Effectiveness of Once-weekly Compared with Thrice-weekly Subcutaneous Epoetin Alpha for the Treatment of Chemotherapy-induced Anemia

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Purpose: The purpose of this study was to compare the effectiveness of once-weekly (20,000 IU) and thrice-weekly (10,000 IU) subcutaneous epoetin alpha (rHuEPO) in the treatment of chemotherapy-induced anemia (hemoglobin, Hb) in Korean cancer patients treated with cisplatin containing chemotherapy regimens.

Methods: This study prospectively collected data on epoetin alpha treatment in 1999-2005 from 10,000 IU (127 patients) and 20,000 IU (81 patients) dosage groups. Patients were treated with oral iron supplements when needed. The primary endpoint was the comparison of Hb changes after the study period of 8 weeks.

Results: At the start of the study, the mean Hb levels were similar in the 10,000 IU and 20,000 IU dosage groups (9.4 g/dL vs. 9.7 g/dL). The increase in Hb levels over 8 weeks was not significantly different between the two groups (1.57±1.39 g/dL vs. 1.68±1.35 g/dL, p=0.59). No significant differences were observed in the effectiveness of epoetin alpha between patients with or without cisplatin-containing regimens.

Conclusion: The results of this study indicate that the use of 20,000 IU epoetin alpha is comparable to 10,000 IU epoetin alpha in treating chemotherapy-induced anemia in Korean patients. Further studies are needed to confirm these findings in larger patient populations.
and blood shortage problem.4) The most commonly used treatment of anemia at present is epoetin alpha or recombinant human erythropoietin (rHuEPO). Epoetin alpha use has been shown to reduce the need for RBC transfusions and guarantee the safest and most effective anemia treatment. The American society of clinical oncology in conjunction with the American society of hematology recently launched the clinical practice guideline of epoetin usage in cancer related anemia patients.5) They recommended a starting dose of either 150-300 unit/kg thrice weekly (TIW) or 40,000 IU once weekly (QW). The pharmacokinetics and pharmacodynamics analysis conducted in healthy adults show that rHuEPO administered once-weekly gives a similar effect to that of thrice weekly regimen. However, the clinical outcome of the two different dosing regimens of epoetin alpha has not yet been evaluated in Korean cancer patients with chemotherapy-induced anemia. Therefore the objective of this study is to compare the effectiveness of once weekly with thrice weekly subcutaneous administration of rHuEPO for the treatment of chemotherapy-induced anemia in Korean cancer patients.

PATIENTS AND METHODS

Study design
Data for this observational study was collected retrospectively from the medical charts of patients who initiated erythropoietic support from March 1, 1999 to March 31, 2005 at the National Cancer Center, Goyang. Patients were scheduled to undergo chemotherapy during the course of this study and were administered rHuEPO 10,000 IU SC TIW or 20,000 IU SC QW while taking 200 mg of oral ferrous sulfate (Feroba-you®, Bukwang) twice daily as needed.

Study population
Patients eligible to participate in this study were those with anemia (Hb level in male < 11.5 g/dL; Hb level in female < 10.5 g/dL) attributable to chemotherapy. Inclusion criteria were patients who were at least 18 years of age and had active, incurable cancer that required treatment with myelosuppressive chemotherapy. Exclusion criteria were Hb level greater than 12 g/dL, uncontrolled hypertension, gastrointestinal bleeding, or hemolysis. Patients were also required not to have been administered RBC transfusions within two weeks of rHuEPO administration. Patients who underwent dose escalation or reduction of rHuEPO were excluded from this study.

Data collection
Patient demographics and clinical characteristics (eg. age, gender, baseline Hb level, disease, type of chemotherapy) were recorded at baseline. The Hb levels of enrolled patients were followed up for a maximum period of eight weeks.

Assessment of efficacy
The primary endpoints were the actual value and the mean change of Hb levels in patients administered with rHuEPO once or thrice weekly for eight weeks.

Statistical analysis
There were three stratification variables as follows: (1) receiving oral ferrous sulfate versus none; (2) receiving platinum-based therapy versus non-platinum based therapy; (3) male versus female. Data were analyzed by MS Excel 2000 and SAS (version 8.0). Mean Hb level change after rHuEPO treatment were compared using a two-sided paired t-test. Values are expressed as mean±S.D. The rHuEPO effect was analyzed by Student’s t-test. P value less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics
A total of 576 patients received rHuEPO for chemotherapy-induced anemia from March 1, 1999 to March 31, 2005 at the National Cancer Center, Goyang. Among the 576 patients, 268 patients received transfusions during the course of the study or were given
altered doses of rHuEPO and so were ineligible for assessment. Of the 208 patients who were assessed for efficacy, 127 patients were administered with 10,000 IU rHuEPO TIW and 81 patients were administered with 20,000 IU rHuEPO QW.

