Anaemia Management Strategies: Optimising Treatment Using Epoetin Beta (NeoRecormon®)

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Abstract
Anaemia has a detrimental impact on quality of life and it is important that this condition is recognised and treated in patients with cancer. Epoetin beta is an effective and well-tolerated treatment of anaemia in patients with a wide range of solid and haematological malignancies. A study in patients with lymphoid malignancies confirms that epoetin beta is equally effective at the same overall weekly dose (30,000 IU weekly) when given once-weekly or three-times weekly. This once-weekly regimen has also proved effective in patients with solid tumours. Once-weekly treatment is more convenient for the patient, potentially improving compliance and is associated with reduced hospital administration costs. The majority of patients with cancer will respond to epoetin therapy with an increase in haemoglobin levels. However, it is of value to identify those patients who are likely to respond, so that cost-effectiveness can be improved. Despite much research into potential predictive factors, follow-up studies are required and clinical judgement remains key to managing the anaemia of cancer. In addition, studies suggest that intravenous iron supplementation can improve response to epoetin therapy in patients with functional iron deficiency. Epoetin beta offers an effective, safe and convenient therapy for the management of anaemia in patients with cancer. Ongoing studies are expected to lead to a greater understanding of the optimal use of epoetins in cancer-related anaemia.

Introduction

Anaemia is common in patients with cancer [1, 2]. The symptoms of anaemia, of which fatigue is the most debilitating, have a profound impact on quality of life (QoL) [3]. Therefore, it is important that anaemia is effectively recognised and patients with cancer are offered optimal treatment for this condition.

Historically, blood transfusions were used to manage anaemia in patients with cancer. However, these are inconvenient, provide only temporary benefits and may be associated with a number of risks, such as infection transmission, allergic reactions and iron overload [4]. With blood supplies becoming increasingly limited, it became apparent that there was a need for an effective and safe anaemia treatment.

Recombinant human erythropoietin was first cloned in the mid 1980s [5] and its efficacy in managing anaemia associated with a variety of conditions was quickly realised [6, 7]. Epoetin beta (NeoRecormon®, F. Hoffmann-
La Roche Ltd, Basel, Switzerland) is a recombinant human erythropoietin with the same structure [8] and function as the endogenous hormone.

Epoetin beta has been used successfully in clinical practice in the management of anaemia for over 14 years. Various studies have confirmed that epoetin beta is effective at increasing haemoglobin (Hb) levels, reducing transfusion requirements and improving QoL of patients with anaemia and a range of non-myeloid malignancies [9–12]. Moreover, studies have suggested that early intervention with epoetin beta has the potential to prevent severe anaemia, reduce transfusion requirements and maintain or improve QoL in patients with cancer receiving concomitant myelosuppressive chemotherapy [13–15].

**Efficacy of Epoetin Beta in Treating Chemotherapy-Induced Anaemia**

A large number of studies have shown epoetin beta to be highly effective in treating anaemia in patients with lymphoproliferative malignancies (multiple myeloma [MM], non-Hodgkin’s lymphoma [NHL], Hodgkin’s disease [HD] and chronic lymphocytic leukaemia [CLL]). For example, Österborg et al. [12] evaluated epoetin beta in a multicentre, placebo-controlled study of anaemic (Hb <10 g/dl), transfusion-dependent patients with NHL, CLL or MM over a period of 16 weeks. In total, 67% of patients treated with epoetin beta (~30,000 IU weekly) showed a Hb response (defined as a Hb increase of ≥2 g/dl from baseline without transfusion need in the previous 6 weeks) compared with only 27% of patients treated with placebo (p < 0.0001). Importantly, patients in the epoetin beta group were significantly more likely to be transfusion free at the end of the study than patients in the placebo group (p = 0.0012). In patients treated with epoetin beta, QoL (assessed using the Functional Assessment of Cancer Therapy [FACT]-Anaemia and FACT-General scales) improved steadily over the course of the study, reaching statistical significance compared with placebo by week 12 (p < 0.05).

