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Serum erythropoietin level in anemic cancer patients

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Anemia is a frequent complication of cancer and its treatment. A defect in erythropoietin production has been advocated as being the main cause of anemia in cancer patients. We studied serum erythropoietin levels in 74 patients with solid tumors and in a control group consisting of 20 otherwise healthy individuals without any malignancy, who have only iron deficiency anemia. Serum erythropoietin levels were measured by enzyme immunoassay in cancer patients without anemia ($n=34$), and in anemic cancer patients ($n=40$); either receiving chemotherapy ($n=21$) or not ($n=19$). Anemic cancer patients were found to have decreased response of erythropoietin for a given hemoglobin level (mean, 40.1 ± 34.7 u/ml), compared with the patients having only iron deficiency anemia (mean, 69.7 ± 68.6 u/ml) ($P<0.05$). In patients with iron deficiency anemia having no malignancy, erythropoietin response was remarkably high and inversely correlated with the level of hemoglobin ($r=-0.69$; $P=0.05$). Although there was no correlation between hemoglobin and erythropoietin response in cancer anemia ($r=-0.07$), serum levels of erythropoietin were found to be higher in anemic cancer patients (mean, 40.1 ± 34.7 u/ml), compared with cancer patients with normal hemoglobin values (mean, 19.96 ± 18.4 u/ml). There was not any statistically significant difference between erythropoietin levels in anemic cancer patients with or without chemotherapy (mean, 43.7 ± 37.7 u/ml and 41.9 ± 30.08 u/ml respectively; $P>0.05$). No difference in serum erythropoietin levels were noted in patients treated with cisplatin or non-cisplatin containing regimens (mean, 48.36 ± 33.12 u/ml and 38.55 ± 43.52 u/ml, respectively; $P>0.05$). In this study, we demonstrated that anemia in cancer patients was caused by blunted erythropoietin response, rather than its quantitative deficiency. Serial measurements, however, should be considered in patients receiving chemotherapy.
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Keywords: cancer; anemia; erythropoietin; iron deficiency

Introduction

Patients with solid tumors are often anemic even before they undergo cytotoxic treatment. Beside chemotherapy induced bone marrow suppression and renal damage,[1] there can be many other causes of anemia in patients with cancer, like blood loss, hemolysis, bone marrow infiltration, renal disorder or nutritional defi-

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ciencies. This type of cancer-related anemia shares many hematological and biochemical similarities with anemias seen in other chronic diseases, which was described by Cartwright as 'Anemia of Chronic Disorders (ACD).[2] Anemia usually causes constitutional symptoms affecting the daily activities of cancer patients, may delay cancer treatment and may also result in complications associated with blood transfusion;[3,4] its treatment can have a significant impact on one's quality of life.[5] Erythropoietin (epo) plays a major role in the control of erythrocyte production.[6] Produced primarily in the kidneys in adults, epo interacts with erythroid precursors in the bone marrow and increases red cell production. Epo is unique amongst the hematopoietic growth factors with its hormone-like functioning, that makes serum measurements of epo possible.[7] Studies reporting on serum levels of epo in anemic cancer patients are conflicting; some of the studies reported normal or high levels of epo in cancer anemia[8,9] whereas some others described low levels of epo, accompanied by a blunted response of epo to the decrease in hemoglobin (hb).[10,11]

In this study, we have studied serum levels of epo in cancer patients with or without anemia, in order to investigate whether a decrease in serum epo level is responsible for cancer anemia and also to determine whether an association exists between hb and epo levels in these patients. We also analyzed the treatment effect on serum epo levels.

Materials and methods

We studied serum epo levels in 74 patients with solid tumors who presented to the outpatient clinic of the university hospital (group 1 and group 2). The control group consisted of 20 otherwise healthy individuals without any malignancy, who were confirmed to have only iron deficiency anemia (group 3). Both in cancer patients and in the control group anemia was defined as hb level of less than 13 g/dl in men, and less than 11.5 g/dl in women. Clinical characteristics of cancer patients are outlined in Table 1. All cancer patients were evaluated for iron deficiency anemia, which could be in part the cause of their anemia. Serum iron and iron binding capacity were measured by colorimetric method (RAICHEM, Reagents Application, Inc.) and ferritin levels were determined by radio-immunoassay (Ferritin RIA Kit, Amersham). Iron deficiency anemia was defined as serum ferritin level less than 17 ng/ml in men or 14 ng/ml in women, or a serum iron level less than 50 μ/dl and serum iron binding capacity greater than 400 μ/dl. Creatinine clearance was determined in all patients to exclude the possibility of renal dysfunction that may affect epo level and cause ACD by some other mechanisms. Serum epo was measured with a commercially available enzyme immunoassay (Clingen Erythropoietin, EIA). With this assay, the range of normal values in adults without anemia is less than 19 u/l.

