Pharmacokinetics and Pharmacodynamics of Weekly Epoetin Beta in Lung Cancer Patients

Yasuhito Fujisaka, Tomohide Tamura, Yuichiro Ohe, Hideo Kunitoh, Ikuo Sekine, Noboru Yamamoto, Hiroshi Nokihara, Atsushi Horiike, Tetsuro Kodama and Nagahiro Saijo

Division of Internal Medicine, National Cancer Center Hospital, Tokyo, Japan

Received December 16, 2005; accepted April 26, 2006; published online August 9, 2006

Background: To assess the pharmacokinetic profile and time-course of trough concentrations and hemoglobin levels associated with subcutaneous weekly administration of epoetin beta in lung cancer patients with chemotherapy-induced anemia.

Methods: Epoetin beta was subcutaneously administered to 15 anemic lung cancer patients once weekly for 8 weeks at doses of 9000, 18,000 and 36,000 IU. Pharmacokinetic parameters (C_{max}, AUC_{inf} and T_{1/2}) were determined after the first single dose administration on a model-independent basis, and the relationship between the dose and these parameters was examined for linearity.

Results: Weekly administration of epoetin beta at 9000, 18,000 and 36,000 IU produced C_{max} values of 308–117 (mean ± standard deviation), 678–86.7 and 1316–766 mIU/ml, and AUC_{inf} values of 15,300–9,524, 54,574–16,265 and 88,501–55,687 hr mIU/ml, respectively, showing dose-proportional increases. Trough concentrations tended to increase in the presence of severe bone marrow suppression induced by chemotherapy or other factors. Extremely high values were seen in three patients, but there was no apparent trend toward an increase with repeated doses. After 8 weeks’ administration at 9000, 18,000 and 36,000 IU, hemoglobin levels were changed by 0.37 ± 1.26, 2.15 ± 1.36 and 2.82 ± 2.17 g/dl, respectively.

Conclusions: Epoetin beta exhibited linear pharmacokinetics when administered to anemic cancer patients at weekly doses of 9000–36,000 IU and did not cause drug accumulation. Hemoglobin levels increased with weekly doses of 18,000 or 36,000 IU.

Key words: anemia – epoetin beta – pharmacokinetics

INTRODUCTION

Cancer patients receiving multicycle chemotherapy and radiotherapy frequently develop anemia, with one clinical study reporting that hemoglobin levels fell to 8–12 g/dl in 75% of patients undergoing these therapies (1). Among patients undergoing chemotherapy, anemia with hemoglobin levels of <8.0 g/dl reportedly occurs in 50–60% of ovarian cancer, lung cancer, non-Hodgkin’s malignant lymphoma or multiple myeloma patients (2).

The etiology of chemotherapy-induced anemia includes the following: myelosuppression of chemotherapy or radiotherapy, reduced production of the bone-marrow-stimulating hormone erythropoietin (EPO), diminished bone marrow response to EPO and cancer cell-induced immune system activation resulting in reduced iron availability (3).

EPO, a hematopoietic hormone mainly produced in the kidneys, acts on erythropoietic precursor cells to promote differentiation and proliferation of erythrocytes and disappears in the bone marrow and spleen. Epoetin beta is a human EPO preparation that is mass-produced by recombinant gene technology and is commonly used in treatment of patients with renal failure-induced anemia. In Europe and the United States, it has already been approved and has also been administered to cancer patients with anemia with demonstrated effects in reducing required blood transfusion volumes, elevating hemoglobin concentrations and improving quality of life (QOL) (4,5). Furthermore, in the US, the American Society of...
Hematology and the American Society of Clinical Oncology jointly issued clinical practice guidelines in 2002 for the use of EPO preparations (6). Thus, the general use of epoetin in anemic cancer patients has been advocated. Meanwhile, in Japan, EPO preparation has not been approved for cancer patients with anemia, but clinical trials are now in progress.

