EUR. J. ONCOL.; Vol. 19, n. 1, pp. 53-57, 2014

Efficacy of epoetin-α administration on improvement of hemoglobin (Hb) values in anemic patients with non-myeloid cancer

Mohammad Forat-Yazdi[1], *Golbarg Mehrpoor*[2]

[1] Department of Internal Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; [2] Department of Internal Medicine, Alborz University of Medical Sciences, Karaj, Iran

Summary. *Background:* Anemia in cancer patients is a common finding; it is caused by decrease in production or response to erythropoietin as a result of primary disease or complications of treatment. Traditionally, blood transfusion has been the treatment of choice in cancer related anemia; however, potential short- and long-term complications have limited its use. This study was designed to evaluate the efficacy of epoetin-α (a form of recombinant human erythropoietin) administration three times weekly on improvement of hemoglobin (Hb) values in patients with non-myeloid cancer suffering from anemia. *Methods:* In this open labeled, non randomized trial, a total of 60 patients were recruited. For all patients the baseline Hb values were measured. The study started with subcutaneous injection of epoetin-α (Eprex) 10,000 U three times weekly and treatment was continued for 12 weeks. *Results:* Hb level rose at the end of the second week in nearly all patients but the difference was not statistically significant compared to baseline Hb (p =0.37). At the end of the first months, Hb values were significant compared with baseline and the second week (p<0.001 and p= 0.002, respectively). Statistical analysis revealed a significant improvement in Hb levels in the third month compared to baseline (p <0.001), second week (p = 0.002) and first month (p < 0.001). *Conclusion:* epoetin-α improves Hb levels in cancer patients with anemia.

Key words: epoetin-α, hemoglobin, anemia, non-myeloid cancer

«Effetti della somministrazione di alfa epoetina nel miglioramento dei valori di emoglobina (Hb) in pazienti anemici con cancro non mieloide»

Riassunto. *Background*: Nei pazienti con cancro si riscontra comunemente l'anemia; essa è causata dalla diminuzione o risposta nella produzione di eritropoetina in conseguenza della malattia primaria o complicanza del trattamento. Tradizionalmente, la trasfusione di sangue è il trattamento di prima scelta per far fronte all'anemia legata al cancro, anche se le complicanze a corto o lungo termine ne hanno limitato l'utilizzo. Il presente studio intende valutare l'efficacia della somministrazione dell'epoetina alfa (una forma ricombinata di eritropoetina umana) tre volte a settimana sul miglioramento dei valori di emoglobina (Hb) in pazienti con cancro non mieloide affetti da anemia. *Metodi:* In questo studio aperto, non randomizzato, sono stati reclutati 60 pazienti. A tutti i pazienti sono stati misurati i valori basali di Hb. Lo studio è cominciato con una iniezione sottocutanea di 10000 unità di Epoetina-α (Eprex) tre volte a settimana e il trattamento è continuato per 12 settimane. *Risultati:* Il livello di Hb è aumentato alla fine della seconda settimana in quasi tutti i pazienti ma la differenza non è stata statisticamente significativa se paragonata al valore Hb basale (p=0.37). Alla fine dei primi mesi, i valori di Hb sono risultati significativi rispetto a quelli basali e a quelli della seconda settimana (p<0.001 and p= 0.002, rispettivamente). Le analisi statistiche hanno rivelato un

miglioramento significativo nei livelli di Hb durante il terzo mese in confronto ai valori basali (p <0.001), a quelli della seconda settimana (p = 0.002) e al primo mese (p < 0.001). *Conclusioni:* L'Epoetina alfa migliora i livelli Hb nei pazienti anemici con cancro

Parole chiave: epoetina-α, emoglobina, anemia, cancro non mieloide

Introduction

Anemia in cancer patients is a common finding. There are many different causes of anemia in people with cancer such as decrease in production or lack of response to erythropoietin as a result of primary disease or complications of treatment (1-3). Anemia in cancer patients often presents with dizziness, palpitations, heart failure, depression, severe impairment of cognitive function and negative effects on the quality of life in these patients (4).

