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Epoetin beta therapy in patients with solid tumours

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Contents

Abstract

Anaemia is a common occurrence in patients with cancer, resulting in symptoms such as fatigue that have a profound impact on quality of life. Anaemia is also associated with poor treatment outcome and overall survival. Epoetin beta, a recombinant human erythropoietin that has the same structure and function as the endogenous hormone, is an effective and safe treatment of cancer-related anaemia. Various studies in patients with solid tumours have shown that this agent effectively increases haemoglobin levels and reduces the need for emergency blood transfusions regardless of the type of concomitantly administered chemotherapy. Epoetin beta also improves the quality of life of anaemic patients with cancer, decreasing fatigue and improving the ability to perform usual daily activities. In addition, epoetin beta prevents severe anaemia and reduces transfusion requirements in patients with a high-risk of developing anaemia during chemotherapy, such as those receiving platinum-based regimens. A meta-analysis of epoetin beta trials showed that epoetin beta has no negative impact on survival or thrombosis-related survival and may reduce the risk of tumour progression in patients with solid or lymphoid malignancies. Another study has shown epoetin beta to be equally effective when administered once weekly or three times weekly. Therefore, epoetin beta offers an effective, safe and convenient therapy for the management of anaemia in patients with cancer.

Keywords: Epoetin beta; Anaemia; Survival; Cancer

1. Introduction

Anaemia is highly prevalent in patients with solid tumours [1,2]. In a recent European survey evaluating anaemia in over 13,000 patients with malignancies, anaemia was observed in 68% of patients at some time during the 6-month survey [3]. The frequency varied according to type of malignancy and treatment. Of patients with solid tumours receiving chemotherapy, the frequency of anaemia ranged from 62% in patients with gastrointestinal/colorectal tumours to 88% in patients with gynaecological tumours (Fig. 1; [3]).

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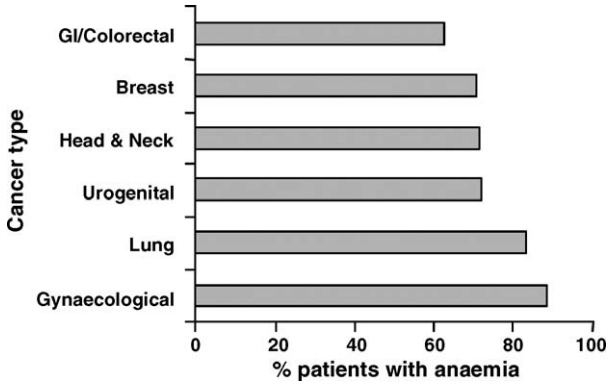

Fig. 1. Percentage of patients with solid tumours receiving chemotherapy who were anaemic at least once during the European Cancer Anaemia Survey (ECAS) (adapted from Ludwig et al. [3]).

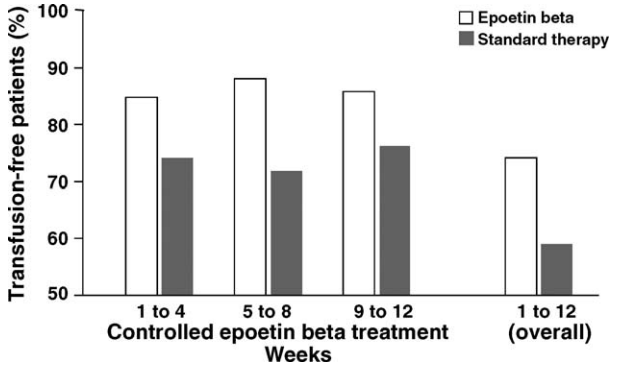

Fig. 2. Reduction in transfusion requirement during treatment with epoetin beta seen within the first 4 weeks of therapy (adapted from Oberhoff et al. [11]).

The manifestations of anaemia, including fatigue, dizziness, headache, shortness of breath, chest pain and depression, impact on the overall quality of life (QoL) of anaemic patients with cancer [4]. Anaemia may also reduce survival and tumour control [5–7].

