

Research Article,

## Application of Rhuepo to Post-Chemotherapy Blood Cancer Patients and Clinical Observation

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### Abstract:

**Aim:** Clinical use of Recombinant Human Erythropoietin (rHuEPO) effectively increases the level of Hemoglobin in blood and improve quality of life of patients.

**Methods:** Blood cancer patients is divided into two groups namely Treatment group and Control group. There is altogether 24 patients in treatment gp to whom both chemotherapy and rHuEPO is given for 4 weeks. rHuEPO is given as 150u/kg, subcutaneously, three times a week. Blood routine checkup is done in every week and iron is prescribed after 2 weeks.

**Result:** After 4 weeks of treatment, patients were evaluated for drugs effectiveness in both groups; total effectiveness were 58.34% and 20% respectively,  $P > 0.05$ ; after 4 weeks of treatment, there was distinct statistical significance. Comparing with pretreatment level, Treatment group has remarkable rise in Hb after 4 weeks ( $81.29 \pm 9.85$ ) 对 ( $65.75 \pm 12.37$ ) , ( $P < 0.01$ , whereas control group has not distinct change in Hb level ( $86.95 \pm 11.61$ ) 对 ( $84.30 \pm 16.25$ ) , ( $P > 0.05$ ).

**Conclusion:** Hb is significantly increased after the use of rHuEPO and side effects were less with well tolerances.

**Key Words:** Cancer, Anemia, Erythropoietin, Recombinant.

Anemia is a lack of red blood cells or hemoglobin that cannot meet the needs of tissues for oxygen supply. In cancer patients, this is a very common complication, especially hematological malignancies. Patients with hematological malignancies (lymphoma, chronic lymphocytic leukemia, multiple myeloma, etc.) Usually develop anemia during the course of the disease. Anemia is reported to be the most common hematologic finding at diagnosis in patients with non-hodgkin lymphoma<sup>1</sup>. In addition, 50% of patients with multiple myeloma have hb  $< 10g/l$ <sup>2,3</sup>. In the past, it was mainly treated by blood transfusion, but there were many complications. The replacement therapy of recombinant human erythropoietin (rhuepo) has achieved good results. Recent clinical studies have confirmed that recombinant human erythropoietin is safe and effective for the treatment of solid tumors<sup>4,14</sup> and anemia due to post-chemotherapeutic malignancies<sup>5,13,15</sup>, and improves the quality of life of patients.

### 1. Materials and Methods:

#### 1.1 Materials:

Patients with malignant tumor-related anemia were admitted to our hospital from August 2006 to January 2008. A total of 44 patients were enrolled in this study; 24 patients in the EPO group (Group A) and 20 patients in the non-EPO group (Group B). Group A has 14 males and 10 females; Group B has 10 males and 10 females. Age 30-68 years old; primary disease: lymphoma 23, multiple myeloma 9, AML 7, CLL 3, and MDS 2. All patients had a clear pathological diagnosis. Hemoglobin (HB)  $\leq 105g/L$  or hematocrit (HCT)  $\leq 0.3$ , or HB decreased after chemotherapy  $\geq 15g/L$ . No blood transfusion or rHuEPO treatment was performed 4 weeks before chemotherapy, and anemia caused by other reasons (blood loss, lack of hematopoietic factors, chronic infection, etc.) or bone marrow metastasis and uncontrolled hypertension

were excluded).

### 1.2 Methods:

Group A Patients were given recombinant human erythropoietin (rHuEPO, produced by a pharmaceutical company) 10,000 u, subcutaneously, 3 times a week for 4 consecutive weeks, and oral iron was given at the same time. Chemotherapy and radiotherapy was required during the treatment with rHuEPO, and the patients received chemotherapy and radiotherapy according to the cycle. After 4 weeks of EPO treatment, the HB increased by 20 g/L was considered to be effective for rHuEPO treatment.

**1.3 Observation Indicators:** (1) Before and after treatment, hemoglobin, hematocrit, platelets, and leukocytes were measured every week; liver and kidney function and coagulation time were measured every 3 weeks; serum ferritin, serum potassium and electrocardiogram were checked before and after treatment. (2) Status of Quality of Life: The main complaints of the patients were recorded, the changes in anemic symptoms and signs were understood, and the standard index was divided into KPS. The increase of KPS by more than 10 was regarded as improvement, and the no change before and after treatment was regarded as stable; the decrease of KPS more than 10 after treatment was regarded as worsen. (3) Observe clinical symptoms and adverse reactions. (4) Allogeneic blood transfusion (HB=<70g/L).

