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ORIGINAL ARTICLE

Early intervention with epoetin beta prevents severe anaemia in patients with solid tumours receiving platinum-based chemotherapy: results of the NeoPrevent study

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Abstract
Background Anaemia is common during platinum-based chemotherapy. This study aimed to evaluate the efficacy and safety of epoetin beta in the prevention of severe anaemia in patients with solid tumours receiving concomitant platinum therapy.
Patients and methods In this open-label, single-arm study, patients ($n = 255$) with solid tumours and haemoglobin (Hb) levels ≤ 13 g/dl (men) or ≤ 12 g/dl (women) received epoetin beta 450 IU/kg (~30,000 IU) weekly until 4 weeks after their last platinum-based chemotherapy cycle.
Results An anaemia prevention response [defined as patients with a Hb response (increase in Hb level > 1 g/dl from baseline) plus patients whose Hb levels remained ± 1 g/dl of baseline throughout the study] was observed in 234 patients (92%). Response to epoetin beta was rapid. Of the 159 patients achieving a Hb response, 139 (87%) had Hb levels > 1 g/dl of baseline within 4 weeks of treatment initiation. Mean Hb levels had improved from 10.8 ± 1.0 g/dl at baseline to 12.2 ± 1.8 g/dl by the final visit. Quality of life measured by linear analogue scale assessment significantly ($P < 0.01$) improved in patients achieving a Hb response ($n = 159$).
Conclusions Epoetin beta effectively prevents anaemia in most patients with solid tumours receiving concurrent platinum-based chemotherapy.

Keywords Anaemia · Epoetin beta · Platinum-based chemotherapy · Solid tumours

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Introduction

Anaemia is a common complication in patients with cancer [1, 2], resulting from the underlying disease and also the effects of anticancer treatment. This condition is particularly common in patients receiving platinum-based chemotherapy, as these regimens damage the renal erythropoietin-producing cells and also have direct myelosuppressive effects [3].

Anaemia has a profound impact on quality of life (QoL), inducing a variety of symptoms, including fatigue, dyspnoea, dizziness, headache, chest pain and depression [4]. Importantly, anaemia is also an adverse prognostic factor in patients with cancer [5], and a number of studies confirm that low haemoglobin (Hb) levels before and/or during anticancer therapy are associated with reduced tumour control and overall survival [6–9].

Epoetin beta is a recombinant human erythropoietin with the same structure [10] and function as the endogenous hormone. Various studies have confirmed that epoetin beta is effective at increasing Hb levels, reducing transfusion requirements and improving QoL of

patients with cancer-related-anaemia and a range of non-myeloid malignancies [11–14]. Moreover, studies have suggested that epoetin beta has the potential to prevent anaemia and reduce transfusion requirements in patients with cancer receiving concomitant myelosuppressive chemotherapy [15, 16]. However, few studies have examined the impact on QoL of early treatment with epoetin beta to prevent anaemia during platinum-based chemotherapy.

The aim of the current study was to determine the efficacy, safety and impact on QoL of early intervention with epoetin beta given to prevent severe anaemia in patients with solid tumours who were receiving concomitant platinum-based chemotherapy.

Methods

This was an open-label, single-arm study carried out in 11 centres throughout Spain.

Patients

Adult patients, aged > 18 years, with histologically or cytologically confirmed solid tumours and receiving platinum-based chemotherapy could be enrolled into the study if their baseline Hb levels were ≤ 13 g/dl (men) or ≤ 12 g/dl (women) or fell to these levels after one or more chemotherapy cycles. All patients provided written informed consent. The study was performed according to the revised Declaration of Helsinki and good clinical practice guidelines, and was approved by local ethical committees and health authorities.

Patients were excluded if they had received blood transfusions in the previous month, anaemia due to blood loss, received treatment with an erythropoietic agent in the previous 3 months, hypertension not controlled with antihypertensive therapy, previous intolerance to epoetin beta or its constituents; cognitive or mental impairment affecting ability to take part in the study.

