Antianemic Effect of Once Weekly Regimen of Epoetin Alfa 40,000 Units in Anemic Cancer Patients Receiving Chemotherapy

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Background: *Anemia is a common problem in the cancer population that is the result of clinical consequences. It also has adverse effects on patients' perceived quality of life. Good management of anemia in the cancer population is therefore essential. A recent published clinical trial has demonstrated statistically significant increases in hemoglobin levels and significantly increased QOL assessment following the administration of recombinant erythropoietin.*

Objective: *To evaluate the effectiveness, the safety, and the 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*

Material and Method: *This was an open label, non-randomized study, in 41 adult male and female anemic cancer patients who had non-myeloid malignancies in the upper area of the body part and hemoglobin ranging from 9-11 g/dL receiving chemotherapy at least 8 weeks with or without concurrent radiotherapy. The subjects were treated with Epoetin alfa 40,000 units once a week subcutaneously. If, the hemoglobin did not increase by > 1.0 g/dl after 4 weeks of treatment, the dose of Epoetin alfa was then increased to 60,000 units per dose subcutaneously at week 5. The Epoetin alfa treatment would continue for a total of 16 weeks. Clinical outcome was evaluated based on quality of life by using the linear analog scale assessment (LASA) and the functional assessment of cancer therapy-anemia (CU-QOL) instrument. Analyses were performed to determine the incremental change in QOL associated with hemoglobin increases.*

Results: *Seventy six percent of patients receiving Epoetin alfa subcutaneously showed good response with hemoglobin increases of $\geq$ 1g/dL (Hb level before and after = 9.82 $\pm$ 0.78 g/dL and 12.56 $\pm$ 1.49 g/dL, respectively; $p < 0.001$). Improvement of all primary cancer- and anemia-specific QOL domains, including energy level and ability to do daily activities evaluated from LASA and fatigue assessed from CU-QOL, were significantly greater ($p < 0.01$) for week 16 (233.94 $\pm$ 56.01 and 18.45 $\pm$ 13.07) compared to the baseline (202.58 $\pm$ 36.74 and 25.09 $\pm$ 11.00). Epoetin alfa was well tolerated in all patients.*

Conclusion: *Once weekly dosing of Epoetin alfa 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 physician should maintain hemoglobin concentration of cancer patients in normal level to improve their quality of life through the chemotherapy period.*

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

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Cancer and treatment-related anemia has received increasing attention, particularly as relationships between anemia and quality of life (QOL) or treatment outcome. The management of anemia has changed over the past 2 decades. Before 1980, improvements in blood banking technology had allowed liberal transfusion practices, with many patients transfused at the hemoglobin thresholds as high as 10 g/dL. The 1980s brought the recognition of infection risks, as well as limits on supply. Consequently, stringent transfusion guidelines were also lowering the threshold for transfusion to 7 to 8 g/dL with the goal of preventing "physiological" complications. In the 1990s, the use of epoetin alfa was approved, providing an alternative way of treatment. In addition, the development of newer agents for cancer treatment shifted the management of malignancy in many cases to that of a more chronic disease. Wider interest in QOL and validated tools for its assessment emerged, and the relationship between fatigue and anemia as one factor impairing QOL in some patients with decreased hemoglobin levels has been suggested[1].

Anemia in cancer patients may be related to the disease itself or the effect of concomitantly administered chemotherapeutic agents. Eprex (Epoetin alfa), a glycoprotein hormone which stimulates red cell production and is manufactured by recombinant DNA technology, has been shown to increase hematrocrit and decrease transfusion requirements after the first month of therapy (months two or three therapy) in anemic cancer patients undergoing chemotherapy[2] 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[3].

Many studies showed clinical data about using epoetin alfa 10,000 units subcutaneous by thrice weekly. One of those studies, Voravud reported about Clinical benefits of epoetin alfa 10,000 units subcutaneously thrice weekly in 40 Thai cancer patients with anemia receiving chemotherapy. The result showed epoetin alfa 10,000 units thrice weekly significantly increased the hemoglobin levels, achieving the target hemoglobin and sustained the level in cancer patients with anemia receiving chemotherapy. Clinical benefits on functional status and quality of life were also improved. The treatment was well tolerated[4].