**1.4 Efficacy analysis:** Effective (hemoglobin increased by  $\geq 20$  g/L compared with the baseline value) and/or hematocrit increased by  $>10\%$  or blood transfusion volume reduced by more than half; Ineffective: no effective standard or deterioration after treatment. See Table 1.

**1.5 Statistical methods:** Excel was used for data entry, and SPSS14.0 statistical software was used. The data were expressed as  $X \pm S$ . The data before and after treatment and between groups were compared by t test for statistical analysis, and the efficacy evaluation was performed by X2 test.

### 2.Result:

**2.1 Clinical efficacy:** The effective rate of the treatment group (the percentage of patients whose hemoglobin increased by  $\geq 20$  g/L compared with the baseline value and who had not received blood transfusion within the previous 4 weeks) was 37.5%, which was significantly higher than the effective rate of the control group of 10 %; In the treatment group, 13 patients were effective, while 16 patients in the control group were ineffective. There was a significant difference in the effectiveness between the two groups ( $P < 0.05$ ). See Table 1.

**Table 1. Comparison of effectiveness of two groups**

Group	Effectiveness (%)	Ineffective (%)
Treatment Group (n=24)	13(54.16%)	11(45.83%)
Control Group (n=20)	4(20%)	16(80%)
Using Pearson's Chi-Square Test $X^2 = 5.37, P < 0.05$ .		

**2.2 Changes of Hb in Pre and Post-treatment in each group:** After 2 weeks of treatment in the treatment group, it was found that Hb increased significantly. Compared with pre- treatment, there was a statistically significant difference in Hb in the 4th week ( $P < 0.01$ ). At the 2nd and 4th week, there was a statistically significant difference between the two groups in hemoglobin rise ( $P < 0.01$ ). See Table 2.

**Table 2. Changes and comparison of hemoglobin between the two groups before and after treatment (g/L,  $\bar{X} \pm S$ )**

Group	Pre-treatment	Post-treatment		Difference	
	Base Value	2 weeks	4 weeks	2 weeks	4 weeks
A GP	65.75±12.37	72.79±9.04 <sup>1</sup>	81.29±9.95 <sup>1</sup>	7.04±9.98	15.54±13.80
B GP	86.95±11.61	82.55±9.35 <sup>2</sup>	84.30±16.25	-4.40±8.52	2.65±16.39
By t test, the comparison between the two groups before and after treatment <sup>1</sup> $P < 0.01$ , <sup>2</sup> $P < 0.05$ after the treatment, the comparison between the two groups at 2, 4 weeks is $P < 0.01$ .					

**2.2 Changes of HCT in each group pre- and post- treatment:** HCT in the treatment group was significantly increased after 4 weeks, and the difference was significant compared with that pre- treatment (P<0.01). The comparison of hematocrit increment between the two groups at the 2nd and 4th week, it was a statistically significant difference (P<0.01). See Table 3.

**Table 3. Changes and Comparison of hematocrit between the two groups before and after treatment (%,( X̄±S)**

Group	Pre-treatment	post-treatment		Difference	
	Base value	2weeks	4weeks	2weeks	4weeks
A GP	21.35±4.14	23.87±3.13 <sup>1</sup>	25.83±2.48 <sup>1</sup>	2.5±3.89	4.48±4.08
B GP	27.52±3.57	25.97±2.84 <sup>1</sup>	25.99±2.79 <sup>2</sup>	-1.55±1.96	-1.53±3.11

By t test, the comparison between the two groups before and after treatment <sup>1</sup>P<0.01, <sup>2</sup>P<0.05. Comparison between the two groups at 2, 4 weeks is P<0.01.

**2.3 Changes of RBC pre- and post- treatment in each group:** RBC was found to be increased in the treatment group after 4 weeks, and the difference was significant compared with pre-treatment group, (P<0.01). The comparison of the increase in red blood cell count between the two groups persisted at 2 and 4 weeks of treatment There was a statistically significant difference (P<0.01). See Table 4.

