Comparison of the serum erythropoietin levels in chemotherapy-naive and cisplatin-treated cancer patients

M. ARSLAN[1], T. EVRENSEL[1], E. KURT[1], M. DEMIRAY[1], I. ERCAN[2], O. KANAT[1], R. ALI[3], A. OZKAN[3], O. MANAVOGLU[1]

[1]Department of Medical Oncology, e-mail: marslan@uludag.edu.tr, Uludag University Faculty of Medicine, Bursa 16059, Turkey; [2]Department of biostatistic, and [3]Department of Hematology, Uludag University Faculty of Medicine, Bursa, Turkey

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There are conflicting data about the effects of cisplatin on erythropoietin (EPO) response to anemia. Aim of our study was to investigate whether endogenous EPO response to anemia in cisplatin treated patients was insufficient in comparison to the anemic chemotherapy-naive cancer patients and non cancer patients with iron deficiency anemia. Patients who had hemoglobin (Hb) levels of less than 110 g/l were included in the study. Fifteen chemotherapy-naive cancer patients were enrolled in Group A. Group B consisted of 15 patients who had been treated with three cycles of cisplatin chemotherapy and then became anemic and in Group C were included 15 patients who had iron deficiency anemia, without any malignancy. The mean Hb values were not different between all groups (102.8 ± 39.8 g/l, 103.1 ± 2.5 g/l and 99.3 ± 3.6 g/l in Group A, Group B and Group C, respectively). However, EPO levels were found to be significantly lower in Group A and Group B than Group C (29.63 ± 9.09 mU/ml, 20.87 ± 2.43 mU/ml and 85.38 ± 25.72 mU/ml, respectively; p=0.017 Group A vs. Group C, p=0.005 Group B vs. Group C). No significant difference was found between Group A and B (p=0.917).

Opposite the iron deficiency anemia, cancer anemia is associated with an inadequate EPO response to anemia and administration of cisplatin does not lead to it further deterioration.

Key words: anemia, erythropoietin, cisplatin, cancer

Anemia occurs in more than 50% of cancer patients and this rate may increase up to 90% in patients with more advanced cancer or in those treated with chemotherapy or radiotherapy [5]. Many factors; such as type of malignancy, direct bone marrow invasion by the tumor, hemolysis, hypersplenism, infections and malnutrition may contribute to the development of anemia. However, neoplastic disorders are often complicated by "anemia of chronic disease" (ACD). This type of anemia is mediated by inflammatory cytokines, which exert inhibitory effects on erythropoiesis and erythropoietin (EPO) production [1, 5, 6].

The peritubular cells of the kidneys produce EPO, which is a growth factor necessary for survival and maturation of erythroid precursors in the bone marrow. Renal hypoxia that may resulted from anemia is a unique factor that is known to increase EPO production [3].

Cisplatin, which is a metal-based anticancer drug, is used in the treatment of wide variety of solid tumors. At the moderate doses, it commonly causes progressive anemia without persistent effects on white blood cells or platelet counts. Cisplatin exhibits some toxic effects on the kidney tubules thus may suppress the EPO production [7, 12]. Therefore, it is generally accepted that cisplatin causes anemia not only by myelosupression but also by inhibition of the EPO response to anemia, which add to negative effects, observed in ACD, on EPO production. However, there are some contradictory results, because some investigators found that cisplatin did not further decrease EPO response to anemia [2, 4, 8, 9]

Aim of our study was to investigate whether endogenous EPO response to anemia in cisplatin-treated patients is inadequate in comparison to anemic chemotherapy-naive cancer patients and non cancer patients with iron deficiency anemia.

Material and methods

The patients with solid tumor, had to meet all of the following inclusion criteria: Hemoglobin (Hb) levels <110

g/l, age ≥ 18 years, normal hepatic and renal functions, Karnofsky performance score ≥ 80. Other causes of anemia such as hemorrhage, hemolysis, hemoglobinopathy, vitamin B_{12} or folic acid deficiency were considered to be exclusion criteria.

A total 45 patients were included in the study in three separate groups. Fifteen chemotherapy-naive cancer patients with chronic cancer anemia were enrolled in Group A. Group B consisted of 15 patients who had been treated with three cycles of cisplatin (50–100 mg/m^2 per cycle) and than became anemic. Group C was constituted of 15 patients who had iron deficiency anemia, without any malignancy. The demographic characteristics of patients are shown in Table 1.

