Once-weekly dose of epoetinum alfa in cancer patients with anemia receiving radiotherapy

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Introduction. **Anaemia is present in 30%-90% of all patients with cancer, and its origin is multifactorial. Human recombinant erythropoietin has been shown to be useful in treating anemia in patients with cancer. The aim of this study was to evaluate the effectiveness of treatment of anaemia with epoetin alfa (EPO) given as a single weekly dose, and its repercussions on quality of life (QoL).**

Materials and methods. **From January to October 2002, a total of 139 patients referred to our service for radiotherapy (RT) had anemia and received treatment with EPO as a single weekly dose of 40,000 IU subcutaneously, with oral iron supplement. If haemoglobin (Hb) values after 1 month of treatment did not increase by ≥1 g/dl, the dose was increased to 60,000 IU/week. Treatment with EPO ended when Hb values reached ≥14 g/dl or one month after the end of RT regardless of Hb values. QoL was evaluated with the Functional Assessment of Cancer Therapy-Anaemia subscale (FACT-An) and the Cancer Linear Analogue Scale (CLAS).**

Results. **Mean Hb at the start of treatment with EPO was 11.49 ± 1.08 g/dl, and the mean value at the end of treatment was 14.52 ± 1.41 g/dl ($p < 0.001$). The mean increase in Hb was 2.97 ± 1.65 g/dl. Mean duration of treatment was 7.13 ± 2.91 weeks. In 11 patients (7.9%) the dose was increased after 4 weeks. In 84 patients (60.4%) EPO treatment was implemented before the commencing of RT. Mean Hb values in this group was 11.34 ± 1.11 g/dl at the start of EPO treatment, 12.69 ± 1.56 g/dl at the start of RT, 13.96 ± 1.54 g/dl at the end of RT and 14.68 ± 1.3 g/dl at the end of EPO treatment ($p < 0.001$). In 55 patients (39.6%) anaemia developed during RT and, therefore, EPO treatment was implemented after commencing of RT. In this group the mean Hb values were 12.29 ± 1.6 g/dl at the start of RT, 11.72 ± 1.01 g/dl at the start of EPO treatment, 13.97 ± 1.53 g/dl at the end of RT and 14.28 ± 1.54 g/dl at the end of EPO treatment ($p < 0.001$). Hemoglobin levels at the start of EPO were lower in patients who commenced EPO before RT ($p < 0.05$). In 60 patients who received combined RT and chemotherapy, mean Hb values were 11.42 ± 1.16 g/dl at the start of EPO and 13.98 ± 1.55 g/dl at the end of EPO ($p < 0.005$). In 75 patients who had received RT alone, the mean Hb values was 11.53 ± 1.05 g/dl at the start of EPO and 14.98 ± 1.17 g/dl at the end of treatment ($p < 0.001$). Patients treated with RT alone had higher Hb levels at the end of RT and at the end of EPO treatment than did patients who had received combined treatment ($p < 0.005$). The duration of EPO treatment was shorter in the group treated with RT alone than in the combined treatment group (6.41 ± 2.99 weeks versus 7.96 ± 2.67 weeks; $p < 0.005$). No significant differences were observed in FACT-An and CLAS scores at the beginning and the end of the study.**

Conclusions. **Treatment with epoetin alfa as a single weekly dose significantly increased Hb levels in patients with cancer who were undergoing radiotherapy. The response was greater in patients treated with radiotherapy alone than in those receiving combined therapy. The duration of EPO treatment was shorter in the group treated with radiotherapy alone than in the combined treatment group.**

Key words: anaemia, radiotherapy, erythropoietin, quality-of-life.

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INTRODUCTION

Anemia is present in 30% to 90% of all patients with cancer depending on tumor type and the definition of anemia used[1]. Its origin is multifactorial, and can in-

volve chronic inflammation, blood loss, nutritional deficiency, hemolysis, bone marrow infiltration by malignant cells, diminished levels of erythropoietin and impaired bone marrow response to erythropoietin[2]. Moreover, most cancer treatments cause anemia[3]. Anemia favors tumoral hypoxia, which can increase tumour aggressivity and curtail the effectiveness of radiotherapy (RT)[4-6]. This makes anemia a prognostic factor in local control and survival[7-11].

