Cancer-related anaemia requires higher doses of epoetin alfa than chronic renal failure replacement therapy

Loretta M. Itri

Genta, Inc., Berkeley Heights, New Jersey, USA

Keywords: anaemia; epoetin alfa

Introduction

Epoetin alfa has been used effectively for over a decade as hormone replacement therapy in the treatment of anaemia in patients with chronic renal failure (chronic kidney disease). In this condition, erythropoietin production is impaired and the resulting deficiency is the primary cause of the normocytic, normochromic anaemia typically observed [1]. The recommended initial epoetin alfa dosages in this patient population are 50–100 U/kg three times weekly (TIW) intravenously (i.v.) or subcutaneously (s.c.) in adults and 50 U/kg TIW i.v. or s.c. in children. Because of the extensive experience with epoetin alfa in the nephrology community, oncologists may seek advice in the use of the drug to treat cancer-related anaemia. It is important to note that the pathogenesis of cancer-related anaemia differs from that of the anaemia of chronic renal failure. While the aetiology of anaemia in patients with cancer can be multifactorial, it closely resembles the anaemia of chronic disease [2,3], with inappropriate low erythropoietin levels for the degree of anaemia compared with iron deficiency anaemia [4,5]. Anaemia of chronic disease is also characterized by excessive release of inflammatory cytokines such
as tumour necrosis factor and interleukin-1, which suppress erythropoietin expression, inhibit erythroid marrow proliferation, and impair iron utilization [2,3,6]. Thus, to stimulate erythropoiesis in the treatment of cancer-related anaemia, higher doses of epoetin alfa (150–300 U/kg TIW or 40 000–60 000 U once weekly) are needed than in the chronic renal failure population.

Cancer-related anaemia and its impact

Anaemia is a common complication of cancer, with numerous potential causes including iron or vitamin deficiency, blood loss, haemolysis, tumour marrow involvement, and myelosuppressive chemotherapy and radiation therapy [7]. The risk of anaemia generally increases with disease duration and extent. Multiple cycles of chemotherapy can impair erythropoiesis cumulatively. The incidence and severity of chemotherapy-related anaemia depend on the type, schedule, and intensity of therapy and whether the patient has received prior myelosuppressive therapy [8]. The incidence of mild-to-moderate anaemia (haemoglobin >8 and <11 g/dl as defined by the World Health Organization) generally ranges from 50 to 80% with the most frequently used single agents and combination chemotherapy regimens [8].

Anaemia symptoms can negatively impact patient quality of life and ability to perform normal daily activities. Fatigue and dyspnoea on exertion are the most frequent patient complaints. Fatigue occurs in most cancer patients and is the symptom with the greatest apparent adverse effect on quality of life and functional capacity [9,10]. Fatigue is generally perceived by cancer patients to be more problematic than pain [9–11] and may be an independent predictor of loss of function [12]. Anaemia symptoms often manifest at higher haemoglobin levels in elderly cancer patients than in anaemic patients without cancer, and symptom severity is related to severity of the anaemia, the type of malignancy, and the patient’s cardiovascular and pulmonary function [2].

Epoetin alfa and cancer-related anaemia

Randomized, double blind, placebo-controlled clinical trials demonstrated almost a decade ago that epoetin alfa (initial dose of 150 U/kg s.c. TIW, increasing to 300 U/kg s.c. TIW after 8 weeks of therapy if the response is inadequate) effectively increases haemoglobin levels and reduces transfusion requirements in anaemic cancer patients treated with cisplatin-containing or non-cisplatin-containing chemotherapy [13–15]. The results of these trials also demonstrated the need for higher epoetin alfa doses in this patient population [13,16]. In a control arm of 105 anaemic cancer patients not receiving chemotherapy treated with epoetin alfa 100 U/kg s.c. TIW, the increase in haematocrit and overall response rate (increase of at least 6 points in haematocrit) were approximately 50% lower than in patients receiving chemotherapy who were treated with epoetin alfa 150 U/kg s.c. TIW [13]. Additionally, there was no statistically significant reduction in red blood cell transfusions in the control group. Similarly, in open-label extensions following the double blind phase of these trials, in which upward epoetin alfa dose titration to as high as 300 U/kg s.c. TIW was allowed, the median dose at response was approximately 450 U/kg s.c. TIW in patients receiving chemotherapy and response rates increased over time [16]. Improvements in quality of life in anaemic cancer patients receiving chemotherapy were also associated with increased haemoglobin and haematocrit levels with epoetin alfa therapy in several studies [13,15,17,18].