Serum EPO and Hb levels were measured in all patients and results were compared. Serum samples were taken one week after completion of third cycle of cisplatin in Group B. Serum EPO was evaluated with immunometric method (Immulite, DPC, LA USA). An automatic blood cell counter (Cell-Dyn3500R, Abbot Lab., IL, USA) was used for Hb measurement. Serum iron and iron binding capacity were measured by an automatic analyzer (Vitros, Ortho Clinical Diagnostics, NY, USA). Measurement of serum ferritin, vitamin B_{12} and folic acid levels were performed by automatic chemiluminescence system (ACS: 180, Bayer, Germany).

All statistical tests were carried out with the computer program SPSS 10.0 for Windows. Data were expressed as mean ± standard error of mean. Statistical analyzes was performed by using Kruskal-Wallis ANOVA test. If significant differences between the groups were found by ANOVA, comparisons between the groups were carried out by the use of Mann Whitney U test. Pearson Correlation Analyze was used for determination of correlation between EPO and Hemoglobin levels in each group.

Results

The mean Hb values were 102.8 ± 39.8 g/l, 103.1 ± 2.5 g/l and 99.3 ± 3.6 g/l in Group A, Group B and Group C, respectively. No significant differences were found between the groups in terms of the mean Hb values. The serum EPO levels were 29.63 ± 9.09 mU/ml, 20.87 ± 2.43 mU/ml and 85.38 ± 25.72 mU/ml in Group A, Group B and Group C, respectively. There was no significant difference between Group A and Group B (p=0.917). Group C had higher EPO levels compared to Group A and Group B (p=0.017, and p=0.005, respectively) (Tab. 2).

There was a significant inverse correlation between Hb and EPO levels in Group C (r=–0.839, p<0.0001). There were, however, weak inverse correlations between Hb and EPO levels in Group A and Group B (r=–0.519, p<0.05 in Group A and r=–0.517, p<0.05 in Group B).

Table 1. Patients' characteristics

	Group A	Group B	Group C
N	15	15	15
Age	56.07 ± 2.55	56.2 ± 2.26	37.2 ± 2.75
Gender			
Male	11	13	1
Female	4	2	14
Organ			
Lung	11 (73.3%)	8 (53.3%)	None
Stomach	1 (6.7%)	3 (20.0%)	
Larynx	1 (6.7%)	1 (6.7%)	
Esophagus	2 (13.3%)	1 (6.7%)	
Skin	–	1 (6.7%)	
Nasopharynx	–	1 (6.7%)	

Table 2. Mean serum EPO and Hb levels of the groups

	GROUP A	GROUP B	GROUP C
Hb (g/l)	102.8 ± 3.98	103.1 ± 2.5	99.3 ± 3.6
EPO (mU/ml)	29.63 ± 9.09	20.87 ± 2.43	85.38 ± 25.72

Discussion

In our study, we found that erythropoietin response to anemia was inadequate in both chemotherapy-naive and cisplatin treated cancer patients (Group A and Group B) compared to the similar degree of anemia caused by iron deficiency (Group C). We also observed that even three cycles of cisplatin administration did not lead to further deterioration of EPO response to anemia compared to the chemotherapy-naive cancer patients.

Plasma EPO level is constant due to basal constitutive EPO production in healthy persons. Serum EPO levels do not exceed normal range until hemoglobin level fall down below 105.0 g/l [11]. In case of the absence of serious inflammatory or malignant disease, proper EPO response to anemia is observed in patients who suffer from metabolic, genetic, or immun disorders of erythrocytes, such as iron deficiency anemia, hemoglobinopathy, blood loss, and aplastic anemia. There are some conflicting data about the EPO response to anemia in cancer patients. While some authors found adequate EPO levels [10, 13]; others observed inadequate EPO response to anemia in patients with cancer [8, 9, 12]. In early studies, in which adequate EPO response to anemia were observed in cancer patients, EPO levels of cancer patients were compared with the levels of non anemic persons [10, 13]. These results were in fact misinterpreted because of the fact that the healthy persons, who were compared with the cancer patients with chronic anemia, did not properly demonstrate EPO response as discussed above. In such situation, it could not be made

a decision whether the EPO response to chronic cancer anemia is adequate or not. Likewise, we found that the EPO response to chronic cancer anemia not as adequate as in the patients with iron deficiency anemia; in spite of similar degree of Hb levels.

