Effect of subcutaneous recombinant human erythropoietin in cancer patients receiving radiotherapy: final report of a randomized, open-labelled, phase II trial

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Summary The purpose of this study was to determine the safety, efficacy and impact on quality of life of recombinant human erythropoietin (r-HuEPO) for cancer patients undergoing radiotherapy (RT). An open-labelled randomized design was used, with patients randomized to either treatment or control arms. Patients in the treatment arm received r-HuEPO given by subcutaneous injection at a dose of 200 units kg⁻¹ day⁻¹ plus oral iron supplements (ferrous sulphate 325 mg p.o. i.i.d.). Entry was restricted to patients with carcinoma of the lung, uterine cervix, prostate or breast who presented for RT with anaemia parameters reflective of 'the anaemia of chronic disease'. Radiotherapy policies (portals, doses, fraction size, etc.) were determined by the site and stage of disease. Complete blood counts (CBCs) were obtained weekly. The target level of haemoglobin was 15 g dl⁻¹ for men and 14 g dl⁻¹ for women. Quality of life (QOL) was assessed weekly by using an analogue scale to judge energy, activities of daily living and overall quality of life. Forty-eight patients were entered in the study, 24 in the treatment arm and 24 in the control arm. The prerandomization demographic characteristics and mean laboratory values were comparable in both arms. The mean haemoglobin at completion was 13.6 g dl⁻¹ for r-HuEPO-treated patients compared with 11.0 g dl⁻¹ for control subjects (mean P = 0.0012). Patients who received r-HuEPO demonstrated a mean weekly haemoglobin increase of 0.41 g dl⁻¹ compared with a decrease in mean haemoglobin level in controls for 6 of the 7 weeks of the study (mean weekly decrease of 0.073 g dl⁻¹). Target levels of haemoglobin were achieved by 41.6% of r-HuEPO-treated patients compared with none of the control subjects. The mean platelet count declined in both arms of the study with RT but the decline from pretreatment was less rapid in r-HuEPO-treated patients (11.2% decrease) compared with controls (26.3% decrease) and was statistically significant during weeks 4–6. Toxicity was minor with only mild irritation at the injection site. Mean quality of life end points were superior in the treatment arm but not statistically significant. r-HuEPO had a beneficial effect on weekly haemoglobin levels in patients undergoing RT with response rates similar to other studies. There was also a less rapid decline in weekly platelet counts in r-HuEPO-treated patients compared with control subjects. Further studies are needed to address the optimum dose and scheduling as well as the impact of r-HuEPO on clinical outcomes.

Keywords: erythropoietin; radiotherapy; anaemia in cancer

Anaemia is a common occurrence in cancer patients at some point in their disease course (Samuels and Bierman, 1956; Hirst, 1986; Abels, 1992a; Leitgeh et al, 1994). The presence of anaemia reflects a reduction in red cell mass and a corresponding decrease in the oxygen-carrying capacity of the blood (Bunn, 1991). Although the severity is variable from patient to patient, anaemia can lead to symptoms of fatigue, dyspnoea and loss of appetite and can cause or aggravate cardiovascular and respiratory problems (Ludwig et al, 1993; Leitgeh et al, 1994). The causes of anaemia in cancer patients are often multifactorial including haemorrhage, haemolysis and iron deficiency as well as tumour infiltration of bone marrow and the toxicities of cancer therapy (radiation and chemotherapy) (Abels, 1992a,b; Spivak, 1992; Longo, 1993). One component may be related to the so-called ‘anaemia of chronic disease’ (Lee, 1983; Abels, 1992a; Longo, 1993). The anaemia of chronic disease results from decreased erythrocyte lifespan (about 80 days rather than the normal 120 days), impaired flow of iron from macrophages to plasma and an inadequate erythropoietin response to anaemia (Miller et al, 1990; Abels, 1992a,b; Kushner, 1992; Dhsrsen and Hossfeld, 1994). In cancer patients erythropoietin production has been found to be particularly depressed compared with patients with either iron deficiency anaemia or other normochromic, normocytic anaemias associated with chronic disease (Miller et al, 1990; Kettelhack et al, 1994). This may be partly related to the inhibitory effect of increased cytokine production of tumour necrosis factor alpha and interleukin 1 on erythropoiesis (Dhsrsen and Hossfeld, 1994; Spivak, 1994). Thus, the anaemia of cancer is at least partially due to a deficiency of erythropoietin (Miller et al, 1990; Abels, 1992a,b; 1993; Spivak, 1992, 1994).

