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Prevention of anaemia by early intervention with once weekly epoetin alfa during chemotherapy

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ARTICLE INFO

Article history:
Received 28 November 2007
Received in revised form
8 February 2008
Accepted 14 February 2008
Available online 17 March 2008

Keywords:
Anaemia
Blood transfusion
Erythropoietin
Haemoglobin

ABSTRACT

This study compared the effects of early intervention with standard use of epoetin alfa on haemoglobin (Hb) levels and transfusion requirements in cancer patients receiving chemotherapy. Patients with Hb > 10 and ⩽12 g/dL were randomised 1:1 to epoetin alfa (40,000 IU, subcutaneously, once weekly), initiated within 7 d of the start of the first on-study chemotherapy cycle (defined as early intervention) versus epoetin alfa when Hb ⩽ 10 g/dL (defined as standard therapy). Increases in Hb values were significantly higher with early intervention compared to standard therapy from week 6 to 10 ($P \leqslant 0.05$) and approached significance at week 15/16 ($P = 0.0531$). Although the percentage of patients receiving blood transfusions was similar in both groups, the amount of blood transfused was almost twice as high in the standard epoetin alfa group (n.s.). Early intervention with epoetin alfa was well tolerated and overall survival did not differ significantly between groups. Initiation of epoetin alfa at the onset of chemotherapy and Hb < 12 g/dL improves Hb levels significantly versus standard therapy.

1. Introduction

Patients with cancer receiving chemotherapy often develop anaemia, which is associated with poor performance status and decreased quality of life (QOL) and is manifested as fatigue and decreased functional capacity.[1,2] Recombinant erythropoiesis-stimulating agents, such as epoetin alfa, are used for the treatment of chemotherapy-induced anaemia in patients with non-myeloid malignancies.[3] Results of several clinical trials and community-based studies have demonstrated the benefits of administration of epoetin alfa to anaemic patients receiving chemotherapy,[4–11] which include correction of anaemia, reduced transfusion requirement and improvement in QOL. The positive effect of epoetin alfa on QOL is independent of disease response and tumour type[12] and directly related to increases in the haemoglobin (Hb) level.[13]

More recent studies have assessed the effects of an early intervention approach. In this approach, the goal is to begin therapy before Hb levels drop below 10 g/dL and to maintain Hb levels between 10 and 12 g/dL. Evidence-based guidelines for epoetin alfa use established by the American Society of Clinical Oncology and the American Society of Hematology (ASCO/ASH) support this approach, as determined by clinical circumstances.[14] The European Organisation for Research and Treatment of Cancer (EORTC) recommends consideration of early intervention with erythropoietin based on the intensity and expected duration of chemotherapy.[3]

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.02.017

In an open-label, community-based study, early initiation of epoetin alfa improved Hb and QOL relative to baseline in patients with breast cancer.[15] Results of several clinical trials evaluating early intervention in comparison with best supportive care demonstrated that early intervention was superior on endpoints including Hb level, transfusion requirement and QOL.[16–21] However, these studies compared early intervention with control arms that received no epoetin alfa treatment making it difficult to draw conclusions about the benefits of early intervention. At the time of the start of this trial, few studies had compared early intervention directly with standard epoetin alfa therapy. Findings from clinical trials that compared early intervention with delayed intervention have become available.[22–24] These studies have shown that early intervention with epoetin alfa at the start of chemotherapy results in higher Hb levels and lower transfusion rates than delayed intervention. In addition, early intervention appears to maintain QOL in patients with only mild anaemia, potentially avoiding the deterioration of QOL associated with increasingly severe anaemia. A systematic review of the literature also demonstrated that early administration of epoetin alfa, before the onset of anaemia in patients with cancer, resulted in significant reduction in transfusion requirements (significantly fewer patients whose Hb levels fell below 10 g/dL) and significant improvements in QOL.[25] The objective of the current study (Clinical Trials Registry: www.clinicaltrials.gov, NCT00216541) was to compare the effects of early intervention with epoetin alfa with standard use of epoetin alfa on Hb levels and transfusion requirements in patients with cancer receiving chemotherapy.

