

Serum Erythropoietin Levels in Leukemia Patients Receiving Cytostatic Treatment

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Anemia is the major stimulus for erythropoietin (Epo) secretion. Various studies have reported increases in Epo levels following chemotherapy. The mechanism has not yet been clarified. In this study, we evaluated serum Epo levels before, during (7 and 14 days), and after (day 25) chemotherapy in patients with acute myeloblastic leukemia (n=13) and lymphoblastic leukemia (n=4). As control group, 12 healthy subjects were evaluated. Epo levels were high in untreated leukemia patients compared to controls and continued to increase following chemotherapy. There was no significant difference in post-treatment values of Epo as compared with pre-treatment levels. In patients with pre-treatment values of Hb \leq 9 g/dl, Epo levels were inversely correlated with Hb (r: 0.552, p < 0.05). This correlation disappeared during and following treatment. There was no correlation between Epo and hematological or biochemical parameters. Therefore, elevated levels of Epo regardless of anemia may be due to a response to tissue hypoxia or increased synthesis of Epo in liver or bone marrow. [Journal of Turgut Özal Medical Center 1997;4(1):50-52]

Key Words: Erythropoietin, leukemia, chemotherapy

Kemoterapi alan lösemili hastalarda serum eritropoietin düzeyleri

Eritropoietin (Epo) sekresyonunda anemi major stimulusdur. Çeşitli çalışmalarda kemoterapiyi takiben Epo düzeylerinin arttığı bildirilmiştir. Bu artışın nedeni henüz tam olarak açıklanamamıştır. Bu çalışmada 17 akut lösemili hastada (13 akut myeloblastik, 4 akut lenfoblastik) kemoterapi öncesi, sırası ve sonrası serum Epo düzeyleri ölçüldü. Kontrol grubu olarak 12 sağlıklı kişi çalışmaya alındı. Tedavi öncesi Epo seviyeleri lösemili hastalarda kontrol grubuna göre yüksek olup, bu yükseklik tedavi sonrası devam etti. Tedavi öncesi ile tedavi sonrası değerler arasında anlamlı bir fark yoktu. Tedavi öncesi Hb ve Epo düzeyleri arasında Hb \leq 9 g/dl olan grupta zıt ilişki vardı (r: -0,52, p < 0,05). Bu ilişki tedavi sırası ve sonrasında kayboldu. Epo ile diğer hematolojik ve biokimyasal parametreler arasında ilişki bulunamadı. Anemi olmadan Epo'nun artışında, kemoterapiye bağlı doku hipoksisi veya karaciğer ve kemik iliği orijinli Epo sentezi gibi diğer nedenlerin rolü olabilir. [Turgut Özal Tıp Merkezi Dergisi 1997;4(1):50-52]

Anahtar Kelimeler: Eritropoietin, lösemi, kemoterapi

Erythropoietin is the main regulator of red blood cell production in humans (1). Epo is synthesized by peritubular capillary endothelial cells in the kidney in response to low arterial oxygen tension (2,3). The

hemoglobin concentration of the blood is one of the main determinants of the production of erythropoietin (4). Elevated levels are found in patients with hypoxic or anemic hypoxia and in a

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few instances in patients with inappropriate Epo secretion from tumors or cysts. Elevated epo levels are found in bone marrow failures because decreased consumption is responsible for high epo levels in aplastic anemia or other syndromes with bone marrow failure (5,6). However, it has been reported that low level of epo was found in mice during nephrotoxic drug administration such as cyclosporin-A (7). Some authors have reported that erythropoietin is inappropriately elevated in acute leukemia patients receiving chemotherapy (8-10). This study was performed for evaluating the probable changes in serum erythropoietin levels before, during, and after the cytostatic treatment of patients with acute leukemia.

MATERIALS AND METHODS

Seventeen patients who received intensive cytostatic treatment were studied. Twelve healthy men and women, who were not receiving any drug, were accepted as control group. 13 of patients had acute myelogeneous leukemia (AML) and 4 of them had acute lymphoblastic leukemia (ALL). Diagnosis of patients was established according to morphology, immunophenotyping, and cytogenetic studies. Erythrocyte concentrate transfusions were administered to maintain the hemoglobin level above 9 g/dl, and platelet transfusions to keep the platelet count above $20 \times 10^9/l$ as a part of the routine care of the patients. Hematological and biochemical tests were monitored every other day during chemotherapy and twice a week after treatment.