Despite the increasing usage of epoetin, its pharmacokinetics have not been adequately investigated at high, once-weekly doses of 30 000 or 40 000 IU that are typically administered subcutaneously to cancer patients with anemia (7). To the best of our knowledge, the literature contains no pharmacokinetic data for epoetin beta in patients with cancer-related or chemotherapy-induced anemia, and the effect of the chemotherapy on serum EPO concentrations was not clear. We therefore studied the pharmacokinetic profile and time-course of trough concentrations and hemoglobin levels associated with subcutaneous weekly administration of epoetin beta in lung cancer patients with chemotherapy-induced anemia.

PATIENTS AND METHODS

PATIENTS

Inclusion criteria were as follows: (i) histological or cytological confirmation of lung cancer diagnosis; (ii) treated with cyclic chemotherapy; (iii) aged between 20 and 79 years; (iv) life expectancy of at least 2 months; (v) anemia (hemoglobin level of ≤11.0 g/dl) considered to be primarily chemotherapy-induced; and (vi) adequate renal and hepatic function.

Exclusion criteria included (i) iron deficiency (Mean corpuscular volume ≤80mm$^3$ or iron saturation [Fe/(Fe+ Unsatuated iron-binding capacity)] × 100] ≤ 15.0%); (ii) blood cell transfusion in the 4 weeks prior to the study; (iii) rHuEPO therapy in the 4 weeks prior to the study; (iv) documented hemorrhagic lesion; (v) pregnancy, breastfeeding or not using adequate birth control measures; (vi) history of myocardial, pulmonary or cerebral infarction, serious drug allergy, uncontrolled hypertension, hypersensitivity to any EPO preparation, any serious complication; and (vii) a primary hematologic disorder as the cause of the present anemia.

The protocol was approved by the institutional review board of the National Cancer Center Hospital, and written informed consent was obtained from all patients who participated in the study.

STUDY DESIGN

This was an open-label, single-arm, dose-escalation study. Patients were assigned sequentially to one of three groups, receiving epoetin beta at either 9000, 18 000 or 36 000 IU per patient. This was administered by weekly subcutaneous injection for 8 weeks. If the patient’s hemoglobin level recovered to 14 g/dl or higher, the treatment was stopped. Chemotherapy and radiotherapy were not performed from 7 days prior to until 4 days following the initial dose, and blood transfusion was not performed until 4 days after the initial dose. Oral iron supplementation (200 mg of ferrous sulfate) was administered daily. Blood samples for detection of epoetin beta antibody were collected before the first administration and 7 days after the last administration. Patients were followed for 1 week after the end of drug administration. Granulocyte colony-stimulating factor administration was allowed to the patients whose neutrophils count was <500 per cubic millimeter or those with neutropenic fever whose neutrophils count was <1000 per cubic millimeter.

SERUM ASSAY

To determine the pharmacokinetic parameters, blood samples were collected immediately prior to and 6, 10, 24, 34, 48, 72, 96 and 168 h after the initial dose of epoetin beta. To investigate the time-course of trough concentrations, samples were also collected immediately prior to the administration of each dose.

Blood samples were allowed to stand at room temperature for ~30 min and then centrifuged at 4°C and 3000 rpm for ~10 min to separate the serum. The resulting serum was stored frozen at below ~20°C until used for measurement of serum EPO concentrations.

Serum EPO concentrations were measured by the RIA method developed and validated by Chugai Pharmaceutical Co., Ltd., Tokyo, Japan. Validation of this assay revealed the following: quantification range, 6–384 mIU/ml; intra-assay precision (repeatability) and accuracy of 2.7–6.3% and −22.1 to −5.5%, respectively; and inter-assay precision (reproducibility) and accuracy of 2.4–7.6% and −18.1–3.0%, respectively. If the assayed value exceeded the upper limit of the quantification range (378 mIU/ml), the sample was diluted for re-measurement.

