Epoetin Beta (NeoRecormon®) Corrects Anaemia in Patients with Hormone-refractory Prostate Cancer and Bone Metastases

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Abstract. Background: Severe anaemia is common in patients with metastatic, hormone-refractory prostate cancer (HRPC). Patients and Methods: We evaluated the efficacy of epoetin beta in correcting anaemia and maintaining haemoglobin (Hb) levels in this group of patients. Patients with HRPC, bone metastases and anaemia (Hb <12 g/dl) were included. Epoetin beta, 30,000 IU per week in three divided doses, was administered subcutaneously, with iron supplementation when needed. If Hb increased by <1 g/dl during the first 4 weeks of therapy, the epoetin dose was increased (increments of 5,000 IU per dose) at fortnightly intervals to a maximum of 60,000 IU per week. Patients with haematopoietic response (Hb increase ≥2 g/dl from baseline or Hb level ≥12 g/dl without blood transfusions) went on to receive epoetin beta 10,000 IU once weekly for up to 24 weeks. Results: All 29 evaluable patients demonstrated a haematopoietic response to epoetin beta treatment. None of the patients required blood transfusions. All patients showed improvements in quality of life (assessed using the EORTC QLQ-C30 questionnaire). Hb levels were maintained for the remainder of the trial. Epoetin beta was very well tolerated. Conclusion: Epoetin beta therapy resulted in a rapid and sustained improvement in Hb levels in patients with HRPC metastatic to bone.

Patients with hormone-refractory prostate cancer (HRPC) metastatic to bones have a median survival rate of less than 1 year and therapeutic approaches are predominantly palliative. Severe anaemia is common in these patients, which may be related to several factors. These include the myelosuppressive effects of chemotherapy or radiotherapy, bone marrow infiltration by tumour, nutritional deficiencies, mucosal bleeding, haemolysis or anaemia of chronic disease (1, 2). Anaemia is also induced by androgen deprivation treatment (3-5).

In patients with cancer, anaemia appears to be a negative prognostic factor for locoregional tumour control and/or survival following therapy (6, 7). In a review of published trials, anaemia was estimated to increase the relative risk of death by 65% overall in patients with cancer and by 47% in patients with prostate cancer (7).

Anaemia affects virtually every organ system in the body and contributes to overall morbidity in patients with cancer. Clinical manifestations of anaemia include fatigue, dizziness, dyspnoea, cold skin, vertigo, loss of appetite, loss of libido, increased episodes of angina, inability to concentrate, falls and depression (8, 9). These manifestations significantly impair the patients’ quality of life (QoL) (9). Consequently, effective treatment of anaemia should be considered an important goal in patients with advanced prostate cancer, owing to their reduced life expectancy. Caring for patients with anaemia may also have significant economic costs both for the patients and for the community as a whole (10).

Traditionally, anaemia has been treated using red blood cell transfusions, but these offer only transient improvements in haemoglobin (Hb) level and have minimal effects on QoL. In addition to the inconvenience for the patient, blood transfusions are associated with potential risks, including immunosuppression, adverse haemolytic reactions and transmission of infectious agents. The development of recombinant human erythropoietin (rHuEPO; epoetin) provided a viable alternative, avoiding the risks associated with transfusion. Numerous clinical studies have shown that epoetin can effectively treat anaemia in patients with various solid or haematological malignancies, increasing Hb levels, decreasing transfusion requirements and improving QoL (11-13). Few studies have evaluated the benefits of anaemia correction specifically in patients with HRPC. The limited data available suggest that epoetin treatment may be beneficial in these patients (14, 15).
The primary objective of the current study was to assess the efficacy and safety of epoetin beta in correcting anaemia in patients with HRPC metastatic to bone. In addition, this study investigated the use of low-dose epoetin beta to maintain Hb response over time.

**Patients and Methods**

This was a single-arm, open-label, 24-week, prospective study. Patients with histologically verified HRPC metastatic to bone and anaemia (Hb <12 g/dl) were included in the study. Patients were required to have adequate renal and liver function. The presence of adequate iron stores was ensured before inclusion by prescription of iron supplementation therapy when necessary. Patients with a life expectancy of less than 3 months were excluded. Other exclusion criteria were non-cancer-related causes of anaemia; more than two red blood cell transfusions within 2 weeks before inclusion; strontium-89 or rhenium-186 treatment within the previous 2 months; active cardiac disease; uncontrolled hypertension and the presence of acute infection.

Various palliative treatments were permitted before and during the study, including hormonal treatment, appropriate analgesics, corticosteroids and palliative radiotherapy. Blood transfusions were given if Hb levels were ≤7.5 g/dl during the study. The study was approved by the regional ethics committees and performed according to good clinical practice. All patients gave their informed consent.