Table 1 Clinical characteristics of cancer patients

Characteristics	*Number of patients*
Sex	
Male	31
Female	43
Cancer type	
Lung	17
Breast	18
Gastrointestinal	26
Others	13
Subgroups of cancer patients	
Group 1 : with anemia	40
1a : chemotherapy +	21
1b : chemotherapy −	19
1aa : cisplatin +	11
1ab : cisplatin −	10
Group 2 : without anemia	34

Group 1 : anemic cancer patients; 1a patients treated with chemotherapy, 1b without chemotherapy, 1aa with cisplatin, 1ab without cisplatin.
Group 2 : cancer patients with normal hb levels.
+ YES; − NO.

Cancer patients had a mean age of 49 (range: 16–76 y), while the iron-deficient control subjects had a mean age of 52 (range: 25–72 y). There were 31 males and 43 females in our study. Primary cancer sites included the gastrointestinal system in 26 patients, breast in 18 patients, lung in 17 patients; the remaining patients had other miscellaneous sites of primary disease. The cancer patients were categorized on the basis of their treatment history and hb status: Group 1; cancer patients with anemia ($n = 40$), who were subdivided into patients currently receiving chemotherapy (group 1a; $n = 21$) or not (group 1b; $n = 19$); patients who had chemotherapy induced anemia were further evaluated on the basis of whether they had been treated with a cisplatin (group 1aa; $n = 11$) or non-cisplatin (group 1ab; $n = 10$) containing regimens. Group 2 patients

consisted of non-anemic cancer patients ($n=34$) (Table 1).

Distribution of serum levels of erythropoietin in relation to concurrent hemoglobin levels was determined by 'analysis of covariance'. Mean hemoglobin and serum epo levels were compared and tested for statistical significance in different subsets of cancer patients with 'Student *t*-test'.

Results

Mean hemoglobin and epo levels in the control group and in cancer patients are summarized in Tables 2 and 3. None of the cancer patients included in the study were found to have superimposed iron deficiency anemia. Mean serum levels of iron, iron binding capacity and ferritin in cancer patients with or without anemia were $124.4\pm50\,\mu g/dl$, $275.8\pm42\,\mu g/dl$, $478.5\pm125\,ng/ml$ and $139.8\pm35\,\mu g/dl$, $325.6\pm73\,\mu g/dl$, $223.9\pm89\,ng/ml$, respectively. Glomerular filtrate rate measured by creatinine clearance was found to be within normal limits in all patients.

Table 2 Erythropoietin levels in anemic cancer patients and in patients with iron deficiency anemia

	Hemoglobin g/dl		
	Male	*Female*	*EPO (u/ml)*
Group 3 ($n=21$)	10.26 ± 1.6	10.2 ± 1.2	69.7 ± 68.6
Group 1 ($n=40$)	10.9 ± 0.9	9.9 ± 1	40.1 ± 34.7
P-value	>0.05	>0.05	<0.05

Group 3: iron deficiency anemia.
Group 1: cancer patients with anemia.

Table 3 Comparison of erythropoietin levels in three different subsets of cancer patients

	Hemoglobin g/dl		
	Male	*Female*	*EPO (u/ml)*
Group 1 ($n=40$)	10.9 ± 0.9	9.9 ± 1	40.1 ± 34.7
Group 2 ($n=34$)	14.18 ± 1	12.84 ± 0.9	19.96 ± 18.4
P value	<0.001	<0.001	<0.01
Group 1a ($n=21$)	10.1 ± 0.7	9.1 ± 1.1	43.7 ± 37.7
Group 1b ($n=18$)	11.3 ± 1	10.7 ± 0.84	41.94 ± 30.08
P value	<0.05	<0.05	>0.05
Group 1aa ($n=11$)	10.57 ± 0.9	9.37 ± 1.1	48.36 ± 33.12
Group 1ab ($n=10$)	10.2 ± 0.6	10.3 ± 0.92	38.55 ± 43.52
P value	>0.05	>0.05	>0.05

Group 1: anemic cancer patients; 1a patients treated with chemotherapy, 1b without chemotherapy, 1aa with cisplatin, 1ab without cisplatin.
Group 2: cancer patients with normal hb levels.

