High Dose Erythropoietin for the Unexplained Anemia in the Elderly

Somchai Insiripong, M.D.*,
Watcharin Yingsitsiri, M.D.*,
Juree Boondumrongsagoon, M.D.*,
Jirawadee Noiwatanakul, M.D.*

Abstract:

Objective: To study the outcome of high dose erythropoietin (EPO) therapy in the elderly with the unexplained anemia Patients and Methods: The 60-year old or older participants with the unexplained anemia are treated with weekly subcutaneous injection of erythropoietin (EPO), seven with 30,000 units of beta-EPO (Recormon®) and one with 40,000 units of alpha-EPO (Eprex®). **Results:** There are eight patients with mean age of 72.4±8.2 years. Every case has complete recovery within 4-16 weeks, mean of hemoglobin level is raised from 9.9±0.6 g% to 13.2±0.6 g%. Four from seven (57.1%) participants of Recormon group respond well within the first four weeks. No side effect or complication is detected. **Conclusion:** High dose EPO can correct the unexplained anemia in all elderly people within 4-16 weeks.

Key words: Erythropoietin, Unexplained Anemia of the Elderly

บทคัดย่อ: **การรักษาภาวะโลหิตจางที่ไม่ทราบสาเหตุในผู้สูงอายุด้วย Erythropoietin ขนาดสูง**

สมชาย อินทรศิริพงษ์, พ.บ.*, วัชรินทร์ ยิ่งสิทธิ์สิริ, พ.บ.*,
จุรี บุญดำรงสกุล,พ.บ.*, จิราวดี น้อยวัฒนกุล, พ.บ.*,
*หน่วยโลหิตวิทยา, กลุ่มงานอายุรกรรม, โรงพยาบาลมหาราชนครราชสีมา, จ.นครราชสีมา, 30000

เวชสารโรงพยาบาลมหาราชนครราชสีมา 2559; 38: 11-20.

* Hematology Unit, Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000

วัตถุประสงค์: ศึกษาผลการรักษาภาวะโลหิตจางไม่ทราบสาเหตุในผู้สูงอายุด้วย erythropoietin (EPO) ความเข้มข้นสูง **ผู้ป่วยและวิธีการ:** ผู้ป่วยอายุมากกว่า 60 ปี ที่มีภาวะโลหิตจางไม่ทราบสาเหตุได้รับการรักษาด้วยการฉีด EPO เข้าใต้ผิวหนัง โดย 7 ราย ฉีดด้วย beta-EPO (Recormon®) 30,000 หน่วย อีก 1 ราย ฉีดด้วย alpha-EPO (Eprex®) 40,000 หน่วย ทุกสัปดาห์ **ผลการศึกษา:** ผู้ป่วยทั้ง 8 ราย อายุเฉลี่ย 72.4±8.2 ปี ทุกรายหายจากภาวะโลหิตจางภายใน 4-16 สัปดาห์, ระดับ hemoglobin เฉลี่ยเพิ่มจาก 9.9±0.6 g% เป็น 13.2±0.6 g% โดยผู้ป่วย 4 ใน 7 รายจากกลุ่ม Recormon (ร้อยละ 57.1) หายภายใน 4 สัปดาห์แรกของการรักษา ไม่พบผลข้างเคียง หรือภาวะแทรกซ้อนใด ๆ **สรุป:** EPO ขนาดสูงทำให้ผู้สูงอายุที่มีโลหิตจางไม่ทราบสาเหตุทุกรายหายได้ ภายใน 4-16 สัปดาห์

คำสำคัญ: erythropoietin, ภาวะโลหิตจางไม่ทราบสาเหตุในผู้สูงอายุ

Introduction

The recombinant human erythropoietin (EPO) is the genetically engineered glycoprotein. In the animal models, it effectively stimulates the erythropoiesis in the normal, uremic or polycythemic animals. It can stimulate the formation of the red blood cells (RBCs) from their committed progenitors and act on the differentiation of the RBCs. With the subcutaneous injection three times a week, and in combination with oral iron therapy, EPO can increase the hemoglobin level of the normal human from 14.2 g% to 16.8 g%[1].

