# Once-weekly epoetin beta therapy in patients with solid tumours and chemotherapy-induced anaemia: a randomized, double-blind, dose-finding study

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HERAS P., KRITIKOS K., HATZOPOULOS A. & MITSIBOUNAS D. (2008) *European Journal of Cancer Care* **17**, 619–623

**Once-weekly epoetin beta therapy in patients with solid tumours and chemotherapy-induced anaemia: a randomized, double-blind, dose-finding study**

Anaemia is common in patients receiving chemotherapy, causing symptoms that have a major impact on quality of life (QoL). Epoetin beta rapidly increases haemoglobin (Hb) levels and improves QoL in anaemic patients with a variety of tumours. This was a randomized, double-blind, parallel-group, dose-finding study assessing the efficacy and safety of once-weekly epoetin beta in patients with solid tumours receiving chemotherapy. Adult patients with anaemia (Hb < 11 g/dL) were randomized to receive epoetin beta 30 000 IU or 20 000 IU once weekly for 12 weeks. All patients received oral iron supplementation. Haemoglobin levels, transfusion need and QoL [Functional Assesment of Cancer Therapy-fatigue (FACT-F) subscale score] were assessed at regular intervals. Fifty patients were randomized; 30 patients received epoetin beta 30 000 IU once weekly and 20 received 20 000 IU once weekly. Mean (± SD) increase in Hb from baseline to week 12 was 1.75 ± 2.15 g/dL in the 30 000 IU group ($P = 0.008$ vs. baseline) and 1.04 ± 1.75 g/dL in the 20 000 IU group (non-significant). Haemoglobin response (increase in Hb ≥2 g/dL from baseline) was observed in 78.3% of patients receiving epoetin beta 30 000 IU and 66.7% receiving epoetin beta 20 000 IU. Improvements in FACT-F subscale score were significantly ($P < 0.001$) correlated with increases in Hb level. Transfusion use was low during the study in both groups. Both epoetin beta regiments were well tolerated and there were no dose-dependant adverse events. Epoetin beta 30 000 IU once weekly is an effective and well-tolerated treatment of anaemia in patients with solid tumours.

*Keywords:* cancer, anaemia, epoetin beta, haemoglobin, quality of life.

## INTRODUCTION

Anaemia is common in patients with solid tumours or haematological malignancies receiving chemotherapy and is caused by a variety of factors, including the underlying cancer, myelotoxic effects of chemotherapy and/or radiation therapy, and impaired iron utilization (Mercadante *et al*. 2000). Depressed erythropoiesis could also result from the disruption of homeostatic mechanisms by the

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Accepted 16 October 2007
DOI: 10.1111/j.1365-2354.2007.00892.x

*European Journal of Cancer Care*, 2008, **17**, 619–623

inflammatory state associated with malignancy, leading to inappropriately low levels of circulating erythropoietin for the degree of anaemia (Miller *et al*. 1990). Anaemia in cancer produces a multitude of debilitating symptoms, with fatigue being one of the most prevalent effects. This leads to functional impairment and to reduced quality of life (QoL) among cancer patients (Cella 1998; Ludwig & Fritz 1998).

Although blood transfusions may correct anaemia in the short term, they are increasingly reserved as an emergency intervention for patients with severe anaemia who require a rapid improvement in haemoglobin (Hb) levels. Single transfusions are not effective for chronic anaemia correction (Osterborg 1998), requiring multiple hospital attendances and consuming significant healthcare recourses and nursing time. Blood transfusion administration can also be inconvenient to patients and may extend the duration of in-patient admission (Barret-Lee *et al*. 2000; Bosanquet & Tolley 2003). Also, transfusion carries the risk of complication, such as transmission of bloodborne infections, haemolytic reactions, allergic-type reactions and iron overload (Provan 1999; Mortimer 2002; Allain 2003; Sandler & Rassai 2003; Ludlam & Turner 2006).

