Original Article

Serum Erythropoietin Level in Anemic and Non-Anemic Patients with Chronic Leukemia

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Abstract

Background: Anemia is a common issue in chronic leukemia, which results in a worse outcome and shorter survival. Inadequate production of erythropoietin (EPO) as compared to the severity of anemia may play a major role in ACD for patients with hematological malignancies. Clarifying the role of EPO may provide a better understanding of its pathogenesis, and proper management of patients. **Objectives:** To determine serum EPO levels and look for any potential link between EPO and the cause of anemia in anemic patients with chronic leukemia in a sample of Iraqi patients in the middle euphrates region. **Materials and Methods:** This is a case control study included 38 patients (19 chronic myeloid leukemia [CML], 19 chronic lymphocytic leukemia [CLL]) who were attending the outpatient clinic of hematology in Baghdad Teaching Hospital, Marjan Teaching Hospital from September 2022 to March 2023, together with 30 adult participants without disease as a control group. All patients involved were diagnosed as having a disease based on a specialist's physical examination, morphological evaluation of peripheral blood films and bone marrow, and flow cytometric immune-phenotypic profile. Blood samples were collected from each subject, and the following investigations were done: CBC, RFT, blood film examination, and ELISA assay for serum EPO. **Results:** The mean age of CML patients was (50.1 ± 12.85) range from 24 to 72, CLL patients (58.2 ± 10.4) range from 38 to 75. The majority of patients were men (N = 23, 60.5%). The participants in the patient group were subdivided into 18 (47.4%) patients with anemia and 20 (52.6%) patients without anemia. The mean differences of EPO concentration (U/L) between study groups demonstrated significant higher level among patient group (49.53 ± 56.82) than control group (12.73 ± 4.72) with P value < 0.0001. The level of serum EPO in anemic patients (89.28 ± 61.95) has been found to be higher than non-anemic patients (13.82 ± 4.43) and it was statistically significant (P < 0.0001). Endogenous EPO production was found to be defective in 10% of CML patients, 50% of CLL patients were judged by a value for the ratio of observed-to-predicted serum EPO levels (observed/predicted ratio) of ≤0.9. **Conclusion:** These findings indicate that anemia associated with hematologic malignancy may result from an inappropriately low EPO response. EPO treatment should benefit in this group of patients.

Keywords: Anemia, chronic leukemia, erythropoietin, middle euphrates

Introduction

Cancer is a major health problem worldwide in terms of morbidity and mortality, but it is especially prevalent in developing countries.[1] The leukemias are a group of diseases characterized by the increase of cancerous white cells in the blood and bone marrow. They are four forms of leukemia including acute or chronic leukemia, which are further split into lymphoid or myeloid leukemia. Because they progress more slowly than acute leukemia, chronic leukemia can be recognized from them.[2] Chronic myeloid leukemia (CML) is a myeloproliferative tumor in which granulocytes and precursors are the main proliferative element. Around half of newly diagnosed CML patients are asymptomatic and are discovered accidently when as high (WBC) count during a routine medical evaluation. Untreated CML has a biphasic or triphasic natural history, with an initial indolent chronic phase followed by an accelerated phase, blastic phase, or both. Since the introduction of tyrosine kinase inhibitors as standard treatment for CML, the rate of progression from chronic

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phase CML to blastic phase CML has been reduced. The Philadelphia chromosome, also known as t(9;22) (q34;q11.2), or its variants, as well as the identification of a BCR-ABL1 fusion, are required for the diagnosis.[3] Chronic lymphocytic leukemia (CLL), which has a male predominance and a diagnostic age of 72 years, is the most common adult leukemia in Western countries. The condition is distinguished by accumulation of monoclonal, mature CD5+ B lymphocytes in the peripheral blood, bone marrow, and secondary lymphoid organs. CLL is 10–20 times more common in Western countries than in Asia, implying that genetic, environmental, or combined factors, which influence the susceptibility of the disease. Following a workup for accidental lymphocytosis, CLL is usually found. The clinical course and presentation are extremely variable, ranging from an asymptomatic, dormant disease that may never need treatment (30% of patients) to an active disease that can cause progressive lymphocytosis, B symptoms (such as loss of weight, sweating at night, and fever), fatigue, recurrent infections, cytopenias (anemia, thrombocytopenia), lymphadenopathy, hepatosplenomegaly, or autoimmune complications.[4] Anemia is a common clinical feature associated with a poor prognosis in individuals with hematological malignancies. It can aggravate cancer at any stage of the disease's progression. Anemia is caused by a variety of reasons, including leukemic bone marrow infiltration, the myelosuppressive action of chemotherapy and inhibitory cytokines, autoimmune disorders, hypersplenism, and a low nutritional condition, which results in folic acid, vitamin B12, and iron deficiency.[5] Most cancer patients have low serum erythropoietin (EPO) levels, which contribute to the anemia of chronic illness produced by cytokine-mediated inhibition of erythropoiesis.[6] Key players in the pathophysiology of ACD are thought to be a reduced red blood cell (RBC) lifespan and the bone marrow's inability to enhance RBC production. EPO is a glycoprotein hormone that regulates the synthesis of RBC in the body. It stimulates red cell progenitors in the bone marrow by acting on particular receptors, resulting in increased proliferation and differentiation of these cells.[7]

