17 months for patients who received epoetin alfa, compared with 11 months for the placebo group. In figure 4 the survival curves for the epoetin alfa- and placebo-treated patients are shown. The investigators concluded that although the study was not designed or powered for survival as an endpoint, the results suggested a survival benefit with epoetin alfa. Other trials designed to try and confirm a survival benefit are needed, since other variables that may have influenced survival, e.g., tumour stage, intensity of chemotherapy, extent of bone marrow involvement, and disease progression, were not controlled for in the original study.

7. Pharmacology of Erythropoietin

Intravenous rHuEpo produces higher peak plasma concentrations and has a substantially shorter elimination half-life compared with subcutaneous rHuEpo. The elimination half-life of subcutaneous rHuEpo is 19 to 22 hours and this route of administration is recommended because of the longer half-life and because subcutaneous administration is more practical for patients who self-administer.

All the previously reported studies in this review used a daily or three-times-weekly dosage schedule for conventional rHuEpo preparations. Recently Gabrilove et al.[18] have reported that a once weekly dose schedule of subcutaneous rHuEpo (starting dose 40 000IU) is as effective as a three times weekly schedule. This was an open-label, nonrandomised trial, which included 3012 patients. No randomised comparison between the administration of rHuEpo one- or three-times weekly has been reported.

Novel erythropoiesis stimulating protein (NESP) is a hyperglycosylated analogue of erythropoietin containing two extra oligosaccharide chains. This prolongs the half life approximately two to three fold compared with erythropoietin although the mechanism of action remains the same. Studies in patients with renal failure and anaemic patients with cancer[25,26] have shown that NESP is effective when given every week or every other week.

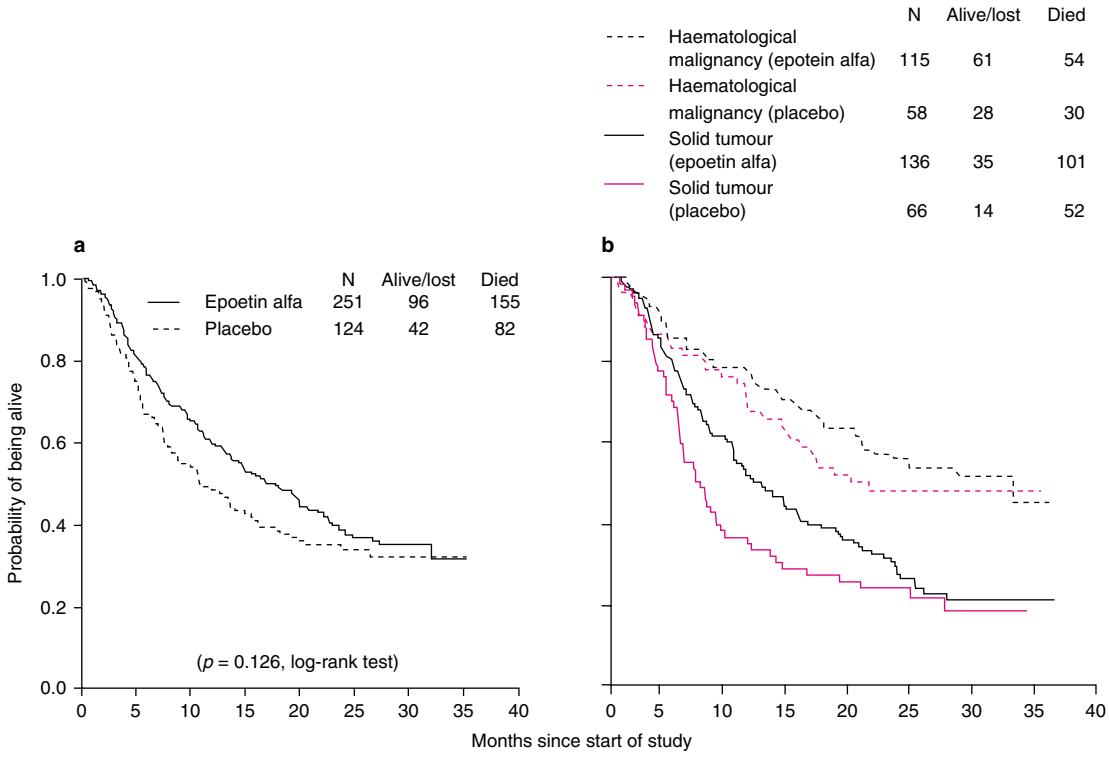

Fig. 4. The Kaplan-Meier survival curves for (**a**) all patients treated with epoetin alfa or placebo and (**b**) patients treated with epoetin alfa or placebo according to the underlying tumour type (reproduced from Littlewood et al.,[20] with permission from Lippincott Williams & Wilkins).