Traditionally, blood transfusions were used to manage anaemia in patients with cancer, the principal benefit being an immediate rise in haemoglobin (Hb) levels. This is particularly important in patients with severe, life-threatening anaemia (Hb <8 g/dl), and transfusions are still commonly used for this reason. However, transfusions may be associated with a number of risks, some of which are serious [8,9]. Consequently, there was a need for an effective and safe anaemia treatment.

Recombinant human erythropoietins (epoetins) have been available for the treatment of cancer-related anaemia for many years and have a proven efficacy and safety record in patients across many different malignancy types, reducing transfusion need and improving QoL. Epoetin beta (NeoRecormon®, F. Hoffmann-La Roche, Basel, Switzerland) is a recombinant human erythropoietin that is identical in structure and function to the endogenous hormone. Epoetin beta has been available for over 14 years, and has proved effective in the management of anaemia in patients with haematological or solid tumours [10–13]. This review describes the efficacy, safety and convenience of epoetin beta therapy in patients across a range of solid tumour types.

2. Benefits of epoetin beta in patients with solid tumours

2.1. Treatment of chemotherapy-induced anaemia

The efficacy and safety of epoetin beta has been evaluated in several studies that enrolled patients with chemotherapy-induced anaemia and a variety of solid tumours [11,12,14–18]. In these studies, epoetin beta has been shown to be safe and effective across a wide range of malignancies, both in patients with early and advanced/metastatic disease. In addition, response to epoetin beta is rapid and is observed in patients receiving non-platinum-based or platinum-based chemotherapy.

A controlled study by Oberhoff et al. [11] evaluated epoetin beta as a 5000 IU daily dose (corresponding to ~450 IU/kg per week) in 218 patients with solid tumours and chemotherapy-induced anaemia (Hb levels of ≤11 g/dl [or ≤13.5 g/dl with a drop in Hb level of ≥1.5 g/dl during the preceding chemotherapy cycle and at least one transfusion in this cycle]). The most common tumour types were gynaecological (36%), breast (25%), urinary tract (10%) and lung (10%). All patients received chemotherapy during the study and more than half were receiving platinum-based regimens. This study demonstrated a significant reduction in the need for transfusion in patients receiving epoetin beta compared with controls (transfusions in 28% versus 42% of patients, respectively; $p = 0.028$) (Fig. 2). This benefit of epoetin beta in reducing transfusion was seen as soon as the first 4 weeks of treatment, with maximal benefit by weeks 5–8. In addition, median Hb levels increased in the epoetin beta group but remained unchanged (in spite of the high level of transfusion use) in the control group.

Boogaerts et al. [14] compared the efficacy, particularly effects on QoL, of epoetin beta 150 IU/kg three times weekly (equivalent to ~30,000 IU per week) with a standard care control group in 262 anaemic patients with lymphoid or solid tumours. In the population as a whole, QoL scores (assessed using SF-36 Physical Component Summary, Functional Assessment of Cancer Therapy [FACT]-fatigue and visual analogue scales) remained stable over time in the control group but improved significantly in the epoetin beta group (Fig. 3). Stratification of patients according to tumour type revealed comparable QoL improvements in patients with solid and lymphoid malignancies. The improvements in QoL could be correlated with improvements in Hb levels during epoetin beta therapy. Overall, epoetin beta therapy for 12 weeks increased median Hb levels by 2.1 g/dl

