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항암치료로 인한 빈혈의 치료에서 Epoetin Alpha 주일회요법과 주삼회요법의 약효 비교 연구

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

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Purpose : 본 연구의 목적은 항암치료로 인한 빈혈환자의 치료에서 epoetin alpha (rHuEPO) 피하주사 시, 주일회요법과 주삼회요법의 헤모글로빈(hemoglobin, Hb) 상승 효과를 비교하는 것이다.
Methods : 본 연구는 1999년 3월부터 2005년 3월까지 국립암센터에서 항암치료로 인한 빈혈로 epoetin alpha를 투여 받은 환자를 대상으로 의무기록의 자료를 후향적으로 수집하여 분석하였다. 연구에 포함된 환자는 rHuEPO 10,000 IU 주삼회투여군(n = 127)과 20,000 IU 주일회투여군(n = 81)으로 구분되었으며, 이들은 필요에 따라 경구용 철분보조제를 섭취하였다. Epoetin alpha 치료 시작 후 최대 8주까지 2주 간격으로 Hb 수치변화를 분석하였다.
Results : 치료 시작 시점의 rHuEPO 10,000 IU 주삼회투여군과 20,000 IU 주일회투여군의 평균 Hb수치는 유사하였다 (9.4 g/dL vs. 9.7 g/dL). Epoetin alpha 치료 후 8주까지 두 그룹간의 헤모글로빈 수치의 상승 정도에는 유의한 차이가 없었다 (1.57±1.39 g/dL vs. 1.68±1.35 g/dL, p=0.59). 또한 경구용 철분보조제 투여여부, cisplatin 포함 항암제 투여여부 및 성별에 따른 군의 분류에 있어서도 rHuEPO 10,000 IU 주삼회투여군과 20,000 IU 주일회투여군의 평균 Hb 상승수치는 유의한 차이를 보이지 않았다.
Conclusion : 한국인에서 항암치료로 인한 빈혈의 치료 시에 rHuEPO 20,000 IU 주일회투여 용법은 10,000 IU 주삼회투여 용법과 유사한 Hb 상승효과를 가진다.

□ Key words - anemia, chemotherapy, Epoetin alpha, Hemoglobin, dosing schedule

Anemia is a common complication of cancer and chemotherapy treatment which can lead to serious impairment on patients' quality of life (QOL) and prognosis.[1,2] In addition to this, the fact that as much as 75% of cancer patients receiving radiation and/or chemotherapy experience mild-to-moderate anemia, defined as hemoglobin (Hb) level of 8 to 12 g/dl,[3] makes it a clinically important condition. A variety of factors are known to be involved in the development of anemia, and these differ depending on the tumor itself (blood loss, bone marrow infiltration, nutritional deficiencies) or the type of chemotherapeutic regimen administered. Red blood cell (RBC) transfusions were traditionally used to treat anemia resulting from the use of myelotoxic agents. However, the use of alternatives have been encouraged given the growing concerns about problems arising from transfusions, increasing rate of transfusion uses,

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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 erythropoetic 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 (Ferobayou®, 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

Table 1. Baseline demographics and characteristics of TIW and QW groups

	TIW (n=127)	QW (n=81)
Age, years		
Mean±S.D. (Range)	62±10.4 (30-85)	49±10.4 (27-76)
Gender, *n* (%)		
Male	86 (67.7)	1 (1.2)
Female	41 (32.3)	80 (98.8)
Tumor type, *n* (%)		
Breast	1 (0.8)	80 (98.8)
Lung	116 (91.3)	0 (0)
Others	10 (7.9)	1 (1.2)
Baseline Hb, g/dL, mean± S.D.	9.4 (9.3-9.5)	9.7 (9.5-9.8)
≤10.5 g/dL, *n* (%)	114 (89.8)	64 (79.0)
>10.5 g/dL, *n* (%)	13 (10.2)	17 (21.0)
Chemotherapy agent, *n* (%)		
Cisplatin-containing	59 (46.5)	6 (7.4)
Others	68 (53.5)	75 (92.6)
Oral iron supplements, *n* (%)		
With oral iron supplements	72 (56.7)	49 (60.5)
Without oral iron supplements	55 (43.3)	32 (39.5)

