

Clinical evaluation of once-weekly dosing of epoetin alfa 40,000 units in anemic cancer patients receiving chemotherapy

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Voravud N. Clinical evaluation of once-weekly dosing of epoetin alfa 40,000 units in anemic cancer patients receiving chemotherapy. *Chula Med J* 2003 Dec; 47(12): 773 - 84

- Background** : *Anemia is a common problem in cancer population, mainly attributed by clinical consequences and possible adverse effects of treatment on patients' perceived quality of life. Good management of anemia in cancer population is therefore essential. Recent published clinical trials have demonstrated statistically significant increases of hemoglobin levels and significantly increased QOL assessment following administration of recombinant erythropoietin.*
- Objective** : *To evaluate the effectiveness, safety and quality of life by using once weekly dosing of epoetin alfa (Eprex[®], Janssen-cilag) 40,000 Units in the treatment of anemia in cancer patients receiving chemotherapy.*
- Setting** : *Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
- Patients** : *This was an open label, non-randomized study, in 25 adult male and female anemic cancer patients who had non-myeloid malignancies in the upper part of the body, whose hemoglobin ranged from 9-11 g/dl and were on chemotherapy for least 8 weeks, with or without concurrent radiotherapy.*

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Methods : The subjects were treated with subcutaneous epoetin alfa 40,000 units once a week. If, the patient's hemoglobin did not increase by > 1.0 g/dl after 4 weeks of treatment, the dose of epoetin alfa would then be increased to 60,000 units per dose subcutaneously at week 5. The epoetin alfa treatment would be continued for 16 weeks. The clinical outcome was then evaluated based on the quality of life accessed by linear analog scale assessment (LASA) and the functional assessment of cancer therapy-anemia (FACT-An) instrument. Analyses were performed to determine the incremental change of QOL associated with the increase of hemoglobin.

Results : Seventy- five percent of the patients who received epoetin alfa subcutaneously showed good responses with the rise of hemoglobin ≥ 1 g/dl (Hb level before and after = 9.95 ± 0.78 g/dl and 12.59 ± 1.83 g/dl, respectively; $P < 0.001$). Improvement of all primary cancer- and anemia-specific QOL domains, including energy level and the patient's ability to do daily activities evaluated by LASA and fatigue assessed from Fact-An, were significantly greater ($P < 0.01$) at week 16 (252.00 ± 38.02 and 13.13 ± 11.28) as compared to baseline (200.00 ± 34.76 and 23.88 ± 11.64). In addition, the hemoglobin levels may be related to LASA and FACT-An scores as tested by Pearson correlation ($P < 0.001$; $r = 0.435$ and < 0.001 ; $r = -0.431$, respectively). Epoetin alfa was well tolerated in all patients. Five patients, however, discontinued their participation before the planned study ended. The most common reason for their discontinuation came out of the patients' choices such as their lack of time or progression of the disease.

Conclusions : Once weekly dosing of epoetin alfa (Eprex[®], Janssen-cilag) 40,000 units therapy is safe and effective in remodeling anemia and significantly improves the quality of life in cancer patients receiving chemotherapy. Therefore, the treatment allows physicians to maintain the hemoglobin concentration of their cancer patients in normal level to improve their quality of life through the course of chemotherapy.

Keywords : Non-myeloid malignancy, Epoetin alfa, Anemia, Quality of life.

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Received for publication. September 15, 2003.