Epoetin beta (NeoRecormon®, F. Hoffmann-La Roche Ltd, Basel, Switzerland) was administered subcutaneously at a dose of 30,000 IU per week in three divided doses. For patients whose Hb had increased by <1.0 g/dl during the first 4 weeks of treatment, the dose of epoetin beta was increased. Dose adjustments by increments of 5,000 IU per dose were performed at fortnightly intervals to a maximum of 60,000 IU weekly in three divided doses. The first dose of study drug was administered under the supervision of a nurse but subsequent doses were self-administered for the rest of the study. Patients who had a haematopoietic response to epoetin beta treatment (defined as an increase in Hb ≥2 g/dl from baseline or subsequent doses were self-administered for the rest of the study. Patients who had a haematopoietic response during epoetin beta treatment. The safety of epoetin beta was assessed throughout the study. All reported adverse events were grouped according to body system using the modified World Health Organization Adverse Reaction Term (WHOART) dictionary.

**Statistical analysis.** Data for continuous variables were summarised using descriptive statistics (mean ± SD, median [range]). Changes from baseline measurements were determined and repeated measures analysis of variance was used to identify significant differences over time. Greenhouse-Geisser F-value was used to calculate within-subjects' effects.

Serum ferritin and iron values at baseline and after 1 month of treatment were compared using paired sample t-test. When deviations from the normal distribution were detected, pre-post comparisons of measures were conducted via the Wilcoxon test. All tests were conducted at a significance level of alpha = 0.05.

Predicted erythropoietin levels for the degree of anaemia were calculated for each patient according to the formula described by Cazzola et al. (16) for patients with haematocrit values ≤38% as follows: log_{10} (predicted serum erythropoietin) = 4.746−(0.093 x Hb)−(0.016 x log_{10} ferritin). An indication of whether endogenous erythropoietin production is sufficient for the degree of anaemia can be obtained by calculating the ratio of observed/predicted (O/P) log_{10} serum erythropoietin levels. An O/P ratio of <0.9 is likely to indicate that the endogenous erythropoietin level is inappropriately low for the degree of anaemia (16).

**Results**

There were 29 evaluable patients included in this study. All 29 patients had data recorded at 12 weeks and 23 patients had data recorded at 24 weeks. Patient demographics and clinical characteristics are shown in Table I.

Hb levels increased significantly during the first 12 weeks of the study (Figure 1) and all patients demonstrated a haematopoietic response during epoetin beta treatment.

**Table I. Patient demographics and baseline clinical characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable patients, n</td>
<td>29</td>
</tr>
<tr>
<td>Age, years</td>
<td>75 ± 6.6</td>
</tr>
<tr>
<td>Time from diagnosis to study enrolment, months</td>
<td>44.9 ± 34.9</td>
</tr>
<tr>
<td>Hb level, g/dl</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>9.9 ± 1.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>10.1 (6.8–11.7)</td>
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<tr>
<td>Haematocrit, %</td>
<td>30.2 ± 3.8</td>
</tr>
<tr>
<td>Reticulocyte count corrected a, %</td>
<td>1.2 ± 1.1</td>
</tr>
<tr>
<td>Median serum ferritin, ng/ml (range)</td>
<td>90.0 (0.8–1000)</td>
</tr>
<tr>
<td>Median serum iron, mg/dl (range)</td>
<td>54.5 (15.0–120.0)</td>
</tr>
<tr>
<td>Median serum Epo b, mU/ml (range)</td>
<td>27.0 (4.1–155.5)</td>
</tr>
<tr>
<td>Median log_{10} O/P Epo (range)</td>
<td>0.41 (0.02–1.35)</td>
</tr>
</tbody>
</table>

aCorrected for haematocrit
bBaseline Epo levels were available for 22 patients

eP = erythropoietin; O/P = observed/predicted ratio of log_{10} transformed serum Epo levels

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**Endogenous erythropoietin levels** were measured at baseline to determine whether they were predictive of likely haematopoietic response. The safety of epoetin beta was assessed throughout the study. All reported adverse events were grouped according to body system using the modified World Health Organization Adverse Reaction Term (WHOART) dictionary.

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**Results**

There were 29 evaluable patients included in this study. All 29 patients had data recorded at 12 weeks and 23 patients had data recorded at 24 weeks. Patient demographics and clinical characteristics are shown in Table I.

**Hb levels increased significantly during the first 12 weeks of the study (Figure 1) and all patients demonstrated a haematopoietic response during epoetin beta treatment.**
Twenty-six patients (90%) had a haematopoietic response at a dose of epoetin beta of 30,000 IU per week. Response in these patients was evident by the time of the first assessment after 4 weeks of epoetin beta therapy. Three patients (10%) had an increase in epoetin beta dose to 45,000 IU per week and had a haematopoietic response at this dose level.

