r-HuEPO appeared to be efficacious in a wide variety of tumour types. Patients with haematological or solid tumours appeared to respond equivalently to r-HuEPO, as did patients with or without evidence of tumour infiltration of the bone marrow. In addition, the significant improvement shown for quality-of-life measures in the r-HuEPO-treated responder subgroup suggests that r-HuEPO can substantially improve functional capacity in anaemic cancer patients when haematocrit increases significantly. This improvement is striking when one considers that the patient population under study was in the late stages of cancer, and that two of the three trial groups were enduring aggressive courses of cyclic chemotherapy.

r-HuEPO therapy was well-tolerated in this patient population, reflected in the similar nature and frequency of reported adverse experiences in the experimental and control patient groups. While statistical comparison of the treatment groups indicated no increased cardiovascular risk to r-HuEPO-treated patients, individual case histories suggest that occasional patients may experience increased blood pressure as haematocrit rises significantly above the baseline level. This is probably related to the fact that many of the patients in this study were older, and so may have had underlying recognised or unrecognised cardiovascular disease. The risk of hypertension, though, appears to be much less than among chronic renal failure patients [7].

## CONCLUSIONS

r-HuEPO increases haematocrit and corrects anaemia in cancer patients whether or not they are receiving chemotherapy, and apparently without regard to type of cancer. In a dose of 150 U/kg three times weekly, r-HuEPO appears to decrease transfusion requirements after the first month of therapy, but not earlier. This therapy also appears to improve functional capacity in those anaemic cancer patients who show a significant increase in haematocrit in response to therapy, which is consistent with observations among chronic renal failure and AIDS patients [9,10]. r-HuEPO also appears to be well-tolerated in this patient population.


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# Erythropoietin Treatment of Chronic Anaemia of Cancer

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## INTRODUCTION

CHRONIC ANAEMIA of cancer occurs in association with solid tumours, lymphomas, and haematological malignancies, although the specific incidence varies with the type of cancer. The probability of chronic anaemia developing generally increases with the duration of the disease, with patients in the advanced stages of malignancy being the most prone to the chronic anaemia of cancer [1]. Once anaemia has become chronic, the chances of overcoming it are slight. Because chronic anaemia results in weakness, fatigue, drowsiness, lethargy, depression and, in extreme situations, respiratory distress and cardiac decompensation, this relatively common problem in cancer patients can significantly impair their quality of life.

Currently, patients suffering from the chronic anaemia of cancer must rely on periodic blood transfusions. Blood transfusions, however, do not sufficiently counter the

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anaemia, and introduce new problems. Most significant is the risk of serious infection with HIV, cytomegalovirus, Epstein-Barr virus, or hepatitis [2]. Transmission of toxoplasmosis and of malaria, although rare, has been documented [3]. Additionally, blood transfusions carry the risks of severe allergic reaction and the problems consequent to iron overload. Finally, transfusions are very costly, and also make the patient dependent on the transfusion centre.

The excellent results achieved with the use of recombinant human erythropoietin (r-HuEPO) in the chronic anaemia of renal insufficiency [4,5] raised the possibility that it might also be able to correct the chronic anaemia of cancer. In an attempt to investigate this possibility, we designed a pilot study to explore several questions. (1) Does r-HuEPO have a positive effect on cancer-associated chronic anaemia? If it does, then: (2) is the benefit general, or is it limited to specific types of cancer? (3) Is the benefit long-lasting? (4) Do responding patients experience an improved quality of life and performance status? (5) is there a correlation between baseline endogenous EPO levels and the response to r-HuEPO?

## PATIENTS AND METHODS

67 patients have been enrolled in the investigation to date (Table 1). There are 40 female and 27 male patients who range in age from 43 to 90 years (median=64.0). Fourteen types of cancers are represented, with multiple myeloma ($n$=18), myelodysplastic syndrome ($n$=14), and breast cancer ($n$=9) predominating. Median duration of the basic disease before r-HuEPO treatment was 26 months (range 1–179 months). Most of these patients (89.2%) had previously received cytostatic chemotherapy and/or radiotherapy. Any such treatment was continued during r-HuEPO therapy. Median haemoglobin level at the start of r-HuEPO therapy was 9.6 g/dl (range 5.3 to 10.9 g/dl).