Boogaerts et al. [11] also evaluated the efficacy and impact on QoL of epoetin beta (~30,000 IU weekly) in a randomised, controlled study including a mixed population of patients with solid or lymphoid malignancies and baseline Hb levels of ≤ 11 g/dl. Over the 12-week study, Hb levels increased by a mean of 2.1 g/dl over baseline in patients treated with epoetin beta (p < 0.001 versus patients treated with standard care [transfusions as required]). Moreover, epoetin beta therapy resulted in significant improvements in QoL compared with standard therapy (fig. 1), particularly with regard to fatigue, physical performance and overall well-being. Importantly, improvements in QoL were experienced rapidly, within three to four weeks of initiating epoetin beta therapy. This study confirmed that anaemic patients with solid tumours responded equally well to epoetin beta as patients with lymphoid malignancies.

Studies performed exclusively in patients with solid tumours have also shown epoetin beta to be highly effective at increasing Hb levels, reducing transfusion requirements and improving QoL [9, 10, 14, 16, 17]. These studies confirm that epoetin beta is an effective and well-tolerated treatment for anaemia across a wide range of malignancies.

**Optimising Treatment Schedules of Epoetin Therapy**

Although the benefits of epoetin therapy in the management of anaemia are well documented, surveys suggest that anaemia is frequently undertreated in patients with cancer [2]. Epoetin was originally administered three-times weekly, a schedule that had already proved effective in patients with renal anaemia. Patients and physicians often perceive the three-times-weekly schedule to be inconvenient, requiring frequent visits to the clinic for patients who choose not to self-administer and representing a substantial burden on clinic time.
Consequently, optimisation of epoetin administration regimens has been the focus of much research. In this regard, Cazzola et al. [18] confirmed that a once-weekly regimen of epoetin beta is just as effective as a three-times-weekly regimen at the same overall weekly dose (30,000 IU weekly).

In this 16-week, randomised study of 241 anaemic patients with lymphoproliferative malignancies and a relative serum erythropoietin deficiency (≤100 mU/ml), the efficacy and safety of epoetin beta 30,000 IU once-weekly was compared with the conventional 10,000 IU three-times-weekly regimen [18]. Both regimens resulted in a median change in Hb level of ≧2 g/dl following 8 weeks of treatment. In addition, there was no significant difference in the primary efficacy variable (time-adjusted area under the Hb curve from weeks 5–16 of the study [Hb-AUC5–16]) between the two treatment regimens (median Hb-AUC5–16 with once-weekly and three-times-weekly treatment were 12.05 g/dl and 12.27 g/dl, respectively). This indicates that the Hb level increases over time were equivalent for the two dosing regimens (fig. 2).

Hb response rates were also similar for the two regimens (72% with once-weekly treatment and 75% with three-times-weekly treatment). In addition, approximately 90% of patients remained transfusion free throughout the study (91% once-weekly; 86% three-times weekly). Response to epoetin beta was rapid with both regimens. The median times to achieve ≥1 g/dl or ≥2 g/dl increases in Hb level from baseline were 4.1 weeks and 8.1 weeks, respectively, with the once-weekly regimen [19]. In addition, both administration regimens of epoetin beta were equally well tolerated. The once-weekly regimen of epoetin beta has also subsequently proved to be effective in patients with solid tumours receiving concomitant chemotherapy [20, 21].

The ability to administer epoetin beta once weekly offers significant advantages over the three-times-weekly regimen. For patients who self-administer, once-weekly administration allows epoetin beta to be given on the same day each week, which may help improve compliance. For patients who choose to attend the clinic for injections, once-weekly administration frees up valuable clinic time and is associated with reduced administration costs and indirect costs, associated with patients/carers taking time off work to attend the clinic.