**Table 4. Changes and comparison of red blood cell counts in the two groups pre- and post-treatment (10<sup>12</sup>/L, X̄±S)**

Group	Pre-treatment	Post-treatment	4wks	Difference	4wks
	Base value	2wks		2wks	
A GP	2.43±0.52	2.64±0.41	3.0±0.33 <sup>2</sup>	0.21±0.42	0.55±0.50
B GP	3.08±0.57	2.89±0.51	2.98±0.58	-0.23±0.41	-0.13±0.59

By t test, the comparison between the two groups before and after treatment <sup>1</sup>P<0.01, <sup>2</sup>P<0.05 after the treatment. The comparison between the two groups at 2, 4 weeks is P<0.01.

**2.4 Changes of KPS in each group Pre- and Post- treatment:** After treatment, the KPS score of the treatment group was improved in 11 patients, stable in 13 patients, and juxtaposed with no worsened. The control group improved in 3 patients and stabilized to 17 patients. There is no significant difference between the two.

**2.5 Adverse reactions:** The main manifestations are neutropenia, nausea and vomiting, fever, diarrhea, fatigue, muscle pain, dizziness, numbness, migraine, and proteinuria, the degree of which is closely related to the chemotherapy regimen and dose. During rHuEPO treatment, 12 patients experienced mild to severe adverse events: 3 patients experienced increased blood pressure, ranging from 150/95 to 180/100 mmHg, 3 patients had fatigue and numbness, 2 patients had recurrent fever, and 4 patients experienced Dizziness, vomiting and chills are all mild. Seven patients in the control group experienced mild to severe adverse events. The overall adverse event rate was 50% in the treatment group and 35% in the control group.

**2.6 Changes in allogenic blood transfusion requirements during treatment:** 12 patients in the treatment group had blood transfusion requirements during 2 weeks of treatment. Blood transfusion was required in 5 cases after 4 weeks of treatment. The blood transfusion requirement rate was 41.66%. In the control group, 3 patients required blood transfusion at 2 weeks of treatment, and 4 patients at 4 weeks of treatment. The blood transfusion requirement rate is 75%.

### 3. Discussion:

Anemia caused by the tumor itself or tumor treatment is common in cancer patients. Approximately 60 to 70 percent of patients with non-Hodgkin lymphoma are reported to be anemic at diagnosis<sup>6</sup>. In addition, almost all patients with multiple myeloma develop or will develop anemia<sup>7</sup>. With the progression of the disease and

the application of chemotherapy drugs, the incidence of anemia is higher. Anemia will adversely affect various systems of the body, and in severe cases, respiratory distress and cardiac insufficiency may occur, which seriously affects the quality of life of patients.

Blood transfusion is the main method of treating anemia in the past, but it will bring many complications<sup>8</sup>. rHuEPO, as an improved method for the treatment of anemia, has achieved good efficacy in patients with renal anemia since its inception, and is currently widely used in clinical practice. Recently, many clinical studies abroad have shown that recombinant human erythropoietin (rHuEPO) has been applied in patients with multiple myeloma, non-Hodgkin's lymphoma and chronic lymphocytic leukemia and other hematological malignancies induced by chemotherapy, can quickly and effectively promote the steady growth of hemoglobin, reduce the amount of blood transfusion and improve the quality of life of patients<sup>8,9,10</sup>.

The main purpose of this study was to confirm the effect of rHuEPO on hematological malignancies (multiple myeloma, non-Hodgkin's lymphoma and chronic lymphocytic leukemia, etc.) with relative erythropoietin deficiency and in patients receiving antimalignant chemotherapy, the efficacy and safety of anemia in adult patients<sup>11,12,16</sup>. Among the 24 patients in the retrospective comparison, 24 entered the rHuEPO treatment group and 20 entered the control group. The results of the study showed that rHuEPO, the effective rate of the treatment group was 54.16%, and that of the control group was 20%. Since the 2nd week, the hemoglobin of the treatment group has begun to increase compared with the base; at the end of the 4th week of treatment, the hemoglobin of the treatment group increased by 14.91 g/L, the control group decreased to 2.15g/L. The increase of hemoglobin in the treatment group was rapid and continuous. The increase was significantly higher than that in the control group; it was proved that rHuEPO could stably and continuously increase the hemoglobin level in patients with anemia in hematological malignancy.

During the whole treatment process, there was no significant difference in reticulocyte count, serum iron and ferritin changes. However, there were significant differences in the frequency and dose of blood transfusion between the two groups. Foreign research and treatment showed that rHuEPO can effectively reduce anemia in cancer patients. The blood transfusion needs of the treatment group and the control group were 41.66 vs 75%<sup>9</sup>. In this study, the two groups of patients were given blood transfusion when the average HB was 61.45-66.20 g/L. The need for blood transfusion may be a sensitive indicator for patients to evaluate the efficacy of EPO.