There are also many studies that investigated the use of epoetin alfa 40,000 Units subcutaneous once a week. The selection of this dose was based both on clinical experience and the results of a published study[5] in which normal volunteers receiving two doses of epoetin alfa 600 U/kg (approximately 40,000 Units) given 10 days apart showed significant increases in hemoglobin levels and reticulocyte counts.

Witzig TE et al reported in their well controlled double blind study that investigated in accrued 344 patients divided into two groups. Group I had received epoetin alfa 40,000 units and group II had received placebo. The result showed that epoetin alfa significantly improved Hb and reduced transfusions in this patients' population. These results support the use of weekly epoetin alfa as an ameliorative agent for cancer-related anemia[6].

A pharmacokinetic/pharmacodynamic study was completed in normal male volunteers that compared 150 U/kg subcutaneous three times weekly with 600 U/kg subcutaneous weekly for 28 days. All subjects received oral iron supplementation. Reticulocytes and hemoglobin were measured. The data indicated that, at 28 days, there was no difference between the two groups in terms of change in reticulocyte count or hemoglobin level[7].

None of the studies showed clinical benefit about using epoetin 40,000 units in Thai cancer patients receiving chemotherapy. The present study was designed to evaluate the effectiveness, safety and quality of life using once weekly dosing of Epoetin alfa 40,000 Units in the treatment of anemia in Thai cancer patients receiving chemotherapy.

Material and Method

Patients

The present study was an open label, non-randomized study. Adult patients eligible for inclusion were aged $\geq$ 18 years with a confirmed diagnosis of non-myeloid malignancy in the upper area of the body part with or without concurrent radiotherapy were scheduled to receive chemotherapy for at least 8 weeks. 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 responsiveness to erythropoietin, acute major illness within 7 days of study

entry, or major infection within 28 days of study entry. All patients gave written informed consent before study entry, and the study protocol and amendments were reviewed by an independent ethics committee.

Study protocol

Patients suitable for inclusion were initial treated with Epoetin alfa 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 for a total of 16 weeks. However, if the hemoglobin rose above 13 g/dL, Epoetin alfa therapy should be withheld until the hemoglobin level decreased to less than 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 a 2-week period. Blood transfusion was permitted during the present study at the discretion of the physician but was to be avoided in patients with a hemoglobin level greater than 8 g/dL, unless clinically indicated. An oral daily dose of 325 mg of ferrous sulfate administered three times a day was recommended to avoid depletion of iron stores 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 last value $\geq$ 1 g/dL). Hemoglobin concentration evaluations were performed at screening and every 4 weeks after the start of the study drug. Secondary efficacy evaluation was changed in QOL scores from baseline to last value. QOL was measured using a patient-completed QOL battery consisting of the Linear Analog Scale Assessment (LASA) and Functional Assessment of Cancer Therapy-Anemia (CU-QOL) scale. The CU-QOL is a 20-item questionnaire measured anemia symptoms, 13 of which assess fatigue symptoms and 7 of which assess non-fatigue-related symptoms. The score of CU-QOL contains 5 grades (0, 1, 2, 3, 4) by 0 as best and 4 as the worst QOL. The LASA consists of three linear analog scales, each 100 mm long, that measure level of energy, the ability to do daily activities, and overall QOL related to cancer symptoms. Subjective QOL assessments were completed before the start of the present study, at weeks 4,8,12 and 16 after 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.

Statistical analysis

Change in hemoglobin level and QOL score from baseline to value in every four weeks through the course of the present study were compared by *t-tests*, and the proportions of responders (patients with an increase in hemoglobin $\geq$ 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 ANOVA with repeated measurement done on all cases that had their complete week.