Treatment

Patients received epoetin beta (NeoRecormon®, F. Hoffmann-La Roche Ltd, Basel, Switzerland) as a prefilled syringe formulation, at a dose of 450 IU/kg (equivalent to ~30,000 IU) weekly divided into three doses. Treatment was continued until 4 weeks after the last chemotherapy cycle.

Patients whose Hb level decreased by > 1 g/dl within the first 4 weeks of treatment initiation had their epoetin dose doubled (to 900 IU/kg weekly in three divided doses); this dose was continued throughout the rest of the study provided that the Hb level increased by > 1 g/dl or remained between ± 1 g/dl of its baseline value. In patients whose Hb level increased to > 14 g/dl during the study, epoetin beta was interrupted and restarted at 50% of the previous dose when the patient's Hb level was ≤ 12 g/dl. Patients whose Hb level decreased by > 1 g/dl despite the dose increase of epoetin beta were withdrawn from the study.

Iron supplementation was given at the discretion of the treating physician. Transfusions were given according to standard centre practice, if deemed necessary by the physician.

Assessments

Treatment efficacy was assessed based on an anaemia prevention response rate (% of patients with a Hb response plus percentage of patients who maintained their Hb level at ± 1 g/dl of baseline). Hb response was defined as an increase in Hb level of > 1 g/dl from baseline. Transfusion requirements were recorded. QoL was determined using separate linear analogue scale assessments (LASA) for energy level, ability to perform daily activities and overall QoL. Each LASA used a scale of 0–10, with higher scores denoting better QoL. Adverse events were monitored throughout the study and for a further 30 days, and were rated according to National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) criteria. Tumour response to chemotherapy was assessed at the final visit, 30 days after study completion.

Statistical analysis

To determine the effectiveness of epoetin beta in the prevention of anaemia and its impact on QoL in patients with cancer treated with platinum-based chemotherapy, the protocol required 365 patients to fulfil the inclusion criteria. This number of patients would allow detection of differences in Hb level between baseline and any of the visits, with a level of significance of 5%, and allow a loss to follow-up of 20% of patients. Although the number actually recruited to the study was 270 patients, this was not expected to impact on the analysis of results: this was a single-arm study, only 8.5% of patients were not included in the analysis population or were lost to follow-up and most patients responded to treatment (see Results).

Data for continuous variables (Hb level, haematocrit, transferrin saturation and ferritin levels) were summarised using descriptive statistics [mean ± standard deviation (SD), median (range)]. Changes in

these parameters from baseline were determined and comparisons were conducted using the Wilcoxon test. Differences in QoL assessments between baseline and the final visit were compared using the paired *t*-test. All tests were conducted at a significance level of alpha = 0.05.

Results

A total of 270 patients were enrolled into this study. Of these, 15 had no follow-up data and were excluded from the analysis. All 255 remaining patients were included in the efficacy and safety evaluations.

Thirty-three patients did not complete the study treatment period and/or the 30 days' follow-up for assessment of adverse events. Eight patients were lost to follow-up. Reasons for withdrawal in the remaining 25 patients were adverse events related to epoetin beta in four patients (1.6%) and patient decision in 16 patients (6%). Only five patients (2%) were withdrawn because of lack of response.

Patient demographic and clinical characteristics are shown in Table 1. Most patients (72.5%) were male and lung cancer was the most common malignancy. Just over half of the patients received cisplatin-based chemotherapy and the remainder received carboplatin or oxaliplatin.

Most patients (64%) were maintained on the starting dose of epoetin beta of 450 IU/kg weekly (10,000 IU TIW) throughout the study (Table 2) with 21% requiring a dose increase and 3% having a dose decrease. The mean duration of epoetin beta therapy was 74.9 ± 39.9 days.