Patient baseline demographics and characteristics are shown in Table 1. Patient mean age in the TIW and the QW group were 62±10.4 and 49±10.4 years, respectively. Patients in the QW group were generally younger in age than patients in the TIW group. The mean Hb level at baseline was similar between the two groups (9.4 g/dL in TIW vs. 9.7 g/dL in QW group).

The most commonly diagnosed cancers were lung and breast cancer. All patients received chemotherapy during the study, with 46.5% of patients in TIW group receiving chemotherapy containing cisplatin (vs. 7.4% in QW group), and the others (53.5%) receiving other anticancer medicine (vs. 92.6% in QW group).

### Efficacy of Epoetin Alpha on Hb level

1) Mean Hb level change from baseline to measurements in TIW and QW groups

The mean (± S.D.) Hb level change from baseline to week 4 was 1.07±1.04 g/dL in the TIW group and 1.08±0.93 g/dL in the QW group (p=0.93). The mean (± S.D.) Hb level change from baseline to week 8 was 1.57±1.39 g/dL in the TIW group and 1.68±1.35 g/dL in the QW group (p=0.59). No significant difference in mean Hb level increase between the two groups from baseline to each measurement points was observed.

Change in mean Hb level was generally proportional to the elapsed time (Table 2). The proportion of patients achieving hematopoietic response (Hb increase from baseline > 0 g/dL) by each study week is shown in Figure 1. At week 2, a greater proportion of patients in QW group achieved response than in TIW group (86.3% vs. 71.6%), but from week 4, the proportion of patients was similar between the two groups.

2) Mean Hb level change from baseline to measurements in other variable groups

56.7% of patients in the TIW group took iron supplements in TIW and QW groups

![Fig. 1. Proportion of patients with hematopoietic response by study week](image)
ments as compared with 60.5% of patients in the QW group. The mean Hb level change of patients in the TIW group taking oral iron supplement or none from baseline to week 4 were 1.07±0.92 and 1.15±0.98 g/dL, respectively (p=0.73); and to week 8 were 1.76±1.15 and 1.60±1.54 g/dL, respectively (p=0.60). There was no significant difference in mean Hb level change in patients with or without oral iron supplement (Table 3).

46.5% of patients in the TIW group received platinum-containing chemotherapy as compared with 7.4% of patients in the QW group. To make up for this difference, the mean Hb level change was compared between patients receiving platinum and those receiving non-platinum-containing chemotherapy. The mean Hb level change in patients receiving platinum and those receiving non-platinum-containing chemotherapy at week 4 in the TIW group were 1.01±1.21 and 1.14±0.88 g/dL, respectively (p=0.51); and in the QW group were 1.57±0.95 and 1.06±0.94 g/dL, respectively (p=0.29). There was no significant difference in mean Hb level change in patients with platinum or non-platinum-containing chemotherapy (Table 4).

As shown in Table 1, the gender ratio in TIW group is a little different from QW group. To make up for this difference, the mean Hb level change was compared in women receiving QW or TIW rHuEPO (Table 5). The mean Hb level changes in the TIW and QW group at Week 4 were 1.21±0.96 and 1.14±0.96 g/dL, respectively (p=0.51); and at Week 8 were 1.42±1.22 and 1.62±1.45 g/dL, respectively (p=0.59). In addition, there was no significant difference in mean Hb level change between male and female in the TIW group (Table 6).

### DISCUSSION

Several double-blind placebo controlled randomized trials and studies conducted in specific communities have documented the therapeutic benefit of epoetin alpha as a treatment for chemotherapy-induced anemia.\(^6\)\(^-\)\(^9\)

Results attained from these studies have been consistent in
demonstrating the significant increase in Hb levels and decrease in blood transfusion incidences with the use of epoetin alpha. However, it must be noted that the TIW dosing regimen of epoetin alpha was initially developed in consideration with the dialysis schedule of patients with chronic renal failure. TIW practices are actually inconvenient for cancer patients because they do not synchronize with typical chemotherapy schedules. A number of studies comparing the benefits of QW and TIW epoetin alpha regimen on cancer patients receiving chemotherapy have been conducted in the past. However, the clinical outcome of TIW versus QW regimen of subcutaneously administered epoetin alpha in Korean cancer patients with chemotherapy-induced anemia has not been evaluated yet.

