Erythrotropin for Treating Anemia in Multiple Myeloma: Response to Treatment and Survival

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Abstract

Background

Anemia is a common complication of multiple myeloma (MM). Recombinant human erythropoietin (rhEPO) and blood transfusions are two general treatments for anemia.

Methods

In a retrospective study, we compared the efficacy and treatment response of rhEPO to those of blood transfusions on anemia and sought to determine its prognostic value in these patients. The 94 patients who received rhEPO were divided into high-dose (≥160,000 U/month) and low-dose (<160,000 U/month) groups; 97 other patients received blood transfusions.

Results

Patients receiving rhEPO had significantly higher hemoglobin concentrations after 3 (112.65 v. 86.10 g/dL) and 6 (128.96 v. 91.41 g/dL) months of treatment (P<0.001 for both comparisons). Furthermore, the high-dose rhEPO group had higher mean hemoglobin concentrations than those of the low-dose group after 3 (41 v. 34 g/L) and 6 (57 v. 49 g/L) months of treatment, respectively. The risks of death and relapse were significantly lower in patients receiving either dose of rhEPO than in the transfusion group. Receiving rhEPO was associated with better overall and progression-free survival (68 v. 52 months, 39 v. 27 months).

Conclusions

We believe rhEPO should be preferred to blood transfusions for treating the anemia associated with MM.

Background

Multiple myeloma (MM) is characterized by clonal proliferation of plasma cells and accounts for 10% to 15% of hematopoietic malignancies.[1] Anemia is a common complication of MM and is often caused when malignant cells infiltrate the bone marrow and with the reduced survival of red blood cells (RBCs), chronic renal insufficiency, cytokine production, and the myelosuppressive effects of chemotherapy. Recombinant human erythropoietin (rhEPO) and blood transfusions are two treatments for the anemia associated with MM. Compared to blood transfusions, which are characterized by transient elevations of hemoglobin concentration, rhEPO corrects anemia constantly and effectively for a long time.[2].

Erythropoietin (EPO) is a hormone produced by the kidney [3] and is important in regulating the production of RBCs by binding to its receptor EPO-R, which is expressed on erythroid progenitors in the bone marrow (BM) and stimulates expansion, differentiation, and decreasing apoptosis of erythroid burst-forming unit cells.[4-6] However, although most research has verified the efficiency of EPO in prolonging survival and improving immunological functions in patients with MM,[7-20] other studies have found contradictory results in anemic patients with MM treated with rhEPO.[21,22] Therefore, we sought to determine whether rhEPO is better than blood transfusions for improving and predicting survival and in anemic patients with MM.

Methods

Patients

We abstracted data from the medical records of patients with a diagnosis of MM and anemia who were seen at West China Hospital, Sichuan University, between January 2009 and December 2014. The diagnosis of MM was based on the World Health Organization criteria,[23] and disease stage was determined by the Durie-Salmon staging system. [24] Anemia was defined as a hemoglobin concentration of less than 90 g/L.

Ethical approval was obtained from the Ethical Committee of West China Hospital before the study began.

Experimental Groups and Treatment

The patients were divided into rhEPO (94 patients) and transfusion (97 patients) groups. The rhEPO group received recombinant human erythropoietin (rhEPO, epoetin alfa) in initial doses of 40,000 to 640,000 U/month but a general dose of 150 to 200 U/kg, three times a week (about 160,000 U/month) in previous clinical treatment. We further divided these patients into high-dose rhEPO (≥160,000 U/month) and low-dose rhEPO (<160,000 U/month) groups. The transfusion group received transfusions to maintain an essential hemoglobin concentration (above 70 g/L). All patients underwent chemotherapy at the beginning of treatment and received 150 to 200 mg/day of thalidomide or 25 mg/day of lenalidomide as maintenance treatment.

Outcomes were defined with International Myeloma Working Group criteria[25]: a stringent complete response, a complete response, a very good complete response, a very good partial response, a good partial response, stable disease, and progressive disease. A very good complete response or better was considered an effective treatment.