Efficacy

An anaemia prevention response was observed in 234 of the 255 evaluable patients (92%; Fig. 1). Of these, 159 patients (62.4%) responded to epoetin beta therapy with an increase in Hb level of more than 1 g/dl. Moreover, response was rapid, with most of these patients (90.5%) responding at the 30,000 IU weekly (10,000 IU TIW) dose level, by the time of the 4-week assessment in 139 (87.4%) patients and by the time of the 5- to 6-week assessment in five (3.1%) patients (in whom no 4-week assessment was made). In addition, a further 75 patients (29.4%) maintained a Hb level of ± 1 g/dl versus baseline despite concomitant platinum-based chemotherapy.

Twenty-nine male patients started treatment having their baseline Hb levels between 12 and 13 g/dL, 70 had their baseline Hb levels between 11 and 12 and 24 female patients were included having their baseline Hb levels between 11 and 12 g/dL. In all these groups of patients the response rate was similar to the main group. Furthermore, there were no apparent differences in response to epoetin beta therapy between patients with the different tumour types included in the study (Table 3).

Table 1 Baseline demographics and clinical characteristics

	Evaluable study population (n = 255)
Gender, *n* (%)	
Male	185 (72.5)
Female	70 (27.5)
Median age, years (range)	61 (19–91)
Most common tumour types, *n* (%)	
Non-small-cell lung cancer	65 (25.5)
Small-cell lung cancer	37 (14.5)
Head and neck	34 (13.3)
Colorectal	26 (10.2)
Ovary	20 (7.8)
Gastric	16 (6.3)
Bladder	15 (5.9)
Other	42 (16.5)
ECOG performance status, *n* (%)	
0	42 (16.5)
1	178 (69.8)
2	32 (12.5)
3	3 (1.2)
Mean Hb level, g/dl (SD)	10.8 (1.0)
Platinum type, *n* (%)	
Cisplatin	133 (52.2)
Carboplatin	93 (36.5)
Oxaliplatin	29 (11.4)
Treatment cycle at start of study, *n* (%)	
Cycle 2	81 (31.8)
Cycle 3	62 (24.3)
Cycle 4	35 (13.7)
Cycle 5	26 (10.2)
Not known	51 (20.0)

ECOG Eastern Cooperative Oncology Group, *Hb* haemoglobin, *SD* standard deviation

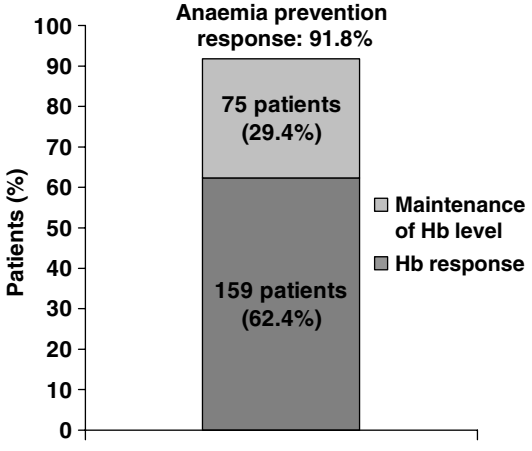

Fig. 1 Anaemia prevention response to epoetin beta therapy during concomitant platinum-based chemotherapy

Table 2 Duration of epoetin beta therapy and dose adjustments in the 255 evaluable patients

Epoetin beta dose	Patients, *n* (%)
Maintained on 450 IU/kg/week (~30,000 IU weekly) throughout	163 (63.9)
Dose increase to 900 IU/kg/week	53 (20.8)
Dose reduction	7 (2.75)
Therapy interrupted because Hb ≥ 14 g/dl	32 (12.55)
Median duration of epoetin beta therapy, days (range)	69 (11–285)

Hb Haemoglobin

The requirement for blood transfusions was low during epoetin beta therapy: only 32 (12.5%) required transfusions at some point during the study. The median number of units transfused in those patients receiving transfusions during the study was 3.0 (range 2–9) units.