A number of studies have also evaluated the efficacy and safety of once-weekly regimens of the two other commercially available epoetins, epoetin alfa and darbepoetin alfa. The first of these studies was an open-label, non-controlled study evaluating a once-weekly schedule of epoetin alfa (40,000 IU weekly) in patients with non-myeloid malignancies [22]. Over the course of the study, a mean increase in Hb level of 1.8 g/dl over baseline was demonstrated with this regimen. In addition, 49% of patients (increasing to 68% when the dose was increased to 60,000 IU weekly) demonstrated a haematopoietic response rate (Hb increase ≥2 g/dl from baseline and/or a Hb level of ≥12 g/dl without transfusion in the previous month). The authors commented that these results were similar to those obtained with a historical control group who received epoetin alfa 10,000 IU three-times weekly [22]. Epoetin alfa 40,000 IU once weekly has subsequently been evaluated in a double-blind, placebo-controlled study of 344 anaemic patients with advanced cancer [23]. Like the study by Gabrilove et al. [22], the 40,000 IU once-weekly regimen of epoetin alfa was shown to increase Hb levels effectively. Over the course of the study, 32% of placebo patients had a Hb increase of ≥2 g/dl compared with 73% of epoetin alfa patients.

Two randomised, placebo-controlled studies have also confirmed that darbepoetin alfa is effective when administered once weekly [24, 25]. These studies evaluated darbepoetin alfa at a dose of 2.25 μg/kg once weekly in patients with lymphoproliferative malignancies or lung cancer. Over the 12-week study period, increases in Hb level
of 1.8 g/dl from baseline were observed in patients with lymphoid malignancies [24]. In addition, a Hb response of 60% was observed in these patients [24], with similar results being reported in patients with lung cancer [25].

**Predicting Response to Epoetin Therapy**

While the majority of patients treated with epoetin for chemotherapy-induced anaemia can be expected to respond effectively with an increase in Hb level of >2 g/dl, there are a number of reasons why a patient may fail to respond. These include inflammation, infection, haemorrhage, complications of chemotherapy, absolute or functional iron deficiency and other nutritional deficiencies (e.g. folate or vitamin B₁₂).

Importantly, the type of tumour does not appear to influence the response to epoetin, provided that there is no other reason for anaemia besides cancer and its treatment. Evidence for this comes from several large-scale studies which show similar response rates to epoetin in anaemic patients with solid or lymphoid malignancies [11, 26, 27]. Likewise, for patients receiving concomitant chemotherapy, there is no significant difference in efficacy of epoetin alfa or epoetin beta between patients receiving platinum-based and non-platinum-based regimens [26, 28, 29].

It is best to direct epoetin treatment at those patients most likely to benefit from it, and there has been some interest in potential factors that could be of value in predicting response, either before or within a few weeks of initiating therapy. This would help avoid unnecessary long-term therapy, allow treatment to be tailored to individual needs and ultimately improve cost-effectiveness.

Several studies have provided evidence that certain baseline parameters influence the response to epoetin; the majority of these have been performed in patients with lymphoid malignancies [11, 12, 24, 30]. These studies have identified similar factors as being important, namely baseline endogenous erythropoietin production and/or early indicators of erythropoietic marrow response to epoetin.

In an exploratory multivariate analysis, Österborg et al. [12] noted that baseline platelet count ≥ 100 × 10⁹ cells/l (which reflects residual bone marrow function), Hb level ≥ 9 g/dl and a lower pre-study transfusion requirement (≤ 2 units in the three months before study entry) were the factors most strongly associated with a higher probability of treatment success. In this study, type of underlying malignancy (MM, NHL or CLL), sex, age, baseline neutrophil count, transferrin saturation, performance status and QoL score had no significant predictive value [12].

Additionally, several studies in patients with haematological malignancies have suggested that a low endogenous erythropoietin concentration (in the region of <70–<100 mU/ml) is also a significant factor for predicting response [11, 24, 30, 31]. Moreover, it has been suggested that low endogenous erythropoietin levels should be interpreted in relation to the degree of anaemia present [32]. To determine whether erythropoietin levels are appropriate or inappropriate for the degree of anaemia, an exponential regression plot of serum erythropoietin levels versus haematocrit has been determined in reference subjects [33]. Based on this regression plot, it is possible to determine the observed/predicted log erythropoietin ratio (O/P ratio) for a given patient (fig. 3). In patients with lymphoid malignancies, an O/P ratio of <0.9 was associated with high response rates, whereas patients with a ratio of >0.9 only benefited rarely from epoetin therapy [34]. In contrast to lymphoproliferative malignancies, studies in patients with solid tumours have found that baseline erythropoietin concentration does not predict response to epoetin [9, 10].