นรินทร์ วรวิมล. การประเมินประสิทธิผลทางคลินิกของการใช้อีพोटิน อัลฟา ขนาด 40,000 ยูนิตนิต ฉีดเข้าใต้ผิวหนังสัปดาห์ละครั้ง ในการรักษาภาวะโลหิตจางในผู้ป่วยมะเร็งที่กำลังได้รับเคมีบำบัด. จุฬาลงกรณ์เวชสาร 2546 ๓.ค; 47(12): 773 - 84

- วัตถุประสงค์** : เพื่อประเมินประสิทธิผล ความปลอดภัย และผลทางคลินิก ของการใช้อีพोटิน อัลฟา (อีเพรกซ์, Janssen cilag) ขนาด 40,000 ยูนิตนิต สัปดาห์ละครั้งเพื่อรักษาภาวะโลหิตจางในผู้ป่วยมะเร็งอวัยวะส่วนบนของร่างกายที่กำลังได้รับยาเคมีบำบัด
- สถานที่ทำการศึกษา** : หน่วยมะเร็งวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
- รูปแบบการวิจัย** : ศึกษาแบบเปิด
- ผู้ป่วยที่ทำการศึกษา** : ผู้ป่วยมะเร็งอวัยวะส่วนบนของร่างกาย ได้แก่ มะเร็งของอวัยวะบริเวณศีรษะและคอ มะเร็งปอด หรือ มะเร็งเต้านม ทั้งเพศชายและหญิง 25 ราย ซึ่งมีแผนการรักษาด้วยยาเคมีบำบัดเป็นเวลาอย่างน้อย 8 สัปดาห์โดยได้รับรังสีรักษาพร้อมด้วยหรือไม่ก็ได้ และมีระดับฮีโมโกลบินระหว่าง 9 - 11 กรัม/เดซิลิตร
- วิเคราะห์ทางสถิติ** : ข้อมูลพื้นฐานรายงานในรูปของสัดส่วนและร้อยละ เปรียบเทียบความแตกต่างของระดับฮีโมโกลบิน และ คุณภาพชีวิตก่อน และหลังการได้รับยาอีพोटิน อัลฟา โดยใช้สถิติวิเคราะห์ t-test ศึกษาความสัมพันธ์ระหว่างระดับฮีโมโกลบิน และคุณภาพชีวิตโดยใช้สถิติวิเคราะห์ Pearson correlation
- ผลการศึกษา** : ผู้ป่วยจำนวนร้อยละ 75 ตอบสนองต่อยาอีพोटิน อัลฟา ได้เป็นอย่างดี โดยมีระดับของฮีโมโกลบินเพิ่มมากกว่าหรือเท่ากับ 1 กรัม/เดซิลิตร หลังได้รับยาโดยการฉีดเข้าใต้ผิวหนัง (ระดับฮีโมโกลบินก่อนได้รับยาคือ 9.95 ± 0.78 กรัม/เดซิลิตร และ ระดับฮีโมโกลบินที่สัปดาห์ที่ 16 หลังเริ่มได้รับยา คือ 12.59 ± 1.83 กรัม/เดซิลิตร) ผู้ป่วยที่ได้รับยาอีพोटิน อัลฟา มีคุณภาพชีวิตที่ดีขึ้น จากการประเมินด้วยแบบสอบถามชนิด LASA และ FACT-AN ($P < 0.01$) โดยแบบสอบถาม LASA ถูกนำมาใช้เพื่อประเมินระดับของกำลัง ความสามารถในการทำกิจวัตรประจำวัน และ คุณภาพชีวิตโดยรวมของผู้ป่วย ขณะที่ FACT-AN ถูกนำมาใช้เพื่อประเมินความเหนื่อยล้าของผู้ป่วย อีกทั้งเมื่อศึกษาความสัมพันธ์

ระหว่างระดับฮีโมโกลบิน และคุณภาพชีวิตของผู้ป่วยที่ได้จากแบบสอบถาม LASA และ FACT-AN พบว่า ระดับฮีโมโกลบินมีความสัมพันธ์เป็นเส้นตรงกับคุณภาพชีวิต ($P < 0.001$; $r = 0.435$ and < 0.001 ; $r = -0.431$, ตามลำดับ). นั่นคือหากระดับของฮีโมโกลบินเพิ่มขึ้น คุณภาพชีวิตของผู้ป่วยจะดีขึ้นเช่นกัน ผู้ป่วยส่วนใหญ่สามารถทนต่อยาอีโพอิติน อัลฟาได้ดี มีผู้ป่วยเพียง 5 รายที่ถอนตัวออกจากโครงการก่อนสิ้นสุดการศึกษาทั้งนี้ส่วนใหญ่เนื่องจากผู้ป่วยมีการดำเนินของโรค มะเร็งรุนแรงขึ้น และผู้ป่วยไม่สามารถมาพบแพทย์ตามนัดได้