Changes in Hb level during epoetin beta therapy are shown in Fig. 2. In the evaluable study population, mean Hb levels improved from 10.8 ± 1.0 g/dl at baseline to 12.2 ± 1.8 g/dl by the final visit. In patients with a Hb response ($n = 159$), mean Hb levels increased by 2.2 g/dl during treatment, whereas there was a small decrease in mean Hb levels (0.4 g/dl) in patients who did not achieve a Hb response ($n = 96$). Changes in haematocrit during epoetin beta therapy mirrored those of the Hb levels (data not shown).

Ferritin levels decreased over the course of the study from a mean of 445.5 ± 462.9 μg/l at baseline to 297.1 ± 384.7 μg/l at study endpoint. Likewise, transferrin saturation decreased from 28.6 ± 18.3% at baseline to 27.9 ± 10.2% at study endpoint.

Effect of epoetin beta on QoL and ECOG performance status

Quality of life was assessed in patients grouped according to whether or not they achieved a Hb response with epoetin beta therapy (Fig. 3). Overall QoL and the assessments of energy levels and ability to perform daily activities significantly ($P < 0.01$ for each) improved in patients who achieved a Hb response and were maintained in patients who did not achieve a > 1 g/dl increase in Hb level ($P \geq 0.337$). In addition, Eastern Cooperative Oncology Group (ECOG) performance status was stable during the study in those who achieved a Hb response ($P = 0.162$), but deteriorated significantly ($P < 0.01$) in patients without a Hb response (Fig. 4).

Table 3 Haemoglobin (Hb) response (defined as an increase in Hb level of > 1 g/dl over baseline) according to tumour type

Tumour type	*n*	Patients with Hb response, *n* (%)
NSCLC	65	36 (55.4)
SCLC	37	25 (67.6)
Head and neck	34	20 (58.8)
Colorectal	26	17 (65.4)
Ovarian	20	16 (80.0)
Other	73	45 (61.6)

Hb Haemoglobin, *NSCLC* non-small-cell lung cancer, *SCLC* small-cell lung cancer

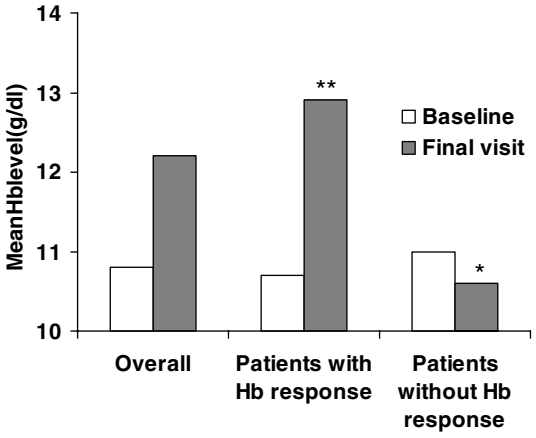

Fig. 2 Change in Hb level during epoetin beta treatment. Data are shown for the overall population ($n = 255$) and for patients with ($n = 159$) and without ($n = 96$) a Hb response (defined as an increase in Hb of > 1 g/dl from baseline during epoetin beta treatment). At final visit, $n = 219$ for the overall population, $n = 151$ for patients with Hb response and $n = 68$ for patients without Hb response

Safety

Epoetin beta was well tolerated in this study. Only six patients (2.4%) had an adverse event that was related to epoetin beta therapy and only four patients were withdrawn because of adverse events. Five adverse events in four patients were rated as possibly related to epoetin beta: cerebral thrombosis in one patient; cerebrovascular accident in one patient; left inferior venous thrombosis and venous thrombosis in the lower limb in one patient; and a skin reaction in one patient. Two adverse events were rated as probably related to epoetin beta therapy: venous thrombosis and arterial ischaemia occurring in one patient each. There were no deaths related to epoetin therapy. In 32 (12.55%) patients, therapy was interrupted because their Hb levels were ≥ 14 g/dl but side-effect rate was not superior in this group.

