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Short communication

Response to the publication: EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer

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The guidelines issued recently by the European Organisation for Research and Treatment of Cancer (EORTC) for the management of cancer-related anaemia [1] are a welcome addition to previously published guidelines [2]. In recent years the impact of anaemia on patient outcomes and quality of life (QOL) has been highlighted *vis-à-vis* the availability of effective anaemia treatments beyond blood transfusion. The recognition that anaemia and resulting fatigue are not inevitable consequences of cancer treatment, and that performance status and QOL are improved when anaemia is controlled, is a great stride forward.

However, the EORTC (2004) Guidelines omit two important publications that dispute the statement, "Despite the common use of epoetin alfa QW [once weekly] (40 000 IU), there is limited evidence to support this dosing schedule (grade C)". In a study published in 2001, Gabrilove *et al.* [3] report the results of a large open-label non-randomised prospective trial that evaluated the efficacy of a QW fixed dose (40 000 IU, increased to 60 000 IU if necessary) of epoetin alfa in anaemic patients ($n = 2964$) with non-myeloid malignancies who received chemotherapy. Overall response rate [hemoglobin (Hb) increase $\geqslant 2$ g/dl or achievement of Hb level of 12 g/dl without blood transfusion] was 68%. Mean Hb increase from baseline was statistically significant after 1 month of treatment ($P < 0.007$), with mean increases remaining significant throughout the 16-week trial. Transfusion requirements were significantly reduced ($P < 0.007$). QOL was significantly improved as measured by the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) ($P < 0.001$) and the Linear Analog Scale Assessment (LASA; also known as CLAS, Cancer Linear Analog Assessment scale) ($P < 0.001$). Moreover, a positive and significant correlation was shown between the increase in overall QOL and the increase in Hb level from baseline in the overall study population, as well as in a hematologic malignancy subgroup ($r = 0.24$; $P = 0.0001$).

The second study, conducted by Shasha *et al.* [4], was an open-label non-randomised prospective trial in anaemic cancer patients receiving radiotherapy either concomitantly or sequentially with chemotherapy. In this study, anaemic patients received a fixed dose (40 000 IU QW, increased to 60 000 IU if necessary) of epoetin alfa; 442 patients were evaluable for hematologic response. Overall response rate (Hb increase $\geqslant 2$ g/dl without blood transfusion) was 74.0%. Mean Hb increase from baseline was statistically significant by week 2 of treatment ($P < 0.05$), and remained significant throughout the 16-week trial. Transfusion requirements were significantly reduced ($P < 0.05$). QOL as measured by LASA was significantly ($P < 0.05$) improved. This study also demonstrated that improvements in QOL were directly correlated with Hb changes, with significant ($P < 0.0023$) differences between QOL changes in patients whose Hb increased 0–2 g/dl. There are also numerous abstracts published between 2002 and 2003 [5–9] that support the efficacy of the 40 000 IU QW epoetin alfa dosage regimens. These data should have led to a "grade B" instead of a "grade C" recommendation for the once weekly 40 000 IU dosing regimen for epoetin alfa.

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Since the August 2004 EORTC publication, two additional randomised studies have been published after the deadline for data inclusion, which would impact the rating given in the EORTC guidelines for the use of erythropoietic proteins. In a trial published by Witzig and colleagues [10], the placebo-controlled, double-blind, randomised study clearly showed that epoetin alfa (40 000 IU QW × 16 weeks), compared with placebo, resulted in a significantly greater increase in improved Hb from baseline in all evaluations ($P < 0.001$), and significantly greater reductions in transfusion requirements ($P < 0.005$) and the number of red blood cell units transfused ($P < 0.001$) in cancer patients experiencing chemotherapy-induced anaemia. Hemoglobin increases of $\geqslant 2$ g/dl were observed in 72.7% of epoetin-treated patients compared with only 31.7% of patients in the placebo group ($P < 0.0001$) [10]. These increases in Hb in patients receiving epoetin are comparable to those observed by Gabrilove [3].

The most recent evidence comes from a randomised phase III report published by Chang *et al.* [11] that demonstrated that breast cancer patients under chemotherapy treatment and given 40 000 IU QW epoetin alfa were better able to maintain Hb levels; required fewer transfusions; and had improved QOL. Week 12 FACT-An scores were significantly higher ($P < 0.001$), as were CLAS scores that measure level of energy ($P < 0.014$); ability to do daily activities ($P < 0.01$); and overall QOL as it relates to cancer symptoms ($P < 0.001$) for patients randomly assigned to receive epoetin compared with those given standard of care. The new information available from these two randomised studies should probably necessitate an update of the EORTC guidelines.

Additionally, the updated NCCN 2005 [12] guidelines included the epoetin alfa 40 000 IU QW option; and the 40 000 IU once per week epoetin alfa dosing regimen has also been recommended in the lymphoma/multiple myeloma guidelines [13] and the multiple myeloma research foundation [14]. Further, a once weekly epoetin alfa regimen is now approved in Europe for treatment of anaemia in adult patients receiving chemotherapy for solid tumors, malignant lymphoma, or multiple myeloma (450 IU/kg QW) [15]; in the United States epoetin alfa once weekly is approved for treatment of patients with non-myeloid malignancies with chemotherapy-associated anaemia (40 000 IU QW) [16].

The Gabrilove and Shasha studies along with the newly published Witzig placebo-controlled double-blind study and the randomised Chang standard of care-controlled study clearly demonstrate that epoetin alfa is effective when administered in a once weekly scheme. Based on these conclusive data, this dosage of epoetin alfa should now receive a "grade A" recommendation in the EORTC guidelines. These guidelines should therefore be adapted to reflect this important new information.

Conflict of interest statement

Dr. Gascón has received honoraria from Amgen Inc., Janssen-Cilag Ltd., Johnson and Johnson Pharmaceuticals LLC, and Roche Laboratories Inc.

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