PHARMACOKINETIC ANALYSIS

Since EPO is an endogenous substance, measurements of serum EPO concentration following the first administration were baseline corrected to account for the presence of endogenous EPO. The corrected values were then used to determine descriptive statistics for drug concentration at each blood sampling time-point and the pharmacokinetic parameters.

The following pharmacokinetic parameters were determined after the initial dose by using WinNonlin Pro v.3.3 (Pharsight Corporation, Mountain View, CA) in a model-independent manner: $C_{\text{max}}$, AUClinf and $T_{1/2}$.

$C_{\text{max}}$ was observed values. AUClinf was calculated by the trapezoidal method with infinite extrapolation by dividing the last plasma concentration by the elimination rate constant ($K_{\text{e}}$). $T_{1/2}$ was calculated as 0.693/$K_{\text{e}}$.

Trough concentrations were not baseline corrected.

PHARMACODYNAMIC ANALYSIS

Hemoglobin levels and platelet counts were assessed weekly.
STATISTICAL ANALYSIS
All statistical analyses were performed using SAS v. 8.2 (SAS Institute, Cary, NC). Descriptive statistics were not calculated if they were to be based on available data from less than half the subjects.

Analyses of dose linearity were performed for $C_{\text{max}}$ and AUC$_{\text{inf}}$. Each analysis used the power model: $\log y = \alpha + \beta \cdot \log \text{dose}$, where $\beta$ is the slope and $y$ represents the pharmacokinetic parameter. Fitting a linear relationship between log $y$ and log dose is an extension of the analysis of variance model. The key feature of the power model is the assumption of linearity between the log-transformed values of parameters and doses. The 95% confidential interval (CI) of the slope of the log-transformed parameters plotted against log dose was estimated, and dose-proportionality was concluded to be present if the 95% CI contained a slope with a value of 1.

RESULTS
PATIENTS’ CHARACTERISTICS
Fifteen patients were enrolled in the study. Their characteristics are shown in Table 1. Participants were 8 men and 7 women, aged 30–78 years (median age, 69.0 years), who were being treated with chemotherapy (containing platinum in 12 cases). Four patients received prior radiation therapy (brain radiation in four cases and thoracic radiation in three cases). Ten patients had small cell carcinoma, four had adenocarcinoma and one had large cell carcinoma. Doses of 9000, 18 000 and 36 000 IU were administered to 3, 6 and 6 patients, respectively. Data from all 15 patients were included for evaluation of pharmacokinetic analysis and hemoglobin response. In all patients, the hemoglobin levels at the time of registration were <11.0 g/dl. Five patients discontinued this study for the following reasons: recovery of hemoglobin level to 14 g/dl or higher, $n = 1$ (36 000 IU); adverse effects (rotary vertigo), $n = 1$ (36 000 IU); withdrawal of consent, $n = 1$ (9000 IU); and disease progression, $n = 2$ (18 000 IU, 36 000 IU).

PHARMACOKINETICS ANALYSIS
The mean baseline serum EPO concentration across all patients was 77.3 mIU/ml, with a median value of 59.9 mIU/ml, a minimum of 23.6 mIU/ml and a maximum of 301 mIU/ml. The 9000 IU group showed the highest mean, attributable to an extremely high value of 301 mIU/ml in one patient (Table 1).

The time-courses of the mean serum drug concentrations by dose group are shown in Fig. 1, and a summary of the pharmacokinetic parameters are given in Table 2.

The power model gave 95% CI of the slope ($\beta$) of the $C_{\text{max}}$-dose and AUC$_{\text{inf}}$-dose curves of 0.551–1.388 and 0.532–1.753, respectively, both including ‘1’.