EPO may have a significant role in the development of anemia, either directly or indirectly. Clarifying this role could lead to a more accurate diagnosis of the etiology of anemia and, as a result, more appropriate management.[8]

Materials and Methods

This study was done on a total of 68 Iraqi adult from two Iraqi centers: Baghdad Teaching Hospital, Marjan Teaching Hospital. We studied 38 patients who attended the outpatient clinic in these hospitals during the period from September 2022 to March 2023. They were diagnosed as having chronic leukemia (CML and CLL). Another 30 adult participants without disease were included and served as a normal control for comparison with the patients' study group; all control members had normal CBC measured at the time of blood sampling. 38 adult patients diagnosed with chronic leukemia (CML = 19 patients, CLL = 19 patients) based on a specialist's physical examination, morphological evaluation of peripheral blood films and bone marrow, and flow cytometric immunophenotypic profile were included in this study. ELISA assays were used to quantify serum EPO levels in the patient and control groups. CBC, reticulocyte count, blood film examination, renal function tests were done for both the patient and control groups. Serum EPO levels should not be quantitated in absolute terms in anemic patients but should be evaluated in relation to the degree of anemia, adequacy of serum EPO level were evaluated based on equation; observed/predicted (O/P) ratio in each patient, EPO O/P ratio was calculated as follows: $\log_{10}$(EPO observed)/$\log_{10}$(EPO predicted).

Log_{10} (EPO predicted) was calculated with the following formula: For Hb values <13 g/dL, the regression equation was log (EPO) = 4.746 − (0.275 × Hb). O/P ratio values ≤ 0.9 indicate an inadequate endogenous EPO concentration with respect to the degree of anemia.[9,10]

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) version 27.0 (IBM, Chicago, IL, USA). Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (means ± SD). Student *t* test was used to compare means between two groups. ANOVA test was used to compare means between three groups or more. Correlation coefficient was used to assess the relationship between two continuous variables. Pearson chi-square was used to find the association between categorical variables. A *P*-value of ≤0.05 was considered as significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. All subjects involved in this work are informed, and agreement had been obtained verbally before sample collection. This study was approved by the committee of publication ethics at College of Medicine, University of Babylon, Iraq under the reference No. BMS/0236/016.

Results

Age

The mean age of patients group was 54.1 ± 12.24 years that ranges from 24 to 75 whereas the mean age of controls group was 55. 8 ± 10.6 years that ranged from 29 to 70, which were statically not significant ($P = 0.42$). The mean age of CML patient was (50.1 ± 12.85) range from 24 to 72, CLL patients (58.2 ± 10.4) range from 38 to 75.

Gender

The majority of patients and control were men ($N = 23/38$, 60.5%) and ($N = 18/30$, 60%), respectively.

Specific diagnosis

19 CML and 19 CLL patients, 10/19 of CML and 8/19 CLL patients were anemic [Table 1].

Staging

All CML patients were in chronic phase except one was in blastic phase [Figure 1], distribution of CLL patients according to modified Rai staging system as in Figure 2.

Laboratory investigations

The comparison between study groups in hematological and biochemical parameters shown in Table 2. The comparison in hematological and biochemical parameters according to patient groups (anemic patients and non-anemic patient) shown in Table 3.