Erythropoietin is the primary regulatory factor in erythropoiesis (Zanjani and Ascensao, 1989). It is an acidic glycoprotein with an estimated molecular weight of 34 000 that is produced primarily in the kidney (Jacobson et al, 1957; Wang et al, 1985; Spivak, 1989; Zanjani and Ascensao, 1986). Tissue hypoxia induces erythropoietin production which stimulates erythroid progenitor cells (Goldberg et al, 1988; Zanjani and Ascensao, 1989; Spivak, 1992, 1994). Recently, through the use of recombinant technology exogenous erythropoietin has become available. Thus, it is now possible

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### Table 1  Demographic characteristics and prerandomization laboratory values

| Demographic characteristics and laboratory data | Control arm | Treatment arm | P-value |
|-----------------------------------------------|-------------|---------------|---------|
| Age (years)                                   | 62.7        | 62.3          | 0.89    |
| Sex                                           |             |               |         |
| Male                                          | 13          | 15            | 0.558   |
| Female                                        | 11          | 9             |         |
| Diagnosis                                     |             |               |         |
| Breast cancer                                 | 5           | 5             | 0.532   |
| Lung cancer                                   | 11          | 7             |         |
| Prostate cancer                               | 6           | 10            |         |
| Cervix cancer                                 | 1           | 2             |         |
| Unknown                                       | 1           |               |         |
| Previous transfusion                          |             |               |         |
| Yes                                           | 3           | 2             | 0.64    |
| No                                            | 21          | 22            |         |
| Haemoglobin (gm dl⁻¹)                         | 10.72       | 12.07         | 0.22    |
| (men 14–18; women 12–16)                      |             |               |         |
| RBC count (x 10⁹ mm⁻³)                        | 3.7         | 3.88          | 0.28    |
| (men 4.6–6.2; women 4.2–5.4)                  |             |               |         |
| WBC count (x 10⁹ mm⁻³)                        | 7.47        | 6.88          | 0.11    |
| (4.8–10.8)                                    |             |               |         |
| Platelets (x 10¹² mm⁻³)                       | 350.7       | 295.38        | 0.11    |
| (159–400)                                     |             |               |         |
| Reticulocyte count (%)                        | 1.29        | 1.31          | 0.94    |
| (0.5–1.5)                                     |             |               |         |
| Serum iron (µg dl⁻¹)                          | 82.58       | 54.95         | 0.43    |
| (men 80–160; women 60–135)                    |             |               |         |
| Serum ferritin (ng ml⁻¹)                      | 347.76      | 223.85        | 0.11    |
| (men 36–262; women 10–155)                    |             |               |         |
| Total iron-binding capacity (TIBC) (µg dl⁻¹)  | 251.39      | 271.05        | 0.33    |
| (250–350)                                     |             |               |         |
| Serum folate level (ng ml⁻¹)                  | 25.04       | 17.76         | 0.7     |
| (2.5–17.5)                                    |             |               |         |
| Serum B12 level (pg ml⁻¹)                     | 667.2       | 633.1         | 0.77    |
| (250–1000)                                    |             |               |         |
| Serum erythropoietin level (IU/l) (4–26)      | 27.52       | 25.96         | 0.91    |

- Units of measurement in parentheses. Normal values in parentheses. *Mean laboratory values. Data not available on all patients.