In clinical practice, it is worldwide accepted to be the standard and effective treatment of anemia of chronic kidney disease (CKD)[2], anemia among non-myeloid cancer patients receiving chemotherapy[3,4] and anemia in zidovudine-treated HIV-infected patients[5]. The EPO in combination with granulocyte-colony stimulating factor is the good treatment of anemia in the low-risk myelodysplastic syndrome and the refractory anemia with ring sideroblasts[6].

For the elderly, anemia is one common symptom. And its three major causes are the iron deficiency with/without folic acid or vitamin B12 deficiency, anemia of chronic diseases and of CKD and the so-called unexplained anemia, of which the phenotype comprise a hypoproliferative mild-to-moderate anemia, Hb 10.5-12.0 g%, the normal mean corpuscular volume (MCV), normal white blood cell and platelet and no increased serum EPO[7,8]. Because the anemia among the elderly is associated with higher mortality, the longer hospitalization and the impaired cognitive function, it should be properly treated. Besides the specific treatment according to the causes, the EPO agents have the therapeutic role in this population[9].

The EPO has many forms, alpha-, beta-EPO and darbepoietin. In our institute, both alpha-EPO and beta-EPO are available in various concentrations, including 40,000 units/syringe for alpha-EPO (Eprex®) and 30,000 units/syringe for beta-EPO (Recormon®). This paper is aimed to describe the experience of using the high dose of Eprex® or Recormon® in the unexplained anemia in the elderly.

Patients and Methods

This prospective descriptive study recruited all patients who were referred from the internists to the hematologist because of the chronic anemia which could not be corrected by the long term iron therapy in the year 2012. All patients had one or more chronic

medical problems such as ischemic heart disease, diabetes and hypertension which had been managed by the specialists in the OPD of medicine, Maharat Nakhon Ratchasima Hospital. Every patient was older than 60 years and the Hb level must be persistently less than 11 g%, normal MCV (80-100 fL) and creatinine was less than 1.5 mg%.

They were all treated with the subcutaneous injection of the high dose of EPO agents, 40,000 units/ week for Eprex® and 30,000 units/week for Recormon®. They would be clinically and hematologically followed every 4-week. The targeted Hb was between 12-13 g% and if it was achieved, the dose interval of EPO would be adjusted to be every two weeks for one month and then every four weeks if the targeted Hb could still be maintained[10]. On contrary, if the Hb was less than 11 g%, the dose interval would be back to every two weeks.

Results

There were eight patients, five women and three men. The ages varied from 63 to 87, mean 72.4±8.2 years. Their concurrent diseases included four with the ischemic heart disease (three of them had also diabetes), two with hyperlipidemia and hypertension), one with inactive rheumatoid arthritis and one with the excision of the small palpebral mass of the extranodal marginal zone B cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type.

The laboratory studies including CBC, the creatinine, ferritin, the Hb typing and the PCR for alpha-thalassemia-1 (SEA and Thai types) were performed and shown in the table 1

While the patients were injected with high dose of EPO, their concurrent drugs for the underlying diseases were still continued. Moreover, ferro-B-Cal and multivitamin, three tablets a day for each were also prescribed for all, except the one who had the excessive serum ferritin >1,000 ng/mL. Every patient would be followed for the clinical and hematological examinations every four weeks. The mean Hb level and hematocrit could be raised from 9.9±0.6 g% and 29.9±1.9%, respectively before EPO therapy to be 13.2±0.6 g% and 40.5±2.3%, respectively and the mean duration from the initiation of treatment till the achievement of the targeted Hb was 7.5 weeks, range 4-16 weeks. Four from seven cases (57.1%) treated with Recormon responded well within the first four weeks while the only one who was treated with Eprex responded in eight weeks. The numbers of injection that the patients needed for acquiring the targeted Hb were shown in the table 2

After achieving the targeted Hb, the dose interval was gradually increased to be 2-4 weeks. Every patient was continually treated with the high dose EPO injection every 4 weeks for at least 3 months. During this 3-month maintenance therapy, the targeted Hb level could be kept in all patients. Every patient could tolerate the EPO well, no adverse effects such as the thromboembolic event, the new onset or the exacerbation of hypertension. No one complained of pain at the injection sites of either Eprex or Recormon.