Anemic cancer patients (group 1) were found to have lower serum levels of epo ($40.1\pm34.7\,u/ml$) than the control group (group 3) with only iron deficiency anemia ($69.7\pm68.6\,u/ml$) ($P<0.05$). No statistically significant difference between the hb levels of two groups was noted ($P>0.05$) (Table 2, Figure 1). In the iron deficiency anemia group, epo response was remarkably high and inversely correlated with the level of hb ($r=-0.69$). However, in anemic cancer patients no correlation was noted between serum levels of epo and hb levels ($r=-0.068$).

Mean serum levels of epo in anemic (group 1) and non-anemic (group 2) cancer patients were $40.1\pm34.7\,u/ml$ and $19.96\pm18.\,u/ml$, respectively ($P<0.01$) (Table 3, Figure 1). There was a weak correlation between hb and serum levels of epo in non-anemic cancer patients ($r=-0.42$). There were no statistically significant differences between serum epo levels in anemic cancer patients receiving chemotherapy (group 1a; $43.7\pm37.7\,u/ml$) or not (group 1b; $41.9\pm30.08\,u/ml$) ($P>0.05$). No difference in serum levels of epo was noted in patients either treated with cisplatin (group 1aa; 48.36 ± 33.12) or non-cisplatin (group 1ab; 38.55 ± 43.52) containing regimens ($P>0.05$) (Table 3, Figure 1).

Discussion

Chronic anemia in cancer patients is caused by several pathophysiologic mechanisms. Shortened erythrocyte survival and failure of erythropoiesis to compensate for the shortened survival of red blood cells appear to be the most probable causes. Inadequate epo production, as well as suppressed erythroid progenitor cells and impaired iron utilization; seem to play a major role in decreased erythropoietic activity in cancer patients with anemia[12,13]

In our study we investigated epo levels in response to anemia in various solid tumors. Epo levels in anemic cancer patients were compared with epo levels in patients with iron deficiency anemia. It is well known that in response to a decrease in hb, epo level increases in iron deficiency anemia[11,14.] Although we found elevated epo levels in anemic cancer patients, this increase in epo levels was less than the increase noted in iron deficiency anemia, especially when hb