### Figure 1

(A) Haemoglobin; (B) platelets; (C) White blood cell count

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To manipulate erythropoiesis independently of endogenous erythropoietin production (Spivak, 1994). Recombinant erythropoietin (r-HuEPO) has previously been shown to increase the haematocrit and reduce the transfusion requirement in patients with end-stage renal disease undergoing haemodialysis (Esbach et al, 1989) and in AIDS patients treated with zidovudine (Fischl et al, 1990). In addition, there are now a number of reports on the use of r-HuEPO to correct anaemia in cancer patients (Plataniotis et al, 1991; Abels, 1992a,b, 1993; Miller et al, 1992; Case et al, 1993; Lavey and Dempsey, 1993; Ludwig et al, 1993, 1994; Vijayakumar et al, 1993; Dusenberg et al, 1994; Leitgeh et al, 1994; deCampos et al, 1995). In the largest randomized trial published to date, Abels (1993) demonstrated that r-HuEPO corrected anaemia and reduced transfusion requirements compared with a control group for patients with a variety of cancers undergoing chemotherapy. However, this particular study excluded patients receiving radiotherapy (RT). In view of the above, a prospective, randomized, open-labelled clinical trial was conducted to determine the safety and efficacy of subcutaneous r-HuEPO in cancer patients undergoing RT. A randomized design was chosen to compare weekly changes in blood cell parameters between the treatment and the control group in a prospective and unbiased manner and to separate the toxicities associated with RT from any unexpected toxicities of r-HuEPO administration in the treatment arm. In addition, we sought to assess quality of life measures between those patients in the treatment and control arms. We have previously reported the interim analysis of the first 26 patients entered (Vijayakumar et al, 1993) and now present the final report of the 48 patients who completed this study.

### METHODS AND MATERIALS

The study was initiated in September 1991 and completed in February 1996. The participating institutions were the departments of radiation oncology at the University of Chicago (UC), the...
University of California in San Francisco (UCSF) and the Joint Center for Radiation Therapy (JCRT) in Boston. Informed consent was obtained from all patients before randomization. Entry was restricted to patients with either carcinoma of the lung, uterine cervix, prostate or breast who presented for radiation therapy with anaemia. Patients were required to have a Karnofsky performance status of ≥ 70 and a life expectancy of at least 3 months. Only patients who would undergo at least 4 weeks of RT were eligible. Although not specifically considered an exclusion criteria, only three patients in the r-HuEPO arm and two of the control patients received concomitant chemotherapy. Thus, impact of r-HuEPO on patients receiving RT cannot be considered confounded by the addition of concomitant chemotherapy. Anaemia was considered to be haemoglobin ≤ 13 g dm⁻¹ in males and ≤ 12 g dm⁻¹ in female patients. So as to best approximate the anaemia of chronic disease, patients with evidence of iron, folate or B₁₂ deficiency or guaiac-positive stool were excluded. Patients were required to have serum iron of > 20%; ferritin > 20 ng ml⁻¹; TIBC < 400 μg dl⁻¹ and be direct Coomb’s test negative. Metastatic disease was not an exclusion criteria except for patients with lung primaries or cerebral metastases.

Patients in the treatment arm received 200 units(U) kg⁻¹ of r-HuEPO (Procrit, Ortho Biotech, Raritan, NJ, USA) subcutaneously, five times a week, until the haemoglobin reached its target level. Injections for up to 7 weeks were allowed considering this to be the maximum length of a radical course of RT for the malignancies in this study. The target levels of haemoglobin were 15 gm dl⁻¹ for men and 14 gm dl⁻¹ for women. Once the target haemoglobin level was achieved, the dose of r-HuEPO was reduced by 50% for maintenance of this level until completion of RT. All patients in the treatment arm received iron (ferrous sulphate, 325 mg. p.o. t.i.d.) supplements during the period of r-HuEPO administration. Iron supplements were used to ensure adequate iron stores during erythropoiesis in order to prevent the development of iron deficiency anaemia (Van Wyck, 1989). Patients in the control arm did not receive iron supplements. Radiotherapy treatment policies were based on the site and stage of the disease and were at the discretion of the treating physician in terms of total dose, fraction size, treatment portals, etc. Complete blood counts (CBC) were obtained prerandomization for baseline values (week 0) and weekly thereafter during the RT. The following parameters were analysed: haemoglobin, total white blood cell count (WBC) and platelets.