A less frequent administration schedule is likely to be preferable to patients and their families and result in reduced costs of administration.

8. Predictors of Response

Because the response rate is around 60% it would be helpful to be able to select those patients who will are likely to respond to therapy in advance so that an expensive drug is not wasted on a patient who is destined not to respond. Various investigators have reported on factors which predict a response. Ludwig et al.[27] suggested that if after 2 weeks of treatment with rHuEpo the serum erythropoietin level is >100 IU/L and the haemoglobin level has increased by <0.5 g/dl the patient will almost certainly not respond. There has not been complete unanimity in the published literature with regards to the predictive role of serum erythropoietin levels but there seems to be substantial agreement that if the haemoglobin increase is >0.5 g/dl after 2 weeks of treatment a response is likely.[12] Other factors which may have a bearing on the likelihood of a patient responding to rHuEpo are the degree of neutropenia and thrombocytopenia.[12,14]

9. rHuEpo and Iron Deficiency

Iron deficiency occurs in many patients treated with rHuEpo. It is standard practise to monitor iron levels and to prescribe supplementary iron by mouth if the transferrin saturation decreases to less than 20%, or the serum ferritin decreases to less

than 100 μg/L. A functional rather than a true iron deficiency may develop in rHuEpo treated patients. This is defined as a situation where body iron stores are normal but iron supply to the erythroid marrow is inadequate for the red cell precursor demand. Macdougall et al.[28] described a simple approach to allow detection of functional iron deficiency. Using an automated blood counter the percentage of hypochromic red blood cells (haemoglobin level < 28 g/L) is usually <2.5%. An increase in the percentage of hypochromic cells to more than 10% during rHuEpo treatment, with apparently normal serum iron levels, would suggest the development of functional iron deficiency. Patients who develop a true or functional iron deficiency should be treated with oral iron supplements. Intravenous iron supplementation is recommended for those who do not respond to oral iron.

10. Myelodysplasia

Anaemia is the most common haematological abnormality in patients with myelodysplasia. Treatment of myelodysplasia with rHuEpo has been investigated in a number of relatively small studies.[29,30] A meta-analysis of 17 trials[31] including 205 patients was published in 1995. In the majority of these studies patients were eligible for treatment with rHuEpo if they had a haemoglobin level of <10.5 g/dl or were transfusion dependent. Response was generally defined as abolition of the need for transfusion or a rise in haemoglobin level of >1.5 g/dl in non-transfusion-dependent patients. The response rate in the 17 trials was 16% (33 of 205 patients) using quite a range of rHuEpo doses given both subcutaneously and intravenously. The median time to response was 8 weeks and some of the responses, with continued rHuEpo administration, were durable. The patients most likely to respond were those who did not have sideroblastic anaemia, those who were not transfusion dependent and those whose serum erythropoietin level was less than 200 IU/L.

Three groups have investigated the impact of combination treatment with rHuEpo and granulocyte-colony stimulating factor (G-CSF) on the anaemia of patients with myelodysplasia.[32-34]

When a complete response (CR) was defined as achieving a haemoglobin level of >11.5 g/dl and partial response (PR) was defined as an increase in haemoglobin level of >1.5 g/dl or a 100% reduction of transfusion need a response rate of 36% (CR 21.4%; PR 14.4%) was seen when the results of the Scandinavian and US studies were pooled.[35] The rHuEpo dose in these studies varied but was often between 100 to 300 IU/kg/day; a substantially higher dose than that used for patients with non-myeloid tumours which significantly increases the cost.

There was no significant difference in erythroid response rates for patients with refractory anaemia, refractory anaemia with ring sideroblasts or refractory anaemia with excess blasts in these studies.