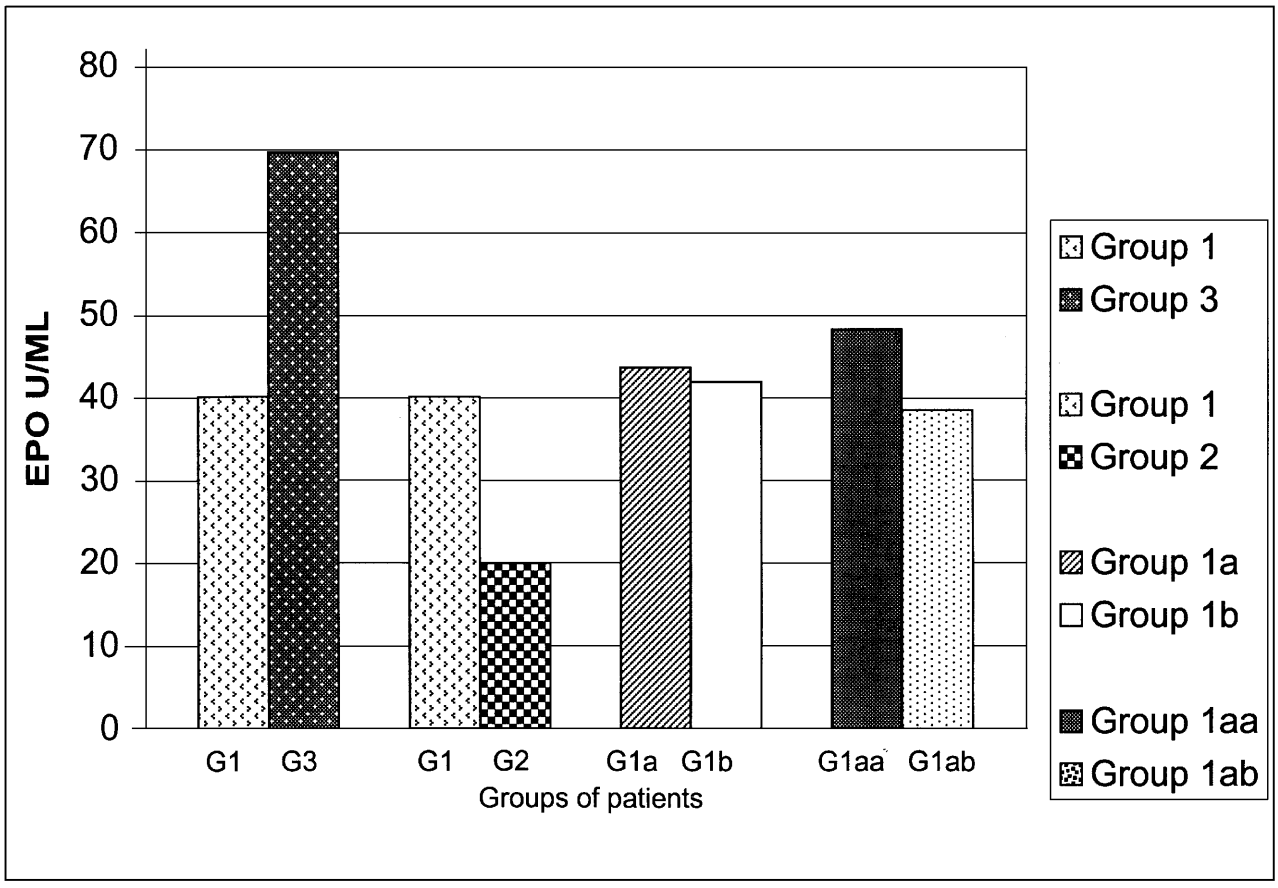

Figure 1 *Comparison of serum erythropoietin level in different subgroups of cancer patients.*

levels were matched. The increase in epo levels was clearly blunted when compared with the increase in epo levels of patients with iron deficiency anemia. We also found a strong negative correlation between hb and epo in iron deficiency anemia, which completely disappeared in cancer patients with anemia. Serum levels of epo were found to be considerably higher in anemic cancer patients, compared with serum epo levels in non-anemic cancer patients. There was also a weak correlation between epo and hb in non-anemic cancer patients, resulting in a decrease in epo, in response to normal hb, which completely disappeared in cancer patients with anemia.

Previous studies investigating epo levels in anemic cancer patients revealed conflicting results; some studies reported adequate epo levels[8,9] and some reported low levels and blunted response of epo to hb decrease.[10,11] In a detailed study of 81 anemic cancer patients, Miller *et al* found apparently elevated, but inappropriately low, epo levels for the degree of anemia, compared to the iron deficiency anemia.[11] His findings are consistent with our results. Studies reporting high epo levels in cancer patients with anemia were in fact misinterpreted since there was no comparison to iron deficiency anemia, which could have shown a blunted response in anemic cancer patients compared to iron deficiency anemia. This would be the case in our study; with higher levels of epo in anemic cancer patients compared to non-anemic cancer patients, but lower levels than in patients with iron deficiency anemia. Several mechanisms are proposed for blunted epo response in cancer anemia. Excessive release of cytokines such as interleukin 1, interleukin 6 and tumor necrosis factor probably both inhibit erythroid marrow proliferation and blunt the normal exponential relationship between hb and serum epo.[15,16]

These findings suggest that normal feedback mechanism, which results in epo production in response to a decrease in hb level, is compromised in patients with cancer anemia.

One of the major causes of cancer anemia is cytotoxic therapy. Mechanisms causing anemia in patients receiving chemotherapy include the direct effect of the chemotherapy on hematopoietic stem cells, the indirect effect on bone marrow micro-environment and renal toxicity associated with deficient epo production.[17] In our study, chemotherapy administration did not have any effect on serum levels of epo, which was in contrary to the previous studies published.[11,18] There were contradictory findings in studies, showing both increased levels of epo[19,20] and inadequate epo response secondary to renal toxicity in cancer patients receiving chemotherapy.[11,21] Changes in serum epo concentration may occur during chemotherapy, which makes serum epo level determination unreliable. Saijo *et al* performed a different approach and obtained serial measurements of epo from a group of lung cancer patients receiving chemotherapy. They described an initial peak of epo levels followed by a rapid or gradual fall to baseline while receiving chemotherapy.[22] The mechanism underlying the initial peak of epo might be related to new synthesis in response to depressed bone marrow, rather than a response to renal hypoxia associated with anemia.

The data in our study support the concept that, rather than an absolute deficiency, lack of an adequate response to anemia plays an important role in cancer anemia. Controversial findings of epo levels in cancer patients under cytotoxic drug treatment should be carefully analyzed, especially considering that these levels were measured randomly in most of the studies. Serial measurements of epo should be explored in patients receiving chemotherapy to find out the dynamic changes in epo levels. Considering multiple factors that may affect serum levels of epo, baseline serum epo levels cannot predict response to recombinant human epo[23] and therefore, high serum levels of epo in cancer patients with anemia should not preclude the administration of recombinant human epo in the supportive treatment of cancer patients. However, the accurate prediction and targeting of recombinant human epo therapy for patients most likely to respond needs to be addressed in subsequent prospective studies.

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