Follow-up and Endpoints
Patients were followed until December 2016. The duration of follow-up was determined from the date of diagnosis to either death or the end of the study. End points were relapse, death, or at the end of the study period.

**Statistical Methods**

All data were analyzed with the SPSS statistical software package (version 21.0; IBM Corporation, Armonk, NY). Normally distributed data are presented as means and standard deviations, and skewed data as medians and interquartile ranges. Categorical data are reported as absolute frequencies and percentages. Chi-square tests and t-tests were used to compare two groups for categorical data and normally distributed data, respectively. The Mann-Whitney U-test was used to compare skewed data or ordinal data. Kaplan–Meier method was used to calculate and present survival rates at 3 and 5 years after the diagnosis of the MM. Survival rates were compared between groups with the log-rank test. Univariate Cox regression analysis was used to identify independent risk factors of death. Variables significant at the 0.10 level were included in a multivariable Cox regression analysis to investigate the independent effect of MM on the outcomes. Hazard ratios (HRs) are presented with 95% confidence intervals. Alpha was set at 0.05, and all tests were two-tailed.

**Results**

**Patient Characteristics**

Median (range) follow-up of all 191 enrolled patients was 42 (4 to 92) months (Table 1). Baseline characteristics did not differ significantly between the rhEPO and transfusion groups. 48% patients were loss to follow up in our study.

**Hemoglobin Concentrations**

Baseline hemoglobin concentrations did not differ significantly between the rhEPO and the transfusion groups (Table 2). However, mean hemoglobin concentrations were significantly higher in of the rhEPO group than blood transfusion group after 3 months (112.65 vs. 86.10 g/L) and 6 months (128.96 vs 91.41 g/L) treatment (Table 2).

Furthermore, subgroup analysis revealed that mean (SD) hemoglobin concentrations were significantly higher in the high-dose group than in low-dose group at 3 months (40.81 vs. 32.62 g/L) and at 6 months (56.98 vs. 49.16 g/L, respectively; Table 3).

**Effective Treatment**

The percentage of effective treatment (a very good complete response or better) was significantly higher in the rhEPO group (49%) than in the transfusion group (36%; Table 2). Subgroup analysis in rhEPO group indicated the dose of rhEPO had no influence on response evaluation (P>0.05).

**Overall and Progression-Free Survival**

The Kaplan-Meier estimate of overall survival for all patients was 74% at 36 months and 52% at 60 months. Estimated progression-free survival rates for all patients were 52% at 36 months and 43% at 60 months (Figure 1).

Estimated overall survival rates were 82% at 36 months and 68% at 60 months in the rhEPO group and 69% at 36 months and 36% at 60 months for the transfusion group. The estimated progression free survival rates were 52% at 36 months and 31% at 60 months for the rhEPO group, and 33% at 36 months and 21% at 60 months in the transplant group. In conclusion, The rhEPO group had significantly longer progression-free and overall survival than did the transfusion group (Figure 1).

Subgroup analysis revealed that the dose of rhEPO was not associated with longer OS and PFS (Figure 2).

**Predictors of Progression-free and Overall Survival**

Univariate analysis identified 5 risk predictors for overall survival (cancer stage III, more than 30% of bone marrow clonal plasma cell, β2-MG >3.5 mg/L, a very good partial response or better, and rhEPO; Table 3). Multivariate analysis indicated that rhEPO treatment was significantly associated with improved overall survival (hazards ratio [HR], 0.44) and progression-free survival (HR, 0.61) after adjusting for cancer stage, bone marrow clonal plasma cells, serum creatinine, β2-MG, and response to treatment.

Otherwise, progression-free survival and overall survival were significantly and inversely correlated with more than 30% BM clonal plasma cells (HR, 1.74 and 1.62, respectively) and more than 3.5 mg/L of β2-MG (HR, 1.97 and 1.82) and was positively correlated with a very good partial response or better (HR, 0.50 and HR 0.60; Table 3).