After achieving the targeted Hb, the dose interval was gradually increased to be 2-4 weeks. Every patient was continually treated with the high dose EPO injection every 4 weeks for at least 3 months. During this 3-month maintenance therapy, the targeted Hb level could be kept in all patients. Every patient could tolerate the EPO well, no adverseewrtf

Table 1 The cinical and laboratiry characterristics of eight patients

Case No.	I	II	III	IV	V	VI	VII	VIII
Gender	F	M	F	F	F	M	F	M
Age (years)	64	77	67	79	63	87	72	70
Hb (g%)	9.9	10.3	9.7	9.1	9.3	10.7	9.3	10.6
Hct (%)	30	31.7	29.2	27.8	29.4	33.6	27.8	29.8
MCV (fL)	87.3	75.5	83.3	89.5	64.4	78.0	90.3	94.6
MCH (pg)	28.7	24.5	27.5	29.4	20.5	24.9	30.3	33.6
Hb A_2 (%)		2.7	2.8	2.6		3.0	2.9	2.1
Hb E (%)	27.1			2.8				
α-thalassemia-1	neg	-	neg	neg	neg	neg	neg	-
WBC (/mm^3)	4400	5300	7200	2500	6300	102	5500	6500
Plt (x10^3/mm^3)	197	275	272	32	546	220	173	193
Ferritin (ng/mL)	397	273	160	127	134	-	369	1260
EPO		17.6	-	32.3	-	22.5	-	-
Cr (mg%)	1.2	1.2	1.1	1.0	0.7	1.4	1.0	1.5

Note : Hb = hermoglobin, Hct = hematocrit, MCV = mean corpuscular volume, MCH = mean corpuscular hermoglobin WBC = white blood cell, Plt = platelet, EPO = serum erythropoietin, Cr = creatinine, - = not preformed

effects such as the thromboembolic event, the new onset or the exacerbation of hypertension. No one complained of pain at the injection sites of either Eprex or Recormon.

Discussion

One proposed mechanism of unexplained anemia in the elderly is the resistance to the action of EPO through the interaction with pro-inflammatory

Table 2 The forms and the numbers of EPO injection

Case No.	I	II	III	IV	V	VI	VII	VIII
Before EPO injection								
Hb (g%)	9.9	10.3	9.7	9.1	9.3	10.7	9.3	10.6
Hct (%)	30	31.7	29.2	27.8	29.4	33.6	27.8	29.8
EPO form	β	β	β	β	β	β	β	α
After EPO injection								
No. of injection	4	8	4	10	16	4	4	8
Hb (g%)	12.6	12.9	14.0	12.8	12.3	13.7	13.7	13.4
Hct (%)	37.9	39.9	43.7	38.4	38.0	43.2	41.8	40.3

cytokines[11] and the elderly patients with anemia have higher levels of inflammatory markers than elderly patients without anemia[12] but at the high dose of exogenous EPO, it can successfully raise the Hb level in every case of the unexplained anemia in the elderly. Moreover, 4 from 7 cases (57.1%) of the Recormon group respond well within the first 4 weeks of therapy. And then the dose interval can be gradually increased and finally maintained at every 4 weeks. With this dose interval increment, it can let more elderly patients with unexplained anemia have a chance to access to this expensive drug.

The side effects of EPO therapy such as the pure red blood cell aplasia, acute myocardial infarction and poorly controlled hypertension have not been found although half of our cases have previous ischemic heart disease whereas two cases have well controlled hypertension. However it seems too early to conclude because of the very small sample size and the duration of EPO therapy is quite limited[13].

In the case of EPO therapy for the anemia of CKD, the targeted Hb level in terms of the improvement of the quality of life without an increase of the adverse reactions from EPO should be 11-12 g%[14] to 12 g%[9], if the Hb level is more than 13 g%, it is more frequently associated with the serious side effects such as thrombotic or vascular events or death. Furthermore, the higher dose of EPO (>20,000 units of subcutaneous injection of alpha-EPO per week) is found associated with the greater mortality rate[15]. The treatment of the unexplained anemia of the elderly is considered necessary because in the elderly without severe co-morbidities, mild anemia is significantly associated with the greater mortality in men[16]. Therefore, the proper indication, the targeted Hb level and the proper dose of EPO for these special dilemmas are in need to be extensively further studied before any conclusion can be established.