Measurement of factors, such as Hb, reticulocyte count and soluble transferrin receptor level increases early during treatment (two to four weeks after initiation of epoetin) have also been useful as predictive markers of epoetin response in patients with solid and lymphoid malignancies. Another approach to predicting response involves a combination of baseline parameters and early changes. For example, a baseline serum O/P erythropoietin ratio of <0.9 and a two-week Hb increase of ≥ 0.3 g/dl was shown to give an 88% response rate [31]. Similar accuracy was observed with low baseline serum erythropoietin levels combined with soluble transferrin receptor increase after two weeks [34].

Certain precautions should be taken when using such factors to predict response. The timing of serum erythropoietin measurement is important, as decreased use of erythropoietin by target cells in the first 2 weeks of chemotherapy results in inappropriately elevated levels of the hormone and, therefore, samples should be taken immediately before starting chemotherapy. In addition, initial Hb increases are of less value in predicting further response in transfused patients or in those receiving epoetin to prevent the occurrence of severe anaemia. In the recently published European Organisation for Research and Treatment of Cancer (EORTC) guidelines, it is highlighted that no predictive factors can be used routinely in clinical practice and the only factor of some importance (in haematological malignancies) is a low serum erythropoietin level [32], because no predictive test identified
Fig. 3. Baseline serum erythropoietin levels can help predict response to epoetin therapy in patients with lymphoid malignancies. O/P EPO = Ratio of observed/predicted log(EPO); normal values 0.8–1.20; EPO deficiency <0.80.

Table 1. Characteristics of functional iron deficiency (FID)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values in FID</th>
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<tr>
<td>Mean corpuscular</td>
<td>All low to normal</td>
</tr>
<tr>
<td>Volume (MCV)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (MCH)</td>
<td>Low</td>
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<tr>
<td>Haemoglobin concentration (MCHC)</td>
<td></td>
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<tr>
<td>Serum iron concentration</td>
<td>Low</td>
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<tr>
<td>Transferrin saturation</td>
<td></td>
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<tr>
<td>Ferritin concentration</td>
<td>High</td>
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<tr>
<td>Soluble transferrin receptor</td>
<td>High</td>
</tr>
<tr>
<td>Red cell protoporphyrin</td>
<td>Low</td>
</tr>
<tr>
<td>Reticulocyte haemoglobin levels</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Hypochromic red blood cells</td>
<td>Abundant</td>
</tr>
<tr>
<td>Iron in bone marrow</td>
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* Compared with expected range in subjects without iron deficiency.

thus far has a very high positive/negative predictive value. Therefore, further investigation into reliable predictive models of response to epoetin is required and in the near future, at least, clinical judgement remains vital to managing patients with cancer and anaemia.

**Improving Outcome of Epoetin Therapy**

Epoetin is highly effective at treating anaemia, but not all patients achieve a meaningful response [35]. An important condition, functional iron deficiency (FID), defined as a failure to provide iron rapidly enough to meet the demands of epoetin-induced erythropoiesis despite the apparent presence of sufficient iron stores, may arise during epoetin treatment and this can reduce the efficacy of therapy [35, 36].

The iron required by developing red blood cells is provided by a labile iron pool in the reticuloendothelial system. This usable iron is in dynamic equilibrium with iron stores. Since large amounts of iron are required during epoetin treatment to support accelerated erythropoiesis, the iron required for epoetin-induced erythropoiesis can quickly exceed the rate of iron mobilisation from iron stores. In addition, inflammatory cytokines associated with the anaemia of chronic disease may inhibit iron storage release, which exacerbates the condition further. Consequently, even when iron stores appear to be adequate, iron supplementation may be necessary to achieve an optimal response to epoetin [37].

