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Effect of Cisplatin on Erythropoietin and Iron Changes

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ANAEMIA SECONDARY to nephrotoxicity, haemolysis, inappropriate erythropoietin response to haemoglobin levels, and interaction of cisplatin, early erythroid progenitors and iron utilisation are the most commonly proposed causes of cisplatin-induced anaemia [1, 2]. A study has been carried out to investigate the effect of cisplatin-containing chemotherapy regimens on serum erythropoietin, iron and ferritin levels. 15 patients with no prior chemotherapy, normal renal function, and a variety of tumours (head and neck 12, osteosarcoma 2, germ cell testicular 1), who received 100 mg/m^2 of cisplatin in a combination for three consecutive cycles, and 9 healthy controls were included in the study. Blood samples were taken by venipuncture prior to and on the 7th day of each course of chemotherapy. Serum erythropoietin levels were determined by sandwich ELISA, ferritin levels by an enzyme immunoassay, and serum iron by a commercially available kit. Although the pretreatment erythropoietin levels were low in 9 cancer patients (60%), the median level was 9.5 mU/ml and not significantly different from that of the controls ($P > 0.05$). The pretreatment median serum ferritin level was 286.9 μg/l which was significantly higher than the controls ($P < 0.001$). The pretreatment median serum iron level was 159.25 μg/dl which was not statistically different from the median level in the control group. During the three consecutive chemotherapy cycles the haemoglobin level decreased by 2 g/dl in 40% of the cycles, however, no patient needed blood transfusions or developed renal failure. After the first cycle, no significant difference in serum erythropoietin, ferritin or iron levels was discovered. Following the second and third cycles, however, statistically significant increases in these levels were observed ($P < 0.001$). The erythropoietin levels were plotted against haemoglobin, and a good correlation was observed, indicating a sufficient erythropoietin response to haemoglobin reduction during treatment.

Severe anaemia secondary to red blood cell sensitisation induced by cisplatin has been described [1], but we did not observe haemolytic anaemia in our patients. Erythropoietin synthesis defect due to renal failure has been advocated in the development of cisplatin-induced anaemia, however, none of the patients in the study developed nephrotoxicity. Inappropriate erythropoietin response to decreased haemoglobin levels and alterations in early erythroid progenitors have been proposed as causes of anaemia [3–8]. Low serum erythropoietin levels in cancer patients with anaemia which further decreased during chemotherapy, was claimed to be independent of therapy-induced nephrotoxicity [7, 8]. Another study revealed a trend towards lower erythropoietin levels with sequential treatment cycles in head and neck cancer patients [9]. The present study has demonstrated a normal erythropoietin response to decreasing levels of haemoglobin with consecutive cycles of cisplatin-containing chemotherapy, and therefore does not agree with the previous reports on inappropriate erythropoietin response. Significant increases in serum iron and ferritin levels were reported during cisplatin therapy, and associated with defective iron utilisation by the erythroid precursors [4, 5]. Decreased iron utilisation was speculated to be the result of a direct and early interaction of cisplatin with iron supply to erythroblastic precursors [3]. Our study has confirmed the finding of increased levels of serum iron and ferritin with successive cycles of cisplatin. The cumulative decrease of the erythroblastic pool may, therefore, be the leading cause of severe anaemia encountered during cisplatin-containing chemotherapy. In conclusion, cisplatin-induced anaemia is not due to an erythropoietin defect, but it may have a direct and early influence on the iron supply to erythroblasts.

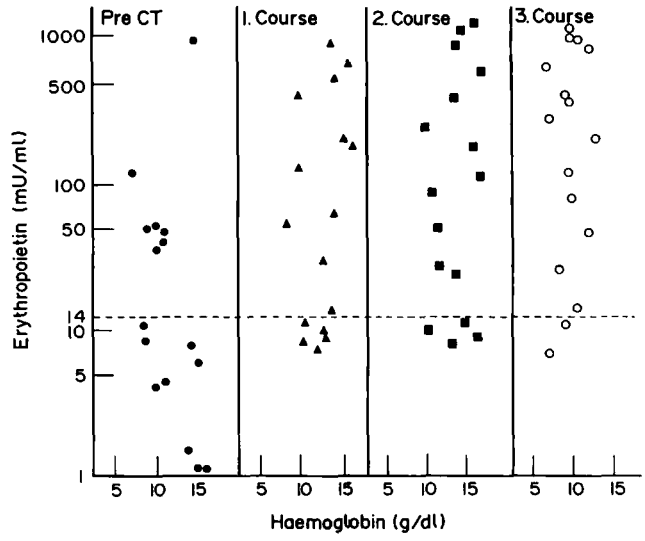

Fig. 1. Serum erythropoietin level changes after each cycle of cisplatin-containing chemotherapy.

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