สรุปผลการวิจัย

: ผู้ป่วยมะเร็งอวัยวะส่วนบนของร่างกายที่มีภาวะโลหิตจางร่วมด้วยจากการได้รับยาเคมีบำบัด หลังจากได้รับยาอีโพอิติน อัลฟา (อีเพรกซ์, Janssen cilag) ขนาด 40,000 ยูนิต ชนิดฉีดเข้าใต้ผิวหนังสัปดาห์ละครั้ง ผู้ป่วยสามารถตอบสนองต่อยาได้ดี โดยระดับฮีโมโกลบินของผู้ป่วยจะค่อย ๆ เพิ่มขึ้นและเข้าสู่ระดับปกติ (12 กรัม/เดซิลิตร) พร้อมทั้งทำให้คุณภาพชีวิตของผู้ป่วยดีขึ้น ดังนั้นการประเมินระดับฮีโมโกลบิน และคุณภาพชีวิตตลอดช่วงที่ผู้ป่วยได้รับยาเคมีบำบัดจึงเป็นสิ่งที่จำเป็นสำหรับผู้ป่วยมะเร็ง

คำสำคัญ

: ผู้ป่วยมะเร็งอวัยวะส่วนบนของร่างกาย, อีโพอิติน อัลฟา, ภาวะโลหิตจาง, คุณภาพชีวิต

Anemia in cancer patients may be directly related to the disease itself or an effect of concomitantly administered chemotherapeutic agents. Eprex® (Epoetin alfa), a glycoprotein hormone which stimulates red cell production and manufactured by recombinant DNA technology, has been shown to increase hematocrit and decrease the requirement of transfusion after the first month of its therapy (months two or three of the therapy) in anemic cancer patients undergoing chemotherapy;⁽¹⁾ and is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy.⁽²⁾

Two recent studies^(3,4) conducted in over 1000 community-based oncology practices to measure clinically relevant outcomes, including evaluations of the quality of life (eg., energy level, activity level, and overall well-being through visual analog scales), hemoglobin changes, and transfusion requirements. Over 4,300 patients, diagnosed with various types of tumors who were anemic and on chemotherapy (2,030 - Study I; 2,289 - Study II), treated with a starting dose of 10,000 units of epoetin alfa subcutaneously three times weekly, which could be doubled (after 8 weeks - Study I or 4 weeks - Study II) if the response was not satisfactory. In Study I, 23 % of the patients and in Study II, 22 % of the treated patients had hematological malignancies, including; lymphoma, multiple myeloma, Hodgkin's disease, and chronic lymphocytic leukemia. The rest had solid tumors including (Study I/Study II); lung cancer (22 % / 24 %), breast cancer (18 % / 17 %), gynecological malignancies (14 % / 13 %), gastrointestinal malignancies (6 % / 9 %), prostate cancer (4 % / 3 %), head and neck tumors (2 % / 2 %), bladder

cancer (2 % / 2 %), and pancreatic, esophageal and renal cancers (1% each of both studies), other (4 % / 5 %) and unknown (1% / 1 %). In both studies, the energy level, activity level, and overall quality of life improved significantly ($p \leq 0.001$) over baseline levels. In addition, these improvements of the quality of life directly correlated with hemoglobin change from baseline. As hemoglobin increased with epoetin alfa treatment, the parameters of the quality of life significantly improved. It is important to note that where there was no increase in hemoglobin, there was no improvement in energy level, activity level, and the overall quality of life.