Tumour response

Data on tumour response were available for 224 patients. About half of these patients were classed as responding to chemotherapy: 16.5% had a complete

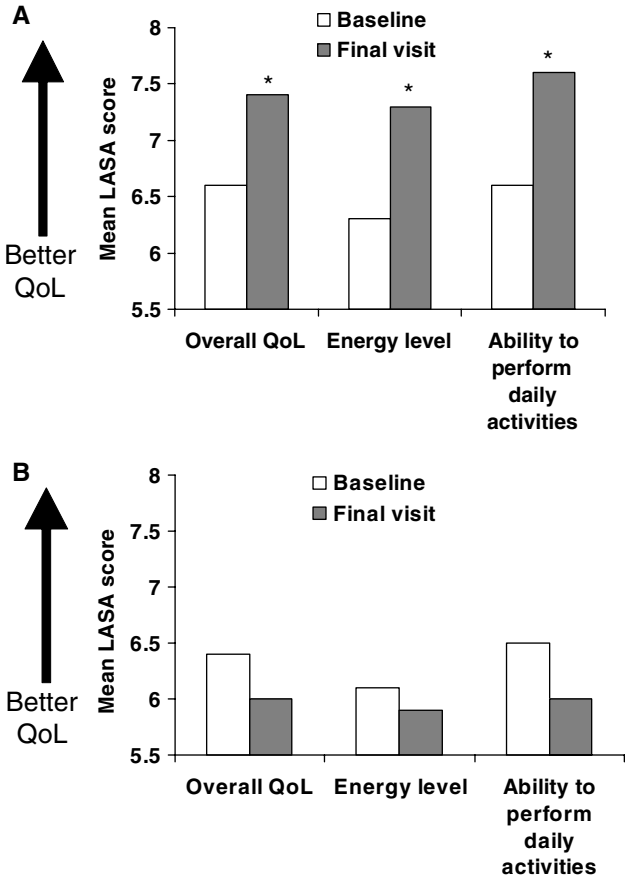

Fig. 3 Changes in overall quality of life (*QoL*) score (LASA) and the individual scales of energy level and ability to perform daily activities during epoetin beta therapy. Higher scores denote better QoL. **a** Patients with a Hb response (Hb increase > 1 g/dl from baseline; $n = 159$ at the baseline assessment and $n = 151$ at the final visit). **b** Patients without a Hb response ($n = 96$ at the baseline assessment and $n = 72$ at the final visit)

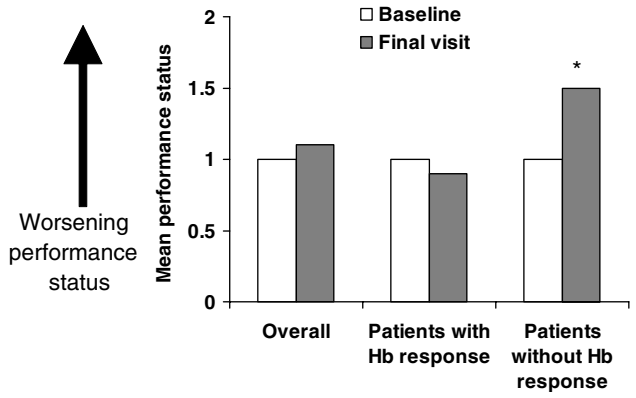

Fig. 4 ECOG performance status during the study (higher scores denote worsening of performance status). Data are shown for the overall population ($n = 255$) and for patients with ($n = 159$) and without ($n = 96$) a Hb response (defined as an increase in Hb of > 1 g/dl from baseline during epoetin beta treatment). At final visit, $n = 225$ for the overall population, $n = 152$ for patients with Hb response and $n = 73$ for patients without Hb response

response and 32.6% had a partial response. In addition, 23.2% had disease stabilisation, while 27.7% had disease progression.