A predictive model for response has been proposed by Hellstrom-Lindberg et al.[35] This model was based on a retrospective analysis from the combined results of the Scandinavian and US groups. Using multivariate analysis the serum erythropoietin level and red cell transfusion need were used to create a scoring system which allowed patients with a high, intermediate or low chance of response to be identified. This model has recently been confirmed and simplified in a prospective study.[36]

Patients with a transfusion need of <2 units per month and a serum erythropoietin level of <500 IU/L had a 74% response rate to combined erythropoietin/G-CSF compared with a response rate of 23 and 7% for those patients with a >2 units per month transfusion need or serum erythropoietin concentration >500 IU/L or both of these risk factors, respectively. These data indicate that the combination of rHuEpo and G-CSF is a more effective combination in anaemic patients with myelodysplasia than rHuEpo alone.

11. Adverse Effects of rHuEpo

All of the studies have confirmed that rHuEpo is well tolerated with an adverse effect profile that is similar to that found with the placebo treated

arms of studies. However, these studies generally recommended a reduction in dose of rHuEpo in responding patients in order to maintain the haemoglobin between 12.0 to 13.0 g/dl. There have been anecdotal reports of venous thrombosis in patients whose haemoglobin rises rapidly and to >15.0 g/dl. Hypertension, which was a common complication in the early trials of rHuEpo in patients with renal failure, occurs much less frequently in patients with malignant disease.

In a recent article[37] pure red cell aplasia, secondary to the development of anti-erythropoietin antibodies, was reported in 13 patients with chronic renal failure. Data reported to the US Food and Drug Administration drug surveillance scheme indicate that, to date, 83 cases of red cell aplasia have occurred in patients treated with rHuEpo.[38] All of the patients were being treated for renal failure. There have been no reported cases in patients with malignant disease so far. Although rare, this serious adverse effect is of concern. One hypothesis is that the antibody is directed against differences in the carbohydrate structure between rHuEpo and naturally occurring erythropoietin.[39]

12. What Can Be Recommended?

Anaemia is a common cause of morbidity in patients with cancer and has an adverse impact on survival. Many patients are left untreated until their anaemia is severe and the commonest approach to treatment is blood transfusion. This has the advantage of being rapidly effective but a number of disadvantages such as cost, inconvenience and not being completely safe.

From the available data there is excellent evidence to recommend the use of rHuEpo in anaemic patients with malignant disorders who are receiving chemotherapy with the aim of maintaining the haemoglobin at >12.0 g/dl.[19] The existing data suggest that treating the patient before severe anaemia develops may be the most cost effective approach[20] but further studies are needed in this area. Similarly, most research has been conducted in patients with malignancies who are receiving concurrent chemo- or radiotherapy. However, anaemic patients with malignant disease who are not being actively treated may also benefit from treatment with rHuEpo.[40]

The possibility that treatment with rHuEpo might enhance survival is intriguing but it would be premature to advise treatment with rHuEpo on this basis. Future studies, both in the laboratory and the clinic, are vital.

In myelodysplasia there are no placebo-controlled, randomised trials. Nevertheless, the data indicate that treating patients with the combination of rHuEpo and G-CSF is effective in the majority of patients whose baseline red cell transfusion need is <2 IU/month and have a serum erythropoietin level of <500 IU/L. Patients meeting neither or just one of these criteria are far less likely to respond much. A trial of treatment in such patients, who have complications from blood transfusion (such as the development of multiple red cell antibodies), making the provision of blood difficult, is a reasonable approach. There are few data on quality of life benefits in patients with myelodysplasia treated with rHuEpo plus G-CSF and no studies to determine whether such treatment might have any impact on life expectancy. The lack of such data makes recommendations about the use of rHuEpo in patients with myelodysplasia uncertain. Further research is needed.

Many physicians were trained that anaemia is not important in patients with malignant disease until it became very severe. This thinking results in patients experiencing substantial morbidity and possible impairment in survival. Effective treatment is available for many patients using rHuEpo but uncertainties about its real worth and its high cost still precludes its use in many healthcare systems.

Acknowledgements

Dr Tim J. Littlewood is a paid consultant to one of the companies manufacturing recombinant human erythropoietin. No funding was used in the preparation of this manuscript.