The starting dose in this study is 40,000 units, subcutaneous once a week. The selection of the dose was based both on clinical experience and the results of a published study⁽⁵⁾ in which normal volunteers received two doses of epoetin alfa 600 U/kg (approximately 40,000 units) given 10 days apart showed significant increases in both hemoglobin levels and reticulocyte counts. A clinical trial⁽⁶⁾, involving subjects undergoing surgical hip and knee replacements surgery with pretreatment hemoglobin values of ≥ 10 to ≤ 13 g/dl, showed patients who received four doses of epoetin alfa 600 U/kg Day - 21, Day -14, Day -7, and Day 0 of surgery had comparable hematology and transfusion response compared with a group which received 15 daily doses of epoetin alfa. A pharmacokinetic/pharmacodynamic study was completed in normal male volunteers that compared 150 U/kg Sc tiw with 600 U/kg Sc qwk for 28 days. All subjects received oral iron supplementation. Reticulocytes and hemoglobin were measured. The data indicate that, in 28 days, there was no difference between the two groups in terms of

change either in reticulocyte count or hemoglobin level.⁽⁷⁾

This study was designed to evaluate the effectiveness, safety of once-weekly dosing of epoetin alfa (Eprex[®], Janssen-cilag) 40,000 units in the treatment of anemia in cancer patients receiving chemotherapy as expressed in their assessed quality of life.

Patients and methods

Patients

This study was an open label, and non-randomized study. Adult patients eligible for recruitment were aged ≥ 18 years with a confirmed diagnosis of non-myeloid malignancy in the upper part of the body and scheduled to receive chemotherapy for at least 8 weeks, with or without concurrent radiotherapy. All patients had a hemoglobin level between 9 – 11 g/dl, serum ferritin more than 100 ng/dl and had a life expectancy of at least 6 months. None of the patients had secondary metastases (other than nodal disease), poorly controlled hypertension, defined as diastolic blood pressure persistently greater than 100 mmHg, hypersensitivity to epoetin alfa or mammalian cell-derived products, pregnancy or lactation, history of seizure, anemia due to other factors (i.e., iron or folate deficiencies, hemolysis, gastrointestinal bleeding, or any active bleeding), presence of chronic inflammatory conditions (e.g. rheumatoid arthritis) or infectious disease which might impair any response to erythropoietin, acute major illness within 7 days prior to the study, or major infection within 28 days of prior to the study. All patients gave their written informed consents before entering the study, and the study protocol and its

amendments were reviewed by an independent ethics committee.

Study procedure

Patients suitable for the recruitment were initially treated with epoetin alfa (Eprex[®], Janssen-cilag) 40,000 units administered subcutaneously once weekly. If, after 4 weeks of therapy, the hemoglobin level did not increase by > 1.0 g/dl, the dose of epoetin alfa was to be increased to 60,000 units subcutaneously once weekly at week 5. The epoetin alfa treatment was continued in total for 16 weeks. However, if the hemoglobin rose above 13 g/dL, epoetin alfa therapy would be withheld until the hemoglobin level decreased below 12 g/dL and then reinstated at 75% of the original dose. The dose of epoetin alfa should also be reduced if there was an increase of hemoglobin of > 13 g/dL in 2-week period. Blood transfusion was permitted during the study at the discretion of the physician but this was to be avoided in patients with a hemoglobin level greater than 8 g/dl unless it was clinically indicated. An oral daily dose of 325 mg of ferrous sulfate administered three times a day was also recommended to avoid depletion of iron storage and to adequately support erythropoiesis by epoetin alfa.

Efficacy Assessments

The primary efficacy end point was the proportion of responders (patients with an increase in hemoglobin level from baseline to the last value ≥ 1 g/dl). Evaluation of hemoglobin concentration was performed every 4 weeks after the start of the study drug. Secondary efficacy evaluation was seen in the change of QOL scores from baseline to the last value.