Result

Patients

Forty-one patients (20 men and 21 women) were included in the study. These patients anemia problem was resolved with Epoetin alfa treatment for 16 weeks. There were no major differences in the demographics and baseline clinical characteristics of patients as illustrated in Table 1. Most patients had advanced disease, and 28 patients (68%) had the stage of disease in grade III or IV. Cancer types of these patients included

Table 1. Demographic and baseline clinical characteristics

Characteristic	Epoetin alfa (n = 41)	
	N (range)	%
Gender		
Male	20	49
Female	21	51
Age, years		
Median	60	
Range	40-76	
Stage of disease		
I	0	0
II	6	15
III	12	29
IV	17	41
Unspecified	6	15
Cancer type		
Lung cancer	30	73
Breast cancer	4	10
Others	7	17
Hemoglobin, g/dL, mean $\pm$ SD	9.82 $\pm$ 0.78	
QOL scores		
LASA	202.58 $\pm$ 36.74	
CU-QOL (20 items)	25.09 $\pm$ 11.00	

lung cancer (73%), breast cancer (10%), and others (17%). Pre-study mean hemoglobin levels at baseline (9.82 ± 0.78 g/dL) were determined to anemia status. Low quality of life of patients was shown as measured by LASA and CU-QOL score (202.58 ± 36.74 and 25.09 ± 11.00, respectively).

Proportion of responder

From the 41 patients, proportions of responders were 31 of 41 patients (76%) as illustrated in Fig. 1. These patients completed the course of the present study (16 weeks) and showed good response (patients who achieved a ≥ 1 g/dL increase in hemoglobin level) after receiving Epoetin alfa. Whereas, 10 of 41 patients had incremental mean hemoglobin concentration less than 1 g/dL compared to baseline although these patients were treated with an additional dose of Epoetin alfa 60,000 Units subcutaneously once weekly.

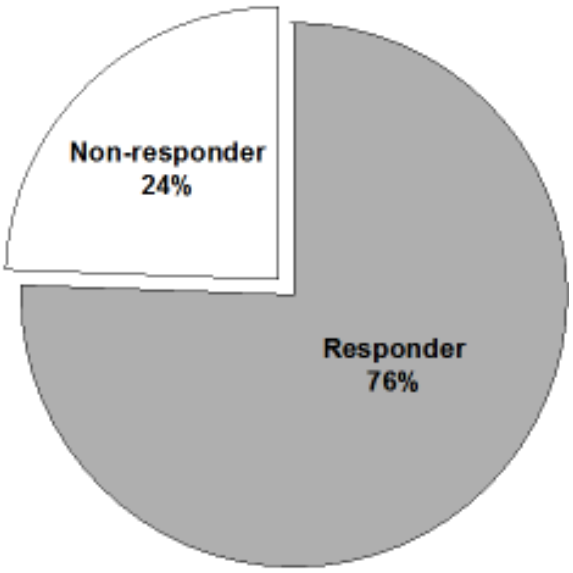

Fig. 1 Proportion of responders to Epoetin alfa

Hematopoietic response

Mean four-weekly hemoglobin values over the 16 weeks of the present study for all cancer patients with anemia treated by Epoetin alfa are shown in Fig. 2. Their mean hemoglobin levels increased gradually from week 4 to reach approximately 12 g/dL by week 8 and were maintained at this level through week 16. The difference significantly in mean hemoglobin level over baseline value was initially found after 1 month of treatment (10.88 ± 1.87 g/dL; *p = 0.01 v baseline*).