Table 1: Distribution of anemic and non-anemic patient among specific diagnosis

Specific diagnosis	No. of anemic patient (%)	No. of non-anemic patient (%)	Sum of specific diagnosis
CML	10	9	19
CLL	8	11	19
Total	18 (47.4%)	20 (52.6%)	38 (100%)

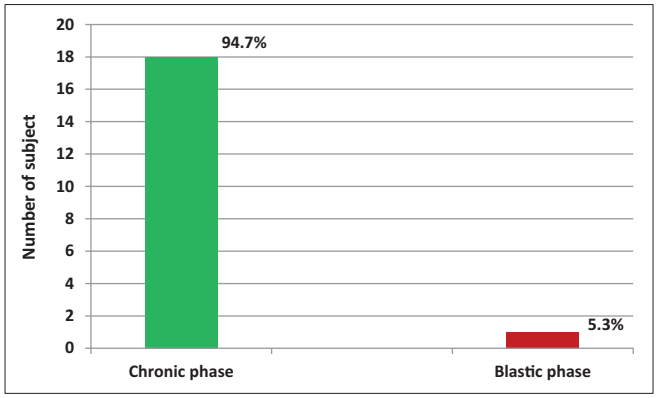

Figure 1: Distribution of patients with chronic myeloid leukemia (CML) according to WHO classification system ($N = 19$)

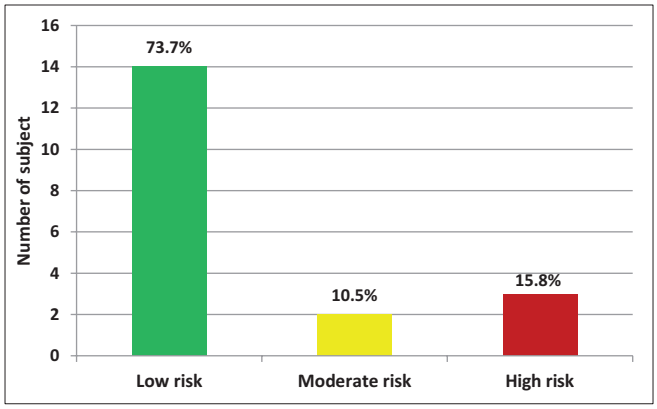

Figure 2: Distribution of patients with chronic lymphocytic leukemia (CLL) according to modified Rai stage ($N = 19$)

EPO

The mean differences of EPO concentration (U/L) between study groups demonstrated significant higher level among patient group (49.53 ± 56.82) than control group (12.73 ± 4.72) with P value <0.0001. The level of serum EPO in anemic patients (89.28 ± 61.95) have been found to be higher than non-anemic patients (13.82 ± 4.43) and its statistically significant ($P < 0.0001$).

Evaluation of adequacy of serum EPO level in anemic patients

We measure adequacy of serum EPO using O/P ratio = $\log_{10}$ (observed/ predicted) EPO for each anemic CML, CLL patient. O/P ratio ≤ 0.9 indicate inadequate EPO for degree of anemia. We found that only 10% of CML and 50% of CLL patients had inadequate EPO for degree of anemia.

Discussion

Anemia is a frequent problem in CML, CLL patients leading to poor outcome and shorter survival. In hematological malignancies, several factors, including inefficient use of iron stores that appear to be adequate, excessive cytokine production (such as the transforming growth factor-β, tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and γ-interferon) and a blunted EPO synthesis, BM infiltration, splenomegaly, radiotherapy, and chemotherapy may contribute to the development of ACD.[10] In this study, we found the mean age of CML patients was 50.1 years range from 24 to 72 years which is comparable to that reported by other Iraqi study at 2019, in which the mean age in their study was 51.7 years.[11] The mean age of CLL patients was 58.2 years range from 38 to 75 years which is comparable to that reported by other Iraqi studies 2019 and 2018, which the mean age in their studies were 57.18 and 59.24 years, respectively.[12,13] Whereas it was lower than that reported in western countries.[14,15] These differences may be related to the effect of geographical, environmental factors, and population structure between Iraq and Western countries that made life expectancy lower among Iraqi population. CML, CLL (male/female) were found to be more in men than women (13/6) (10/9), respectively. This finding is consistent with a studies conducted in Karbala 2019, Baghdad 2021, respectively.[16,17] The real cause of male predominance is unknown.[18]

Staging system distribution

According to WHO classification system most CML patients were in chronic phase (90%), whereas the

Table 2: The mean differences of hematological and biochemical parameters in study groups