Human recombinant erythropoietin has been shown useful in the treatment of anemia, increasing hemoglobin (Hb) levels and reducing the need for transfusions in patients with chronic anemia caused by cancer. In addition, human recombinant erythropoietin improves quality of life and performance status, and is well tolerated[12,13]. The best results have been obtained when erythropoietin is administered subcutaneously[14].

The usual dose of epoetinum alfa (EPO) in patients with cancer is 150 IU/kg 3 times per week subcutaneously, with doubling of the dose after 4 weeks if Hb values have not increased by 1 g/dl. However, pharmacokinetic and pharmacodynamic studies have shown dose equivalence with a 40,000 IU/week subcutaneously[15]. In 2001 Gabrilove et al[16] published the results for 3,012 patients with nonhematological cancer treated with chemotherapy who received EPO at a dose of 40,000 IU/week, which was increased to 60,000 IU/week after 4 weeks if no response was seen. They concluded that this form route of administration increased Hb levels, decreased the need for transfusions, and improved quality of life in patients with cancer and anemia who were receiving chemotherapy. Their results were similar to those obtained previously with regimens of three doses per week.

Here we report the results of a prospective study that investigated the effects of a single weekly dose of EPO in patients with cancer and anemia who were receiving RT.

MATERIALS AND METHODS

Between January and October 2002, 139 patients referred to our radiation oncology department for RT and who became anemic at any time during RT were included in the study. Laboratory values for Hb and blood counts were obtained for each patient on the day of the simulation, the first day of RT and weekly during RT. If any Hb value was <13 g/dl in men or <12 g/dl in women, treatment with EPO was started. Treatment consisted of a single weekly dose of 40,000 IU subcutaneously with oral iron supplements. If after 4 weeks the Hb value did not increase by >1 g/dl, the dose was increased to 60,000 IU/week. Treatment with EPO ended when the Hb value reached ≥14 g/dl, or 4 weeks after RT ended regardless of the Hb value. We compared changes in Hb values and transfusion needs during EPO treatment and during RT.

Quality of life was evaluated with two previously validated instruments: the 21-item Functional Assessment of Cancer Therapy-Anemia (FACT-An)[17] and the Cancer Linear Analog Scale (CLAS)[18], a visual analog scale of 0 to 100 that evaluates the dimensions energy level, ability to perform daily living activities, and overall quality of life.

Statistical analyses were done with SPSS version 10.0 software. The distribution of the variables for the two groups was compared with chi-squared tests. To compare mean values for independent groups, the type of distribution of each variable was first checked, and nonparametric tests (Mann-Whitney U test or Kruskal-Wallis H test, depending on the number of groups) or parametric tests (Student's t test, analysis of variance or Bonferroni test for multiple comparisons) were chose accordingly. For related samples we used Student's t test, Wilcoxon's test or Friedman's test depending on the type of variable and size of the available sample.

RESULTS

The total sample of 139 patients who participated in the study is described in table 1. More than half of the patients (patients 84 [60.4 %]) began EPO treatment before RT started, and 55 patients (39.6%) began EPO treatment after RT had started. Of this group, 40 patients (28.8 %) began EPO during the first week of RT, 9 patients (6.5%) during the second week, 3 patients (2.2%) during the third week, and the 3 remaining patients started EPO treatment during weeks 4, 5 and 6 of RT. Comparison of the descriptive characteristics of all patients who developed anemia before or during RT showed that the only significant difference was in the type of tumour: anemia was present most frequently before RT in patients with head and neck or with breast cancer, whereas anemia appeared most frequently during RT ($p < 0.05$) in patients with prostate cancer. We found no significant differences between patients in prior treatments for cancer.

In 11 patients (7.9 %) Hb levels did not increase by ≥1 g/dl after 4 weeks of EPO treatment, so the dose was raised to 60 000 IU /week. The dose was not reduced in any of the patients.

The reasons for stopping EPO administration were attainment of optimum Hb levels during RT in 94 patients (67.7 %); 1 month after the end of RT in 10 patients (7.2%), transfer to another centre in 13 patients (9.4%), missed appointment in 4 patients (2.9%), death in 3 patients (2.2 %) and allergic reaction in 1 patient (0.7%). The reason for ending EPO treatment was not recorded for 10 patients.

Mean duration of EPO treatment was 7.13 ± 2.91 weeks (range 1 to 16 weeks).