QOL

The LASA and CU-QOL questionnaires were answered in the present study at baseline, 4, 8, 12 and 16 weeks after start of treatment with Epoetin alfa. Baseline scores for the LASA and CU-QOL were compared to the obtained score every four weeks in order to evaluate the improvement of quality of life. For the LASA scale, the score increased significantly in all of the three items including level of energy, ability to do daily activities, and overall QOL related to cancer symptoms after the patients received Epoetin alfa (Fig. 3). Correspondingly, the anemia symptoms in cancer patients measured by CU-QOL score was statistically

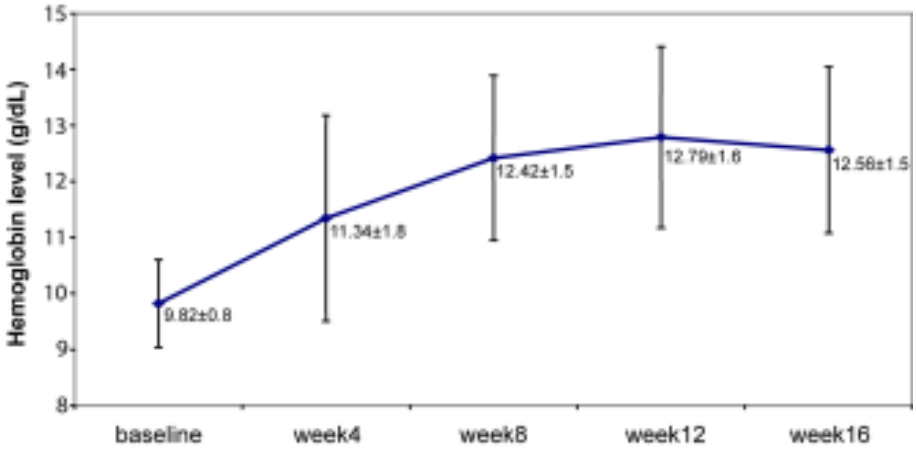

Fig. 2 Mean hemoglobin during treatment with Epoetin alfa (mean ± SD) (Using ANOVA with repeated measurement)

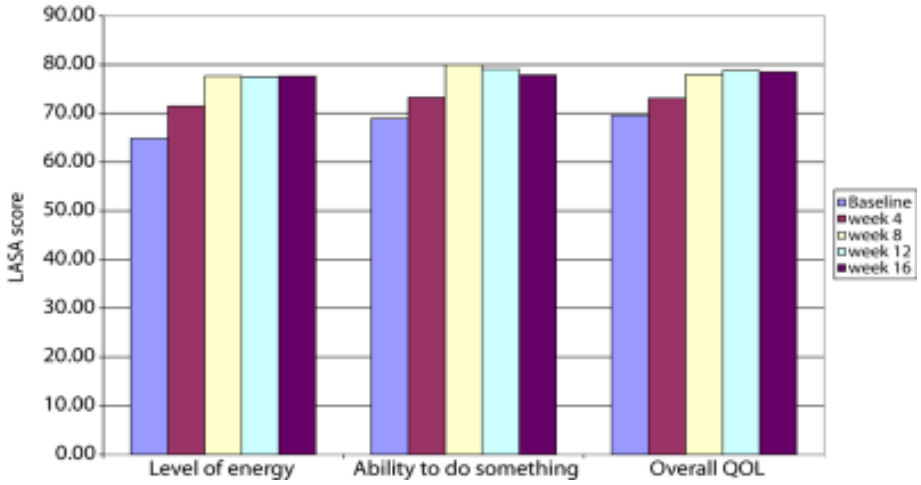

Fig. 3 Baseline and change from baseline in linear analog scale assessment (LASA)
* Statistically significant difference at $p < 0.05$