A patient self-assessed, subjective quality of life assessment was also obtained on all patients on a weekly basis. Patients were asked to mark their assessment of quality of life in a visual analogue format. Three aspects of quality of life were addressed: energy level, ability to perform activities of daily living and overall quality of life. A computer program was written for converting the subjective quality of life assessment to numerical objective values. At the completion of RT blood counts were obtained on those patients available for follow-up with a maximum follow up time of 18 months.

Patients were randomized between r-HuEPO and control by creating random numbers separately by disease site and treatment centre in bins of 10 by a computer. The differences between the control and treatment arm of the various CBC parameters were analysed by subtracting the weekly parameter from the baseline value for each patient. A mean of all patients’ incremental/decremental values for each parameter was calculated and the difference between the control and treatment arm was tested. Statistical analyses were carried out with the two-tailed t-test for two variables and the chi-square test for multiple variables.

### Table 2: Mean changes in weekly haemoglobin levels for the treatment and control arms

| Week studied | Control  | r-HuEPO  | P-value |
|--------------|----------|----------|---------|
| Baseline     | 10.72    | 12.07    | 0.220   |
| Week 1       | 10.37 (16)| 12.51 (16)| 0.030   |
| Week 2       | 10.39 (16)| 13.02 (20)| 0.001   |
| Week 3       | 10.55 (19)| 13.4 (22) | 0.0004  |
| Week 4       | 10.79 (16)| 13.85 (23)| 0.001   |
| Week 5       | 10.67 (15)| 14.38 (21)| 0.00007 |
| Week 6       | 10.63 (17)| 14.38 (19)| 0.0004  |
| Week 7       | 10.52 (15)| 14.69 (13)| 0.0002  |

*Number in parentheses is sample size for that week.

### Table 3: Weekly mean change in haemoglobin level (g dm⁻¹) subtracted from the previous week’s mean level

| Week studied | Control  | r-HuEPO  | P-value |
|--------------|----------|----------|---------|
| Week 1       | -0.347 (16)| 0.44 (16) | 0.03    |
| Week 2       | -0.07 (15) | 0.679 (16)| 0.003   |
| Week 3       | -0.069 (16)| 0.361 (19)| 0.18    |
| Week 4       | 0.309 (16) | 0.525 (22)| 0.32    |
| Week 5       | -0.169 (13)| 0.433 (21)| 0.015   |
| Week 6       | -0.162 (13)| 0.21 (18) | 0.17    |
| Week 7       | -0.029 (14)| 0.1 (12)  | 0.73    |

*Number in parentheses is sample size for that week.

### Table 4: Mean changes in weekly platelet levels for the r-HuEPO and control arms

| Week studied | Control  | r-HuEPO  | P-value |
|--------------|----------|----------|---------|
| baseline platelet level | 351 | 295 | 0.11 |
| Week 1 change | 27.2 (15) | -33.0 (16) | 0.17 |
| Week 2 change | -2.1 (15) | -23.4 (18) | 0.57 |
| Week 3 change | -52.6 (18) | -1.2 (20) | 0.06 |
| Week 4 change | -82.2 (14) | -7.9 (22) | 0.03 |
| Week 5 change | -88.3 (14) | -9.8 (18) | 0.004 |
| Week 6 change | -106.8 (16) | -49.3 (18) | 0.05 |
| Week 7 change | -102.1 (15) | -66.8 (13) | 0.190 |

*Number in parentheses is sample size for that week.