Blood transfusion was the traditional treatment for cancer-related anemia (5), but mounting concern about the risk of infection, exposure to allogeneic blood products, transient effects on hemoglobin (Hb) levels and its high cost (6, 7), have resulted in a change of treatment strategy focusing on erythropoietic agents.

Erythropoietin is a hormone mainly produced by the kidney that stimulates and regulates red blood cell (RBC) formation in bone marrow (8), epoetin-α and beta are the two forms of recombinant human erythropoietin (9). Several clinical trials have revealed the efficacy of epoetin-α administration in improving Hb levels, quality of life and decreasing transfusion requirement in cancer patients with related anemia (10). The European Medicines Agency (EMA) registered alpha-epoetin only for treatment of anemia in cancer patients receiving chemotherapy and to reduce the need for blood transfusions (11)

This study was designed to evaluate the efficacy of epoetin-α administration three times weekly on improvement of Hb values in patients with non-myeloid cancer suffering from anemia.

Materials and methods

In this open labeled, non randomized study, a total of 60 patients were recruited. Patients were included in the study if they met the following criteria: (1) diagnosis of non-myeloid cancer; (2) Hb levels <11g/dl; (3) normal iron profile; (4) history of chemotherapy; and (5) more than 6 months life expectancy.

Patient were excluded from the study if they had : (1) iron deficiency anemia; (2) uncontrolled hypertension; (3) brain metastases; (4) uncontrolled seizure; (5) history of thrombosis; (6) known hypersensitivity to epoetin-α or any other mammalian derived products.

For all patients, baseline Hb concentrations were measured. The study started with subcutaneous injection of epoetin-α (Eprex) 10,000 U three times weekly (the injection performed in three minutes each time); treatment was continued for 12 weeks. During this period, the Hb levels were measured three times: at the end of second week, first month and third month as the end point. Beside epoetin-α all patients received supplements of ferrous sulfate, 325 mg three times a day in order to avoid depletion of iron stores.

Statistical analysis

Statistical analyses were performed using SPSS software version 17 for Windows (SPSS Inc. Chicago, IL, USA). Continuous variables are presented as means ± standard deviation (SD). Categorical variables are shown as percentages. For comparing treatment results between different periods of study, repeated measure analysis of variance (ANOVA) was used. In all analyses, a p value of less than 0.05 was considered statistically significant.

Results

A prospective study was conducted to evaluate the response of Hb values to epoetin-α administration in patients with cancer-derived anemia. Patients with cancer of non-myeloid origin who received chemo-

therapy and had hemoglobin levels of 11 g/dl were included. In all patients the level of serum iron, ferritin and total iron binding capacity (TIPC) were checked to exclude patients with iron deficiency anemia.

A total of 60 patients were enrolled, 31 (52%) of whom were women and 29 (48%) men. The mean age of study participants was 61.03±19.4 months (with a range of 3 to 78 months). The demographic characteristics of the patients are presented in table 1.

Throughout the study all patients received a supplement of iron and folic acid. A total of 19 (31%) patients had a history of transfusion before the study.

The level of Hb was assessed four times during the study, at the beginning (before epoetin-α administration), at the end of the second week, first month and third month of the study (Tab. 2). Hb levels rose at the end of the second week in nearly all patients but the difference was not statistically significant compared with baseline Hb (p=0.37). Hb values at the end of the first month were significantly higher than baseline or the second week (p <0.001 and p=0.002, respectively). Statistical analysis revealed a significant improvement in Hb levels in the third month compared to the beginning (p<0.001), second week (p=0.002) and first month (p<0.001).

No side effects like pure red cell aplasia or aplastic syndromes were seen among the study population.

Table 1. Demographic characteristics of the study patients

	n (%)
Sex (male/female)	29/31
Age	61.03±11.14
Duration of disease	20.93±19.04
Primary origin of malignancy	15 (25%)
Lung	16 (26%)
Breast	13 (21%)
Prostate	6 (10%)
Lymphoma	5 (5%)
Head and neck	2 (3%)
Sarcoma	2 (3%)
Ovary	1 (1.3%)
Germ cell	?