The treatment regimen is as follows: 1; induction treatment for acute myelogeneous leukemia: idarubicin 15 mg/m^2 days 1-3, Ara-C 100 mg/m^2 days 1-7 for five patients or Ara-C 100 mg/m^2 days 1-10, daunorubicin 45 mg/m^2 days 1-3, etoposide 100 mg/m^2 days 1-5 for five patients or Ara-C 2 g/m^2 days 1-4, mitoxantrone 12 mg/m^2 days 1-3 for one patient or Ara-C 100 mg/m^2 days 1-7, mitoxantrone 12 mg/m^2 days 1-3 for two patients, 2; induction treatment for acute lymphoblastic leukemia: L-asparaginase 5000 U/m^2 days 1-15, daunorubicin 25 mg/m^2 days 1, 8, 15, 22, methylprednisolone 60 mg/m^2 days 1-28, vincristine 1.4 mg/m^2 days 1, 8, 15, 22 for three patients and mitoxantrone 12 mg/m^2 days 1, 8, 15, 22, vincristine

1.4 mg/m^2 days 1, 8, 15, 22, methyl prednisolone 60 mg/m^2 days 1-28 for one patient.

All patients were hospitalized and blood samples were drawn the day before treatment and on the days 7, 14, and 25 after the treatment. The venous blood samples without anticoagulant were kept at room temperature and then samples were stored at -20°C until analysis. Serum levels of erythropoietin were measured by enzyme-linked immunosorbent assay (ELISA) (R&D Systems Diagnostics, Catalog number ADC 06096, Minnesota, USA).

Statistical analysis was performed by correlation analysis and 't' test.

RESULTS

In the pre-treatment period, Epo levels in study group were higher than controls (49.8 ± 14.1 and $19.3 \pm 1.9 \text{ mU/ml}$, respectively, $p < 0.05$), while the Hb was lower in study group than control group (10.5 ± 0.6 and $13.6 \pm 0.2 \text{ g/dl}$, respectively $p < 0.05$). At the time of diagnosis, according to Hb levels ($\text{Hb} \leq 9 \text{ g/dl}$), there was an inverse relation between Hb and serum levels of Epo ($r = 0.552$, $p < 0.05$). This correlation disappeared during and following the treatment. The serum Epo levels were found to be excessively elevated during the treatment and fell to the pretreatment levels after the treatment. Serum levels of Epo were $677.2 \pm 68.7 \text{ mU/ml}$ at first week, $342.2 \pm 64.1 \text{ mU/ml}$ at second week and $66.3 \pm 20.2 \text{ mU/ml}$ at the end of the treatment (Table 1). Hb did not change during the treatment because of transfusion of packed red cells. There was no significant difference in post-treatment values of Epo as compared with pre-treatment levels. A correlation between the serum Epo levels and the levels of Hb, hematocrit, WBC, platelet count, BUN, creatinin, AST, and ALT could not be found during the treatment. After the treatment, a correlation between the serum Epo levels and WBC ($r = 0.731$, $p < 0.01$) and Plt ($r = 0.614$, $p < 0.05$) levels was found. Complete

Table 1. Correlation between Epo levels and Hb

	Pre-treatment 1 st week	Peri- 2 nd week treatment	Post- treatment
Hb (g/dl)	10.5 ± 0.6	10.7 ± 0.5	10.5 ± 0.3
	$p > 0.05$	$p > 0.05$	$p > 0.05$
Epo (mU/ml)	49.8 ± 14.1	677.2 ± 68.7	342.2 ± 64.1
	$p < 0.001$	$p < 0.001$	$p < 0.001$

remission was achieved in twelve patients. There was no correlation between complete remission and failure to treatment in patients.