There are also some contradictory results whether cisplatin leads to further deterioration of the EPO response to anemia. Some authors found that EPO response was further decreased in patients treated with cisplatin [7, 12]. On the contrary, others found that cisplatin did not lead to further decrease of EPO response to anemia [2, 4, 8, 9] as demonstrated in our study. These conflicting results may be related to the time of taking blood samples for the measurement of serum EPO level. It was observed that, serum EPO levels markedly increase within two weeks, then decline towards the baseline values after chemotherapy administration. This event is observed throughout the each administration of cisplatin [2, 4]. The mechanism of this issue is not clear. However, It might be associated with the cisplatin-induced bone marrow inhibition that stimulates new EPO synthesis in the kidneys in early period and/or a decreased mass of erythroid precursors that causes disruption of the usual EPO degradation pathway and reduced EPO consuption may lead to prolonged EPO lifespan and it's concentration and/or cytotoxic therapy causes direct injury to EPO producing cells in the kidney in manner that mimics hypoxia [2]. If blood samples are taken immediately after cisplatin administration, EPO levels may be found to be higher due to increasing of EPO levels in this period. In most of studies, EPO levels were measured randomly. We took blood samples one week after completion of third cycle of cisplatin for avoiding time-related changes. A study, which monitories EPO levels meticulously in cisplatin-treated patients and compares with normal EPO response to anemia, is clearly needed.

Although it was very weak, we observed that the inverse relationship between EPO and Hb levels protected in the chemotherapy-naive and cisplatin treated patients as in patients with iron deficiency anemia. These findings are not consistent with the previous data, in which the inverse relationship between EPO and Hb levels was not observed [8, 9]. However the background of this result is unclear, our findings suggest that EPO response to anemia may be not completely depressed in chemotherapy-naive and cisplatin-treated cancer patients.

In conclusion, present study demonstrates that cancer anemia is associated with an inadequate EPO response to anemia and administration of cisplatin does not lead to it's further deterioration. However; a new study, in which EPO levels will be followed up very closely in cisplatin-treated patients and will be compared with the EPO levels of the anemic patients, without cancer, is needed.

References

[1] BEGUIN Y. Erythropoietin and anemia of cancer. Acta Clin Belg 1996; 51(1): 36–52.

[2] CANAPARO R, CASALE F, MUNTONI E, ZARA GP, DELLA PEPA C et al. Plasma erythropoietin concentrations in patients receiving intensive platinum or nonplatinum chemotherapy. Br J Clin Pharmacol 2000; 50: 146–153.

[3] FISHER JW. Erythropoietin: physiologic and pharmacologic aspects. Proc Soc Exp Biol Med 1997; 216(3): 358–369.

[4] HASEGAWA I, TANAKA K. Serum erythropoietin levels in gynecologic cancer patients during cisplatin combination chemotherapy. Gynecol Oncol 1992; 46(1): 65–68.

[5] HENRY DH. Supplemental iron: A key to optimizing the response of cancer- related anemia to rHuEPO? The Oncologist 1998; 3: 275–278.

[6] LUDWIG H, FRITZ E. Anemia in cancer patients. Semin Oncol 1998; 25(7): 2–6.

[7] MATSUMOTO T, ENDOH K, KAMISANGO K et al. Effect of recombinant human erythropoietin on anticancer drug-induced anemia. Br J Haematol 1990; 75: 463–468.

[8] MILLER CB, JONES RJ, PIANTADOSI S, ABELOFF MD, SPIVAK JL. Decreased erythropoietin response in patients with the anemia of cancer. N Engl J Med 1990; 322(24): 1689–1692.

[9] OZGUROGLU M, ARUN B, DEMIR G, DEMIRELLI F, MANDEL NM et al. Serum erythropoietin level in anemic cancer patients. Med Oncol 2000; 17: 29–34.

[10] SCHREUDER WO, TING WC, SMITH S, JACOBS A. Testosterone, erythropoietin, anemia in patients with the disseminated bronchial cancer. Br J Haematol 1984; 57: 521–526.

[11] SPIVAK JL. The biology and clinical applications of recombinant erythropoietin. Semin Oncol 1998; 25(7): 7–11.

[12] WOOD PA, HRUSHESKY JM. Cisplatin-associated anemia: an erythropoietin deficiency syndrome. J Clin Invest 1995; 95: 1650–1659.

[13] ZUCKER S, FRIEDMAN S, LYSIK RM. Bone marrow erythropoiesis in the anemia of infection, inflammation and malignancy. J Clin Invest 1974; 53: 1132–1138.