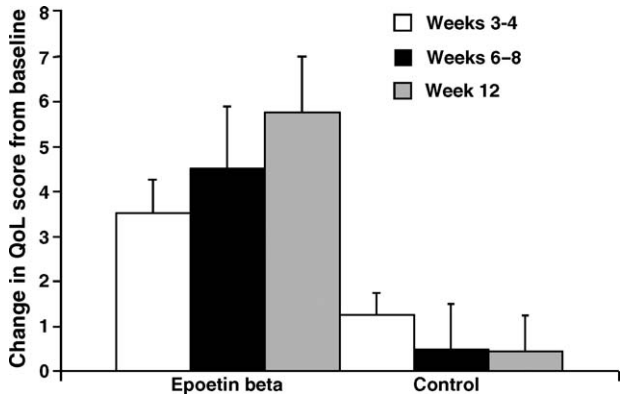

Fig. 3. Improvement in quality of life (QoL) score occurs throughout the epoetin beta treatment period (Functional Assessment of Cancer Therapy (FACT)-fatigue subscale). Median change in FACT-fatigue score from baseline to study end: $p = 0.001$ vs. control (Boogaerts et al. [14]).

from baseline compared with an increase of only 0.9 g/dl in the control group ($p < 0.001$). The same differences were observed with epoetin beta and control therapy for the solid tumour subgroup (although no p-value was quoted for this subanalysis).

Numerous studies have evaluated the efficacy of epoetin beta in patients with a single primary tumour type. Olsson et al. [15] investigated the effect of epoetin beta on haematological parameters and QoL in 180 patients with metastatic breast cancer. The majority (78%) of patients enrolled received chemotherapy (taxane- or anthracycline-based) during the study but 19% received hormonal therapy as their only treatment. Hb levels increased during epoetin beta treatment (15,000–30,000 IU weekly in three divided doses for 24 weeks) and as many as 83% of patients receiving epoetin beta 15,000–30,000 IU weekly demonstrated an improvement in Hb level of at least 2 g/dl. Global QoL (assessed using the EORTC QLQ-C30 questionnaire) improved during epoetin treatment and patients also experienced less fatigue and tiredness while receiving epoetin beta than they had before the study. The effects on QoL were rapid, becoming apparent within 4 weeks of starting treatment. This is an important finding considering the limited life expectancy of the patients enrolled in this study.

Similarly, Glimelius et al. [16] evaluated the efficacy of epoetin beta in 100 anaemic patients with advanced gastrointestinal cancers, most of whom (84%) were receiving chemotherapy. Hb levels improved rapidly in patients receiving epoetin beta 30,000 IU weekly, reaching a mean of 12.5 g/dl after 6 weeks of treatment. Increases in Hb level of >1 and >2 g/dl were observed in 73 and 63% of patients, respectively. A favourable tumour response was seen in 44% of the patients in the study and all of these had a Hb improvement of at least 1 g/dl with epoetin beta 30,000 IU weekly.

Epoetin beta has also been evaluated in a study of anaemic patients with lung cancer (37% small cell lung cancer [SCLC], 63% non-[N]SCLC), three-quarters of whom were receiving platinum-based chemotherapy and the remainder non-platinum regimens [17]. In a preliminary report of this study, epoetin beta 30,000 IU weekly was found to be well tolerated and 68% of patients had a >1 g/dl increase in Hb level.

Finally, the efficacy and safety of epoetin beta (30,000 IU weekly) was assessed in a study of 29 anaemic patients with hormone-refractory prostate cancer (HRPC) metastatic to bone and mean Hb levels of 9.9 g/dl [12]. Various palliative treatments were permitted before and during the study, including androgen-ablation therapy and palliative radiotherapy. In this study, epoetin beta rapidly corrected anaemia. All patients had a haematopoietic response (defined as Hb ≥12 g/dl or Hb increase ≥2 g/dl without blood transfusion), which occurred within 4 weeks in the majority of patients. Moreover, all patients showed QoL improvements using the EORTC QLQ-C30 questionnaire. The rapid effect of epoetin beta in this study is an important finding since patients with HRPC metastatic to bone have short life expectancies.