In terms of safety, the overall adverse event rate was 50% in the treatment group and 35% in the control group. There was no statistical difference between the two groups. During treatment with rHuEPO, 12 patients in the treatment group had mild-to-severe adverse events and 7 patients in the control group had mild-to-severe adverse events. Blood pressure in both groups remained stable during treatment. It was demonstrated that rHuEPO is well tolerated and can be safely used in patients with hematological malignancies.

#### 4. Conclusion:

From the results of the above efficacy and safety parameters, rHuEPO can stably and continuously increase the hemoglobin level in patients with anemia of hematological malignancies, and it is well tolerated. Therefore, rHuEPO is used in the treatment of hematological malignancies (multiple myeloma, Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, etc.) have relative erythropoietin deficiency and an effective and safe approach in anemia in middle-aged patients receiving anti-malignancy chemotherapy.

#### 5. Reference:

- [1] Moulet I, Bouafia F. et al. Frequency and significance of anemia in non-Hodgkin's lymphoma patients. *Ann Oncol*, 1998;Oct(10):1109-15.
- [2] Conté L G, Figueroa M G, et al. Clinical features and survival of Chilean patients with multiple myeloma. *Rev Med Chil*, 2007;Sep135(9):1111-7.
- [3] Bladé J, Rosiñol L. Complications of multiple myeloma. *Hematol Oncol Clin North Am*, 2007 Dec;21(6):1231-46,xi. Review. PMID: 17996596 [PubMed]
- [4] Thatcher N. Management of chemotherapy-induced anemia in solid tumours. *Semin Oncology*, 1998;25:23-26.

- [5] García-Sanz R, Mateos MV, San Miguel JF. Multiple myeloma. Med Clin (Barc). 2007 Jun 16;129(3):104-15. Review Spanish. PMID: 17594862 [PubMed]
- [6] Knight K,Wade S, Balducci L. Prevalence and outcomes of anemia in cancer:a synamic review of the literature. Am J Med.2004 April5(116)Suppl7A:11s-26s.
- [7] Mittelman M,Zeidman A,Fradin Z,et al. Recombinant human erythropoietin in the treatment of multiple myeloma associated anemia. Acta hematol 1997;Sept(8):204-210.
- [8] Osterborg A, Boogaerts MA, Cimino R, et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lym- phoma- a randomized multcenter study[J]. Blood, 1996(7):2675-2682.
- [9] Boogaerts M,Coiffier B,Kainz C.et al.Impact of epoetinbeta on quality of life in patients with malignant disease.Br J Cancer 2003 Apr 7;88(7):988-95.
- [10] Littlewood TJ,Bajetta E,Nrtier JW,et al. Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial.J Clin Oncol. 2001 Jun 1;19(11):2865-74.
- [11] Dammacco E, Castoldi G, Rower S. Efficacy of epoetin alfa in the treatment of anaemia of multiple myeloma[J]. Br J Haematol.2001,113(1):172-179.
- [12] Shasha D, George MJ, Harrison L. Once-weekly dosing of epoetin-alpha increases hemoglobin and improves quailty of life in anemic cancer patients receiving radiation therapy either concomitantly or sequentially with chemotherapy [J]. Cancer.2003, 98(5):1072-1079.
- [13] Thews O, Kelleher DK, Vaupel P. Erythropoietin restores the anemia-induced reduction in cyclophosphamide cytotoxicity in rat tumors. Cancer Res.2001,Feb15;61 (4): 1358-61.
- [14] Hudis CA, Van Belle S, Chang J, Muenstedt K. rHuEPO and treatment outcomes: the clinical experience.Oncologist.2004;9 Suppl 5:55-69. Review.
- [15] Blackwell K, Gascón P, Sigounas G, Jolliffe L. rHuEPO and improved treatment outcomes: potential modes of action.Oncologist. 2004;9 Suppl 5:41-47. Review. PMID: 15591421.
- [16] Giraldo P, Nomdedeu B, Loscertales J, Requena C, de Paz R, Tormo M, Navarro P, Benedit P, Gasquet JA; Aranesp in Myelodysplastic Syndromes (ARM) Study Group. Darbepoetin alpha for the treatment of anemia in patients with myelodysplastic syndromes. Cancer. 2006; Dec 15;107(