### RESULTS

A total of 48 patients were entered in the study. Half of the patients were men and half women. There were 37 patients from UC, ten patients from UCSF and one patient from the JCRT. The breakdown by cancer is as follows: lung cancer, 18 patients; breast cancer, ten patients; prostate cancer, 16 patients; and uterine cervix cancer, three patients. There was one patient whose primary diagnosis was unknown. There were six patients who were treated palliatively, the remainder were treated with curative intent. Two patients refused r-HuEPO injections after randomization; one refused after 3 days of injections and the second before any drug had been administered. These patients are excluded from the analysis.

The demographic characteristics and prerandomization laboratory results are shown in Table 1. The only notable laboratory value is the baseline mean haemoglobin level, which is greater by more than 1 g in the treatment arm (12.0 g dl⁻¹) than in the control arm (10.7 g dl⁻¹). However, this difference is not statistically
significant \( P = 0.22 \). In general, the two arms are well balanced without significant differences in baseline characteristics. The mean values represented by this table demonstrate a fairly classic picture of the anaemia of chronic disease, specifically, the mean iron and total iron binding capacity (TIBC) values are low—normal and the reticulocyte count and ferritin levels are in the normal range. The mean serum erythropoietin level for the entire group was 26.7 IU ml\(^{-1}\). The normal range in adults without anaemia is 4—26 IU per l (Mendenhall et al., 1984; Egrice et al., 1987). Thus, the endogenous erythropoietin level similarly represents the classic picture of the anaemia of malignancy with a value that is elevated but below what would be expected for iron deficiency anaemia (Mendenhall et al., 1984).

Figure 1A shows the treatment and control arms for the weekly haemoglobin levels. The mean haemoglobin in the patients who received r-HuEPO demonstrated a gradual increase from the baseline level during the weeks of the study as shown by the upward slope. The haemoglobin levels of patients in the control arm demonstrated no significant change in mean haemoglobin during this time period and have a static curve. The mean haemoglobin at completion was 13.6 g dl\(^{-1}\) for the treated patients compared with a week 0 level of 12.0 g dl\(^{-1}\). For the control patients, the completion mean haemoglobin level was 11.0 g dl\(^{-1}\) compared with a baseline of 10.7 g dl\(^{-1}\). The differences between the r-HuEPO group and control mean haemoglobin levels were statistically significant for each week of the study. These data are also presented in Table 2.

These results might be considered misleading because the higher baseline haemoglobin of the treated patients compared with the control patients (12.0 g dl\(^{-1}\) vs 10.7 g dl\(^{-1}\)) inflates the difference in the mean haemoglobin levels, especially during the later weeks of the study. However, this baseline difference is eliminated when the week-to-week changes in haemoglobin are analysed. This is demonstrated in Table 3 where the weekly mean haemoglobin level of the treatment and control patients is subtracted from the previous week’s level during each of the 7 weeks of the study and the differences between the two groups tested. For example, the haemoglobin level obtained in week 1 is subtracted from the baseline (week 0) haemoglobin, the haemoglobin from week 2 is subtracted from week 1, etc. This table shows that for each of the 7 weeks of the study there is an increase in haemoglobin from the previous week for those patients who were treated with r-HuEPO. The average net increase in haemoglobin per week is 0.41 g dl\(^{-1}\) and is greatest between weeks 0 and 5 before levelling off. The maximum increase for 1 week is between weeks 1 and 2, when the mean haemoglobin increases 0.68 g dl\(^{-1}\). Patients in the control arm show a decrease in haemoglobin from the previous week’s reading for 6 of the 7 weeks of the study with a range of between 0.03 and 0.35 g dl\(^{-1}\).