TABLE 1. **Specimen's descriptive characteristics**

Age (years)		Mean 62.32 ± 13.47, range 24-88	
Sex	Men	93	67.4%
	Women	46	33.3%
Tumour	Ear-Nose-Throat	32	23%
	Breast	26	18.7%
	Rectum	26	18.7%
	Prostate	15	10.8%
	Lung	9	6.4%
	Gynecological	8	5.7%
	Other digestive tract	6	4.3%
	Bladder	5	3.5%
	Other	12	8.6%
Stage	I	13	9.4%
	II	38	27.3%
	III	49	35.3%
	IV	17	12.2%
Primary tumour		126	90.6%
Local recurrence		7	5%
Location of metastases		3	2.2%
Prior treatment for cancer	Neoadjuvant CT	29	20.9%
	Surgery	66	47.5%
	Adjuvant CT	26	18.7%
	HT	18	12.9%
	Other	8	5.8%
	None	24	17.3%
Current oncological treatment	RT + sequential CT	5	3.6%
	RT + concurrent CT	42	30.2%
	RT + CT radiosensitizing	13	9.4%
	RT alone	75	53.9%
Intention of RT	Radical	64	46%
	Adjuvant	55	39.6%
	Neoadjuvant	12	8.6%
	Palliative	6	4.3%

CT: chemotherapy; HT: hormone therapy; RT: radiotherapy.

Changes in hemoglobin values

The mean Hb value was 11.49 ± 1.08 g/dl at the start of EPO treatment and 14.52 ± 1.41 g/dl at the end of treatment ($p < 0.001$), for a mean increase in Hb value of 2.97 ± 1.65 g/dl. Mean Hb value was 12.55 ± 1.58 g/dl at the start of RT and 13.97 ± 1.52 g/dl at the end of RT ($p < 0.001$). Changes in Hb values during the study period are shown in figure 1.

Changes in hemoglobin values depending on when epoetinum alfa treatment was started

Mean Hb value at the start of EPO treatment in the 84 patients who started EPO treatment before RT began was 11.34 ± 1.11 g/dl. This value had increased to 12.69 ± 1.56 g/dl at the start of RT, and increased further to 13.96 ± 1.54 g/dl by the end of RT and 14.68 ± 1.3 g/dl by the end of EPO treatment ($p < 0.001$) (fig. 2). In the 55 patients who started EPO treatment during RT, mean Hb level at the start of RT was 12.29 ± 1.6 g/dl, and this value decreased to 11.72 ± 1.01 g/dl during RT. After EPO treatment, Hb levels increased to 13.97 ± 1.53 g/dl by the end of RT, and to 14.28 ± 1.54 by the end of EPO treatment ($p < 0.001$). When we compared patients who started EPO treatment before or during RT, the only statistically significant difference was the lower Hb level at the start of EPO treatment in patients who had anemia before RT ($p < 0.05$).

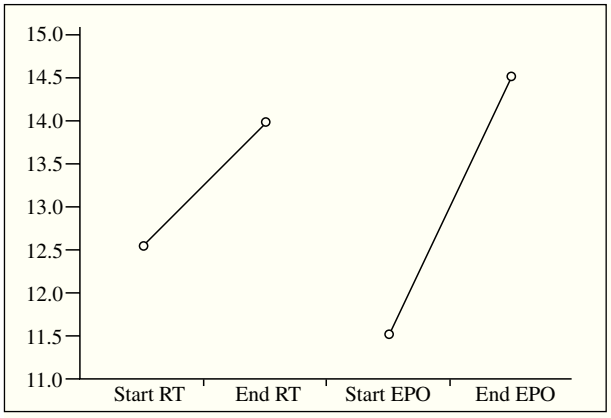

Fig. 1. Changes in Hb values during the study period.

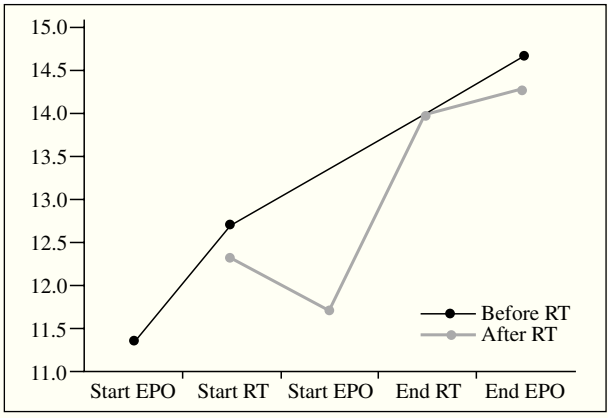

Fig. 2. Changes in hemoglobin values depending on when epoetinum alfa treatment was started. Stadistically significant difference was the lower Hb level at the start of EPO treatment in patients who had anemia before RT (p < 0.05).