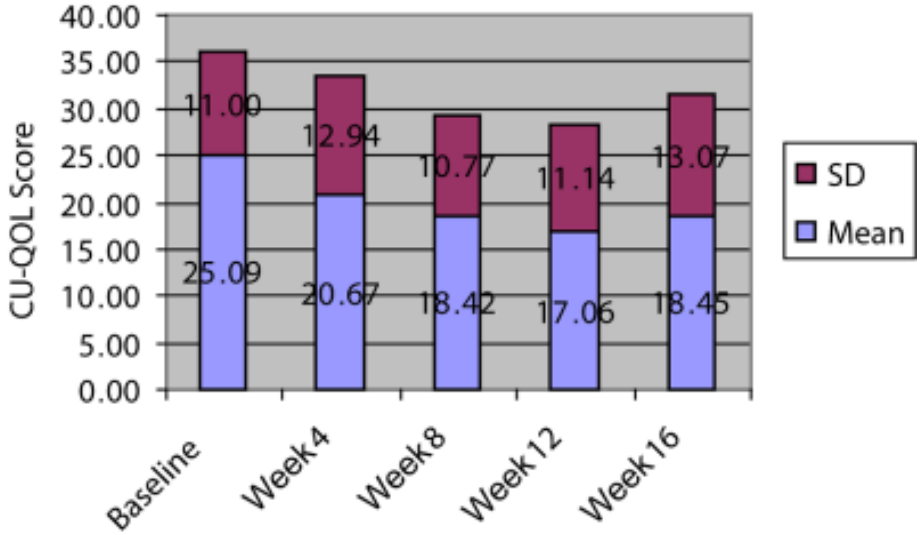

Fig. 4 Baseline and change from baseline in functional assessment of cancer therapy-anemia (CU-QOL) (mean ± SD)

significantly improved over baseline level after receiving Epoetin alfa (25.09 ± 11.00 and 18.45 ± 13.07 at baseline and week 16, respectively) as illustrated in Fig. 4. Moreover, the improvement of quality of life of cancer patients was significantly apparent over baseline level at first month after starting the Epoetin alfa.

Safety

Treatment with Epoetin alfa was well tolerated. The most common adverse event was fatigue. Five patients (12%) had fatigue during the present study and a patient (2%) had a cough. Nevertheless, patients discontinued the treatment because of side effects.

Discussion

The results of this non-randomized, an open label trial demonstrated that most cancer patients with anemia had good response by a ≥ 1 g/dL increase in hemoglobin level when administered Epoetin alfa 40,000-60,000 Units once weekly via subcutaneous route. Additionally, mean hemoglobin concentration of patients gradually increased to normal level (12 g/dL)

within week 8 after the start of the present study treatment with Epoetin alfa. An increase in 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 the graph shown in Fig. 1, the patients had hemoglobin concentration almost 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 present study procedure. The CU-QOL and LASA scales are cancer-specific and have demonstrated sensitivity to hemoglobin[4,5]. 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. Nevertheless, QOL of patients including level of energy, the ability to do daily activities, and overall QOL related to cancer symptoms determined by LASA and fatigue symptoms evaluated by CU-QOL scale had also been improved after receiving Epoetin alfa. Interestingly, when the correlation between hemoglobin level and QOL score was considered, it was found that the hemoglobin concentration and QOL score from LASA and CU-QOL illustrated the strong relationship. The consequence could explain why anemia may be one of the factors which reduces the quality of life in cancer patients undergoing chemotherapy. Therefore hemoglobin level and QOL measurement was a valuable evaluation 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 chemotherapy period.

Conclusion

This finding suggested that Epoetin alfa 40,000 Units once weekly subcutaneously was the safe and effective dosage and administration in remodeling anemia and significantly improving the quality of life in cancer patients receiving chemotherapy.

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การประเมินประสิทธิผลทางคลินิกของการใช้อีโพอิติน อัลฟ่า ขนาด 40,000 ยูนิต ชนิดฉีดเข้าใต้ผิวหนังสัปดาห์ละครั้ง ในการรักษาภาวะโลหิตจางในผู้ป่วยมะเร็งที่กำลังได้รับเคมีบำบัด

นรินทร์ วรวุฒิ, วิโรจน์ ศรีอุฬารพงศ์, หฤษฎ์ สุวรรณรัศมี

วัตถุประสงค์: *เพื่อประเมินประสิทธิผล ความปลอดภัย และ ผลทางคลินิก ของการใช้ยาอีโพอิติน อัลฟ่า (อีเพรกซ์, Janssen cilag) ขนาด 40,000 ยูนิตสัปดาห์ละครั้งเพื่อรักษาภาวะโลหิตจางในผู้ป่วยมะเร็งอวัยวะส่วนบนของร่างกายที่กำลังได้รับยาเคมีบำบัด*