Discussion

Platinum-based chemotherapy regimens are widely used and are the treatment of choice in many solid tumour types. However, the platinum agents (cisplatin, carboplatin and oxaliplatin) are associated with a high rate of anaemia [1], as a result of direct myelosuppressive effects and damage to the renal cells responsible for production of endogenous erythropoietin.

Previous studies have shown the efficacy of epoetin beta in the prevention of anaemia during platinum chemotherapy [15, 16]. Other studies also suggest the effectiveness of erythropoietic agents in this setting, as well as with other myelosuppressive therapies [17–19].

The current, large-scale study confirms the feasibility of early initiation of epoetin beta to prevent severe anaemia in patients with solid tumours receiving platinum-based chemotherapy. Epoetin beta ~30,000 IU weekly (10,000 IU TIW) effectively prevented anaemia in most patients in the study. A total of 92% of patients had an increase in Hb level of > 1 g/dl or maintained their Hb levels within ± 1 g/dl of baseline, despite the use of concomitant platinum-based chemotherapy. Furthermore, QoL was significantly ($P < 0.01$) improved and performance status was maintained in those patients responding to epoetin beta with a > 1 g/dl increase in Hb level.

In addition, the need for blood transfusions was low, with 87.5% of patients remaining transfusion-free throughout the study. This is an important finding since transfusions are common in patients receiving platinum-based chemotherapy without the support of erythropoietic therapy. Studies suggest that as many as 56% of patients with cancer receive transfusions during cisplatin therapy [18, 20]. In our opinion this is an important finding of the present study because only 12.5% of patients received transfusions. Moreover, transfusions are inconvenient and are associated with various risks (such as infection transmission, allergic reactions, iron overload and immunosuppression). Consequently, avoidance of transfusions has become an important goal of epoetin therapy [21].

Although epoetin beta was administered according to a three-times-weekly schedule in the current study, other studies in patients with lymphoid malignancies

have confirmed that the same overall weekly dose of epoetin beta (30,00 IU weekly) given once-weekly is just as effective [22]. This once-weekly regimen has also proved to be effective in patients with solid tumours [23]. Thus, the once-weekly administration regimen of epoetin beta is likely to replace the three-times-weekly regimen in patients with solid tumours, as it is more convenient for the patient without compromising efficacy, and it is associated with reduced hospital administration costs.

To achieve the greatest benefits in terms of QoL and treatment outcome, it is important to consider the most appropriate Hb level for intervention in patients with cancer-induced anaemia. Recent European Organization for Research and Treatment of Cancer (EORTC) guidelines advocate the initiation of epoetin at Hb levels of 9–11 g/dl in patients with cancer receiving myelosuppressive chemotherapy [21]. Besides reducing transfusion requirements, the guidelines confirm that a major goal of epoetin therapy in patients with cancer is to improve QoL. In accordance with these guidelines, the current study showed epoetin beta fulfils both of these goals: there was a very low rate of blood transfusion during the study and QoL significantly ($P < 0.01$) improved in patients responding to epoetin beta therapy.

Recently, there has been some debate on whether epoetin therapy has a negative effect on survival in patients with cancer [24, 25]. A meta-analysis of nine, controlled studies of epoetin beta conducted in patients with cancer found no evidence of reduced survival in patients treated with epoetin beta [26]. In addition, the meta-analysis suggested a trend towards reduced risk of tumour progression among patients treated with epoetin beta [26]. Furthermore, a second, independent meta-analysis of all epoetin trials published up to the end of 2001 has suggested that the treatment of anaemia with epoetin may have a beneficial effect on survival in patients with cancer [27].