The target level of haemoglobin of 15 g dl\(^{-1}\) for men and 14 g dl\(^{-1}\) for women was achieved by 41.6\% (10 out of 24) of the patients in the r-HuEPO arm. This includes six men and four women. The mean time to normalization of haemoglobin was 4.2 weeks for men and 3.9 weeks for women. None of the patients in the control group reached these target haemoglobin levels. If the target level of haemoglobin was considered to be 14 g dl\(^{-1}\) for men and 13 g dl\(^{-1}\) for women, as is the case in some laboratories, then 65.2\% of the r-HuEPO patients achieved this haemoglobin level compared with only one control patient (5.2\%). The type of cancer did not have a predictive value on either the pre-RT haemoglobin level or progression of haemoglobin during the RT for either the r-HuEPO or the control group (data not shown).

Follow-up haemoglobin levels were obtained on a subset of patients. The number of patients continually decreased as the interval from the completion of RT increased because of patients dying or being lost to follow-up. As demonstrated in Figure 2, with a maximum interval of 18 months, the mean level of haemoglobin in the r-HuEPO patients is consistently higher than in the control patients. However, the small number of patients in which follow-up haemoglobin levels were available preclude this difference from showing statistical significance.

Figure 1B and C show the changes in platelets and WBC respectively. The mean platelet count in the control patients demonstrated a progressive decline with RT from a week 0 level of 350 to an end of treatment level of 258, a 26.3% decrease. The
mean platelet count in the r-HuEPO patients was 295 at the commencement of RT and 262 at completion, only an 11.2% decrease. A t-test for the differences between the pre- and post-RT platelet values for the r-HuEPO and control groups indicates a significantly different rate of decline (P = 0.03). This 'positive' effect of r-HuEPO on platelets is shown in Figure 1B as an initial minimal increase in mean platelet count and then a levelling off during weeks 3–5 with a more gradual decline during the final 2 weeks of RT. Table 4 demonstrates that the weekly changes in mean platelet count for the r-HuEPO patients achieve borderline significance during week 3 (P = 0.060) and are statistically significant during weeks 4–6 when compared with controls. Figure 1C demonstrates the lack of effect of r-HuEPO on the WBC values. White blood cell counts decreased in both arms of the study with RT. A comparison of the pre- and post-RT parameters for the treatment and control arm are summarized in Table 5.

**Adverse effects/quality of life**

One patient in the treatment arm developed pruritis, which cleared within 2 days, and he subsequently continued r-HuEPO administration without further difficulties. Five other patients experienced adverse effects during the trial that were considered unrelated to r-HuEPO. Three patients developed herpes zoster in dermatomes within the radiotherapy field (two were in the control arm and one in the treatment arm). Two patients complained of dyspepsia, attributed to iron supplements, although none discontinued taking iron tablets. No increased skin or other side-effects were observed during RT in the treatment arm.

A quality of life (QOL) survey was completed weekly during RT by all patients. Three aspects of quality of life were addressed: energy level, ability to perform activities of daily living and overall quality of life. Our results demonstrate that the answers for all patients were highly correlated for the three aspects meaning an individual patient generally recorded a similar score for each of the three questions. Thus, the results are presented as a single QOL parameter. Table 6 shows the weekly mean QOL scores for the treatment and control groups. Note that for each week of the study there is a more favourable numerical assessment of QOL in the r-HuEPO arm compared with the control arm. These weekly differences did not achieve statistical significance, however, because there was a large variation in individual QOL scores in the control arm. Nevertheless, as the table demonstrates, there is a strong trend towards better QOL in patients who received r-HuEPO.

