Weekly Administration of Epoetin Beta for Chemotherapy-induced Anemia in Cancer Patients: Results of a Multicenter, Phase III, Randomized, Double-blind, Placebo-controlled Study

Masahiro Tsuboi¹, Kohji Ezaki², Kensei Tobinai³, Yasuo Ohashi⁴ and Nagahiro Saijo⁵

¹Department of General Thoracic and Thyroid Surgery, Tokyo Medical University Hospital, Tokyo, ²Department of Internal Medicine, Fujita Health University School of Medicine, Aichi, ³Hematology and Stem Cell Transplantation Division, National Cancer Center Hospital, Tokyo, ⁴Department of Biostatistics, School of Public Health, University of Tokyo, Tokyo and ⁵National Cancer Center Hospital East, Chiba, Japan

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Objective: The efficacy and safety of weekly administration of epoetin beta (EPO) for chemotherapy-induced anemia (CIA) patients was evaluated.

Methods: One hundred and twenty-two patients with lung cancer or malignant lymphoma undergoing chemotherapy were randomized to the EPO 36 000 IU group or the placebo group. Hematological response and red blood cell (RBC) transfusion requirement were assessed. Quality of life (QOL) was assessed using the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire.

Results: Mean change in hemoglobin level with EPO increased significantly over placebo (1.4 ± 1.9 g/dl versus 0.8 ± 1.5 g/dl; P < 0.001). The proportion of patients with change in hemoglobin level ≥2.0 g/dl was higher for EPO than those for placebo (P < 0.001). After 4 weeks of administration, the proportion of RBC transfusion or hemoglobin level <8.0 g/dl was significantly lower for EPO than those for placebo (P = 0.046). The changes in the FACT-An total Fatigue Subscale Score (FSS) were less deteriorated with EPO than those with placebo. Progressive disease (PD) did not influence the change in hemoglobin level but there was less decrease in FSS in non-PD patients. No significant differences in adverse events were observed. Thrombovascular events and pure red cell aplasia related to EPO were not observed. Retrospective analysis of survival showing the hazard ratio of EPO to placebo was 0.94.

Conclusion: Weekly administration of EPO 36 000 IU significantly increased hemoglobin level and ameliorated the decline of QOL in CIA patients over the 8-week administration period.

Key words: anemia – erythropoietin – cancer – chemotherapy-induced anemia – quality of life – survival

INTRODUCTION

One of the causes of anemia in cancer patients is myelosuppression due to chemotherapy or radiation therapy (1). Anemia occurs at a high frequency when using platinum agents, taxanes or anthracyclines often used in cancer patients, especially in patients with lung cancer and malignant lymphomas. Clinical symptoms associated with anemia such as tachycardia, palpitations, fatigue, vertigo and dyspnea are observed in patients with hemoglobin level <10.0 g/dl, and quality of life (QOL) patients is markedly reduced.

In Japan, only red blood cell (RBC) transfusions have been approved for the treatment of chemotherapy-induced anemia (CIA). However, although the safety of RBC transfusions has improved, there are still concerns about viral infections and graft-versus-host disease, as well as adverse effects on survival prognosis. Erythropoiesis-stimulating agents (ESAs) were approved for the treatment of CIA in the 1990s in the United States and in Europe, but they have still not

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been approved for this indication in Japan. It has been reported that the requirement for RBC transfusion can be reduced and QOL improved by increasing the hemoglobin level by ESA administration (2–7). In the United States, ‘Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology’ (8) (the ASH/ASCO guidelines) was published in 2002. The present placebo-controlled, double-blind, comparative study was planned in 2003 based on the ESAs guidelines and applications for ESAs in the United States and Europe for reference. Since 2003, however, several clinical studies have reported that ESAs worsened prognosis in cancer patients (9–16), and the risks of ESAs were investigated by three meetings of the Oncologic Drugs Advisory Committee (ODAC) (May 2004, May 2007 and March 2008). Since 2007, a safety alert (17) including a change in the upper hemoglobin limit has been issued, and the package inserts have been revised. The ASH/ASCO guidelines were also revised in 2007 (18). The effects of ESAs on cancer patient prognosis are not clear at present, and the US Food and Drug Administration (FDA) revised the labeling for ESAs imposed additional restrictions.

As a result of a previous dose-finding study, once a week epoetin beta (EPO) 36 000 IU was recommended for Japanese cancer patients (19). In this prospective, placebo-controlled, double-blind comparative study, the efficacy and safety of weekly administration of EPO 36 000 IU was evaluated. Efficacy was assessed based on the hematological response and QOL. In addition, considering the recent regulatory conditions in the United States and in Europe, a survival survey was retrospectively performed, and survival in the EPO group and in the placebo group was compared.