In the present study, there was no significant difference in mean Hb level increase from baseline to the end point between the QW and TIW groups. Although the proportion of patients achieving hematologic response (Hb increase from baseline > 0 g/dL) was a little higher in the QW group than in the TIW group at week 2, similar responses were observed from week 4. This trend could be explained by the fact that epoetin alpha requires at least two weeks of treatment before an increase in Hb level can be observed. Therefore, a less frequent dosing of epoetin alpha could still be implicated to maintain Hb levels within a range suggested by clinical practice guidelines.

A number of recent studies conducted to show the response to epoetin alpha therapy support this observation. Wing Cheung et al. found that the Hb level increase with 150 IU/kg TIW was similar to 40,000 IU QW dosing regimen despite the large difference in pharmacokinetic parameter such as AUC of serum erythropoietin. The results suggested that erythropoiesis was occurring at a similar rate from exposure to erythropoietin in the serum after both dosing regimens.

In addition to this, a recent pharmacokinetic data showed that the half life of circulating epoetin alpha is dependent on the specific patient population being studied. When epoetin alpha was administered intravenously to chronic kidney disease patients, the circulating half-life in the blood ranged from 4 to 13 hrs, but in contrast to this, patient with chemotherapy induced anemia demonstrated a considerably longer circulating half-life averaging 40 hrs (16–67 hrs) with epoetin alpha dosage regimens of either 150 U/kg SC TIW or 40,000 U SC QW. Therefore it is justifiable to alternate either regimen depending on the clinical situation.

Within the given time frame, approximately one-fifth of the patients in this study did not respond to standard epoetin alpha doses. Various factors are thought to affect the efficacy of epoetin alpha, and the use of concomitant iron supplement is considered as one of the important few. For this reason, mean Hb level change was compared between patients receiving oral iron supplements versus those without any, but results failed to demonstrate a significant difference between the two groups. Other studies have given coinciding results to this specific observation. These studies demonstrated that oral iron supplementation does not provide iron quickly enough to support the accelerated erythropoiesis that occurs with epoetin alpha. IV iron, on the other hand, appears to adequately support erythropoiesis during epoetin alpha therapy by supplying sufficient iron at the required rate. This might be the reason why intravenously administered iron is better than oral ones when adequate rate of hemoglobin increase is required in anemic patients receiving anticancer chemotherapy.

The limitations of this study are that a little difference between patient characteristics in the TIW and the QW group was present and that there wasn’t a safety evaluation (Table 1). To make up for this weakness, we compared the groups according to different variables (platinum-based chemotherapy versus non-platinum-based chemotherapy; male versus female). There was no significant difference in mean Hb level change between the respective groups. Also the difference of mean age between the two groups could be acceptable considering that many analyses and a large cohort study recently published confirmed that erythropoietic agents are equally effective irrespective of age.
Although it is difficult to show the safety data of QW and TIW epoetin alpha regimen because this study evaluated retrospectively, many previous studies agreed with that the QW regimen was safe and well-tolerated and that the adverse effects of QW regimen are similar with TIW regimen.\(^7\,20,\,21\)

In dealing with the treatment of chemotherapy-induced anemia, economical aspect of it cannot be overlooked because epoetin alpha is considered as a relatively expensive medication. The results of this study support a possible potential of switching the dosing regimen of epoetin alpha from TIW to QW without affecting Hb level change. With the practice of QW dosing regimen, the less frequent administration of high-dose epoetin alpha will provide practical advantages such as better compliance and improved quality of life to patients and healthcare workers. Economical benefit is also expected from this regimen, since the price per unit of high-dose epoetin alpha preparation is cheaper than that of the low dose preparation.

In conclusion, rHuEPO 20,000 IU SC QW is as effective as rHuEPO 10,000 IU SC TIW for the treatment of chemotherapy-induced anemia for up to eight weeks of therapy. The ability to administer rHuEPO less frequently not only enhances the management of chemotherapy-induced anemia, but also provides patients with convenience and relief from having to stick needles in their body more often.

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**REFERENCES**

administered every three weeks is effective for the treatment of chemotherapy-induced anemia. Oncologist 2006; 11: 409-17.