It is difficult to assess FID because markers may be affected by confounding factors. For example, serum ferritin is useful for assessing absolute iron deficiency but is less reliable for FID. Ferritin levels increase with acute or chronic inflammation and abnormally high levels may be seen in cancer patients with the anaemia of chronic disease. Therefore, to test for FID, it is important to assess iron stores and a combination of biochemical and haematological factors (table 1).

Thomas and Thomas [38] examined various markers to determine their role in differentiating between iron
Fig. 4. Diagnostic plot to determine functional iron deficiency (FID) in patients not currently receiving epoetin (Reproduced with permission from Clinical Chemistry, Thomas & Thomas [38]. Copyright 2002, American Association for Clinical Chemistry). Iron supply is depleted if soluble transferrin receptor/log ferritin (sTR-F index) is >1.5 in patients with C-reactive protein (CRP) ≤ 5 mg/l and >0.8 in patients with CRP >5 mg/l. Patients in quadrants 2 or 3 should be administered iron supplementation; response indicated by data point shifting from quadrant 3 to 2 within 10 days, and from quadrant 2 to 1 within four to six weeks. Anaemic patients in quadrants 1 and 4 can be treated effectively with epoetin; for quadrant 4, response-limiting factor is functional iron deficiency and iron supplementation should be administered; for quadrant 1, epoetin may be started without iron supplementation, but if data points shift to quadrants 3 or 4, iron supplementation must be initiated.

Iron supplementation can be administered orally or intravenously (IV), although both routes are perceived as having significant disadvantages. When administered orally, iron is poorly absorbed and patients often complain of gastrointestinal-related side effects, which result in poor patient compliance. Although IV administered iron is highly efficient, there are concerns over potentially serious adverse events. Anaphylactic reactions with iron dextran preparations have been reported in 0.7% of patients with chronic kidney disease [39]. However, allergic reactions are to the dextran portion of the preparation rather than iron itself and, consequently, iron-dextran preparations have been superseded by dextran-free preparations, such as iron sucrose that are associated with a much lower rate of adverse events [40]. There are also concerns that IV iron preparations may be associated with “free-iron” reactions in the liver and myocardium [40], although these will not be encountered provided that the maximum weekly dose is respected (300 mg for iron sucrose and 125–187.5 mg for iron gluconate). In the longer term, concerns over IV iron include the possibility that iron may increase the rate of infection and that free iron may lead to increased oxidative stress and cardiovascular disease. Moreover, there are also concerns that increased body stores of iron may increase the risk of cancer [41, 42]. It should be pointed out, however, that none of these concerns have been proven in the clinical setting. The theoretical risks of cancer and infection are only a concern with chronic large doses of iron, capable of main-

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taining high iron availability in the plasma. No study has shown an increased risk of infection or cancer with IV iron (although this has not been assessed prospectively) provided that iron is only given when required. There is no evidence of increased cancer risk in patients with chronic kidney disease receiving long-term IV iron [37]. In addition, a recent review of IV iron in patients with end-stage renal disease suggests that use of dextran-free iron compounds optimises epoetin therapy with no direct evidence of any short- or long-term complications [40]. Therefore, the only two contraindications to IV iron are a high-normal–high transferrin saturation and active sepsis.

IV iron supplementation has been shown to increase the efficacy of epoetin in patients with renal anaemia [43]. In this study, patients receiving IV iron (even those considered to be iron replete) had greater increases in Hb level and better maintenance of iron stores than those patients receiving oral iron or no iron supplementation. In addition, patients receiving IV iron had lower epoetin dosage requirements. This has led to iron supplements also being recommended in cancer-related anaemia [44], although further research in this area is required.