*Table 1. Patient characteristics*

| | |
|---|---|
| Sex | Male=27; female=40 |
| Age (years) | Median 64, range 43-90 |
| Disease duration (months) | Median 26, range 1-179 |
| Pretreatment haemoglobin (g/dl) | Median 9.6, range 5.3-10.9 |
| Haematologic disease ($n$=40) | |
| Multiple myeloma | 18 |
| Myelodysplastic syndrome | 14 |
| Chronic lymphatic leukaemia | 4 |
| Non-Hodgkin lymphoma | 2 |
| CML | 1 |
| OMF | 1 |
| Solid tumours ($n$=27) | |
| Breast | 9 |
| Colon | 6 |
| Renal | 3 |
| Oesophageal | 3 |
| Lung | 2 |
| Prostate | 2 |
| Ovarian | 1 |
| Melanoma | 1 |

r-HuEPO was administered subcutaneously three times weekly at an initial dosage of 150 U/kg body weight. Response to the hormone was arbitrarily defined as an increase of haemoglobin ≥2 g/dl above the pretreatment level. At 3-week intervals for the first 9 weeks, dosage for any patients not yet responding by that point was increased by 50 U/kg up to an eventual maximum of 300 U/kg. Duration of r-HuEPO therapy was formally scheduled for 12 weeks, but could be extended at the patient's request.

Occurrence of transfusions, as well as mortality data, were recorded. Endogenous serum erythropoietin level was recorded at baseline, then weekly for the first 12 weeks of treatment. To evaluate effects of r-HuEPO therapy on performance status, the WHO performance score was determined by the treating physician before therapy began and again after 2 months of therapy.

## RESULTS

*Responsiveness*

Of the 60 patients currently evaluable for responsiveness to r-HuEPO therapy, 43.3% ($n$=26) were responders, with the period of time required for a response to appear varying from 1 week to 20.3 weeks (Table 2). 24 of these patients were early responders, responding to r-HuEPO administration within the initial 12-week period. Most of this group responded between the first 4 to 6 weeks of r-HuEPO therapy, with a median response time of 4.7 weeks. 2 patients initially in the non-responder group, one with breast cancer and one with multiple myeloma, benefitted from prolonged treatment (Tables 2,3). They were among the 50% of initial non-responders electing to continue on r-HuEPO therapy after the initial 12-week period despite a lack of haemoglobin response, compared to 77% of the early responders who chose to continue (Table 3). Improvement in these two late responders appeared after 15.6 and 20.3 weeks, respectively. The remaining patients in the initial non-responder group, who received r-HuEPO therapy for periods ranging from 14 to 52 weeks, did not show a haemoglobin response that met the criterion for responsiveness.

*Table 2. Response rate to r-HuEPO treatment*

| | $n$ (%) | Median weeks to response (range) | No. transfusions/ no. patients |
|---|---|---|---|
| Early responders (≤12 weeks) | 24 (40.0) | 4.7 (1–12.0) | 6/3* |
| Late responders (>12 weeks) | 2 (03.3) | 15.6 and 20.3 | 0/0 |
| Total responders | 26 (43.3) | 4.9 (1–20.3) | 6/3 (12%)† |
| Non-responders | 34 (56.7) | — | 59/21 (62%) |

*Only within the first 2 weeks of therapy. †Difference between total responders and non-responders in percent of patients requiring transfusion is highly significant ($P$ <0.00001).

*Table 3. Patients choosing to continue r-HuEPO treatment beyond 12 weeks**

| | Elected to continue *n* (%) | Total weeks treatment (range) |
|---|---|---|
| Early responders (*n*=22) (≤12 weeks) | 17 (77%) | 14–74 |
| Initial non-responders (*n*=16) | 8 (50%) | — |
| Non-responders (*n*=6) | — | 14–52 |
| Late responders (*n*=2) (>12 weeks) | — | 42–58 |

*This is based on the 38 patients who completed the 12-week observation period. Of the 60 patients who were evaluable for efficacy during this period, by the end of this period 12 had died, 6 had been lost to follow-up or had been dropped due to lack of compliance, and 4 had not yet reached the 12-week point.

*Table 4. Response rate by diagnostic group*

| | Responders *n*/N (%) | Median weeks to response (range) |
|---|---|---|
| Haematologic disease | | |
| Multiple myeloma | 14/18 (77.8) | 4.7 (2.7–20.3) |
| Myelodysplastic syndrome | 2/11 (18.2) | 4.6 (3.1–6.0) |
| Chronic lymphatic leukaemia | 1/3 (33.3) | 5.4 |
| Non-Hodgkin lymphoma | 0/2 | — |
| CML | 0/1 | — |
| OMF | 0/1 | — |
| Total | 17/36 (47.2) | 4.7 (2.7–20.3) |
| Solid tumours | | |
| Breast | 4/9 (44.4) | 3.6 (1.0–15.6) |
| Colon | 2/6 (33.3) | 4.0 (2.0–6.0) |
| Renal | 0/3 | — |
| Oesophageal | 2/3 (66.7) | 7.7 (5.1–10.3) |
| Prostate | 0/1 | — |
| Ovarian | 0/1 | — |
| Melanoma | 1/1 (100.0) | 5.7 |
| Total | 9/24 (37.5) | 5.0 (1.0–10.3) |
| Total | 26/60 (43.3) | 4.9 (1.0–20.3) |