All 29 evaluable patients entered the maintenance phase of the study. In the 23 patients for whom data were available, Hb levels remained stable during the remainder of the 24-week study period at the reduced dose of 10,000 IU once weekly. Moreover, Hb levels were maintained in four patients who received rhenium-186 as palliative treatment during this period. One of these patients had also received localised radiotherapy for painful bone lesions. None of the patients required blood transfusions.

Like Hb levels, mean haematocrit values increased significantly during epoetin beta treatment (p<0.001 for all time points compared with baseline). At 12 weeks, mean haematocrit was 42.3% (SD, 6.0) and this level of improvement was maintained for the remainder of the study. Similarly, reticulocyte counts corrected for haematocrit increased during epoetin beta therapy and measurements were significantly greater than baseline at the 4- and 24-week assessments (data not shown). Furthermore, global QoL scores improved during epoetin beta treatment (Figure 2).

All patients had adequate serum iron and ferritin levels during epoetin beta treatment (data not shown). However, 16 patients (55%) had baseline iron levels of <70 mg/dl and, according to protocol, received iron supplementation initiated simultaneously with epoetin beta. An additional analysis was performed on these patients to determine whether low baseline iron status had any effect on the rate of increase of Hb. Improvements in Hb level were similar in the low iron subgroup to the population as a whole (Figure 1).

Serum erythropoietin levels were recorded for 22 patients (76%) at baseline. Baseline serum erythropoietin levels could not predict response to epoetin beta in these patients. Twenty patients had O/P ratios <0.9 and only two patients had O/P >0.9. The two patients with O/P >0.9 had an early haematopoietic response to epoetin beta 30,000 IU per week, within 4 weeks of study initiation.

Thirty-nine patients were originally enrolled in the study. Ten of these discontinued after 4 weeks, owing to progression of their underlying disease. Although these patients could not be evaluated for response to epoetin beta therapy, safety was assessed in all patients. Epoetin beta was well-tolerated during the study. Any adverse events were consistent with those expected in a population of patients with advanced HRPC and were not considered related to study medication.

Discussion

At the time of diagnosis, a significant proportion of patients with prostate cancer and skeletal metastases already have anaemia, with Hb levels <12 g/dl (17). Testosterone is involved in the stimulation of erythropoietin production and activation of haematopoietic stem cells (18). Consequently, androgen ablation manipulation, the treatment of choice for advanced prostate cancer, exacerbates the anaemia further and, therefore, blood transfusion is common in patients with advanced prostate cancer (14). Moreover, patients receiving combined androgen blockade should be screened for anaemia at regular intervals (4) and appropriate treatment initiated if anaemia is diagnosed.
The results of the present study show that epoetin beta at a dose of 30,000 IU per week in three divided doses is safe and can effectively increase Hb levels in most patients with HRPC, without the need for blood transfusions. Recent studies have suggested that this dose can be given once weekly (19), increasing patient convenience.

An early increase in Hb level was achieved in all but three patients in the current study within the first 4 weeks of treatment. The three patients who had a Hb increase of <1 g/dl during this time had decreasing Hb levels during the month before study entry and had received red blood cell transfusions (two patients had received 2 units and one patient had received 3 units of packed red cells). All three patients subsequently achieved a haematopoietic response to epoetin beta when the dose was increased after 4 weeks to 45,000 IU per week in three divided doses.

Global QoL improved in all patients during epoetin beta treatment. This finding is of important clinical significance, considering the limited life expectancy of these patients and the need to ensure the highest possible QoL (17).

Since all patients achieved a haematopoietic response during epoetin beta therapy, they were all eligible to enter the maintenance phase of the study, during which epoetin beta was administered at a dose of 10,000 IU once weekly. Mean Hb levels remained stable during the maintenance phase at this reduced dose. Moreover, epoetin beta continued to be effective at this reduced dose level in patients who received palliative treatment with rhenium-186 and localised radiotherapy. Likewise, epoetin beta was effective in patients with initial serum iron levels <70 mg/dl (normal values: 70-160 mg/dl). Therefore, baseline iron levels do not appear to affect response to epoetin beta, provided that patients are given adequate iron supplementation. No blood transfusions were required during the study, despite the need for more than one blood transfusion in the month before study entry in three patients.

There have been few other studies of epoetin in patients with prostate cancer. Beshara et al. (15) showed promising results for epoetin in a pilot study of nine patients with HRPC metastatic to bone. Another study evaluating two results for epoetin in a pilot study of nine patients with prostate cancer. Beshara et al. (15) showed promising results for epoetin in a pilot study of nine patients with prostate cancer. Beshara et al. (15) showed promising results for epoetin in a pilot study of nine patients with prostate cancer. Beshara et al. (15) showed promising results for epoetin in a pilot study of nine patients with prostate cancer. Beshara et al. (15) showed promising results for epoetin in a pilot study of nine patients with prostate cancer. Beshara et al. (15) showed promising results for epoetin in a pilot study of nine patients with prostate cancer.

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