Auerbach et al. [45] evaluated the impact of iron supplementation on the efficacy of epoetin in 157 patients with a wide range of malignancies and chemotherapy-induced anaemia. As in patients with renal anaemia, the results of this open-label, randomised study suggest that patients receiving IV iron supplementation (iron dextran repeated 100 mg IV bolus injection or iron dextran total dose infusion) have a greater response to epoetin when compared with patients receiving oral iron (ferrous sulphate 325 mg twice daily) or no iron (fig. 5). Hb levels increased significantly from baseline during epoetin treatment in all groups, but the magnitude of this increase was greatest in patients in the IV iron groups (2.4–2.5 g/dl) compared with the no iron (0.9 g/dl) and oral iron (1.5 g/dl) groups (p < 0.02 for the two IV iron groups vs. the no iron and oral iron groups). In addition, energy and activity levels and overall QoL improved in patients treated with IV iron, whereas there was only a small increase in energy levels and no change in activity levels and overall QoL in patients treated with oral iron. In contrast, the no iron group showed decreases in these QoL measures. Seven of the 157 patients experienced adverse events that were considered related to treatment but there were no discontinuations due to adverse events. This study suggests that correction of FID, as well as absolute iron deficiency, with IV iron supplementation improves the response to epoetin therapy in patients with chemotherapy-related anaemia.

Similar results have been reported by Henry et al. [46], who compared IV iron supplementation (ferric gluconate 125 mg IV weekly for 8 weeks), oral iron (ferrous sulphate 325 mg three times daily) or no iron supplementation in patients with chemotherapy-induced anaemia treated with epoetin. In this study, increases in Hb level from baseline were significantly greater with IV iron (2.4 g/dl) than with oral iron (1.6 g/dl) or no iron supplementation (1.5 g/dl). A greater proportion of patients receiving IV iron (73%) had a Hb response (≥2 g/dl increase in Hb level) compared with patients receiving oral iron (46%) or no iron (41%). Transferrin saturation at baseline appeared to have an impact on the Hb response rates. To enter the study, patients with low transferrin saturation (<15%) had to have serum ferritin values above 100 ng/ml. Low transferrin saturation with high ferritin is a classic indicator of anaemia of chronic disease. Patients with transferrin saturation <20% had a particularly good Hb response to IV iron (81%), compared with oral iron (37%) or no iron groups (27%). In contrast, the oral iron and no iron groups appeared to respond better to epoetin when baseline transferrin saturation was >20%, indicating the presence of greater iron availability.

In addition, an ongoing study with epoetin beta has been designed to further our understanding of the utility of iron supplementation during epoetin therapy of pa-
tients with chemotherapy-related anaemia. This open-label, randomised, 16-week study, the NeoRecomron with Intravenous Iron (Fe [NFe]) study, will assess the efficacy and safety of epoetin beta 30,000 IU once weekly with or without IV iron sucrose 100 mg once weekly in anaemic patients with lymphoid malignancies.

Conclusions

Epoetin beta effectively increases Hb levels, reduces the need for emergency transfusions and improves QoL in anaemic patients with a wide range of solid and haematological malignancies. Research into the most appropriate treatment schedules has confirmed that epoetin beta is equally effective at the same overall weekly dose whether administered according to a once-weekly or three-times-weekly schedule.

Although most patients will respond to epoetin therapy with an increase in Hb levels, it is useful to be able to predict those patients most likely to respond. In patients with lymphoid malignancies, a low endogenous erythropoietin level (<100 mIU/ml) or low O/P erythropoietin ratio (<0.8–0.9) has been verified to be of some importance in predicting response to epoetin therapy. However, further refinement and follow-up studies are still required in this area and clinical judgement remains vital in managing anaemia in patients with cancer. In addition, FID can limit the response to epoetin therapy. Studies suggest that IV iron supplementation can improve response to epoetin therapy in patients with FID. An ongoing study with epoetin beta should further our knowledge of iron supplementation in anaemic patients with cancer.

Anaemia is a common but frequently undertreated condition in patients with cancer. It is important to optimise management strategies to allow more patients to receive treatment for this condition, so avoiding the negative effects of anaemia on QoL and treatment outcome. Epoetin beta is an effective, well-tolerated and convenient therapy for the management of anaemia both in patients with solid tumours and those with lymphoid malignancies.

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medyan S, Laufman I, Ferranti Cancer 

Study Group: Intravenous ferric gluconate 

(FG) for increasing response to epoetin (EPO) 

in patients with anemia of cancer chemother-

apy – results of a multicenter, randomized tri-


Glaspy/Beguin