**Discussion**

Anemia is a common symptom of MM, being reported in up to 70% of patients.[26-27] Hemoglobin concentrations are important in determining the stage of MM and are closely linked to patient quality of life and tolerance to subsequent chemotherapy or stem cell transplantation.[28-29] For most patients, anemia is reduced when the disease responds to chemotherapy. When this reduction does not occur, treatment options are blood transfusions or rhEPO administration.[30] Blood transfusions are characterized by a transient elevation of hemoglobin concentrations, whereas rhEPO corrects anemia constantly and effectively for long periods.[2]
In our study, patients treated with rhEPO had better responses to treatment and longer survival time than those treated with blood transfusions. Also, rhEPO was an independent protector of better prognosis, as reported in other studies.[15,17,18. Importantly, we studied more patients than did these related studies. (there 46 patients in Prutchi-Sagiv’s study and 127 patients in Baz’ study).

Recombinant human erythropoietin suppresses tumor growth and induces tumor regression through a variety of mechanisms, accelerates treatment response, and lengthens survival.[7-20,31,32] It mainly affects the immune system and even influences the proliferation of myeloma.[7-13] The erythropoietin receptor is expressed on the surface of myeloma cell lines, and activating receptor signaling reduced the viability of myeloma cell in vitro. [20] Mean serum concentrations of IgG2b and kappa light chain increased in MM mice injected with MM cells and significantly decreased in MM mice treated with EPO.[19,32] Several studies in MM mouse models have reported that EPO induced tumor regression and prolonged survival. [14,19]

In the current study, rhEPO clearly improved anemia in patients with MM, but we focused on its prognostic value and effect on clinical outcomes. On the one hand, anemia improved and allowed patients to better cope with further treatment;[33] on the other, rhEPO improved prognosis through various mechanisms. Our results confirm that rhEPO slows the progression of MM and prolongs survival.

Although rhEPO effectively treats anemia associated with MM, the optimal dose has not been determined.[34,35] We found that high-dose rhEPO was more effective than blood transfusions in treating anemia; mean hemoglobin concentrations were higher in the rhEPO group at 3 and at 6 months. Nevertheless, high-dose rhEPO did not improve treatment response or prognosis in our study and in others.[19]

We identified 4 predictors of response-to-treatment: later cancer stage, renal insufficiency, more than 30% BM clonal plasma cells, and a β2-MG concentrations greater than 3.5 mg/L We also found that a very good partial response or better was independently protective of both progression-free and overall survival.[36-40]

**Conclusions**

In the patients we studied, both prognosis and clinical outcomes were better with rhEPO than with blood transfusion. We believe our results support the recommendation that rhEPO should be preferred to blood transfusions for treating anemia in patients with multiple myeloma.

**Abbreviations**

MM: multiple myeloma
rhEPO: recombinant human erythropoietin
EPO: erythropoietin
RBCs: red blood cells
BM: bone marrow
CR: complete response
VGCR: very good partial response PR: good partial response
SD: stable disease
PD: progressive disease
HR: hazard ratio
LDH: lactate dehydrogenase β2-MG: beta-2 microglobulin

**Declarations**

**Ethics approval and consent to participate**: Ethical approval was obtained from the Ethical Committee of West China Hospital before the study began. Number: 2019year(218).

**Consent to publish**: Not applicable.

**Availability of data and materials**: The datasets generated and analysed during the current study are not publicly available due to privacy protection of patients but are available from the corresponding author on reasonable request.

**Competing interests**: There is no competing interests.

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Tables

| Characteristic                        | rhEPO group, n=94 | Transfusion group, n=97 | P Value |
|--------------------------------------|-------------------|-------------------------|---------|
| Sex, Male/Female, n/n                | 55/39             | 53/44                   | 0.59    |
| Age at onset, mean (SD), years       | 63 (11)           | 61 (10)                 | 0.20    |
| Disease stage(I~II/III), n/n         | 17/77             | 11/86                   | 0.19    |
| Hemoglobin, mean (SD), g/L           | 75.50 (14.76)     | 71.96 (12.52)           | 0.08    |
| Renal insufficiency, yes/no, n/n     | 19/75             | 25/72                   | 0.36    |
| Chemotherapy, n                      |                   |                         | 0.89    |
| melphalan+prednisone                 | 32                | 29                      |
| bortezomib+dexamethasone             | 38                | 43                      |
| vincristine+doxorubicin+dexamethasone| 13                | 12                      |
| cyclophosphamide+melphalan+vincristine+prednisone | 11                | 13                      |
Table 2: Comparison of the hemoglobin levels and response evaluation of rhEPO group and blood transfusion group