PATIENTS AND METHODS

PATIENT POPULATION

The study protocol was approved by the institutional review board at each study site, and written informed consent was obtained before study-related procedures were begun. Patients eligible for this study were required to be patients of age ≥20 to <80 years, who had lung cancer or malignant lymphoma, were receiving a platinum-, taxane- or anthracycline-containing chemotherapy regimen with at least two cycles of chemotherapy scheduled after the first study drug administration and had CIA (8.0 g/dl ≤ hemoglobin level ≤ 11.0 g/dl), an Eastern Cooperative Oncology Group performance status (PS) ≤2, life expectancy ≥3 months as well as adequate renal and liver function. Exclusion criteria included iron-deficiency anemia (serum iron saturation <15% or mean corpuscular volume (MCV) <80 μm³), history of myocardial, pulmonary or cerebral infarction, severe hypertension beyond control by drug therapy, pregnancy, obvious hemorrhagic lesions or other severe complications, myeloid malignancy or ESA/RBC transfusion within 4 weeks before the first study drug administration.

STUDY DESIGN

Patients were randomized 1:1 to receive EPO 36 000 IU or placebo subcutaneously once a week for 8 weeks. The planned number of patients was 120 (60 in each group). Randomization was conducted by central registration system and a dynamic balancing method using tumor type, PS, age and institution as the adjusting factors. Administration was terminated if the hemoglobin level reached 14 g/dl or more. Oral iron-supplementing drugs were administered if serum iron saturation fell below 15% or MCV fell <80 μm³.

Hemoglobin level and clinical laboratory tests were monitored weekly until 1 week after last study drug administration. RBC transfusion was allowed at the discretion of the investigator during the study.

STUDY ENDPOINTS

The primary endpoint was change in hemoglobin level from baseline, and the last evaluation was performed 8 weeks after the first study drug administration or at study discontinuation. The last observation carried forward method was used for evaluation of the change in hemoglobin level. The secondary endpoints were change in the Functional Assessment of Cancer Therapy Anemia total Fatigue Subscale Score (FSS) (0–52, where a higher score means less fatigue) from baseline to last evaluation, RBC transfusion requirement, nadir hemoglobin level, proportion of patients who achieved a hemoglobin level increase ≥2.0 g/dl from baseline, proportion of the patients with hemoglobin level <8.0 g/dl during the study and incidence of either RBC transfusion or hemoglobin level <8.0 g/dl. Safety was assessed by National Cancer Institute – Common Toxicity Criteria, ver. 2, translated by the Japan Clinical Oncology Group. Anti-erythropoietin antibodies were measured by enzyme-linked immunosorbent assay and radioimmunoprecipitation assay, and compared with the data of the first study drug administration with the data of the last observation. Detection by either method was judged as positive. A retrospective analysis of survival was performed.

STATISTICS

Efficacy analyses were performed using the full-analysis-set (FAS) population, comprising all eligible patients who received a study drug. In both EPO and placebo groups, changes in hemoglobin level and changes in FSS at the last evaluation were compared using Student’s t-test. Stratified analyses in the groups with baseline FSS >36 and ≤36, respectively, were also performed.
RESULTS

PATIENT DISPOSITION

One hundred and twenty-two patients were recruited from February 2004 to March 2005 at 11 sites in Japan. Sixty-five patients had lung cancer and 57 had malignant lymphoma. The patients were randomly assigned to the EPO group (n = 63) or the placebo group (n = 59). One patient in each group never received a study drug, one patient in each group never received chemotherapy and one patient in the placebo group did not have laboratory data after administration. Thus, the FAS population was 117 patients (61 patients in the EPO group, 56 patients in the placebo group).

DEMOGRAPHICS, CLINICAL AND BASELINE CHARACTERISTICS

Patient demographics were well balanced between the two groups, except for baseline hemoglobin levels and serum erythropoietin concentrations (Table 1). The mean hemoglobin level in the EPO group was slightly lower than in the placebo group (10.0 versus 10.4 g/dl). The baseline hemoglobin level did not influence the evaluation of the primary endpoint by analysis of covariance.

HEMATOLOGICAL EVALUATIONS

Mean change in hemoglobin level at the last evaluation significantly increased in the EPO group (1.4 ± 1.9 g/dl) than in the placebo group (−0.8 ± 1.5 g/dl) (P < 0.001). The hemoglobin level started to elevate in the EPO group at 3 weeks after the first administration (Figs 1 and 2). After 4–8 weeks of administration, the proportion of patients who achieved changes in hemoglobin level ≥2.0 g/dl from baseline was 42.6% (26/61) for the EPO group and 1.8% (1/56) for the placebo group (P < 0.001).