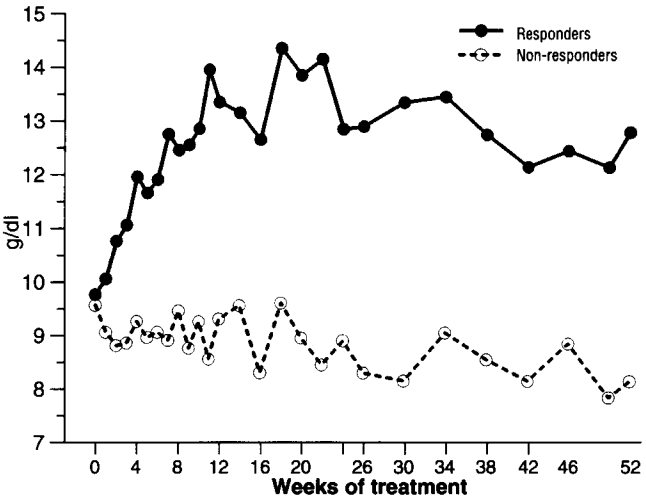


**Fig. 1. Comparison of median haemoglobin values during r-HuEPO therapy for responders and non-responders.**

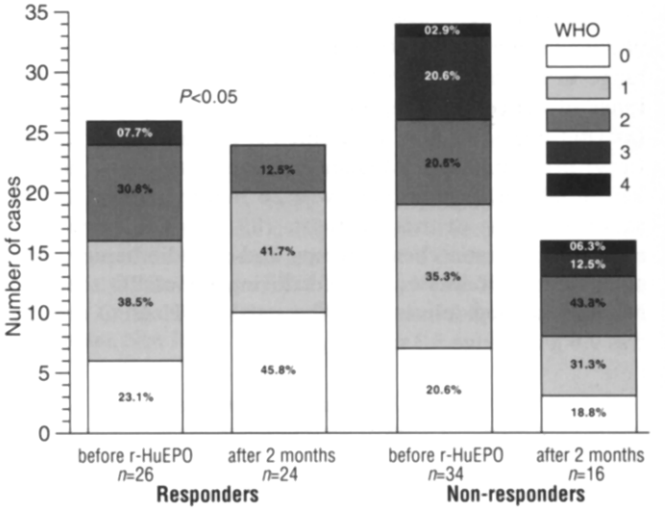


**Fig. 2. Comparison of WHO evaluation at baseline and after 2 months of r-HuEPO therapy within the responder group and the non-responder group.**

Haemoglobin levels (Fig. 1) demonstrate that, in responders who chose to continue r-HuEPO therapy beyond the 12-week period, the benefit was maintained for at least 1 year. (The study, which is still in progress, now shows that a stable significant increase in haemoglobin can continue even beyond this point.) Patients temporarily lost their ability to respond to r-HuEPO therapy, however, following surgery or during an episode of severe infection. Haemoglobin values would drop despite continued treatment, and then rise again once the patient was stable. Responders who developed progressive disease also lost their ability to respond to r-HuEPO therapy.

The 43% overall response rate was not representative of individual diagnostic groups (Table 4). 14 of the 18 patients with multiple myeloma (77.8%) showed adequate improvement in their haemoglobin concentration. The patient group with oesophageal cancer showed a 66.7% (2 out of 3) response rate, while breast cancer patients showed the third highest response rate at 44.4% (4 out of 9). Responsive patients in the chronic lymphatic leukaemia and colon cancer groups were only 33.3% (1/3 and 2/6, respectively). Patients with the remaining types of cancer showed minimal or no effect from r-HuEPO therapy.

*Transfusion requirements*

Transfusion requirements of responders and non-responders were markedly different (Table 2). Only 3 of the 26 responders (11.5%) required transfusions, and then only within the first 2 weeks of treatment. In contrast, 21 of the 34 non-responders (61.8%) required transfusions, nor was this need limited to the initial treatment period. This minimal and brief transfusion need in the responder group of patients corresponds with the clinical observation that symptoms of anaemia subsided, or at the least improved considerably, in all patients in this group.