Hematological variable	Study group	*N*	Mean ± SD	*t* test	*P*-value
Total WBC count (×10⁹/L)	Patient	38	11.98±13.35	2.10	0.04*
	Control	30	7.36±1.84		
Absolute lymphocyte count (×10⁹/L)	Patient	38	6.62±12.32	2.335	0.02*
	Control	30	1.95±0.53		
Hb level (g/dL)	Patient	38	12.45±1.96	–4.573	<0.0001*
	Control	30	14.37±1.32		
RBC count (×10⁹/L)	Patient	38	4.10±0.83	–4.899	<0.0001*
	Control	30	4.96±0.54		
Platelet count (×10⁹/L)	Patient	38	212.34±78.37	–1.746	0.085
	Control	30	243.90±68.00		
B.Urea (mg/dL)	Patient	38	4.45±1.32	–1.922	0.35
	Control	30	4.72±1.19		

*$P \leq 0.05$ was significant

Table 3: The mean differences of hematological and biochemical parameters in patient groups

Hematological variable	Patient group	*N*	Mean ± SD	*t* test	*P*-value
Total WBC count (×10⁹/L)	Anemic patient	18	8.46±6.78	–1.633	0.11
	Non-anemic patient	20	15.14±16.85		
Absolute lymphocyte count (×10⁹/L)	Anemic patient	18	3.53±3.41	–1.57	0.13
	Non-anemic patient	20	9.41±16.37		
Hb level (g/dL)	Anemic patient	18	10.86±1.51	–7.301	<0.0001*
	Non-anemic patient	20	13.89±0.95		
RBC count (×10⁹/L)	Anemic patient	18	3.59±0.62	–4.362	<0.0001*
	Non-anemic patient	20	4.56±0.72		
Platelet count (×10⁹/L)	Anemic patient	18	187.22±87.91	–1.943	0.06
	Non-anemic patient	20	234.95±62.54		
Urea (mg/dL)	Anemic patient	18	4.18±1.35	–1.681	0.9
	Non-anemic patient	20	4.74±1.25		

*$P \leq 0.05$ was significant

remaining in blastic phase (10%) [Figure 1], these results are consistent with study conducted in Karbala 2021.[19] This can be explained as most of the patients were diagnosed for a long time on treatment, whereas according to modified Rai staging system, most CLL patients were in low-risk stage (73.3%) followed by high-risk stage (15.8%). Whereas the lowest percent was found in moderate risk stage (10.5%) [Figure 2], these results are consistent with a study in Barcelona 2017 which found that the majority of patients were at low-risk stage.[20] This may be attributed to the early in seeking medical advice.

Hematological and clinical assessment

In the assessment of hematological parameters, the mean WBC count in CML patients (7.47±5.95) was not statically significant different from control group, and these results are consistent with a study conducted in Baghdad 2020, which the means WBC count was 7.9±3.17.[21] These due to most CML patients (90%) in our study were in chronic phase on treatment, while the mean WBC count in CLL patients (16.49±16.97), absolute lymphocyte count (11.24±16.31) were statically significant higher from control group respectively which were a diagnostic criteria for CLL. This result was consistent with a study conducted in Erbil in 2018.[22] The mean platelet count in patients group was 212.34±78.37; it was with nearly similar to the result as with other studies.[21,23] The mean hemoglobin level for CML patient was 12.47±1.76 mg/dL, and this result was consistent with a study conducted in Baghdad 2020.[21] The number of anemic patients was 10 (52.6%), which was comparable with other study conducted in USA 2004.[24]

The mean hemoglobin level for CLL patient was 12.44±2.2 mg/dL and this result was consistent with a study conducted in Al Mosul in 2022.[25] The number of anemic patients was 8 (42.1%) and this result was consistent with a study conducted in Croatia in 2011,[26] which is higher than other study; this difference could probably be because of the small sample size of CLL patients in our study. This parameter (anemia) representing a determinant for high-risk stage in Binet and modified Rai staging systems.[27,28]