During the study, the proportion of patients with the hemoglobin level increased 12.0 g/dl or more was evaluated in the patients with hemoglobin level below 12.0 g/dl at baseline, the proportion was higher in the EPO group than in the patients with hemoglobin level 8.0 g/dl at baseline, the proportion was 11.9% (7/61) versus 12.5% (7/56), P = 0.865) or from Week 5 to Week 8 [8.2% (5/56) versus 12.5% (7/56), P = 0.443]. However, the incidence of RBC transfusion or hemoglobin level <8.0 g/dl from Week 5 to Week 8 was significantly lower in the EPO group than those in the placebo group [16.4% (10/61) vs. 32.1% (18/56), P = 0.046], and fewer RBC transfusion units were required in the EPO group (10 units, n = 5) than in the placebo group (26 units, n = 7).

QUALITY OF LIFE

At the last observation, the FSS data for two patients were missing because of progressive disease (PD). The missing scores were substituted by the maximum decrease in score.

Table 1. Patient demographics of full-analysis-set population

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n = 56)</th>
<th>EPO group (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>62.1 ± 9.6</td>
<td>61.8 ± 11.9</td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
<td></td>
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<tr>
<td>Lung cancer</td>
<td>30</td>
<td>32</td>
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<tr>
<td>Small cell lung cancer</td>
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<td>8</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
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<td>24</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
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<td>Hodgkin lymphoma</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
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<tr>
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<td>1st line</td>
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<tr>
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<tr>
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<td>26</td>
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<tr>
<td>2</td>
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<tr>
<td>Weight (kg), mean ± SD</td>
<td>54.5 ± 8.8</td>
<td>55.2 ± 10.0</td>
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<tr>
<td>Hemoglobin (g/dl), mean ± SD</td>
<td>10.4 ± 1.0</td>
<td>10.0 ± 1.0</td>
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<td>Serum endogenous erythropoetin (mU/ml), mean ± SD</td>
<td>49.1 ± 33.4</td>
<td>67.3 ± 72.0</td>
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<td>MCV (fl), mean ± SD</td>
<td>93.5 ± 6.0</td>
<td>91.9 ± 5.5</td>
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<tr>
<td>Transferrin saturation (%), mean ± SD</td>
<td>29.4 ± 19.8</td>
<td>32.4 ± 22.0</td>
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<td>Baseline QOL: FACT-An</td>
<td></td>
<td></td>
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<tr>
<td>Fatigue subscale (0–52), mean ± SD</td>
<td>33.9 ± 10.0</td>
<td>35.5 ± 9.7</td>
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<tr>
<td>≤36</td>
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SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; QOL, quality of life; FACT-An, Functional Assessment of Cancer Therapy-Anemia; MCV, mean corpuscular volume; EPO, epoetin beta.
for all patients. This substitution was decided before blinded data review. The changes in FSS from baseline were less in the EPO group than those in the placebo group (Mean $\pm$ SD: $20.5 \pm 9.4$ versus $24.5 \pm 10.0$, $P = 0.031$). But excluding these two patients with missing data at the last observation, the change in FSS from baseline was not significant in the EPO group and in the placebo group ($20.5 \pm 9.4$ versus $23.6 \pm 9.0$, $P = 0.082$). The factors that influenced the change in FSS were baseline FSS, change in hemoglobin level, treatment group and PS at the last observation (analysis of variance). It has been suggested that if the baseline FSS is higher than 36, the change in FSS will decrease after administration of ESA because of the high baseline and the lack of symptoms (ceiling effect and regression to the mean) (20,21). Thus, we also analyzed patients whose baseline FSS was $\leq 36$. In the baseline FSS $\leq 36$ patients, change in FSS was $2.1 \pm 11.7$ in the EPO group and $-1.3 \pm 9.6$ in the placebo group, so the EPO group showed improvement in FSS ($P = 0.225$). However, in the baseline FSS $>36$ patients, the change in FSS was $-2.9 \pm 5.9$ in the EPO group and $-7.9 \pm 4.4$ in the placebo group ($P = 0.016$), so the EPO group showed suppression of the decline in FSS (Fig. 3). In subset analysis of the EPO group, the mean change in hemoglobin level did not differ in PD and non-PD patients ($1.3 \pm 1.8$ versus $1.4 \pm 2.0$ g/dl), but PD patients showed a more marked decrease in FSS than non-PD patients ($-6.8 \pm 9.4$ versus $0.2 \pm 9.2$).