Two large, prospective, open-label community-based clinical studies were performed in the US to evaluate effectiveness of epoetin alfa and its effects on functional outcomes and quality of life in anaemic cancer patients receiving chemotherapy in the setting of actual clinical practice [19,20]. The first study enrolled 2342 patients [19]. The initial dose of epoetin alfa was 150 U/kg s.c. TIW; if the haematologic response was inadequate after 8 weeks, the dose could be increased to 300 U/kg s.c. TIW. Treatment was continued for up to 16 weeks. Patients self-rated their energy level, activity level, and overall quality of life using the linear analogue scale assessment (LASA). Data were available for 2030 patients, of whom 1047 patients completed the study. Epoetin alfa therapy was associated with a significant increase in mean haemoglobin and a significant decrease in the proportion of patients requiring transfusions (P < 0.001). Significant increases in mean scores for all three quality of life parameters occurred in patients demonstrating a response to epoetin alfa; the size of the increase in mean quality of life scores correlated with the magnitude of increase in haemoglobin and was independent of tumour response, which was assessed retrospectively. The data also suggested that most patients who had an increase in haemoglobin ≥1 g/dl from baseline to week 4 of therapy were likely to have a substantial increase by the end of the study.

A subsequent prospective, community-based study was undertaken to further assess the impact of tumour response and the effects of epoetin alfa [20]. In this study, the initial epoetin alfa dose was 10 000 U s.c. TIW; if the increase in haemoglobin was <1 g/dl after 4 weeks, the dose was increased to 20 000 U s.c. TIW. If the increase in haemoglobin remained <1 g/dl after an additional 4 weeks, epoetin alfa was discontinued. Treatment was continued for up to 16 weeks. If haemoglobin levels exceeded 13 g/dl, epoetin alfa was discontinued until haemoglobin decreased to 12 g/dl; when epoetin alfa therapy was resumed, the dose was reduced by 25% and titrated as necessary. The study enrolled 2370 patients; 2289 patients were evaluable for efficacy. This study used two different quality of life measurements, LASA and the Functional Assessment of Cancer Therapy-Anemia (FACT-An)
questionnaire. The results supported the first community-based study and demonstrated that improved functional status and quality of life were independent of tumour response in patients responding to epoetin alfa.

In an incremental analysis of the clinical and outcomes data from the combined results of both community-based studies, a significant ($P < 0.01$), non-linear relationship between haemoglobin level and quality of life over the haemoglobin range of 8–14 g/dl was identified [21]. The largest improvement in quality of life for each 1 g/dl change in haemoglobin was observed when haemoglobin increased from 11 to 12 g/dl (range 11–13 g/dl), levels that traditionally have been not led to therapeutic intervention because a clinically relevant adverse impact on the patient’s well-being and functional ability was not fully recognized [22]. These and other recent data [23] also suggest that haemoglobin levels in anaemic cancer patients should be increased to a target level of 12 g/dl and subsequently maintained at this level to attain optimum benefits, similar to current recommendations in treating the anaemia of chronic renal failure [24].

**Once-weekly epoetin alfa dosing**

The inconvenience and challenges associated with TIW dosing in uses other than anaemic patients on dialysis,
prompted evaluation of alternative epoetin alfa dosing regimens [25–27]. Results of these studies suggested that comparable haematologic responses could be obtained with epoetin alfa s.c. doses of 600 U/kg at intervals of 7 days. This provided the basis for evaluating an initial once-weekly epoetin alfa dose of 40 000 U (with titration to 60 000 U if the response is inadequate) in the cancer population. This dosing regimen was recently evaluated in a large, prospective, multicentre, open-label, non-randomized study that enrolled 3012 anaemic cancer patients undergoing chemotherapy [28]; 2964 patients were evaluable for efficacy. Once-weekly epoetin alfa therapy was associated with significant increases in haemoglobin and decreases in transfusion requirements, as well as significant improvements in functional status and quality of life that correlated with increased haemoglobin (P < 0.001). The haematologic response and improvements in quality of life were comparable with those observed with the TIW dosing schedule [19,20]. The once-weekly regimen also exhibited a safety profile similar to the TIW dosing regimen. Once-weekly dosing has also shown similar results in cancer patients undergoing sequential or concurrent radiation plus chemotherapy [29]. The once-weekly regimen appears to offer an effective, well-tolerated, and more convenient regimen for patients and oncologists, and has widespread use.

Summary

The substantial beneficial effects of epoetin alfa therapy on quality of life were first described in patients with anaemia of chronic renal failure [30]. The use of epoetin alfa to treat cancer-related anaemia has provided a better understanding of the adverse impact of mild-to-moderate anaemia on patient functional ability and quality of life, providing a new perspective on this frequent complication in cancer patients. Maintaining quality of life and ability to perform daily activities are important goals in this patient population. More aggressive treatment of cancer-related anaemia appears to be warranted to help achieve these goals [8,21,22]. With expertise in the use of epoetin alfa, clinical nephrologists can offer the oncology community insight on the need for higher doses in the treatment of cancer-related anaemia. Figure 1 provides dosing options for the use of epoetin alfa in this patient population.

References


29. Shasha D, George MJ, Harrison LB. Once-weekly dosing of epoetin alfa increases hemoglobin and improves quality of life in anemic cancer patients receiving radiation therapy either concomitantly or sequentially with chemotherapy [abstract 1866]. *Blood* 2000; 96 [11 Pt 1]: 434a