Methodological issues, including inclusion of patients with more adverse prognostic factors in the epoetin groups compared with the placebo groups, have complicated interpretation of the studies by Leyland-Jones [24] and Henke et al. [25]. The negative results of these studies may also be partially explained by a higher risk of thromboembolic complications in patients treated with epoetin, as well as the use of epoetin outside approved indications to achieve high target Hb levels. Although the current study was initiated before this debate began, it provides additional evidence of the safety of epoetin beta in patients with cancer. Epoetin beta was particularly well tolerated, with only 2.4% of patients experiencing treatment-related adverse events and only four of the 255 evaluable patients (1.6%) withdrawing from the study because of adverse events. Moreover, the incidence of thromboembolic events was very low during the study. There were only four episodes of thrombosis in three (1%) patients and no episodes of thrombosis-related mortality. These results are consistent with the aforementioned meta-analysis of nine controlled epoetin beta trials, which included 800 patients treated with epoetin beta and 613 patients receiving control treatment [28]. In this meta-analysis, epoetin beta was shown to be a safe and effective treatment of anaemia. The incidence of thromboembolic events in patients receiving epoetin beta was shown to be only slightly elevated compared with control patients and there was no difference in thromboembolic-related mortality between the two groups.

Although the treatment criteria of the present study allowed epoetin beta to be initiated at Hb levels of ≤ 13 and ≤ 12 g/dl in men and women, respectively, the actual mean baseline Hb levels when the therapy was initiated were 10.8 ± 1.0 g/dl. This clearly demonstrates that many patients experience anaemia during initial chemotherapy cycles (56% entered the study at cycles 2 or 3), and this supports the principle of early anaemia correction in these patients. Furthermore, there was an obvious delay in initiating administration of epoetin beta by the participating clinicians, either because of custom, prudence or a tendency to prescribe epoetin at lower Hb levels than those permitted in the present study.

Nevertheless, the slightly higher threshold Hb for initiating treatment with epoetin beta permitted in the present study, compared with the guidelines recently published by the EORTC [21], which recommend the initiation of treatment at Hb levels of < 11 g/dl, could have a favourable effect for correction of anaemia. In the current study, a rapid response to epoetin beta was observed and this had a beneficial impact on maintaining performance status and improving QoL. A total of 87% of patients with a Hb response increased their Hb levels by > 1 g/dl within 4 weeks of treatment initiation.

Furthermore, early intervention to prevent severe anaemia may lead to additional benefits in patients receiving platinum-based chemotherapy. Data presented by Crawford et al. [29] suggest that Hb levels below 12 g/dl are associated with diminished QoL in patients with cancer. They found that, with epoetin therapy, the greatest incremental improvement in QoL occurred in patients who had Hb increases from 11 to 12 g/dl, and these results have been confirmed in later studies [30]. These findings suggest that clinicians should consider early and effective anaemia manage-

ment, in accordance with EORTC guidelines, to maintain patients' Hb levels at 12–13 g/dl during myelosuppressive cancer therapy. Indeed, in the present study, the mean Hb levels of 12.2 ± 1.8 g/dl at the final visit are within the recommended EORTC range.

As part of the European Cancer Anaemia Survey (ECAS), Barrett-Lee et al. [31] identified various factors that could predict the development of anaemia during chemotherapy. Several characteristics, including baseline Hb (≤ 12.9 g/dl in women and ≤ 13.5 g/dl in men), intention-to-treat with platinum-based chemotherapy, female gender and persistent/recurrent tumours, increased the risk of developing anaemia. There was an additive risk in patients with more than one of these characteristics. Assessing patients for these risk factors before beginning chemotherapy would identify those who are likely to become anaemic during treatment and would therefore benefit most from early anaemia intervention.

Conclusions

Epoetin beta effectively prevents severe anaemia in most patients with solid tumours, despite the use of concurrent platinum-based chemotherapy. A total of 92% of patients in this study had improvements in Hb levels of > 1 g/dl or maintained their Hb levels within ± 1 g/dl of baseline. Moreover, there was a low rate of transfusions in the study and QoL was improved in those patients responding to epoetin beta therapy. Epoetin beta 30,000 IU weekly is effective and safe for the early treatment of anaemia in patients with solid tumours receiving platinum-based chemotherapy. However, randomized trials are needed to achieve the optimal strategy to administer erytropoietic agents.

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