Changes in hemoglobin values in patients receiving radiotherapy and chemotherapy

For 60 patients, RT was combined with chemotherapy (sequential, concomitant or radiosensitizing). In this group, mean Hb value was 11.42 ± 1.16 g/dl at the start of EPO treatment, 12.29 ± 1.47 g/dl at the start of RT, 13.42 ± 1.55 g/dl at the end of RT and 13.98 ± 1.55 g/dl at the end of EPO treatment ($p < 0.005$). Mean duration of EPO treatment was 7.96 ± 2.67 weeks. In the 75 patients who were treated with RT only, mean Hb value was 11.53 ± 1.05 g/dl at the start of EPO treatment, 12.71 ± 1.66 g/dl at the start of RT, 14.34 ± 1.41 g/dl at the end of RT, and 14.89 ± 1.17 g/dl at the end of EPO treatment ($P < 0.001$). Mean duration of EPO treatment in this group was 6.41 ± 2.99 weeks. When we compared these two groups (fig. 3), we found that they differed significantly in mean Hb value at the end of RT ($p < 0.005$) and at the end of EPO treatment ($p < 0.005$), and in mean duration of EPO treatment ($p < 0.005$).

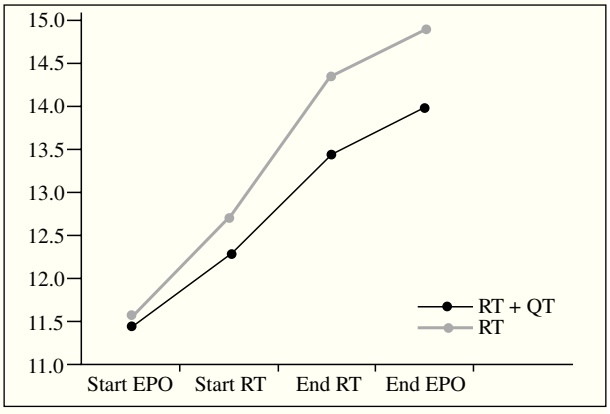

Fig. 3. Changes in hemoglobin values in patients receiving radiotherapy and chemotherapy. Differed significantly in mean Hb value at the end of RT (p < 0.005) and at the end of EPO treatment (p < 0.005).

Transfusion requeriments

Only 9 patients (6.5 %) needed transfusions, and a total of 11 transfusions were given (one patient needed 3 transfusions). Mean Hb value before transfusion was 8.1 ± 0.8 g/dl, and the mean post-transfusion value was 10.4 ± 0.6 g/dl. One patient had not started EPO treatment at the time of transfusion; the other 8 patients continued to receive EPO after their transfusion.

Toxicity of epoetinum alfa treatment

During EPO treatment only one patient had an allergic reaction that motivated suspension of treatment. No other toxic reactions were observed.

Changes in quality of life

Mean score on the FACT-An was 1.11 ± 0.68 at baseline and 1.10 ± 0.63 at the end of the study. On the CLAS, mean baseline score for energy level was 55.2 ± 23.7, and mean score at the end of the study was 54.8 ± 23.4. For ability to perform daily living activities, mean baseline score was 57.9 ± 24.4 and mean score at the end of the study was 55.5 ± 24.7. For overall quality of life, the mean scores were 57.1 ± 24.5 and 57.8 ± 24.1, respectively. None of the differences between baseline and final scores was statistically significant.

DISCUSSION

In 2002, Shasha et al[19] published a retrospective study that evaluated the prevalence of anemia in patients with cancer who were receiving RT. They found a global prevalence of anemia (Hb <12 g/dl), among the 574 patients whose data could be analyzed, of 41% (28% in men, 54% in women) at the start of RT, and 54% (43% men, 63% women) at the end of RT. In patients with cervical cancer the prevalence of anemia before

the start of RT was high (75%), and in patients with prostate, colorectal, lung, and head and neck cancer the prevalence of anemia increased markedly during RT. Of the 139 patients included in the present study, 84 (60.4%) had Hb levels consistent with the criteria for anemia before RT was begun, and 55 patients (39.6%) developed anemia during RT. Patients with head and neck tumours or breast cancer most frequently had anemia before RT, whereas patients with prostate cancer developed anemia most frequently during RT.