Androgen-ablation therapy is the treatment of choice for advanced prostate cancer. At diagnosis, 30% of patients with prostate cancer and bone metastases have anaemia (Hb <12 g/dl) [19]. Androgens stimulate erythropoiesis [20] and, therefore, standard androgen-ablation therapy can exacerbate this anaemia. Bogdanos et al. [19] followed the development of anaemia in 42 patients with advanced prostate cancer treated with combined androgen blockade. Six of 42 patients (14.3%) developed a severe and symptomatic anaemia (mean Hb level 10.2 g/dl) over a period of 6 months of this therapy. This anaemia was easily treatable with epoetin beta: all of these patients had Hb levels of ≥13 g/dl within 4 weeks of initiation of epoetin beta (50 IU/kg three times weekly).

2.2. Prevention of severe anaemia

In the past, epoetin treatment of chemotherapy-induced anaemia was delayed until Hb levels had fallen to ≤10 g/dl, despite the fact that anaemia is commonly defined as a Hb level of <11–12 g/dl. However, studies show that patients gain maximal incremental improvement in QoL at a Hb level of 12 g/dl (over the Hb range of 11–13 g/dl) [21], suggesting that early and effective management strategies should be considered to maintain Hb levels at ≥12 g/dl. Recent EORTC guidelines on the use of erythropoietic therapy in patients with cancer recognise these findings and recommend initiation of therapy in patients with chemotherapy-induced anaemia at Hb levels of 9–11 g/dl, with a target Hb level of 12–13 g/dl [22].

A number of studies have suggested that declining Hb levels during treatment and low nadir Hb levels have a significant impact on survival of patients with cancer [23,24]. In addition, poor tolerance to chemotherapy is often observed in patients with anaemia and this may result in missing treatment or treatment delays. The association between anaemia and reduced QoL and survival of patients with cancer suggests that the early use of epoetin to prevent severe anaemia

during myelosuppressive therapy may result in better patient outcomes.

A number of studies have indicated that epoetin beta has the potential to prevent severe anaemia and reduce the need for emergency transfusions in patients with cancer receiving platinum-based chemotherapy. Anaemia is a particularly common complication of platinum-containing regimens because these agents have direct toxic effects on the renal cells responsible for production of endogenous erythropoietin, as well as myelosuppressive effects.

Ordóñez et al. [18] conducted a study to determine whether epoetin beta treatment could prevent severe anaemia and transfusion need in a mixed solid tumour population receiving platinum-based chemotherapy. The study also assessed the impact of epoetin beta on QoL. Patients had Hb levels ≤13 g/dl (men) or ≤12 g/dl (women) and received epoetin beta 450 IU/kg weekly until 4 weeks after the last chemotherapy cycle. The mean Hb level at baseline was 11 g/dl (S.D. ± 1.0 g/dl) (F. Hoffmann-La Roche, data on file). In total, 89% of patients showed a response (defined as a Hb increase of >1 g/dl or maintenance of a baseline Hb level of ±1 g/dl) during epoetin beta therapy. Furthermore, only 10% of patients received transfusions during the study (F. Hoffmann-La Roche, data on file). Using an asthenia visual analogue scale, significant improvements from baseline in overall QoL scores were seen in patients responding to epoetin beta. In addition, performance status was maintained in patients responding to epoetin beta but deteriorated in patients who did not achieve a >1 g/dl improvement in Hb level.

In addition, ten Bokkel Huinink et al. [25] evaluated the ability of epoetin beta (150 or 300 IU/kg three times weekly (approximately 30,000 or 60,000 IU weekly) to prevent anaemia (defined in this study as a Hb level of <10 g/dl) and reduce transfusion need during six cycles of platinum-based chemotherapy in a controlled study of 120 patients with stage II–IV ovarian cancer. There were no significant differences in efficacy between the two dose levels of epoetin beta, although the dose was interrupted or reduced more often in patients receiving the 300 IU/kg epoetin dose. The median Hb level at randomisation was around 12 g/dl in the two epoetin beta dosing groups and the control group. During every cycle of chemotherapy, anaemia was observed in fewer patients treated with epoetin beta than in controls. After six chemotherapy cycles, 82% treated with epoetin beta 30,000 IU and 70% treated with 60,000 IU remained anaemia free compared with 50% of control patients. Throughout the study a greater proportion of epoetin-treated patients than control patients remained transfusion free: 89% versus 57% at 6 months, respectively.