Erythropoietin

In order to determine whether impaired EPO synthesis causes anemia, the measurement of serum EPO levels is helpful. We discovered that EPO level was significantly higher in patient group compared to control group (*P*-value < 0.0001). This result was in agreement with other workers in many previous studies which reported a higher mean of EPO in CML, CLL patients.[29,30] Furthermore, anemic patients had statically significant higher ($P < 0.0001$) EPO levels compared to non-anemic patients. Similar findings have been reported by other studies.[31,32] This is most likely due to EPO response to anemia in anemic patients. Serum EPO levels were inappropriately low for the degree of anemia in (10%) CML patients whereas 90% of the patients have adequate EPO for degree of anemia (O/P > 0.9) and these findings were in agreement with other study.[29] This might be explained based on fact that there were multiple factors which contribute in the development of anemia other than EPO, and myelosuppression occurs in up to 50% of patients with CML who are treated with imatinib and ≥ Grade 3 myelosuppression is reported in approximately 10% of patients which may lead to higher serum EPO.[24] Serum EPO levels were inappropriately low for the degree of anemia in 50% of CLL patients (O/P ≤ 0.9) and these finding in were comparable with other studies.[10,33,34] Many factors were responsible for blunt EPO production including cytotoxic drugs, as well as excessive production of cytokines such as TNF and IL-1. The blunted EPO response is unlikely to be the only factor responsible for anemia. Erythroid marrow can be inhibited directly by suppressor cytokines and by chemo or radiotherapy.[35] The percent of defective EPO production for the degree of anemia was lower than in other studies[36] which might be due to small sample size. All high-risk CLL patients had higher serum EPO level, but still low for degree of anemia and this indicates that blunt EPO response may play the major role in developing anemia.

Conclusion

These findings indicate that anemia associated with hematologic malignancy may result from an inappropriately low EPO response. EPO treatment should benefit in this group of patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Najem NA-A, Hussein A. Trends and characteristics of childhood cancer in Al-Najaf Governorate, 2012–2020. Med J Babylon 2022;19:37.
2. Bain BJ. Hoffbrand AV, Steensma DP. Hoffbrand's Essential Haematology. 8th ed. Oxford: Wiley Blackwell; 2020.
3. Chen Z, Hu S, Wang SA, Konopleva M, Tang Z, Xu J, *et al*. Chronic myeloid leukemia presenting in lymphoblastic crisis, a differential diagnosis with Philadelphia-positive B-lymphoblastic leukemia. Leuk Lymphoma 2020;61:2831-8.
4. Burger JA. Treatment of chronic lymphocytic leukemia. N Engl J Med 2020;383:460-73.
5. Bhuyan A, Hazarika P, Deka R. Clinicopathological features of pancytopenia in adults and the role of bone marrow study in etiological categorization: A one-year cross-sectional study. Med J Babylon 2022;19:415.
6. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood, J Am Soc Hematol 2019;133:40-50.
7. Kaushansky K, *et al*. Williams Hematology. 9th ed. New York: Faculty Bookshelf; 2016. p. 72. Available from: https://hsrc.himmelfarb.gwu.edu/books/72.
8. Beguin Y. Prediction of response and other improvements on the limitations of recombinant human erythropoietin therapy in anemic cancer patients. Haematologica 2002;87:1209-21.
9. Beguin Y, Yerna M, Loo M, Weber M, Fillet G. Erythropoiesis in multiple myeloma: Defective red cell production due to inappropriate erythropoietin production. Br J Haematol 1992;82:648-53.
10. Siakantaris MP, Angelopoulou MK, Vassilakopoulos TP, Dimopoulou MN, Kontopidou FN, Pangalis GA. Correction of disease related anaemia of B-chronic lymphoproliferative disorders by recombinant human erythropoietin: Maintenance is necessary to sustain response. Leuk Lymphoma 2000;40:141-7.
11. Khazaal MS, Hamdan FB, Al-Mayah QS. Association of BCR/ABL transcript variants with different blood parameters and demographic features in Iraqi chronic myeloid leukemia patients. Mol Genet Genomic Med 2019;7:e809.
12. Ahmed AA. Immunohistochemical expression of CD27 in bone marrow biopsies of chronic lymphocytic leukemia patients. Iraqi J Cancer Med Genet 2018;11:27.
13. Aljabban A, Alalsaidissa J. The expression of human telomerase reverse transcriptase gene and its activity in patients with b-cell chronic lymphocytic leukemia and its impact on clinical staging. Glob J Health Sci 2018;10:167.
14. Parikh SA, Rabe KG, Kay NE, Call TG, Ding W, Schwager SM, *et al*. Chronic lymphocytic leukemia in young (≤55 years) patients: A comprehensive analysis of prognostic factors and outcomes. Haematologica 2014;99:140-7.
15. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, *et al*. Chronic lymphocytic leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26:v78vi50-v84.
16. Mjali A, Al-Shammari HHJ, Abbas NT, Azeez ZD, Abbas SK. Leukemia epidemiology in Karbala province of Iraq. Asian Pacific J Cancer Care 2019;4:135-9.
17. Al-Saadi EAKD, Abdulnabi MA. The prevalence of lymph proliferative disorders in a group of Iraqi patients and its relation to blood indices parameters. Onkol I Radioter 2021;15:2.
18. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300.
19. Mjali A, Abba SK. Imatinib mesylate adherence in chronic myeloid leukemia patients: Data from middle euphrates region of Iraq. Syst Rev Pharm 2021;12:83-7.
20. Delgado J, Doubek M, Baumann T, Kotaskova J, Molica S, Mozas P, *et al*. Chronic lymphocytic leukemia: A prognostic model comprising only two biomarkers (IGHV mutational status and FISH cytogenetics) separates patients with different outcome and simplifies the CLL-IPI. Am J Hematol 2017;92:375-80.
21. Alagele MH, Alwash MM, Ahmed AA. Vascular endothelial growth factor receptor 2 (VEGFR2) gene polymorphism and treatment outcome following imatinib therapy in Iraqi patients with chronic myeloid leukemia. Eur J Mol Clin Med 2020;7:4847-57.
22. Hasan KM. Clinical aspects, immunophenotypic analysis and survival rate of chronic lymphocytic leukaemia patients in Erbil City, Iraq. Sultan Qaboos Univ Med J 2018;18:e461-7.
23. Santi RM, Ceccarelli M, Bernocco E, Monagheddu C, Evangelista A, Valeri F, *et al*. Khorana score and histotype predicts incidence of early venous thromboembolism in non-Hodgkin lymphomas. Thromb Haemost 2017;117:1615-21.