*Quality of life*

After 2 months of r-HuEPO therapy, the WHO performance scores of the 24 responders still available for evaluation were significantly improved compared to baseline ($P < 0.05$), while the 16 non-responders showed only a slight improvement at the poorest end that failed to reach significance (Fig. 2). The group of responder patients also experienced significant improvement in subjectively rated sense of well-being and quality of life (data not shown). It should also be noted from Fig. 2 that the responder group as a whole exhibited better baseline WHO scores compared to the non-responder group.

*Responders vs. non-responders*

In terms of a pretreatment parameter, baseline endogenous erythropoietin level differed between responders and non-responders (Fig. 3). Use of a partial point biserial correlation procedure to eliminate any possible influence of cancer type on this association produced a correlation statistic significant at $P < 0.02$. In the group of responders, pretreatment serum levels were consistently below 200 units/l. Although non-responders showed a median pretreatment level somewhat under 200 units, they actually showed a biphasic distribution, with a considerable proportion presenting with serum levels under 200 units/l and the others showing a broad range of high initial levels. During treatment, serum erythropoietin levels in the responder patient group remained consistently low and displayed very little variability throughout the 12-week therapy period. In the non-responder group, however, the average level climbed substantially during therapy, with variability increasing still further.

The survival curves of the responder and non-responder patient groups for approximately 2 years after treatment began, presented in Kaplan-Meier survival curves (Fig. 4), indicate that survival of non-responders declined significantly more rapidly during this observation period ($P < 0.01$). Median survival was 19.1 months in responders as compared to only 9.2 months in non-responders.

*Safety*

No undesirable side-effects of r-HuEPO therapy were observed throughout the extended observation period. In particular, there was not a single episode of hypertension. Deaths during the observation period were due to the disease process or related consequences.

## DISCUSSION

Close to half of the 60 patients currently evaluable for efficacy showed substantial improvement of their chronic anaemia during treatment with r-HuEPO three times a week. In agreement with published reports [6-8], this improvement was observed in both general cancer categories, i.e. in 47.2% of patients with haematological cancers and in 37.5% of those with solid tumours.

Dramatic differences were observed in patient responsiveness to r-HuEPO therapy among the specific types of cancer represented in this pilot study. As would be expected from the experimental literature [9-11], the most responsive group comprised patients with multiple myeloma, with more than three-fourths showing a positive haemoglobin response. Two-thirds of the oesophageal cancer patients were responders, just under half of the breast cancer patients were responders, and one-third of the patients with chronic lymphatic leukaemia or colon cancer were responders. The remaining diagnostic groups showed little or no response. This included patients with myelodysplastic syndrome, of whom less than one-fifth responded. This agrees with the observations of other investigators [12-13].

The response rates of the two largest diagnostic groups—77.8% of the 18 multiple myeloma patients and 18.2% of the 11 myelodysplastic syndrome patients—are highly suggestive of differential response rates associated with diagnostic type. Due to the pilot nature of this study, however, other diagnostic types were only minimally represented, with exceedingly small patient groups, i.e. three 3-patient groups, one 2-patient group, and five groups containing only 1

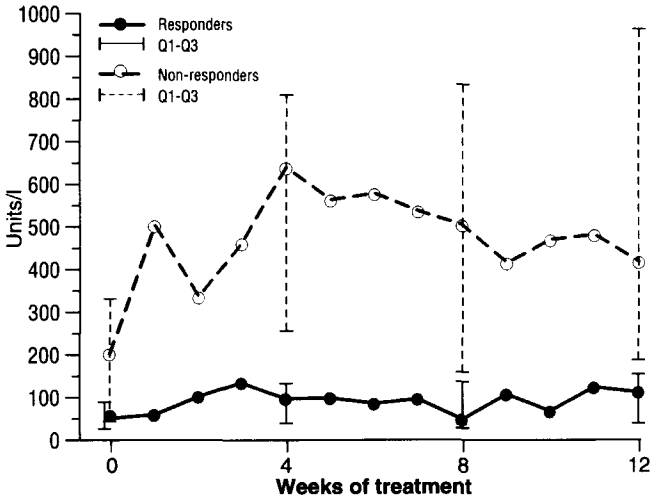


**Fig. 3. Comparison of median serum erythropoietin levels for responders and non-responders. The extremely high values attained by some non-responders required the range of values shown at baseline and weeks 4, 8, and 12 to be limited to those between the first quartile (25%) and third quartile (75%) in order to show the modest variation in the curve for the responder group.**