QOL was measured by patient-completed QOL battery consisting of the Linear Analog Scale Assessment (LASA) and Functional Assessment of Cancer Therapy-Anemia (FACT-AN) scale. The FACT-AN is a 20-item questionnaire evaluating the symptoms of anemia: 13 of which assess fatigue symptoms and 7 of which assess non-fatigue-related symptoms. The score of FACT-AN contains 5 grades (0,1,2,3 and 4) by 0 as best and 4 as worst QOL. The LASA consists of three linear analog scales, each was 100 mm long, that measures the level of energy, ability to do daily activities, and overall QOL related to cancer symptoms. Subjective QOL assessments were completed before the start of the study, at weeks 4,8,12 and 16 after the treatment with epoetin alfa. Patients scored their own perceptions of these domains by placing a mark along the line, with 0 as worst and 100 as best QOL. The FACT-AN and LASA scales are cancer-specific and have been demonstrated to be sensitivity to hemoglobin levels.^(3,4,9) Therefore the two scales were considered particularly suitable for detecting any change in QOL due to administration of epoetin alfa and subsequent increase in hemoglobin.

Statistical Analysis

Change in hemoglobin level and QOL score from baseline to value in every four weeks through the course of study were compared by t-tests, and the proportions of responders (patients with an increase in hemoglobin ≥ 1 g/dl) were observed. Pearson correlation coefficients were calculated to assess the relationship between hemoglobin level and QOL scores. For all statistical analyses, $P < 0.05$ was considered significant.

Results

Patients

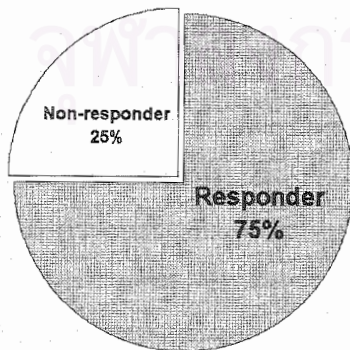
In total, there were 25 patients (13 men and 12 women) recruited into the study. The anemia problem of the patients was resolved after 16 weeks of treatment with epoetin alfa. There were no major differences in the demographics and baseline clinical characteristics of the patients as illustrated in Table 1. Most patients were in their advanced stages of malignancies: 23 patients (92 %) were in either grade III or IV. Cancer types of these patients included, namely: lung cancer (60 %), breast cancer (16 %), head & neck cancer (4 %) and others (20 %). Prestudy means of hemoglobin levels and hematocrit levels at baselines (9.95 ± 0.78 g/dl and 29.93 ± 2.34 %, respectively) determined their status of anemia. Low quality of life of the patients was showed as measured by LASA and FACT-AN score (200.00 ± 34.76 and 23.88 ± 11.64 , respectively).

Proportion of responder

Of the total 25 patients, five patients dropped out from the study (20 %). Their reasons for refusing to participate included, namely: their lack of time and disease progression. At the end of the study, the proportions of responders were 15 of 20 patients (75 %), illustrated in Figure 1. These patients completed the course of the study (16 weeks) and showed good response (patients who achieved an increase of ≥ 1 g/dl in hemoglobin level) after receiving epoetin alfa. Whereas, 5 of 25 patients had incremental mean of hemoglobin concentration less than 1 g/dl, compared to baseline although these patients were treated with additional dose of epoetin alfa 60,000 units subcutaneously once a week.

Table 1. Demographic and Baseline Clinical Characteristics.