There are 2 from 8 cases (25%) having Hb E trait ($\alpha_2\beta_2^{26GlurLys}$), and one responds well within the first 4 weeks of EPO therapy while the other needs 16 weeks to do so. In the EPO treatment of anemia of CKD with the underlying beta hemoglobinopathy such as sickle cell disease, the patients appear more resistant and need more EPO dosage (150 units/kg twice weekly[17]). But the dosage of EPO in our study is > 300 units/kg weekly, and with this much higher dose, it seems the Hb E heterozygosity does not affect the response to the EPO therapy in cases of the unexplained anemia of the elderly.

Conclusion

Eight patients who are diagnosed as an unexplained anemia of the elderly, one is treated with subcutaneous injection of α-EPO 40,000 units / week (Eprex®) and the rest are treated with 30,000 units / week of β-EPO (Recormon®). Everyone responds well, the mean Hb level can be raised from 9.9+0.6 to 13.2+0.6 g% without side effect. Four of seven of Recormon group (57.1%) achieve targeted Hb level, 12-13 g%, within the first four weeks. The dose interval of EPO is increased and finally maintained at every four weeks whereas the targeted Hb can still be kept.

References

1. Lundby C, Olsen NV. Effects of recombinant human erythropoietin in normal human. J Physiol 2011; 589: 1265-71.
2. Tilkian EE, Tzekov VD, Pandeva SM, et al. Epoetinbeta (Recormon-Roche) in the treatment of renal anemia in patients with

chronic renal failure. Folia Med (Plodiv) 2000; 42: 11-5.

3. Bokemeyer C, Aapro MS, Courdi A, et al. ZEORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. Eur J Cancer 2007; 43: 258-70.
4. Ohashi Y, Uemura Y, Fujisaka Y, et al. Meta-analysis of epoetin beta and darbepoetin alfa treatment for chemotherapy-induced anemia and mortality: Individual patient data from Japanese randomized, placebo-control-led trials. Cancer Sci 2013; 104: 481-5.
5. Henry DH, Beall GN, Benson CA, et al. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. Overview of four clinical trials. Ann Intern Med 1992; 117: 739-48.
6. Balleari E, Rossi E, Clavio M, et al. Erythropoietin plus granulocyte colony-stimulating factor is better than erythropoietin alone to treat anemia in low-risk myelodysplastic syndromes: results from a randomized single-centre study. Ann Hematol 2006; 85: 174-80.
7. Teawtrakul N. Anemia in the older adults. J Hematol Transfus Med 2011; 21: 267-72.
8. Artz AS, Thirman MJ. Unexplained anemia predominates despite an intensive evaluation in a racially diverse cohort of older adults from a referral anemia clinic. J Gerontol A Biol Sci Med Sci 2011; 66: 925-32.
9. Agarwal N, Prchal JT. Erythropoietic agents and the elderly. Semin Hematol 2008; 45: 267-75.
10. Pljesa S. The use of erythropoietin beta, two to three times per week, once per week and once every other week: meta-analysis of two clinical trials. Med Pregl 2007; 60: 123-7. (Article in Serbian)
11. Ershler WB. Biological interactions of aging and anemia: a focus on cytokines. Am J Geriatr Soc 2003; 51 (3 suppl): S18-21.
12. Price EA, Schrier SL. Unexplained aspects of anemia of inflammation. Advance hematol 2010; Article ID 508739, 5 pages doi: 10.1155/2010/508739
13. Most common Recormon adverse events reported to the FDA. Available at: http://www.drugcite.com/?q= RECORMON
14. Berns JS. Anemia of chronic kidney disease: Target hemoglobin/hematocrit for patients treated with erythro-poietic agents. In: UpToDate, Basow DS (Ed), UpToDate, Waltham MA, 2008.
15. Zhang Y, Thamar M, Stefanik K, Kaufman J, Cotter DJ. Epoetin requirements predict mortality n hemodialysis patients. Am J Kidney Dis 2004; 44: 866-76.
16. Endres HG, Wedding U, Pittrow D, et al. Prevalence of anemia in elderly patients in primary care: impact on 5-year mortality risk and differences between men and women. Curr Med Res Opin 2009; 25: 1143-58.
17. Tomson CR, Edmunds ME, Chambers K, et al. Effect of recombinant human erythropoietin on erythropoiesis in homozygous sickle-cell anaemia and renal failure. Nephrol Dial Transplant 1992; 7: 817-21.