24. Cortes J, O'Brien S, Quintas A, Giles F, Shan J, Rios MB, *et al*. Erythropoietin is effective in improving the anemia induced by imatinib mesylate therapy in patients with chronic myeloid leukemia in chronic phase. Cancer Interdiscip Int J Am Cancer Soc 2004;100:2396-402.
25. Abdulrazzaq UI, Alwash MM. Evaluation of serum level of CXCL12 in correlation with several clinical and hematological parameters in patients with chronic lymphocytic leukemia. Iraqi J Cancer Med Genet. 2022;15:44.
26. Županić-Krmek D, Lang N, Jurčić D, Ljubić N, Bilić A. Analysis of the influence of various factors on anemia in patients with lymphoid malignancies. Acta Clin Croat 2011;50:495-500.
27. Binet JL, Auquier A, Dighiero G, Chastang C, Piguet H, Goasguen J, *et al*. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.
28. Rai K. A critical analysis of staging in CLL. Chronic Lymphocytic Leuk Recent Prog Futur Dir 1987:253-64.
29. Ishikawa M, Yagasaki F, Okamura D, Maeda T, Takahashi N, Kawai N, *et al*. Serum erythropoietin dose not participate in anemia that persists in CML patients after MMR achievement by imatinib mesylate therapy. Blood 2008;112:4274.
30. Han B, Shi YK, Zhu J, He XH, Lin NJ, Li SL, *et al*. Study on serum erythropoietin levels in patients with hematologic malignancies. Zhonghua xue ye xue za zhi= Zhonghua Xueyexue Zazhi 2006;27:543-5.
31. Birgegård G, Gascón P, Ludwig H. Evaluation of anaemia in patients with multiple myeloma and lymphoma: Findings of the European Cancer Anaemia Survey. Eur J Haematol 2006;77: 378-86.
32. Li LB, Luo RC. Clinical significance of serum erythropoietin detection in patients with cancer-related anemia. Di 1 jun yi da xue xue bao = Acad J First Med Coll PLA 2003;23:954-5.
33. Cazzola M, Ponchio L, Beguin Y, Rosti V, Bergamaschi G, Liberato NL, *et al*. Subcutaneous erythropoietin for treatment of refractory anemia in hematologic disorders. Results of a phase I/II clinical trial [see comments]. Blood 1992;79:29-37.
34. Tisi MC, Bozzoli V, Giachelia M, Massini G, Ricerca BM, Maiolo E, *et al*. Anemia in diffuse large B-cell non-Hodgkin lymphoma: The role of interleukin-6, hepcidin and erythropoietin. Leuk Lymphoma 2014;55:270-5.
35. Erslev AJ. Erythropoietin. N Engl J Med 1991;324:1339-44.
36. Cazzola M, Messinger D, Battistel V, Bron D, Cimino R, Enller-Ziegler L, *et al*. Recombinant human erythropoietin in the anemia associated with multiple myeloma or non-Hodgkin's lymphoma: Dose finding and identification of predictors of response. Blood 1995;86:4446-53.