Characteristic	Epoetin alfa (n=25)	
	N (range)	%
Gender		
Male	13	52
Female	12	48
Age, years		
Median	63	
Range	18-81	
Body weight, kg, mean \pm SD	55.87 \pm 7.47	
Stage of disease		
I	0	0
II	2	8
III	12	48
IV	11	44
Cancer type		
Lung cancer	15	60
Breast cancer	4	16
Head & Neck cancer	1	4
Others	5	20
Hemoglobin, g/dl, mean \pm SD	9.95 \pm 0.78	
Hematocrit, %, mean \pm SD	29.93 \pm 2.34	
QOL scores		
LASA	200.00 \pm 34.76	
FACT-AN (20 items)	23.88 \pm 11.64	

**Figure 1.** Proportion of responder to Epoetin alfa

Hematopoietic response

The mean hemoglobin values measured every four-weeks throughout the 16 weeks of the study for all cancer patients with anemia treated by epoetin alfa were shown in Figure 2. Their mean hemoglobin levels increased gradually from week 4 to approximately 12 g/dl by week 8 and were maintained at this level through week 16. The significant difference in the mean hemoglobin level over the baseline value was initially found after 1 month of treatment (10.88 ± 1.87 g/dl; $p = 0.01$ v. baseline).

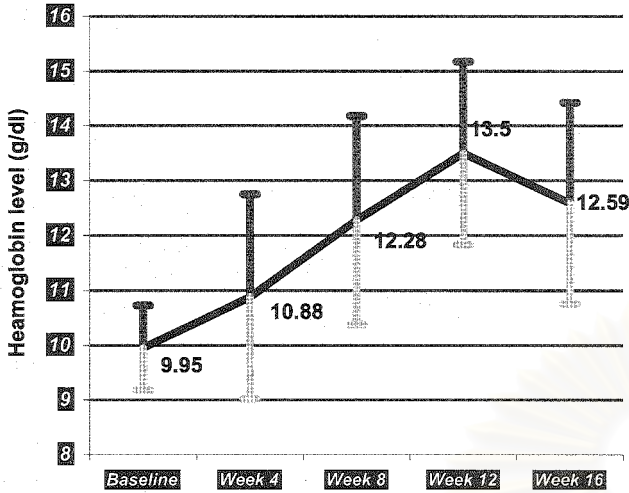


Figure 2. Mean Hemoglobin during Treatment with Epoetin alfa

QOL

The LASA and FACT-AN questionnaires were answered in the study at baseline, 4, 8, 12 and 16 weeks after start of treatment with epoetin alfa. Baseline scores of LASA and FACT-AN were compared

to obtained score every four weeks in order to evaluate the improvement of the quality of life. As for the LASA scale, the score increased significantly in all of three items including the level of energy, ability to do daily activities, and overall QOL related to cancer symptoms after the patients received epoetin alfa (Figure 3). Accordingly, the anemic symptoms in cancer patients measured by FACT-AN score was statistically significantly improved over the baseline level after receiving epoetin alfa (23.88 ± 11.64 and 13.13 ± 11.28 at baseline and week 16, respectively) as illustrated in Figure 4. Moreover, the improvement of the quality of life of the cancer patients was significantly apparent over the baseline level at the end of the first month after the start of epoetin alfa. When QOL of responders and non-responders was particularly considered, it was found that QOL of non-responders didn't improve in both LASA scale and FACT-AN as shown in Figure 5 and 6.

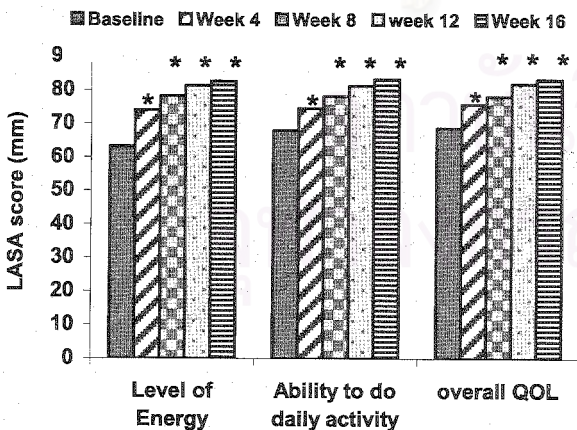


Figure 3. Baseline and Change From Baseline in Linear Analog Scale Assessment (LASA)