Guidelines from the European Organization for Research and Treatment of Cancer (EORTC) recommend treatment of cancer-related anaemia with erythropoietic protein (recombinant human erythropoietin) at Hb levels of 9–11 g/dL (Bokemeyer *et al*. 2004). A target maintenance Hb level of 12–13 g/dL is also advocated, which is supported by data showing a maximal incremental gain in QoL when the Hb level is maintained in the range of 11–13 g/dL (Crawford *et al*. 2002).

Epoetin beta has been shown to improve Hb levels rapidly and effectively, reduce the need for transfusions and improve QoL in patients with solid and haematological cancers (Oberhoff *et al*. 1998; Ten Bokkel *et al*. 1998; Osterborg *et al*. 2002; Boogaerts *et al*. 2003; Cazzola *et al*. 2003; Bogdanos *et al*. 2004). In patients with lymphoproliferative malignancy, once-weekly administration of epoetin beta 30 000 IU was shown to have comparable efficacy to the administration of 10 000 IU three times weekly (Cazzola *et al*. 2003). In this randomized, double-blind study, once-weekly administration of epoetin beta was evaluated to determine its efficacy and safety in improving Hb levels and QoL in patients with solid tumours receiving chemotherapy.

## PATIENTS AND METHODS

This randomized, double-blind, parallel-group, dose-finding study was conducted at the Department of Internal Medicine of the General Hospital of Kos from January 1999 till September 2004. The design and conduct of the study complied with the ethical principles of good clinical practice, in accordance with the Declaration of Helsinki and local legal requirements. The study was approved by an independent ethics committee and all patients gave written informed consent before any study-specific procedures were initiated.

### Patients

For entry into the study, adult patients (≥18 years were required to have a diagnosis of solid tumour malignancy and at least 4 additional months of planned cytotoxic chemotherapy (chemotherapy may have been ongoing at the time of randomization). Also, patients were graded according to World Health Organization performance status grade 0–2. Eligible patients had Hb levels <11 g/dL, life expectancy ≥24 weeks, no communication difficulties due to aphasia or confusion, and adequate cognitive function. Patients were excluded if they had received red blood cell transfusions in the 2 weeks before study commencement or had received epoetin beta therapy previously. Other exclusion criteria included therapy-resistant hypertension, acute or chronic bleeding requiring treatment in the 2 months before study commencement, thrombocytopenia or thrombocytosis (platelet count <50 or >450 × $10^9$/L respectively), or iron (transferin saturation <20%), vitamin B12 or folic acid deficiencies. Haemolysis, epilepsy, pregnancy or lactation were also excluded.

### Study procedures

The initial screen was undertaken before the first epoetin beta dose was administerd. Patients eligible for inclusion were randomized 3:2 to receive epoetin beta (NeoRecormon®, F. Hoffmann-La Roche, Basel, Switzerland) 30 000 IU or 20 000 IU administered by subcutaneous injection once weekly for a maximum of 12 weeks. Oral iron supplementation, 800 mg twice daily, was administered to all patients. If Hb exceeded 14 g/dL, epoetin beta treatment was suspended until the Hb level declined to ≤12 g/dL when therapy was reinstated at 75% of the previous dose. Blood transfusion was avoided at Hb levels >8.5 g/dL, unless medically indicated. Haemoglobin level was measured at screening, at the end of the first 4 weeks and every 4 weeks afterwards during the study and during a follow-up period of up to 4 months after the last dose of study drug. Clinical changes, disease progression, changes in therapy regimen and transfusion use since last study visit were also evaluated at these time-