**DISCUSSION**

For cancer patients receiving RT, anaemia has been correlated with unfavourable outcomes when compared with non-anaemic patients for a number of disease sites (Dische, 1991). Most of the literature concerns malignancies of the uterine cervix (Evans and Berigo, 1965; Hierlhy et al, 1969; Vigerio et al, 1973; Bush et al, 1978; Dische et al, 1983; Mendenhall et al, 1984; Bush, 1986; Girinski et al, 1989; Rader, 1990) and head and neck (Blitzer et al, 1984; Overgard et al, 1989; Dubray et al, 1996). How anaemia is causally related to poor outcome is not entirely clear but it is probably both a marker of advanced tumour and indicative of some degree of tissue hypoxia. Because it is an axiom in radiobiology that hypoxic cells are less radiosensitive than aerated cells (Gray et al, 1953; Palic and Skarsgard, 1984), it has been standard treatment to transfuse anaemic cancer patients to some arbitrary haemoglobin level in an effort to improve tissue oxygenation as well as to enhance patient comfort (Poskitt, 1987). Despite this practice, the routine use of blood transfusion to improve serum haemoglobin level has risks, including viral infection (HIV and hepatitis) and transfusion reaction (Bove, 1987; Poskitt, 1987; Levine and Vijayakumar, 1993). In addition, there is the potential down-regulation of host cellular immune function with transfusion (Blumberg and Heal, 1990). A number of retrospective reviews have documented adverse outcomes (inferior overall and disease-free survival) in patients receiving blood transfusions for a variety of malignancies including colon/rectum, lung, prostate, uterine cervix, breast and soft tissues (Rosenberg et al, 1985; Tarter et al, 1985; Arnoux et al, 1988; Blumberg et al, 1988; Corm an et al, 1988; Heal et al, 1988; Moores et al, 1989; Wobbes et al, 1989; Little et al, 1990; McClinton et al, 1990; Casper et al, 1991). Thus, although transfusion can improve tissue oxygenation and potentially enhance the effectiveness of RT, any radiobiological gain might be mitigated by the adverse effects of transfusion on tumour immunosurveillance (Levine and Vijayakumar, 1993). Recombinant erythropoetin offers the possibility of correcting cancer-related anaemia without subjecting patients to the risks of transfusion.

The results of this study demonstrate the use of r-HuEPO in improving the haemoglobin levels in anaemic cancer patients undergoing RT with an average increase of about 0.4 g dl⁻¹ per week during treatment. This improvement in haemoglobin was seen in every week of the study and was greatest during the second week with a mean increase of 0.68 g dl⁻¹. Although the mean haemoglobin level at completion was 13.6 g dl⁻¹, which is below the targeted levels of 15 g dl⁻¹ for men and 14 g dl⁻¹ for women, this represents an improvement over patient in the control arm who showed no change with RT. Furthermore, when the target levels are reduced to the more realistic values of 14 g dl⁻¹ for men and 13 g dl⁻¹ for women, 65% of the r-HuEPO patients achieved these values compared with only 5.2% of control patients.

These findings in our randomized study confirm the erythropoietic effect of r-HuEPO demonstrated in previous non-randomized studies of anaemic cancer patients undergoing RT as well as our preliminary report (Lavey and Dempsey, 1993; Vijayakumar et al, 1993; Dusenbery et al, 1994). Lavey and Dempsey (1993) described an improvement in mean haemoglobin level from 11.9 g dl⁻¹ to 15.1 g dl⁻¹ in 20 patients who received r-HuEPO while undergoing RT for supradiaphragmatic tumours (Kushner, 1992). This is an approximate haemoglobin increase of 0.45 g dl⁻¹ per week over a 7-week RT treatment course. Similarly, Dusenbery et al (1994) showed an improvement in mean haemoglobin from 10.3 to 13.2 g dl⁻¹ in 15 patients with uterine cervix cancer who received r-HuEPO during RT, which is an increase of 0.5 g dl⁻¹ per week (Dusenbery et al, 1994). These studies demonstrate an increase in mean haemoglobin that is slightly greater than the average weekly haemoglobin increase in our study of 0.41 g dl⁻¹. This may be explained by the fact that patients in each of these studies received r-HuEPO as early as 10 days before the start of RT, whereas patients in our study started r-HuEPO during the first week of RT.