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

Table 2. Mean Hb level change from baseline to measurements in TIW and QW groups

Time	TIW (g/dL, mean±S.D.)	QW (g/dL, mean±S.D.)	*p*
Week 2	0.50±0.90	0.60±0.60	0.38
Week 4	1.07±1.04	1.08±0.93	0.93
Week 6	1.33±1.15	1.46±1.17	0.41
Week 8	1.57±1.39	1.68±1.35	0.59

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 supple-

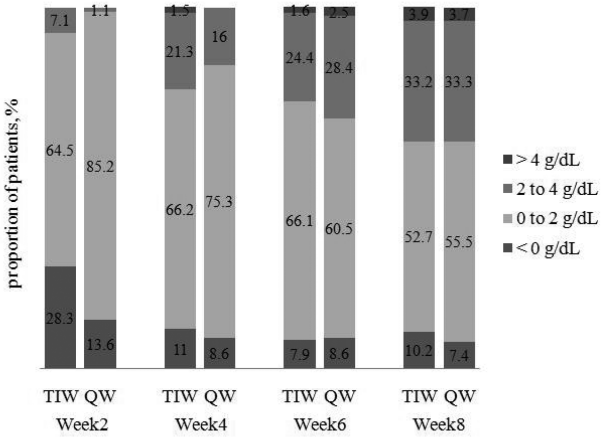

Fig. 1. Proportion of patients with hematopoietic response by study week

Table 3. Mean Hb level change from baseline to measurements in patients with or without oral iron supplements

	with oral iron supplements (g/dL, mean±S.D.)	without oral iron supplements (g/dL, mean±S.D.)	*p*
TIW			
Week 4	1.07±1.10	1.07±0.97	0.86
Week 8	1.62±1.50	1.50±1.24	0.64
QW			
Week 4	1.07±0.92	1.15±0.98	0.73
Week 8	1.76±1.25	1.60±1.54	0.60

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±1.10 and 1.07±0.97 g/dL, respectively (p=0.86); and to week 8 were 1.62±1.50 and 1.50±1.24, respectively (p=0.64). In the QW group, the mean Hb level change in patients 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

Table 4. Comparison of mean Hb level change from baseline to measurements in patients receiving platinum or non-platinum-containing chemotherapy

	Platinum (g/dL, mean±S.D.)	Non-platinum (g/dL, mean±S.D.)	*p*
TIW			
Week 4	1.01±1.21	1.14±0.88	0.55
Week 8	1.44±1.48	1.72±1.30	0.27
QW			
Week 4	1.57±0.95	1.06±0.94	0.29
Week 8	1.70±1.25	1.64±1.33	0.15

Table 5. Comparison of mean Hb level changes from baseline to measurements in women receiving QW or TIW rHuEPO

	TIW, n=41 (g/dL, mean±S.D.)	QW, n=80 (g/dL, mean±S.D.)	*p*
Week 2	0.57±0.71	0.61±0.60	0.76
Week 4	1.21±0.87	1.10±0.93	0.53
Week 6	1.19±0.90	1.49±1.15	0.15
Week 8	1.56±1.16	1.71±1.33	0.53

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±0.87 and 1.10±0.93 g/dL, respectively (p=0.53); and at Week 8 were 1.56±1.16 and 1.71±1.33 g/dL, respectively (p=0.53). 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

Table 6. Comparison of gender differences in mean Hb level change from baseline to measurements for patients in TIW group

	Female, n = 41 (g/dL, mean±S.D.)	Male, n = 86 (g/dL, mean±S.D.)	*p*
Week 2	0.55 ± 0.71	0.47 ± 0.98	0.67
Week 4	1.14 ± 0.96	1.03 ± 1.08	0.58
Week 6	1.13 ± 0.96	1.42 ± 1.22	0.19
Week 8	1.48 ± 1.26	1.62 ± 1.45	0.59

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.[10] 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.[11] 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.[11] 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.[12] 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.[13] 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.[13-15] 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.[14, 15]

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[16, 17-19]

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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