2. Patients and methods

2.1. Study patients and design

Eligible patients were $\geqslant$18 years of age with a confirmed diagnosis of cancer who were to receive chemotherapy (platinum- or non-platinum containing) in 1-, 2-, 3-, or 4-week schedules for at least 8 or 9 weeks. Patients were included in the study before the start of the first or second chemotherapy cycle if Hb levels >10 g/dL and $\leqslant$12 g/dL during the 14-d period before the start of the first on-study chemotherapy cycle; the Eastern Cooperative Oncology Group (ECOG) performance score was 0, 1 or 2; and the life expectancy was at least 6 months, based on the investigator's clinical judgement. Females were required to be post-menopausal for at least 1 year, sterilised, or, if of childbearing potential, practising an acceptable method of birth control, based on the investigator's clinical judgement.

The original study protocol was amended as follows: after the first 5 patients were enrolled in the study, stricter Hb boundaries were applied (Hb $\leqslant$ 12 g/dL at randomisation and 13 g/dL as the upper limit for administration of epoetin alfa). The inclusion of patients with non-platinum containing chemotherapy and patients starting their second cycle of chemotherapy was also allowed by amendments to the protocol during the study. Finally, the collection of overall survival data was also added by amendment.

Patients with any of the following characteristics were excluded from the study: clinically significant or uncontrolled disease or dysfunction of any body system not attributable to underlying malignancy or chemotherapy, including uncontrolled or severe cardiovascular disease, myocardial infarction within 6 months, uncontrolled hypertension (diastolic blood pressure >95 mm Hg), congestive heart failure, or uncontrolled or unexplained seizures; planned surgery within the first 8–9 weeks of study entry that was judged by the investigator as expected to influence Hb levels; major illness or infection within 1 month of the beginning of the study; highly increased risk of thrombotic or other vascular events, as judged by the investigator; androgen therapy within 2 months of study entry; anaemia due to factors other than cancer or chemotherapy; blood transfusion within 14 d before study entry; participation in any other investigational drug trial or therapy relating to anaemia within 30 d of study entry; current inclusion in any other research project involving unlicensed or experimental medications that would interfere with this study; known hypersensitivity to epoetin alfa or one of its components; pregnancy or currently lactating. Each patient provided written informed consent after the study was fully explained and before any study-related activity was performed.

This was a randomised, open-label, explorative, sequential, multicentre study, with a screening, treatment and end-of-treatment phase (or early withdrawal). Study visits were planned to coincide as much as possible with routine visits for chemotherapy. The protocol and associated amendments were approved by an accredited central independent ethics committee/institutional review board (METOPP, Tilburg, the Netherlands) according to the Dutch Medical Research in Human Subjects Act. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines.

The screening visit took place within 14 d before the start of the first on-study chemotherapy cycle, and the following items were collected: informed consent; relevant medical history; chemotherapy, radiotherapy, surgery and transfusion data for the 3 months prior to enrollment; disease symptoms; blood sample for anti-erythropoietin antibody analysis; vital signs; ECOG performance score and concomitant therapy. In addition, the stage of the patient's malignancy was determined, and clinical laboratory tests were carried out.

After screening, patients were randomised 1:1 to receive early intervention (early group) or standard therapy (standard group) according to the adapted minimizations method, after they were determined to fulfil all inclusion criteria by contacting the central randomisation centre. The starting dose of epoetin alfa (Eprex®; Ortho Biotech/Janssen-Cilag, High Wycombe, United Kingdom; [also marketed in the United States as Procrit®; Ortho Biotech Products, L.P., Bridgewater, NJ]) was 40,000 IU, s.c., once weekly (QW). Patients in the early group received their first dose within 7 d after day 1 of the first on-study chemotherapy cycle. Patients in the standard group received their first dose as soon as their Hb was $\leqslant$10 g/dL. All patients received epoetin alfa until 1, 2, 3, or 4 weeks after the start of their last chemotherapy cycle (for patients receiving chemotherapy every 1, 2, 3, or 4 weeks, respectively), up to a maximum of 24 weeks. A gradual increase in Hb of up to 2 g/dL per month during treatment was recommended, epoetin alfa was not to be administered at Hb levels above 13 g/dL, and Hb levels were not to rise above 14 g/dL; therefore, Hb was monitored at least every 2 weeks.