A number of clinical studies have reported Hb levels during RT to be associated with local control of the tumour and survival in patients with cervical cancer[20-23], bladder cancer[24] and head and neck tumours[7,25-27]. In their meta-analysis of 60 published studies, Caro et al[28] found that when anemia appeared, the relative risk of death increased by 19% for lung cancer, 75% for head and neck cancer, 47% for prostate cancer, and 67% for lymphoma. The global increase in risk of death was estimated at 65%.

Many studies have shown that epoetinum alfa at a dose of 10,000 IU three times per week is effective in raising Hb values in patients with cancer who are receiving chemotherapy, RT or combined therapy[4,14,29,30]. However, few studies have been published on the efficacy of epoetinum alfa in a single weekly dose in patients with cancer who are receiving RT. At the 1999 meeting of the American Society of Clinical Oncology, Rosen et al[31] reported preliminary results of a randomized multicenter phase II trial of patients with locally advanced cancer of the head and neck treated with chemotherapy with or without EPO in a single weekly dose, but they did not analyze changes in Hb values. In an earlier study at our centre, we compared the usefulness of EPO 10,000 IU three times per week and EPO 40,000 IU once per week to treat anemia in cancer patients who were receiving RT[32]. We concluded that both dose regimens were equally effective in increasing Hb values.

The results of the present study show that a single weekly dose of epoetinum alfa significantly increased Hb levels in patients with cancer who were receiving RT with or without concomitant chemotherapy. The mean increase in Hb level was 2.97 ± 1.65 g/dl. Increasing the dose to 60 000 IU per week was necessary in only 11 patients (7.9%); in other words, 92.1% of the patients responded to EPO treatment with a single weekly dose. Grabilove et al[16] used EPO 40,000 IU once a week in patients with cancer who were receiving chemotherapy with or without RT, and reported a mean increase in Hb of 1.8 g/dl. This increase was smaller than the one seen in our patients, despite the fact that Grabilove et al used an initial Hb value of <11 g/dl as the criterion for starting EPO treatment whereas in our patients, EPO was started when Hb levels fell below <13 g/dl in men or below 12 g/dl in women. The response rate in the study by Grabilove et al was also lower than in the present report. Their initial response rate of 49.2% increased to 68% when the dose was increased in patients who did not respond to the single weekly dose. The differences between our results and those of Grabilove et al are probably related with the fact that all patients in their study were receiving chemotherapy, whereas only 60 patients in the present study were receiving this mode of treatment.

In preclinical studies, correcting anemia improved radiosensitivity and chemosensitivity[33]. In a meta analysis of 27 clinical trials, Bohlius et al[34] reported that the treatment of anemia with EPO tended to improve survival. Nevertheless, randomized clinical trials in patients with metastatic breast cancer reported by Leyland-Jones et al in 2003[35] and a study of patients with head and neck cancer reported by Henke et al[36] appeared to show a negative impact on survival. However, both these studies were sharply criticized because of methodological shortcomings, and their results should thus be regarded with caution. At the present time there is no clinical evidence of the impact of correcting anemia with erythropoietic agents[37].

Erythropoietin reduced transfusion requirements[2,12,13,38]. Although no control arm could be included in the present study, it is noteworthy that only 9 patients (6.5%) needed transfusions during the study period.

Although earlier studies found that correcting anemia correlated with improvements in quality of life[39,40], we found no significant differences in scores on the FACT-An and CLAS instruments before and after EPO treatment.

CONCLUSIONS

A single weekly dose of epoetinum alfa significantly increased hemoglobin concentration in patients with cancer who were receiving radiotherapy alone or combined with chemotherapy, regardless of whether EPO treatment was started before or during radiotherapy. The overall response rate was 92.1%. The response was greater, and mean duration of EPO treatment was shorter, in patients who were receiving radiotherapy alone than in those receiving both radiotherapy and chemotherapy. Correcting anemia did not correlate with improvements in quality of life in the present study.

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