References

1. San Miguel JF, Garcia-Sanz R, Gonzalez M, et al. A new staging system for multiple myeloma based on the number of S-phase plasma cells. Blood 1995; 85 (2): 448-55
2. Coiffier B. Anemia associated with non-platinum chemotherapy (CT) for Hodgkins lymphoma (HL) or non-Hodgkins lymphoma (NHL) [abstract]. European Cancer Conference (ECCO) 10 Programme 1999; 35: S19
3. Barrett-Lee PJ, Bailey NP, O'Brien MER, et al. Large scale UK audit of blood transfusion requirements and anaemia in patients receiving cytotoxic chemotherapy. Br J Cancer 2000; 82: 93-7
4. Groopman JE, Itri LM. Chemotherapy induced anemia in adults: incidence and treatment. J Natl Cancer Inst 1999; 91: 1616-34
5. Spivak JL. Recombinant human erythropoietin and the anaemia of cancer. Blood 1994; 84: 997-1004
6. Miller CB, Jones RJ, Piantadosi S, et al. Decreased erythropoietin response in patients with the anemia of cancer. N Engl J Med 1990; 322 (24): 1689-92
7. Cazzola M, Mercuriali F, Brugnara C. Use of recombinant erythropoietin outside the setting of uraemia. Blood 1997; 89: 4248-67
8. Curt GA, Breithart W, Cella D, et al. Impact of cancer related fatigue on the lives of patients: new findings from the fatigue coalition. Oncologist 2000; 5: 353-60
9. Vogelzang NJ, Breitbart W, Cella D, et al. Patient, caregiver and oncologist perceptions of cancer-related fatigue: results of a tripart assessment survey. Semin Hematol 1997; 34 Suppl. 2: 4-12
10. Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. Cancer 1999; 86: 1528-36
11. Glaser C, Millesi W, Kornek GU, et al. Impact of hemoglobin level and use of recombinant erythropoietin on efficacy of preoperative chemoradiation therapy for squamous cell carcinoma of the oral cavity and oropharnyx. Int J Radiat Oncol Biol Phys 2001; 50: 705-15
12. Ludwig H, Fritz E, KotzmannH, et al. Erythropoietin treatment of anemia associated with multiple myeloma. N Engl J Med 1990; 322: 1693-9
13. Cazzola M, Messinger D, Battistel V, et al. Recombinant human erythropoietin in the anaemia associated with multiple myeloma or non-Hodgkin's lymphoma: dose finding and identification of the predictors of response. Blood 1995; 86: 4446-53
14. Osterborg A, Boogaerts MA, Cimino R, et al. Recombinant human erythropoietin in transfusion-dependent anaemic patients with multiple myeloma and non-Hodgkin's lymphoma-a randomised multicentre study. Blood 1996; 87: 2675-82
15. Dammaco F, Castoldi G, Rodjer S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma. Br J Haematol 2001; 113: 172-9
16. Glaspy J, Bukowski R, Steinberg D, et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with non-myeloid malignancies during cancer chemotherapy in community oncology practice. J Clin Oncol 1997; 15 (3): 1218-34
17. Demetri GD, Kris M, Wade J, et al. Quality-of-life benefit in chemotherapy patients treated with epoetin alfa is independent of disease response or tumor type: results from a Prospective Community Oncology study. J Clin Oncol 1998; 16 (10): 3412-25
18. Gabrilove JL, Einhorn LH, Livingston RB, et al. Once-weekly dosing of Epoetin alpha is similar to three-times-weekly dosing in increasing haemoglobin and quality of life. J Clin Oncol 2001; 19 (11): 2875-82
19. Cleeland CS, Demetri GD, Glaspy J, et al. Identifying haemoglobin level for optimal quality of life: results of an incremental analysis [abstract]. Proc Am Soc Clin Oncol 1999; 18: 2215
20. Littlewood TJ, Bajetta E, Nortier JW, et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2001; 19: 2865-74
21. Kelleher DK, Matthiensen U, Thews O, et al. Blood flow, oxygenation and bioenergetic status of tumors after erythropoietin treatment in normal and anemic rats. Cancer Res 1996; 56: 4728-34
22. Molls M, Stadler P, Becker A, et al. Relevance of oxygen in radiationoncology: mechanisms of action, correlation to low hemoglobin levels. Strahlenther Onkol 1998; 174 Suppl. IV: 13-6
23. Teicher BA, Holden SA, Al-Achi A, et al. Classification of antineoplastic treatments by their differential toxicity toward putative oxygenated and hypoxic tumour subpopulations in vivo in the FSaIIC murine fibrosarcoma. Cancer Res 1990; 50: 3339-44
24. Höckel M, Schlenger K, Hockel S, et al. Association between tumor hypoxia and malignant progression: the clinical evidence in cancer of the uterine cervix. In: Vaupel P, Kelleher DK, editors. Tumor hypoxia. Stuttgart; Wissenschaftliche Verlagsgesellschaft mbh, 1999: 65-74
25. Glaspy J, Bukowski R, Steinberg D, et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with non-myeloid malignancies during cancer chemotherapy in community oncology practice. J Clin Oncol 1997; 15: 1218-34
26. Glaspy J, Colowick A, Heatherington A. Novel erythropoiesis stimulating protein exhibits a prolonged serum half life ($t_{1/2}$) in oncology patients [abstract]. Proc Am Soc Clin Oncol 2000; 19: 210
27. Ludwig H, Fritz E, Leitgeb C, et al. Prediction of response to erythropoietin treatment in chronic anaemia of cancer. Blood 1994; 84: 1056-63
28. Macdougall IC, Cavill I, Hulme B, et al. Detection of functional iron deficiency during erythropoietin treatment: a new approach. Br Med J 1992; 304: 225-6
29. Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. A randomised double-blind placebo controlled study with subcutaneous recombinant human erythropoietin in patients with low risk myelodysplastic syndromes. Br J Haematol 1998; 103: 1070-4
30. Stein RS, Abels RI, Krantz SB. Pharmacologic doses of recombinant human erythropoietin in the treatment of myelodysplastic syndromes. Blood 1991; 78: 1658-63
31. Hellstrom-Lindberg E. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. Br J Haematol 1995; 89: 67-71
32. Negrin RS, Stein R, Vardiman J, et al. Treatment of the anaemia of myelodysplastic syndromes using recombinant human granulocyte colony stimulating factor in combination with erythropoietin. Blood 1993; 82: 737-43
33. Hellstrom-Lindberg E, Ahlgren T, Beguin E, et al. Treatment of anaemia in myelodysplastic syndromes with granulocyte colony stimulating factor plus erythropoietin: results from a