SAFETY

The incidence of adverse events was evaluated for the 120 patients who receive a study drug. Adverse events were observed in 62 patients (100%) in the EPO group and 57 patients (98.3%) in the placebo group, and no significant differences were found between the two groups ($P = 0.299$). The adverse events related to the study drug were 24 events in the EPO group (17 of 62 patients, 27.4%) and 19 events in the placebo group (11 of 58 patients, 19.0%) ($P = 0.274$). Adverse drug reactions observed in at least 3% of the patients in the EPO group were increased blood pressure (6.5%), increased lactate dehydrogenase (3.2%) and increased urinary glucose (3.2%). In the placebo group, rash (3.4%), increased blood pressure (3.4%) and decreased activated partial thromboplastin time (3.4%) were reported. Grade 3 abdominal pain and Grade 3 liver dysfunction were both observed in the same patients in the EPO group. Five patients (5 events) in the EPO group and five patients (12 events) in the placebo group experienced serious adverse events. Of these, only Grade 3 liver dysfunction was considered related to EPO treatment (Table 2). One thrombovascular event (TVE), a lacunar infarction, was reported in the EPO group. No other TVEs were reported in either group. No anti-erythropoietin antibodies were reported.

SURVIVAL

A retrospective analysis of survival was performed. The median follow-up duration was 670 days for the EPO group.

Figure 1. Hemoglobin level during the treatment period. A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org. SD, standard deviation; EPO, epoetin beta.

Figure 2. Change in hemoglobin level during the treatment period. A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.

Figure 3. Mean change in FACT-An total fatigue subscale score stratified by baseline total fatigue subscale score ($\leq 36$, $>36$). A colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org. FACT-An, Functional Assessment of Cancer: Therapy-Anemia.
and 641 days for the placebo group. The 1-year survival population based on Kaplan–Meier estimates was 64.9% in the EPO group and 65.9% in the placebo group. The hazard ratio was 0.94 for the EPO group relative to the placebo group (95% CI: 0.57–1.53).

DISCUSSION

Improvements in hemoglobin level were observed in Japanese patients with CIA on administration of EPO 36 000 IU once a week for 8 weeks. In the evaluation of QOL, it is necessary to consider the effects of scores at baseline, such as the ceiling effect and regression to the mean (20). It has been reported that in patients with less symptoms as baseline FSS is more than 36, the change in FSS became negative (21). The results of a stratified analysis of groups with baseline FSS \( \leq 36 \) and \( >36 \) (performed for reference) showed that in patients with baseline FSS \( \leq 36 \) (severe anemia symptoms), the symptoms of anemia improved in the EPO group, but worsened in the placebo group. In patients with baseline FSS \( >36 \) (mild anemia symptoms), worsening occurred in both groups, but the worsening was significantly inhibited in the EPO group compared with the placebo group. In the United States, at present, the FDA has not approved the use of ESAs to improve QOL, but the results of this study suggest that EPO may be useful in the prevention of worsening of symptoms of anemia.

In the United States, it has been stressed that the purpose of using ESAs is to treat CIA in order to avoid RBC transfusions. In the present study, the incidence of RBC transfusion during administration was low and the hemoglobin level when RBC was transfused was 5.5–8.8 g/dl. In Japan, most physicians and patients are reluctant to use RBC transfusions, but in the United States and in Europe, RBC transfusions are often started when the hemoglobin level is 8.0–10.0 g/dl (22). In this study, the proportion of patients with either severe anemia requiring a RBC transfusion or hemoglobin level of \(<8.0 \text{ g/dl (NCI-CTC Grades 3 and 4)}\) was examined. Evaluation of this proportion from 4 weeks after the start of administration, when ESAs exhibited hematopoietic effects (23–25), indicated that this proportion was significantly lower in the EPO group (16.4%, 10 of 61 patients) than in the placebo group (32.1%, 18 of 56 patients) \((P = 0.046)\).

One TVE was observed in this study, a lacunar infarction (Grade 1) in one patient (69-year-old male with lung cancer) in the EPO group. The investigator judged without causal relationship to the study drug but by aging, because the event was observed 1 day after the first study drug administration. No other TVEs were reported. Increased blood pressure and hypertension occurred in 10 patients (six in the EPO group, four in the placebo group). Marked differences from the placebo group were not observed for other adverse events.

The FDA has issued several safety alerts regarding data that demonstrated adverse survival outcomes in ESA-treated cancer patients. In this study, however, based on the results of a survey of overall survival, the 1-year survival proportion showed no significant difference between the groups. The effects of ESAs on survival of cancer patients have been examined by the ODAC and other groups since 2007, based on new clinical trial reports. So far, the reported safety data have been insufficient to rule out the risk of mortality in chemotherapy-treated patients, but ESAs are considered a therapeutic option for the management of CIA. Clinical studies based on the doses and hemoglobin levels recommended on the labels will continue to accumulate evidence on the effects of ESAs on survival.

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Conflict of interest statement
The author, Yasuo Ohashi, receives consultation fee from Chugai Pharmaceutical Co., Ltd.: the author advises on design and data analysis of clinical trials.

References