The efficacy of epoetin beta was further compared in a meta-analysis of three controlled clinical trials in 454 patients with solid tumours receiving either platinum or non-platinum based chemotherapy [11,14,25]. Here, epoetin beta (150–300 IU/kg three times weekly or 5000 IU daily) provided a significantly superior and beneficial Hb response in both groups compared with the control group; furthermore, there was no significant difference in the Hb response to epoetin beta between the platinum and non-platinum based chemotherapy groups [26].

These observations confirm that, as for the treatment of chemotherapy-induced anaemia, a weekly dose of epoetin beta 30,000 IU (∼450 IU/kg) is appropriate for the prevention of severe anaemia and the reduction of transfusion need during concomitant administration of platinum-based chemotherapy regimens.

Several investigators have looked for baseline characteristics that could be used to identify patients who have a high likelihood of developing anaemia during anticancer treatment [27,28]. A number of factors including low baseline Hb levels and an early decrease in Hb level of >1.5 g/dl, intention to treat with platinum-based chemotherapy, type of tumour (anaemia was most common in patients with ovarian and lung cancers and lymphomas), persistent/recurrent tumours, prolonged chemotherapy and prior blood transfusions increased the risk of developing anaemia. Assessing patients for these risk factors before beginning anticancer treatment would identify those patients most likely to develop anaemia and who would, therefore, benefit the most from early anaemia intervention.

2.3. Safety of epoetin

Several studies have suggested that erythropoietic therapy may improve survival and tumour control in patients with solid tumours receiving chemotherapy or chemoradiotherapy [29–35]. In contrast, only two studies have reported reduced overall survival with epoetin in patients. The first of these was a double-blind, placebo-controlled study by Henke et al. [36] in 351 patients with head and neck cancer receiving radiotherapy. Epoetin beta increased Hb levels but was associated with reduced locoregional progression-free survival and overall survival versus placebo. However, the results need to be interpreted with caution [37,38] for a number of reasons. Imbalances in prognostic factors at baseline could explain the study results, often favouring greater survival in the placebo group (i.e. fewer smokers and patients with relapsed and stage IV disease were included in the placebo group compared with the epoetin beta group. Differences in tumour progression between treatment groups were also limited to a few patients with cancer of the hypopharynx, where baseline imbalances particularly favoured the placebo group) [37]. Furthermore, high baseline Hb values suggest that a large proportion of patients were not anaemic at study start. This, together with double the normal starting dose of epoetin beta used, meant that very high Hb increases were seen with epoetin treatment. Vaupel et al. [38] calculated that around 16% of patients may have had Hb levels above 17 g/dl after 9 weeks of treatment, well-beyond the 12–14 g/dl range considered optimal for tumour oxygenation [39,40].

In the second study, Leyland-Jones [41] reported a lower 12-month survival rate in patients with metastatic breast

cancer receiving epoetin alfa versus placebo (70% versus 76%, respectively, $p = 0.01$). As most deaths occurred in the first 4 months, the higher mortality rate in the epoetin alfa group seems unlikely to be related to epoetin therapy because of the short treatment duration [41]. Rather, it is attributed to the increased incidence of disease progression in the epoetin alfa group versus placebo (6% versus 3%, respectively). Baseline imbalances favouring the placebo group may also help to explain this increased mortality.

In a separate meta-analysis of pooled data from nine controlled epoetin beta studies, including 800 patients treated with epoetin beta and 609 control patients, there was no negative association between the risk of mortality and epoetin beta treatment. Importantly, this analysis also showed a trend towards a reduced risk of tumour progression associated with epoetin beta therapy [42]. A similar meta-analysis of studies with epoetins in 3287 patients with cancer [43] also suggested that epoetins may improve overall survival (hazard ratio = 0.81, 95% CI: 0.67, 0.99).