Despite the favourable effect on mean haemoglobin levels seen in these studies the optimum dose and scheduling of r-HuEPO for cancer patients has not been established. Our study used 200 units kg⁻¹ for 5 consecutive days as the initial dose and then decreased the dose by 50% once the anaemia was corrected. This was similar to the dose and scheduling of Dusenbery et al (1994) and reflects the favourable results of patients with chemotherapy-induced...
anaemia reported by Plataniats et al (1991) in a dose escalation study of r-HuEPO that demonstrated the highest response rates in patients who received either 200 or 300 U kg$^{-1}$ for 5 days rather than lower dose levels. However, Lavey and Dempsey (1993) used 300 U kg$^{-1}$ three times only during the first week and then 150 U kg$^{-1}$ (three times a week) for the remainder of the RT. This dosing schedule is fairly close to that used in the two largest experiences of r-HuEPO in patients with cancer-related anaemia (Abels, 1992a,b, 1993; Ludwig et al, 1993, 1994) including patients receiving combination chemotherapy (Case et al, 1993). Response rates in these studies are defined differently but are approximately in the 40 to 50% range of patients tested, which is similar to our results. Thus, the correct r-HuEPO dose for RT-treated cancer patients is probably at least 150 U kg$^{-1}$ given three times per week and preferably at least 1 week before the commencement of RT. The dose can be reduced once the anaemia is corrected for the remainder of the RT.

There were no adverse effects related to the r-HuEPO in our patients, except for minor irritation at the injection site. This was similar to the experience of Lavey and Dempsey (1993). Dusenbery et al (1994) did describe deep venous thrombosis (DVT) occurring in 4 of 15 patients either during or just thereafter r-HuEPO administration (Dusenbery et al., 1994). Plataniats et al (1991) also reported DVT occurring in two of the eight patients treated at the highest dose level (300 U kg$^{-1}$) of r-HuEPO and Miller et al (1990) had 1 patient out of 21 develop DVT, although this was in the lowest dose group (25 U kg$^{-1}$). In a placebo-controlled trial by Case et al (1993) the only statistically significant difference in the incidence of any adverse effect in r-HuEPO-treated patients compared with controls was diarrhoea and diaphoresis. Other reports have similarly shown the drug to be fairly well tolerated at the dose levels used for cancer patients (Abels, 1993; Ludwig et al., 1993; deCampos et al, 1995).

We compared quality of life end points between r-HuEPO-treated and control patients and found that for each week of study there was a more favourable QOL assessment in the treated patients, although wide variation of responses in the control group precluded statistical significance. Nevertheless, this trend toward improved QOL in r-HuEPO-treated patients is reflected in the literature with most (Abels, 1992a, 1993; Case et al, 1993; Ludwig et al, 1993; Leitge et al, 1994) but not all (Dusenbery et al, 1994) series showing a benefit in various quality of life parameters over concurrent or historical controls.

One unexpected finding in our study was the positive effect of r-HuEPO on platelets. The gradual decline in platelets with partial body irradiation has been previously reported (Yang et al, 1995). Although the r-HuEPO-treated patients in this study demonstrated a decline in mean platelet level with RT there was clearly seen a less rapid decline than in the control group. This effect has also been described by de Campos et al (1995), who noted fewer platelet transfusions in patients with small-cell-lung cancer treated chemotherapy and RT who received r-HuEPO compared with patients who did not. This thrombopoietic effect of r-HuEPO and its therapeutic implications has been discussed in detail by one of us (SV) in a separate communication (Vijayakumar et al, 1998).

In summary, this study confirms the findings of our preliminary report of the beneficial effect of r-HuEPO on haemoglobin levels in patients undergoing RT for a variety of malignancies. The mean haemoglobin increase in those patients who received r-HuEPO was 0.41 g dl$^{-1}$ per week. By our stringent definition of response (target haemoglobin level of 15 g dl$^{-1}$ for men and 14 g dl$^{-1}$ for women), 41.6% of patients responded, which is equivalent to other studies of anaemic cancer patients. Further, r-HuEPO was found to be safe at the dose levels used and had a favourable impact on quality of life end points. Future studies need to address the optimum dose and scheduling for RT patients and to prospectively compare outcomes from treatment of patients receiving r-HuEPO with control patients.

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