| Group   | Response evaluation | 3-month Hg Mean(SD).g/L | 6-month Hg Mean(SD).g/L | 3-month Hg increase Mean(SD).g/L | 6-month Hg increase Mean(SD).g/L |
|---------|---------------------|--------------------------|--------------------------|----------------------------------|----------------------------------|
|         | ≥CR | VGPR | PR | SD | PD |         |         |         |         |         |
| rHuEPO  | 21  | 25   | 31 | 12 | 5  | 113.28(16.36) | 128.96(11.86) |                |                |
| High-dose |     |      |    |    |    | 41.04(18.80)   | 56.83(15.82)   |                |                |
| Low-dose | 16  | 19   | 35 | 14 | 13 | 86.10(16.74)   | 91.41(10.82)   |                |                |
| P       | 0.04| <0.0001 | <0.0001 | 0.03 | 0.02 |                |                |                |                |

Abbreviations: CR, complete response; VGCR, very good partial response; PR, good partial response; SD, stable disease; PD, and progressive disease.

Table 3: Univariate analysis and Multivariate analysis for the risk factors in multiple myeloma

| Risk factors | Univariate analysis(OS) | Multivariate analysis(OS) | Univariate analysis(PFS) | Multivariate analysis(PFS) |
|--------------|-------------------------|---------------------------|--------------------------|-----------------------------|
|              | HR (95 % CI)            | P                         | HR (95 % CI)            | P                           |
| Male, n      | 1.084(0.722~1.627)      | 0.6965                    | 1.061(0.746~1.510)      | 0.7412                      |
| Age>60 years | 1.188(0.789~1.789)      | 0.4083                    | 1.025(0.727~1.471)      | 0.8509                      |
| Stage(stage III) | 1.845(1.045~3.403)     | 0.0346                    | 1.742(0.931~3.268)      | 0.0824                      |
| Serum creatinine >176 umol/L | 1.439(0.910~2.028) | 0.1197                    | 1.631(1.099~2.421)      | 0.0151                      |
| Serum calcium>2.75mmol/L | 1.460(0.870~2.451)    | 0.1527                    | 1.233(0.784~1.942)      | 0.3655                      |
| Bone marrow clonal plasma cells>30% | 1.938(1.264~2.967) | 0.0024                    | 1.739(1.120~2.703)      | 0.0138                      |
| Elevated LDH | 1.412(0.929~2.151)     | 0.1067                    | 1.081(0.758~1.543)      | 0.6660                      |
| β2-MG>3.5mg/L | 2.096(1.359~3.236)   | 0.0008                    | 1.968(1.266~3.067)      | 0.0026                      |
| Osteolytic lesion | 1.488(0.968~2.283)  | 0.3097                    | 1.314(0.912~1.894)      | 0.1420                      |
| Use bortezomib in Chemotherapy | 0.719(0.471~1.099)  | 0.1275                    | 0.759(0.530~1.088)      | 0.1335                      |
| Response evaluation ≥VGPR | 0.465(0.303~0.713)   | 0.0005                    | 0.498(0.321~0.772)      | 0.0018                      |
| Using rhEPO | 0.539(0.357~0.815)    | 0.0034                    | 0.435(0.282~0.672)      | 0.0002                      |

Abbreviations: HR, hazard ratio; LDH, lactate dehydrogenase; β2-MG, beta-2 microglobulin.

Figures
Figure 1
Comparison of the progression free survival and overall survival of rhEPO group and blood transfusion group.

Figure 2
Subgroup analysis of patients with rhEPO treatment showed that high dose rhEPO is not associated with longer overall survival (p=0.141) or progression free survival (P=0.224).