สถานที่ทำการศึกษา: *หน่วยมะเร็งวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย*

รูปแบบการวิจัย: *ศึกษาแบบเปิดไม่ทำการสุ่ม*

วัสดุและวิธีการ: *ผู้ป่วยมะเร็งอวัยวะส่วนบนของร่างกาย ได้แก่ มะเร็งของอวัยวะบริเวณศีรษะและคอ มะเร็งปอด หรือมะเร็งเต้านม ทั้งเพศชายและหญิง 41 ราย ซึ่งมีแผนการรักษาด้วยยาเคมีบำบัดเป็นเวลาอย่างน้อย 8 สัปดาห์โดยได้รับรังสีรักษาร่วมด้วยหรือไม่ก็ได้ และมีระดับฮีโมโกลบินระหว่าง 9-11 กรัม/เดซิลิตร ข้อมูลพื้นฐานรายงานในรูปของสัดส่วนและร้อยละ เปรียบเทียบความแตกต่างของระดับฮีโมโกลบิน และคุณภาพชีวิตก่อนและหลังการได้รับยาอีโพอิติน อัลฟ่า โดยใช้สถิติวิเคราะห์ t-test ศึกษาความสัมพันธ์ระหว่างระดับฮีโมโกลบิน และคุณภาพชีวิตโดยใช้สถิติวิเคราะห์ Pearson correlation*

ผลการศึกษา: *ผู้ป่วยจำนวนร้อยละ 76 ตอบสนองต่อยาอีโพอิติน อัลฟ่า ได้เป็นอย่างดีโดยมีระดับของฮีโมโกลบินเพิ่มมากกว่าหรือเท่ากับ 1 กรัม/เดซิลิตร หลังได้รับยาโดยการฉีดเข้าใต้ผิวหนัง (ระดับฮีโมโกลบินก่อนได้รับยาคือ 9.82 $\pm$ 0.78 กรัม/เดซิลิตร และระดับฮีโมโกลบินที่สัปดาห์ที่ 16 หลังเริ่มได้รับยาคือ 12.56 $\pm$ 1.49 กรัม/เดซิลิตร) ผู้ป่วยที่ได้รับยาอีโพอิติน อัลฟ่า มีคุณภาพชีวิตที่ดีขึ้น จากการประเมินด้วยแบบสอบถามชนิด LASA และ CU-QOL ($p < 0.01$) โดยแบบสอบชนิด LASA ถูกนำมาใช้เพื่อประเมินระดับของกำลัง ความสามารถในการทำกิจวัตรประจำวัน และ คุณภาพชีวิตโดยรวมของผู้ป่วย ขณะที่ CU-QOL ถูกนำมาใช้เพื่อประเมินความเหนื่อยล้าของผู้ป่วย*

สรุป: *ผู้ป่วยมะเร็งอวัยวะส่วนบนของร่างกายที่มีภาวะโลหิตจางร่วมด้วยจากการได้รับยาเคมีบำบัด หลังจากได้รับยาอีโพอิติน อัลฟ่า ขนาด 40,000 ยูนิต ชนิดฉีดเข้าใต้ผิวหนังสัปดาห์ละครั้ง ระดับฮีโมโกลบินของผู้ป่วยจะค่อย ๆ เพิ่มขึ้นและเข้าสู่ระดับปกติ (12 กรัม/เดซิลิตร)ในสัปดาห์ที่16 หลังเริ่มได้รับยา พร้อมทั้งทำให้คุณภาพชีวิตของผู้ป่วยดีขึ้น การประเมินระดับฮีโมโกลบินและ คุณภาพ ชีวิตตลอดช่วงที่ผู้ป่วยได้รับยาเคมีบำบัดเป็นสิ่งที่จำเป็นสำหรับผู้ป่วยมะเร็ง*