Table 2. Hemoglobin levels at different times of the study

Time	Hb levels	P value
Baseline	9.33±0.64	
Second week	9.63±1.41	P=0.37[a]
First month	10.27±0.77	P<0.001[b]
		P=0.002[c]
Third month	10.98±0.85	P<0.001[d]
		P=0.002[e]
		P<0.001[f]

a. P value calculated for comparison of Hb values between second week and baseline
b. P value calculated for comparison of Hb values between first month and baseline
c. P value calculated for comparison of Hb values between first month and second week
d. P value calculated for comparison of Hb values between third month and baseline
e. P value calculated for comparison of Hb values between third month and second week
f. P value calculated for comparison of Hb values between third month and first month

Discussion

We performed a prospective study to evaluate the efficacy of epoetin-α in the treatment of malignancy-associated anemia. A total of 60 patients with cancer were recruited and epoetin-α was administered three times weekly for 3 months. epoetin-α administration significantly improved Hb values.

Our findings are in agreement with previous reports. Littlewood *et al.* (12) studied 375 patients with cancer-related anemia; they performed a randomized trial and administered 150-300 IU/kg erythropoietin three times a week. They concluded that epoetin-α can significantly decrease the transfusion requirement, increase Hb levels and improve patients' quality of life.

A multicenter, non-randomized study was performed by Gabrilove *et al.* (13). They administered 40,000 U of epoetin-α once weekly in 3,012 patients with non-myeloid malignancies. It was shown that epoetin-α can significantly increase Hb levels, decrease transfusion requirement and improve patients' functional status. They concluded that administration of epoetin-α once a week results in as much benefit as three times weekly administration.

Crawford *et al.* (14) used the results of two open labeled community-based trials to evaluate the relationship between Hb level and quality of life in anemic cancer patients. They enrolled 4,382 patients, and used

linear analog scale assessment (LASA) and functional assessment of cancer therapy-anemia (FACT-An) to measure quality of life. They observed that there is a non-linear relationship and significant positive correlation between improvement of Hb level and high LASA and FACT.

Previous studies evaluated patients with any non-myeloid cancer who received chemotherapy. Another study was performed by Henke *et al.* (14) on patients with head and neck cancer undergoing radiotherapy. They investigated 351 anemic patients diagnosed with malignancy, and randomly assigned them into two groups. Epoetin-β 300 IU/kg three times weekly was administered to the patient group and was compared with placebo. The percentage of patients who achieved 140g/L Hb concentration was higher in the epoetin-β group but loco-regional progression-free survival was poorer in this group than in the placebo group. They concluded that epoetin-β can increase the Hb level but has little beneficial on cancer control or survival.

Cella *et al.* (15) compared the FACT –An data from an internet survey (on the general population) with 1,400 participants with quality of life data gathered from a randomized trial of 375 cancer patients receiving epoetin-α. The result showed that epoetin-α can significantly improve the quality of life of anemic cancer patients compared with the general population. Some other studies revealed the same results and concluded that epoetin-α has no impact on or even significantly improves (ambiguous: rephrase) the quality of life in cancer patients with disease-related anemia (16-18).

Collectively, our study, along with previous studies, shows that administration of epoetin-α can significantly improve Hb levels in patients with malignancy-associated anemia. But in long-term follow-ups there is some evidence as to the impact of epoetin-α on overall survival and mortality. Bohlius, during a Meta-analysis of clinical trials and after including all published and unpublished studies, assessed the data from 13,933 patients and concluded that Erythropoiesis-stimulating agent treatment in cancer patients increased mortality and worsened overall survival (19). Based on data from studies included in this systematic review, increased mortality was most clearly detected in non small cell lung, breast, head and neck, lymphoid and cervical cancers. Inclusion criteria for this meta analysis were studies on long-term follow-ups regardless of anti-cancer treatment. The authors of this manuscript noticed that the patients had many different forms of cancer and many different anti-cancer treatments and said that they could not identify the incidence of decreased survival of each cancer subgroup or treatment regimen on survival.

Our overall knowledge on the long-term effects of erythropoietin on patient survival is low and more studies focusing on specific cancers with different treatment regimens are needed. Of course, for many poor prognosis cancers with low survival rates the quality of life is more important than increasing survival by short periods of time and of course more studies focusing on the superiority and benefit of these two issues are likewise needed.