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Item</th>
<th>Total</th>
<th>9000 IU</th>
<th>18 000 IU</th>
<th>36 000 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Histology</td>
<td>Small cell</td>
<td>10</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Large cell</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>ECOG* performance status</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>12</td>
<td>2</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>None</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Non platinum based</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Platinum based</td>
<td>12</td>
<td>3</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median</td>
<td>69.0</td>
<td>78.0</td>
<td>69.5</td>
<td>68.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>30–78</td>
<td>53–78</td>
<td>54–75</td>
<td>30–71</td>
</tr>
<tr>
<td>Hemoglobin** (g/dl)</td>
<td>Mean</td>
<td>9.4</td>
<td>9.1</td>
<td>9.2</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>6.8–11.4</td>
<td>6.8–11</td>
<td>7.5–10.3</td>
<td>7.1–11.4</td>
</tr>
<tr>
<td>Serum Fe (µg/dl)</td>
<td>Mean</td>
<td>76.8</td>
<td>111.3</td>
<td>69.5</td>
<td>66.8</td>
</tr>
<tr>
<td>Serum ferritin (ng/ml)</td>
<td>Mean</td>
<td>371.9</td>
<td>533.8</td>
<td>254.8</td>
<td>408.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>68.3–786</td>
<td>68.3–786</td>
<td>99.7–509.7</td>
<td>79.6–608.8</td>
</tr>
<tr>
<td>Serum endogenous erythropoietin (mIU/ml)</td>
<td>Mean</td>
<td>77.3</td>
<td>122.7</td>
<td>70.9</td>
<td>60.1</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>23.6–301</td>
<td>26.9–301</td>
<td>23.6–158</td>
<td>41.5–74.1</td>
</tr>
</tbody>
</table>

*Eastern Cooperative Oncology Group.
**The hemoglobin levels show the values just before the first administration of erythropoietin.
TROUGH CONCENTRATIONS

Time-courses of trough concentrations are shown by dose group in Fig. 2. Considerable variations in trough concentration occurred over the 8 week period. EPO concentration did not increase with repeated doses of epoetin beta, suggesting that drug accumulation did not occur. In some patients, trough concentrations were extremely high after chemotherapy (Fig. 3).

RELATIONSHIP OF TRough CONCENTRATION WITH BONE MARROW SUPPRESSION

Time-courses of trough concentrations, hemoglobin levels and platelet counts in the three patients with markedly elevated trough concentrations are shown in Fig. 3. In these patients, hemoglobin level and platelet count fell during the period in which trough concentration increased rapidly.

PHARMACODYNAMICS RESULTS

The time-course of mean hemoglobin levels is shown in Fig. 4. Hemoglobin levels were unchanged at a dose of 9000 IU, but tended to increase at doses of 18000 and 36000 IU. At 8 weeks, the change of hemoglobin levels from baseline was $-0.37 \pm 1.26$ g/dl in the 9000 IU group, $2.15 \pm 1.36$ g/dl in the 18000 IU group and $2.82 \pm 2.17$ g/dl in the 36000 IU group. One patient receiving 9000 IU and two patients receiving 18000 IU underwent blood cell transfusion. Only one patient (who received 36000 IU weekly) exceeded predetermined threshold levels of hemoglobin for discontinuation of the study.

SAFETY

Once-weekly dosing of epoetin beta was well tolerated in all study patients, with no life-threatening toxic effects occurring during the trial. Leucopenia was the most frequent adverse event (13 of 15), followed by nausea (9 of 15). Other frequent adverse events were anorexia (7 of 15), diarrhea (7 of 15), thrombocytopenia (6 of 15), alopecia (5 of 15), fatigue (5 of 15), constipation (4 of 15), elevated serum lactate dehydrogenase (4 of 15), insomnia (3 of 15), dizziness (3 of 15), vomiting (3 of 15), back pain (3 of 15) and elevated aspartate aminotransferase (3 of 15). These adverse events are typical for this patient population receiving chemotherapy, and none occurred in an epoetin dose-dependent manner. Adverse events possibly associated with epoetin beta occurred in six patients, and these events were manageable. These adverse events consisted of grade 3 hypertension and vertigo, grade 2 increased bilirubin, constipation and hyperkalemia and grade 1 headache, nausea, vomiting, insomnia, diarrhea, mouth dryness, fatigue, neck pain, rash, hyperventilation, cardiomegaly, hyperkalemia, hyponatremia, increased phosphorus and increased aspartate aminotransferase. Only one patient in the 9000 IU cohort showed grade 3 hypertension from the 7th day of the first administration to the 65th day. One serious adverse event (rotary vertigo) occurred in a patient (a 31-year-old woman); it remitted after around 2 weeks and resolved after 5 weeks. This event was considered by the investigator to be related to epoetin beta, and the patient therefore discontinued the study. No antibodies to epoetin beta were detected.