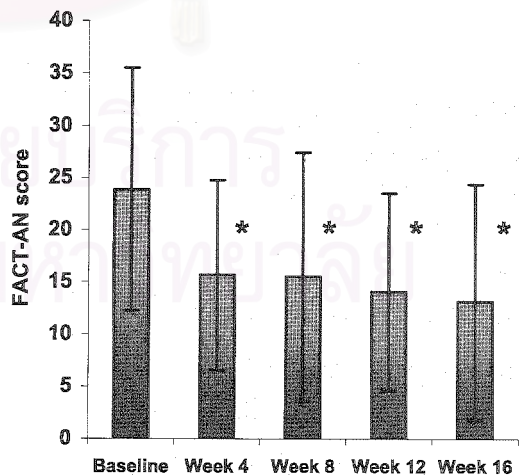


Figure 4. Baseline and Change From Baseline in Functional Assessment of Cancer Therapy-Anemia (FACT-AN)

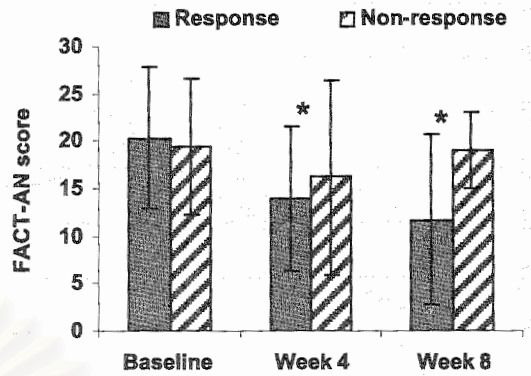
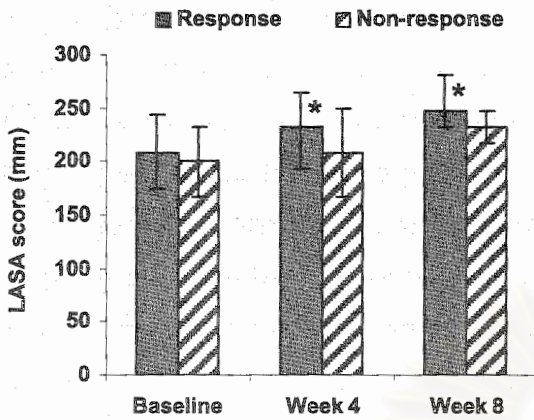


Figure 5. Baseline and Change From Baseline in Linear Analog Scale Assessment (LASA) between responders and non-responders

Figure 6. Baseline and Change From Baseline in Functional Assessment of Cancer Therapy-Anemia (FACT-AN) between responders and non-responders

Analog Scale Assessment (LASA)

Relationship between Hemoglobin levels and QOL

The relationship between hemoglobin levels and QOL scores calculated from LASA and FACT-AN among the patients also suggested that patients with higher hemoglobin levels experienced better QOL. The association between hemoglobin level and

QOL was examined by Pearson correlations analysis as illustrated in Figure 7 and 8. There were strong and statistically significant correlation in linear pattern between hemoglobin concentration and QOL score in both LASA and FACT-AN variables ($P \leq 0.001$; $r = 0.435$ for LASA and $P \leq 0.001$; $r = -0.431$ for FACT-AN).