It is well documented that cancer itself is linked to an increased risk of thrombosis, related to advancing age, surgery, decreased activity, cancer therapies (e.g. chemotherapy and tamoxifen) and use of venous catheters [44]. The incidence of thrombosis was therefore also evaluated in the above meta-analysis of epoetin beta studies [45]. Here, the incidence of thromboembolic events was marginally higher in the epoetin beta group (6%) compared with the control group (4%), but the increase was well within rates typically reported in the literature for patients with cancer [44]. Moreover, a similar slight elevation in the incidence of thromboembolic events is also observed with the other commercially available epoetins [32,41]. Notably, intervention with epoetin beta was not associated with a significantly increased risk of thromboembolic events, and the proportion of patients who died as a result of such events was exactly the same for the two groups (1.1%) [45].

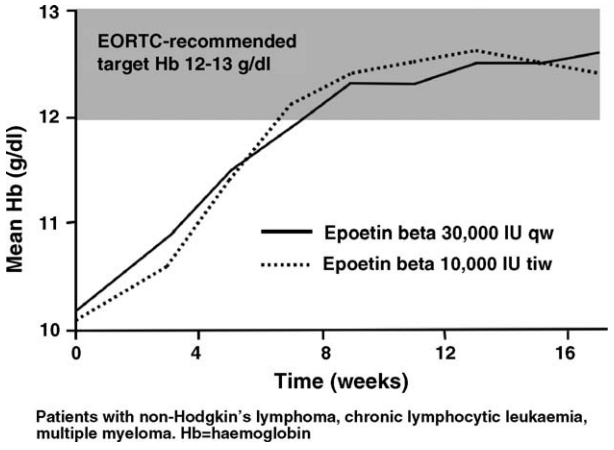

Fig. 4. Time course of mean haemoglobin (Hb) level in anaemic patients with lymphoproliferative malignancies treated with epoetin beta 30,000 IU once weekly (qw) or 10,000 IU three times weekly (tiw) (Cazzola et al. [10]).

3. Improving the convenience of epoetin beta therapy

Historically, epoetins were administered three times weekly SC at a dose of 10,000 IU per injection. A study in patients with lymphoproliferative malignancies has shown that epoetin beta is equally effective in increasing Hb levels and reducing transfusion need when given once weekly at the same overall weekly dose as the three times weekly regimen (Fig. 4) [10].

The once weekly regimen is also effective in patients with solid tumours. Preliminary results from a study of patients with metastatic breast cancer receiving anthracycline- and/or taxane-based chemotherapy reported an increase in Hb from a median of 11.6 g/dl at baseline to 13.5 g/dl during 24 weeks of treatment with SC epoetin beta 30,000 IU once weekly. In contrast, the median Hb level dropped during the study from 11.6 to 11.4 g/dl in the standard therapy control group [46].

4. Conclusions

Anaemia is common in patients with all types of solid tumours. Anaemia results in a reduction in QoL and is associated with poor treatment outcome and reduced survival. Epoetin beta is an effective and convenient treatment of anaemia and has a proven record of efficacy and safety in patients with a wide range of solid tumour types, irrespective of chemotherapy type. In patients with solid tumours and anaemia, epoetin beta treatment rapidly improves Hb levels, reduces the need for emergency transfusion and improves QoL. In addition, epoetin beta is effective in preventing severe anaemia in patients receiving concurrent platinum-based chemotherapy.

A recent meta-analysis of nine trials in patients with cancer has confirmed the safety of epoetin beta. The meta-analysis showed that epoetin beta has no detrimental effect on survival or thrombosis-related survival and may reduce the risk of tumour progression.

A study in patients with lymphoproliferative malignancies has confirmed that epoetin beta is equally effective when given once weekly or three times weekly at the same overall weekly dose. This convenient once weekly administration regimen of epoetin beta is also effective in patients with solid tumours.

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