DISCUSSION

Serum EPO levels are reported to be higher in cancer patients than in healthy adults (8). The results of this study were in accordance with this, showing higher baseline serum EPO concentrations in patients than in healthy adults ($8.40 \pm 3.82, 8.62 \pm 5.83$ mIU/ml) (9) or renal anemia patients ($23.05 \pm 16.63$ mIU/ml) (10). In addition, serum EPO concentrations in cancer patients exhibited wide variation, from typical levels in healthy adults to extremely high levels. Overall, this suggests that the predose endogenous EPO exhibited high mean serum levels and wide individual differences in cancer patients with anemia.

In the present study, we have investigated the pharmacokinetic characteristics of epoetin beta after the initial dose of 9000, 18000 and 36000 IU and have studied the time-course
Figure 2. Time-course of trough concentrations of erythropoietin in each dose group. (A) 9000 IU, (B) 18,000 IU, (C) 36,000 IU. Trough concentrations of erythropoietin did not increase with repeated doses of epoetin beta, suggesting that drug accumulation did not occur.

Figure 3. Time-course of trough concentrations of erythropoietin, hemoglobin levels and platelet counts in three patients with extremely high trough concentrations. The elevation of trough concentration is correlated with decrease of platelet counts and Hb levels, which may be associated with bone marrow suppression.
of trough concentrations after once-weekly repeated dose subcutaneous administration in anemic lung cancer patients. The study provides evidence that epoetin beta has almost linear, dose-dependent pharmacokinetics following subcutaneous administration at doses of 9000–36,000 IU in cancer patients.

During the period of once-weekly administrations of epoetin beta, trough concentrations transiently increased after cancer chemotherapy in many patients, but did not appear to continue to increase with repeated administration of epoetin beta. Some patients showed extremely high trough concentrations that were correlated with periods of marked thrombocytopenia. Increases in trough concentrations may be associated with bone marrow suppression, and this finding is in agreement with reports showing that busulfan-induced bone marrow ablation increases serum EPO concentrations (11) and that chemotherapy increases EPO concentrations in patients with leukemia (12,13). Jelkmann reported that elimination of EPO occurs mainly in bone marrow (14). It is conceivable that the function of bone marrow could be damaged by chemotherapeutic agents after chemotherapy. Elimination of EPO could decrease in the damaged bone marrow, thereby the trough levels of EPO could increase.

At 8 weeks, mean changes in hemoglobin levels from baseline were −0.37 ± 1.26, 2.15 ± 1.36 and 2.82 ± 2.17 g/dl for 9000, 18,000 and 36,000 IU, respectively. Hemoglobin levels increased with repeated doses of 18,000 IU or more. A dose-finding study conducted by Sakai et al. (15) in Japanese patients with lung cancer or malignant lymphoma revealed a similar pattern of hemoglobin change (0.64 ± 1.98, 1.04 ± 1.75 and 1.75 ± 2.15 g/dl for 9000, 18,000 and 36,000 IU doses of epoetin beta) and concluded that the recommended dose was 36,000 IU in chemotherapy-induced anemic patients. Taken together, these results suggest that epoetin beta is sufficiently effective for cancer patients with anemia.

In conclusion, subcutaneous administration of epoetin beta at doses of 9000–36,000 IU in cancer patients with anemia yielded pharmacokinetic linearity, with no drug accumulation caused by repeated doses. Epoetin beta administration at 18,000 IU or higher is therefore anticipated to raise hemoglobin levels without compromising safety.

References