Acknowledgement

We are thankful to Dr Behnam Baghianimoghadam for his help in submission and revision of the manuscript.

References

1. Ludwig H, Van Belle S, Barrett-Lee P, *et al.* The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer 2004; 40: 2293-306.
2. Ozguroglu M, Arun B, Demir G, *et al.* Serum erythropoietin level in anemic cancer patients. Med Oncol 2000; 17: 29-34.
3. Miller CB, Jones RJ, Piantadosi S, *et al.* Decreased erythropoietin response in patients with the anemia of cancer. N Engl J Med 1990; 322: 1689-92.
4. Crawford J, Cella D, Cleeland CS, *et al.* Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancerpatients receiving epoetin-α therapy. Cancer 2002; 95: 888-95.
5. Rizzo JD, Lichtin AE, Woolf SH, *et al.* Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol 2002; 20: 4083-107.
6. Schrijvers D. Management of anemia in cancer patients: transfusions. Oncologist 2011; 16: 12-8.
7. Aapro MS, Link H. Sep 2007 update on EORTC guidelines and anemia management with erythropoiesis-stimulating agents. Oncologist 2008; 13: 33-6.

8. Penna F, Busquets S, Toledo M, *et al.* Erythropoietin administration partially preventsadipose tissue loss in experimental cancer cachexia models. J Lipid Res 2013
9. Lövey J, Bereczky B, Gilly R, *et al.* Recombinant human erythropoietin alpha improves the efficacy of radiotherapy of a human tumor xenograft,affecting tumor cells and microvessels. Strahlenther Onkol 2008; 184: 1-7.
10. Bokemeyer C, Aapro MS, Courdi A, *et al.* European Organisation for Research and Treatment of Cancer(EORTC) Taskforce for the Elderly.EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. Eur J Cancer 2007; 43: 258-70.
11. The European public assessment report (EPAR) for epoetin-α Hexal. European Medicines Agency. Accessed at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000726/human_med_000768.jsp&mid=WC0b01ac058001d124
12. Littlewood TJ, Bajetta E, Nortier JW, *et al.* Effects of epoetin-α on hematologic parameters and quality of life in cancer patients receiving non platinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2001; 19: 2865-74.
13. Gabrilove JL, Cleeland CS, Livingston RB, *et al.* Clinical evaluation of once-weekly dosing of epoetin-α in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. J Clin Oncol 2001; 19: 2875-82.
14. Henke M, Laszig R, Rübe C, *et al*. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet 2003; 362: 1255-60.
15. Cella D, Zagari MJ, Vandoros C, *et al*. epoetin-α treatment results in clinically significant improvements in quality of life in anemic cancerpatients when referenced to the general population. J Clin Oncol 2003; 21: 366-73.
16. Cabanillas ME, Kantarjian H, Thomas DA, *et al*. epoetin-α decreases the number of erythrocyte transfusions in patients with acute lymphoblastic leukemia, lymphoblastic lymphoma, and Burkitt leukemia/lymphoma: results of a randomized clinical trial. Cancer 2012; 118: 848-55.
17. Warm M, Kates R, Dick M, Thomas A, *et al*. Optimized pro-active management of anemia by epoetin-α in pre-operative chemotherapy for primary breast cancer. Oncol Rep 2009; 21: 777-85.
18. Wilson J, Yao GL, Raftery J, *et al*. A systematic review and economic evaluation of epoetin-α, epoetin beta and darbepoetin-α inanaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess 2007; 11: 1-202.
19. Bohlius J, Schmidlin K, Brillant C, *et al*. Erythropoietin or Darbepoetin for patients with cancer--meta-analysis based on individual patient data. Cochrane Database Syst Rev 2009; (3): CD007303.

Received: 22.10.2013
Accepted: 9.1.2014
Address: Mohammad Forat-Yazdi,
Department of Internal Medicine,
Shahid Sadoughi Hospital,
Ibn Sina BLVD, Yazd, Iran
Tel. 98-8224100, +98-09131518076
E-mail: foratyazdi@yahoo.com