randomized phase II study and long term follow up of 71 patients. Blood 1998; 92: 68-75
34. Mantovani L, Lentini G, Hentschel B, et al. Treatment of anaemia in myelodysplastic syndromes with prolonged administration of recombinant human granulocyte colony-stimulating factor and erythropoietin. Br J Haematol 2000; 109: 367-75
35. Hellstrom-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposals for a predictive model. Br J Haematol 1997; 99: 344-51
36. Hellstrom-Lindberg E, Ahlgren T, Dahl I, et al. A final decision model for treating the anemian of myelodysplastic syndromes (MDS) with Epo and G-CSF [abstract]. Blood 2000; 96: 2347
37. Casadevall N, Nataf J, Viron B, et al. Pure red cell aplasia and anti erythropoietin antibodies in patients treated with recombinant erythropoietin. N Engl J Med 2002; 346: 469-75
38. Gershon SK, Luksenburg H, Cote TR, et al. Pure red-cell aplasia and recombinant erythropoietin [letter]. N Engl J Med 2002; 346: 1584-5
39. Bunn HF. Sugar in erythropoietin: clinical and forensic implications [comment]. Blood 2002; 99: 1503
40. Quirt I, Robeson C, Lau CY, et al. Epoetin alfa increases hemoglobin levels and improves quality of life in patients with cancer-related anemia who are not receiving chemotherapy and patients with anemia who are receiving chemotherapy. J Clin Oncol 2001; 19: 4126-34

Correspondence and offprints: Dr *Tim J. Littlewood*, Department of Haematology, John Radcliffe Hospital, Oxford, OX3 9DU, UK.
E-mail: tim.littlewood@orh.nhs.uk