DISCUSSION

Epo production is stimulated both by anemia and low arterial oxygen tension and therefore it has been concluded that the tissue oxygen tension regulates Epo production. No other mechanism stimulating Epo production than tissue hypoxia has been found (9). The relationship between Epo and Hb has been studied in patients suffering from leukemia and ulcerative colitis (11). We speculate that plasma levels of Epo depend not only on the Hb concentration of the blood but also on the marrow that is responsiveness to the hormone. Similar results have been achieved in another study (12). Increase in Epo levels during the treatment has been considered result of anemia secondary to cytostatic drugs (13). Some authors have suggested that increased Epo levels during the treatment do not depend on Hb levels (8-10,14,15). Decreased consumption by a suppressed bone marrow and an increase in the production of extrarenal erythropoietin have been suggested as a possible explanation for elevated levels of Epo during the treatment (8). Another explanation has been proposed that the cytostatic drugs cause an increase in Epo production regardless of anemia, possibly initiated by a cytostatic effect on the kidneys or by an unknown stimulatory factor, responsive to the bone marrow inhibition (9). The cause of the rapid rise in serum Epo after chemotherapy remains controversial. Interestingly, although there were no significant changes Hb levels during the treatment due to regular erythrocyte transfusions, the serum Epo levels increased abnormally during the treatment. As a result, not only the Hb levels but also the response of the bone marrow to hormone may affect the Epo production. In addition, we suggest that hypoxia of the kidney and the extrarenal Epo production from the macrophages of the liver and the bone marrow may play a role in the elevation of Epo levels during cytostatic treatment.

REFERENCES

1. Goldwasser E. Erythropoietin and red cell differentiation. In: Control of Cellular Differentiation and Development.

2. Cunningham D, Goldwasser E, Watson J, Fox CF (Eds). New York: Alan R Liss, 1981: 487-502.
3. Koury ST, Bondurant MC, Koury MJ. Localization of erythropoietin synthesizing cells in murine kidney by in situ hybridization. *Blood* 1988; 71: 524-7.
4. Bauer C. Physiologic determinants of erythropoietin production. *Seminars in Hematology* 1991;28(Supl 3):9-13.
5. Jelkmann W. Renal erythropoietin: Properties and production. *Rev Physiol Biochem Pharmacol* 1986; 104: 139-215.
6. Erslev AJ, Wilson J, Caro J. Erythropoietin titers in anemic, nonuremic patients. *J Lab Clin Med* 1987; 109: 429-33.
7. Schrezenmeier H, Noe G, Raghavachar A, Rich IN, Heimpel H, Kubanek B. Serum erythropoietin and transferrin receptor levels in aplastic anemia. *Br J Haematol* 1994; 88: 286-94.
8. Vannucchi AM, Grossi A, Bosi A, et al. Impaired erythropoietin production in mice treated with cyclosporin A. *Blood* 1991; 78: 1615-8.
9. Piroso E, Erslev AJ, Caro J. Inappropriate increase in erythropoietin titers during chemotherapy. *Am J Hematol* 1989; 32: 248-54.
10. Birgegard G, Wide L, Simonson B. Marked erythropoietin increase before fall in Hb after treatment with cytostatic drugs suggests mechanism other than anaemia for stimulation. *Br J Haematol* 1989; 72: 462-6.
11. Helebostad M, Marstrand J, Slordahl SH, et al. Serum immunoreactive erythropoietin in children with acute leukemia at various stages of disease- and the effects of treatment. *Eur J Haematol* 1990; 44: 159-64.
12. Johannsen H, Jelkmann W, Wiedemann G, Otte M, Wagner T. Erythropoietin/haemoglobin relationship in leukemia and ulcerative colitis. *Eur J Haematol* 1989; 43: 201-6.
13. Jelkmann W, Wiedemann G. High serum immunoreactive erythropoietin in leukaemic patients with bone marrow insufficiency of erythropoiesis. *Eur J Haematol* 1990;44: 271-2.
14. Schapira L, Antin JH, Ransil BJ, et al. Serum erythropoietin levels in patients receiving intensive chemotherapy and radiotherapy. *Blood* 1990; 76: 2354-9.
15. Bowen DT, Janowska-Wieczorek A. Serum erythropoietin following cytostatic therapy. *Br J Haematol* 1990;74:372-3.
16. Grace RJ, Kendall RG, Chapman C, Hartley AE, Barnard DL, Norfolk DR. Changes in serum erythropoietin levels during allogeneic bone marrow transplantation. *Eur J Haematol* 1991; 47: 81-5.

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