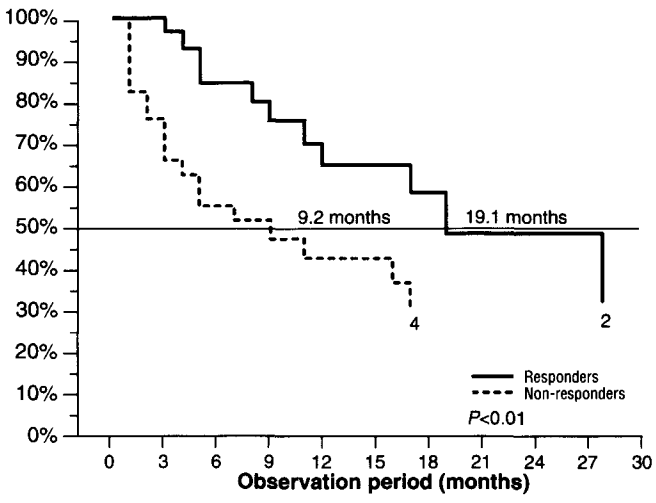


**Fig. 4. Kaplan-Meier cumulative survival curves for responders and non-responders from the start of r-HuEPO treatment show a median survival time of 19.1 months for responders and 9.2 months for non-responders. This difference is significant at $P < 0.01$.**

patient each. Although the data clearly warrant further research into differential haemoglobin response rates to r-HuEPO therapy associated with different cancers, these low numbers make any conclusions premature.

It would appear that there are both early and late responders, with all but a few responsive patients falling into the "early" category. Most responders were identified between weeks 4–6 of the protocol. The median haemoglobin response time was 4.9 weeks. 2 patients did not show a response until 15.6 and 20.3 weeks, substantially beyond the 12-week point at which the experimental therapeutic period had formally ended. Because 50% of the non-responder patients chose not to continue with r-HuEPO therapy beyond the 12-week experimental period, there is no way of knowing whether or not the initial non-responder group actually held more than two late responders. Further investigations should utilize a therapeutic period of sufficient duration to permit all late responders to be identified.

Duration of this significant amelioration of chronic anaemia can be substantial. Although it is temporarily abrogated by any condition which temporarily disrupts the patient's stability—usually surgery and/or severe infection—the positive effects of r-HuEPO therapy otherwise continue until progressive disease intervenes. Patients remaining free of progressive disease in this pilot study continue to manifest a stable, significant increase in haemoglobin concentration more than 1 year after therapy was initiated.

The benefits of this successful amelioration of cancer-associated chronic anaemia in the responder group of patients were multiple. The significant improvements in WHO performance scores and in overall quality of life reflect patients who have been able to regain some sense of value, involvement and pleasure in their lives [14]. The dramatically reduced need for blood transfusions has avoided the attendant risks and stress factors, as well as the economic drain.

In this study, baseline serum erythropoietin appeared to be a partially helpful pretreatment index of responsiveness to r-HuEPO therapy. Although the group of patients presenting with initial levels below 200 units/l represented both eventual responders and non-responders, not a single patient who has presented with a serum erythropoietin level above 200 units/l has thus far achieved sufficient responsiveness. This pretreatment index of responsiveness [15] can aid in weeding out patients who are unlikely to benefit from r-HuEPO therapy.

Additional baseline data would be needed to determine the actual cause(s) of the observed difference in survival time between responders and non-responders. This statistical association between survival time and responsiveness to r-HuEPO treatment may reflect either a variable common to both (e.g. relatively better health at baseline), or some sort of causal relationship. The better baseline WHO scores shown by the responders does suggest that they were in better health at the outset compared to the non-responders. If it is, in fact, the case that responders are those in relatively better health when r-HuEPO therapy first starts, then relative health at baseline can also become incorporated in a pretreatment index of anticipated responsiveness.

Serum erythropoietin level during treatment clearly differed between the responder and non-responder patient groups. Serum erythropoietin level remained relatively constant in responders, while increasing in non-responders. This might be explained by a mechanism that could also explain the response difference, i.e. in responding patients the hormone is rapidly bound to free receptors, while in non-responding patients a saturated receptor population, or other defect of utilization, leaves the added hormone in circulation.

## CONCLUSIONS

In conclusion, our interim results indicate that the administration of r-HuEPO three times a week resolves, or substantially improves, the chronic anaemia of a significant proportion of cancer patients, with meaningful quality of life benefits directly attributable to this improvement. No adverse effects were observed. Responsiveness appears to continue as long as the patient's basic stability is not permanently compromised. A pretreatment serum erythropoietin level substantially above 200 units/l is a possible predictor for unresponsiveness to r-HuEPO therapy. Relatively poorer health at treatment inception may also help to identify unresponsive patients. At this interim stage of the investigation, response rate to r-HuEPO therapy also appears to be partly associated with type of cancer.


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