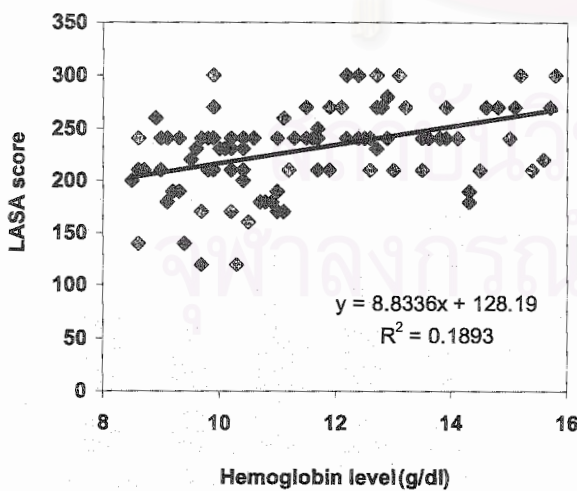


Figure 7. Correlation between change in quality of life (QOL; measured by linear assessment analog scales) and hemoglobin (Hb) level in cancer patients treated with Epoetin alfa.

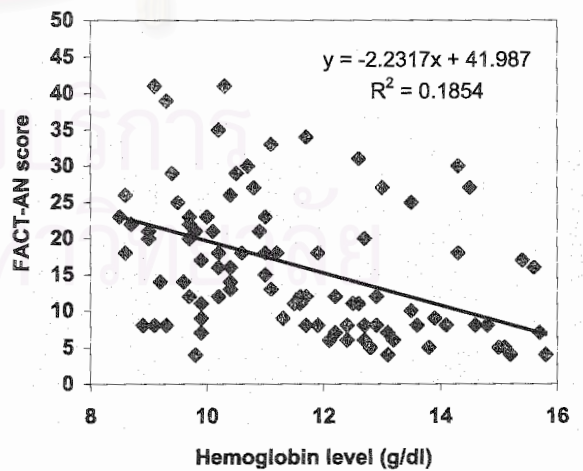


Figure 8. Correlation between change in quality of life (QOL; measured Functional Assessment of Cancer Therapy-Anemia) and hemoglobin (Hb) level in cancer patients treated with Epoetin alfa.

Safety

Treatment with epoetin alfa was well tolerated. The most common adverse event was fatigue. Of the In total 25 patients, 5 patients (20 %) had fatigue during the study and a patient (4 %) had cough. Nevertheless, there was not patient who discontinued their participation in study because of side effect of the treatment.

Discussion

The results of this non-randomized, open label trial demonstrated that most cancer patients with anemia had good response by an increase ≥ 1 g/dl increase in hemoglobin level when administered epoetin alfa 40,000 - 60,000 units once weekly via subcutaneous route. Additionally, the mean hemoglobin concentration of the patients gradually increased to normal level (12 g/dl) within week 8 after the start of the treatment with epoetin alfa. An increase of hemoglobin concentration to normal level had to be taken for a period because epoetin alfa is a glycoprotein that as a mitosis-stimulating factor and differentiating hormone stimulates erythropoiesis pathway. From graph shown in Figure 1, the patients had hemoglobin concentration over 13 g/dl at week 12 of treatment therefore epoetin alfa was withheld to reduce hemoglobin level to 12 g/dl approximately at week 16. This condition was mentioned in the study procedure. Nevertheless, QOL of the patients including the of energy, ability to do daily activities, and overall QOL related to cancer symptoms determined by LASA and fatigue symptoms evaluated by FACT-AN scale were also improved after receiving epoetin alfa. Interestingly, when the correlation between hemoglobin level and QOL score was considered, it was found

that hemoglobin concentration and QOL score from LASA and FACT-AN illustrated a strong relationship. The consequence could be explained that anemia might be one of the factors that reduce quality of life in cancer patients who were on chemotherapy. Therefore hemoglobin level and QOL measurement were crucial evaluations for patients receiving chemotherapy. Additionally, the physician should maintain hemoglobin concentration of cancer patients in normal level to improve their quality of life through the course of chemotherapy.

This finding suggested that epoetin alfa (Eprex[®], Janssen-cilag) 40,000 - 60,000 units once-weekly subcutaneously was safe and effective in remodeling anemia which significantly improved the quality of life in cancer patients receiving chemotherapy.

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