points. The primary efficacy variable was the change in Hb from baseline to end of study (12 weeks). Secondary efficacy parameters included the Hb response defined as an increase in Hb level ≥2 g/dL from baseline without transfusion, change in QoL. Quality of life was evaluated with the 100 mm Linear Analogue Self-Assesment (LASA) scales of energy level, ability to perform activities of daily living and overall QoL (Priestman & Baum 1976). Each patient completed the LASA scale questionnaire at the beginning of the study and every 4 weeks afterwards. Changes in QoL were also assessed with the Functional Assesment of Cancer Therapy-fatigue (FACT-F) subscale (Yellen *et al*. 1997). The FACT-F consisted of 13 items related to fatigue: fatigue, weakness, listlessness, tiredness (four items), energy, ability to perform daily activities, limitation of social activities (three items) and need for sleep during the day. Patients completed the FACT-F questionnaire before the administration of epoetin beta therapy (on day 1 of chemotherapy), during the study (at 7–11 weeks) and at the end of the study (at 12 weeks). Safety was assessed in terms of adverse events, laboratory safety parameters and vital signs.

### Statistical analysis

Baseline values for all variables were compared with the respective values obtained during the study (at weeks 4, 8 and 12) using paired *t*-tests. Changes in Hb level between baseline and week 12 and corresponding changes in the FACT-F subscale score were calculated using the chi-squared test. The differences between baseline and post-treatment Hb values and LASA subscale scores were calculated using the Wilcoxon Signed Rank test. All statistics were conducted using the Statistical Package for the Social Sciences (SPSS) software for Windows version 10.0. A *P*-value of <0.05 was considered to be necessary for statistical significance.

## RESULTS

A total of 50 patients were enrolled in the study, including 23 men and 27 women aged 35–70 years old (mean age: 59.7) with solid tumours. Thirty patients were randomized to receive epoetin beta 30 000 IU once weekly and 20 received 20 000 IU once weekly for 12 weeks. None of the patients were withdrawn during the study. Mean baseline Hb values were similar for both treatment groups. Mean (±SD) increase in Hb from baseline to week 12 was 1.75 ± 2.15 g/dL in the 30 000 IU group ($P = 0.008$ versus baseline) and 1.04 ± 1.75 g/dL in the 20 000 IU group (non-significant $P > 0.07$). Haemoglobin response (Hb increase ≥2 g/dL from baseline) was observed in 78.3% of patients receiving epoetin beta 30 000 IU and 66.7% receiving epoetin beta 20 000 IU. The FACT-F subscale scores at baseline were comparable in both treatment groups. Similar changes in FACT-F subscale score were observed in both groups during the study. In both treatment groups combined the mean increase in FACT-F subscale score correlated significantly with the mean increase in Hb level at week 12 ($r = 0.434$, $P < 0.01$). The mean FACT-F subscale score at week 12 was significantly greater in the groups of patients with Hb responses compared with non-responding patients (2.2 versus – 3.2; $P = 0.011$). Multiple regression analysis also showed that the increase in FACT-F subscale score correlated significantly with the Hb increase ($P < 0.001$). The FACT-F subscale score at week 12 also correlated significantly with the FACT-F score at the start of epoetin beta therapy ($P < 0.001$). Improvements in QoL were also measured with the use of the LASA scores for energy, activity and overall QoL. After treatment with epoetin beta, all LASA parameters were statistically significantly improved from baseline ($P < 0.001$). The largest improvement was measured on the subscale of ability to perform activities of daily living ($P < 0.001$). All LASA improvements were significantly ($P < 0.001$) and positively correlated with Hb level increases. Transfusion use was low during the study in both groups. Transfusion rates during the first 4 weeks of the study were 0% in the 30 000 IU group and 16.8% in the 20 000 IU group. Treatment with epoetin beta was well tolerated. There were no dose-dependant adverse events (mainly nausea in five patients, constipation in three and low-grade fever in nine patients). All these patients were treated with usual medical procedures. There were no withdrawals from the study due to treatment-related events.

## DISCUSSION

Previous studies have shown that epoetin beta is effective at rapidly increasing Hb levels in patients with solid tumours and cancer-related or chemotherapy-induced anaemia (Boogaerts *et al*. 2003; Bogdanos *et al*. 2004), irrespective of the type of chemotherapy (platinum or non-platinum) (Boogaerts *et al*. 2006). Studies conducted in patients with solid and haematological cancers have also demonstrated a reduced need for transfusion and improved QoL following epoetin beta treatment (Oberhoff *et al*. 1998; Ten Bokkel *et al*. 1998; Osterborg *et al*. 2002; Boogaerts *et al*. 2003; Cazzola *et al*. 2003; Bogdanos *et al*. 2004). Furthermore, a trial of patients with lymphoproliferative malignancy showed that once-weekly administra-

tion of epoetin beta 30 000 IU has comparable efficacy to the administration of 10000 IU three times weekly (Cazzola *et al.* 2003). There is also some evidence to suggest that epoetin beta may provide the fastest time to Hb response and may be associated with less discomfort on subcutaneous administration than the other epoetins available for once-weekly administration (Pujade-Lauraine & Topham 2005). The ability to administer epoetin beta once weekly is more convenient for improved compliance and self-administration by patients.

The current study assessed the effectiveness and safety of once-weekly administration of epoetin beta in the management of chemotherapy-induced anaemia in patients with solid tumours. Two once-weekly doses were tested (30 000 IU and 20 000 IU) for efficacy in increasing Hb levels and improving QoL. The QoL of patients was evaluated using the 100-mm LASA subscales, energy level, ability to perform activities of daily living and overall QoL, and the FACT-F subscale. The LASA and FACT-F subscales were shown previously to be valid and reliable measures of QoL in patients with cancer (McCormack *et al.* 1988; Yellen *et al.* 1997).

The results of our study were similar to those of previous studies of epoetin beta treatment in patients with cancer- or chemotherapy-related anaemia and support use of the epoetin beta 30 000 IU once-weekly regimen. In comparison with baseline, epoetin beta 30 000 IU once-weekly treatment significantly increased mean Hb level ($P < 0.01$) and decreased need for transfusion ($P < 0.003$). More than three-quarters (78%) of patients had an Hb response to epoetin beta 30 000 IU once-weekly treatment. This response rate is similar to the 72% response rate reported in a multicentre study of the same epoetin beta regimen in 119 patients with lymphoproliferative malignancy (Cazzola *et al.* 2003). Transfusion rates decreased within 4 weeks of initiation of treatment, with further decreases in weeks 9–12 and during the follow-up period (weeks 13–16). The hospital admission rate due to anaemia-induced complications also decreased significantly from baseline ($P < 0.002$).

Previous epoetin beta studies have shown significant improvements in QoL in patients with cancer in comparison with placebo or standard care (Osterborg *et al.* 2002; Boogaerts *et al.* 2003). In our study, significant improvements in QoL were also observed, as measured with the LASA subscales, energy, ability to perform activities of daily living and overall QoL ($P < 0.001$). The largest improvement was measured on the subscale, ability to perform activities of daily living ($P < 0.001$). Improvements in QoL were also detected with the FACT-F scale, and these improvements correlated significantly ($P < 0.001$) with increases in Hb level. A similar finding was reported in a study of 349 patients with haematological cancers, which found a significant correlation ($P = 0.001$) between Hb level and change in FACT-anaemia subscale score (Osterborg *et al.* 2002).

Once-weekly administration of epoetin beta was safe and well tolerated by the patients in this study. The incidence of adverse events that could be directly related to epoetin beta was very low, and no patients withdrew from the study due to treatment-related events.

The results of this study show that once-weekly administration of epoetin beta 30 000 IU is an effective and safe treatment for anaemia in patients with solid tumours receiving chemotherapy. This epoetin beta regimen significantly increased Hb level, reduced transfusion need, and improved QoL. Despite the small sample size of this study, these data correlate well with results of previous multicentre studies of epoetin beta treatment. Along with the improved convenience and reduced administration costs associated with once-weekly treatment, the results of this study support the use of once-weekly epoetin beta 30 000 IU patients with solid tumours.

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