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Changes in serum iron levels following very high-dose cisplatin*

C. F. Pollera[1], F. Ameglio[2], S. Reina[2], M. Nardi[1], M. R. Abbolito[2], and C. Parracino[2]

[1] Division of Medical Oncology I and
[2] Laboratory of Clinical Pathology, Regina Elena Institute for Cancer Research, Rome, Italy

Summary. A four-fold ($P<0.001$) mean increase in iron levels was found in 18 patients (a total of 36 courses of therapy) with ovarian cancer at the end of a 5-day course of cisplatin (40 mg/m^2 per day every 4–5 weeks). The kinetics of these modifications began very early (24–48 h after initiation of therapy): they reached their maximum on the 4th–5th day, coinciding with the last drug administration, and basal levels were recovered after the 10th day.

A subsequent eight-fold average increase ($P<0.001$) in ferritin serum levels, beginning 2 days after the iron changes, was observed, but showed a slower regression (after the 15th day). Reticulocyte counts were lowered ($P<0.001$) with the same time-course of the iron increases, but returned to pretreatment levels within 2 weeks. Total bilirubin and serum glutamate-pyruvate transaminase showed significantly delayed increases compared with iron.

The results are in keeping with a reduced iron utilization by the erythroid precursors, but other mechanisms cannot be excluded. There is no statistical correlation between the early iron increases and the subsequent hemoglobin nadir values.

Introduction

Increased iron levels and inhibited erythropoiesis have already been reported for the following cytotoxic agents: mechlorethamine [5, 12], methotrexate, 5-FU, dactinomycin, hydroxyurea [2] and vinca alkaloids [18]. A post-treatment increase in serum iron concentrations in patients receiving high-dose cisplatin and vindesine has recently also been reported [10]. Although many hypotheses have been suggested regarding these iron increase, the physiopathologic mechanism(s) is still not clear.

The aim of the present study was better definition of the time-course of the iron serum level modifications in patients receiving very high-dose cisplatin. The relationship between iron and other related variables, and some erythropoietic and hepatic indexes, have also been studied.

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Offprint requests to: C. F. Pollera, Istituto Regina Elena, Viale Regina Elena, 291, I-00161 Roma, Italia

Materials and methods

Between September 1984 and December 1985, a total of 18 patients (average age 47.9 years ± 12.7 standard deviation) with stages III and IV epithelial ovarian cancer were entered into the study. The patients reveived one to three courses (a total of 36) of very high-dose cisplatin (40 mg/m^2 per day for 5 days in 3% hypertonic saline together with an intensive hydration program) as either primary or salvage chemotherapy [6].

During the 6 weeks before the first course of chemotherapy, neither cytotoxic drugs nor blood transfusions or iron therapy were administered. In all cases the pretreatment creatinine clearance levels were greater than 50 ml/min (85.9 ± 23 ml/min).

Blood samples were withdrawn at three different times: on the morning just before the first drug administration (day 0), on the 7th day and after 4 weeks from the start of therapy.

Furthermore, 9 of the patients (18 courses of therapy) were monitored daily for the first 10 days of treatment.

The following analyses were performed: iron (Fe) (IRON, Roche, colorimetric method) and total iron-binding capacity (TIBC and UIBC = TIBC – Fe) (IBC test, Roche, colorimetric method), ferritin (FER) (Ferrizyme, Abbott, ELISA test), transferrin (TRF) and haptoglobin (HPT) (Beckman ICS II, automated immunonephelometer), bilirubin (BIL) and serum glutamate-pyruvate transaminase (SGPT) (Biochemia, Boeringwerke for 705 Hitachi, automated system), red blood cells (RBC), hemoglobin (Hb) and hematocrit (HT) (automatically determined with TOA CC800 instrument) and finally reticulocyte (RET) (conventional method) count.

Before starting chemotherapy and weekly thereafter, the patients were submitted to a complete set of routine biochemical and hematological analyses (data not presented). Quality controls were routinely performed for all the above-mentioned tests throughout the study.

Blood samples were obtained from the patients by venipuncture at 7 a. m. before the cisplatin administration. After adequate coagulation and centrifugation at room temperature these were analyzed within a few hours or frozen at −20 °C until determination.

To verify any possible cisplatin interference with the iron evaluation by the method employed, increasing quantities of this drug (0.2–48 μg/ml) were added to different fractions of a pool of human sera. No differences

were found in the iron levels determined in the cisplatin ranges tested, which mostly exceeded the reported serum values [6] (data not presented).

The normal reference ranges for each of the variables studied were: Fe: 49–151 μg/dl; UIBC: 186–260 μg/dl; FER: 5–270 ng/ml; TRF: 204–360; HPT: 27–139; SGPT: below 31 IU/l; BIL: below 1 mg/dl.

To compare the differences in the values obtained before and after treatment, two-way analysis of variance and Student's paired *t*-test were employed. In some cases the correlation coefficient *R* was also calculated [3].

Results

Table 1 shows the means and standard deviations for serum Fe, FER, TRF, HPT, UIBC, RBC, Ht, Hb, BIL and SGPT determined in the 18 patients studied at the three predetermined times.

Between days 0 and 7, highly statistically significant differences were found for Fe, FER, and UIBC ($P<0.001$), but no variations were evident for TRF and HPT. At the end of the observation period (4th week), the Fe and FER concentrations returned to pretreatment levels. The differences found between day 0 and the 4th week were not statistically significant. An eightfold average increase in FER (peak on day 8; range 2.5–30) was observed, together with less pronounced iron increases (peak on day 5, average increase of 4, range 2.1–6.8).

The average levels of RBC, Hb, and Ht were significantly higher on day 7 (at the end of an intensive hydration program) but again decreased within the 2nd week.

BIL concentrations increased significantly ($P<0.01$), being above normal limits in 44% of cases but exceeding 2 mg/dl in only 2 patients. When the levels were abnormal both the direct and the indirect quotas were higher (data not shown). A complete regression of these changes was observed within 2 weeks.

One week after chemotherapy was started the serum levels of SGPT were evidently higher, and 93% of the subjects had pathologic levels ($P<0.001$). Within 2 weeks, serum SGPT levels returned to pretreatment values.

For better definition of the earliest changes and the relationships between the variables considered, 9 patients (18 courses) were studied daily during the first 10 days of treatment.

Figure 1a–d shows the time-courses of the following variables: Fe, FER, RET, and SGPT. The mean value and standard deviation for each variable are also presented.

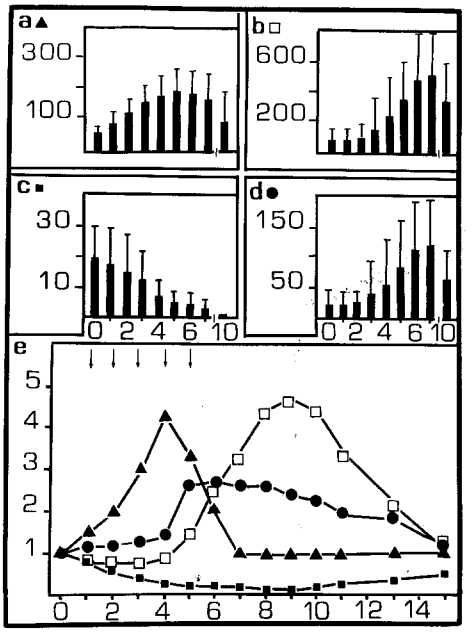

Fig. 1a–d. Mean values and standard deviations of four variables: **a** iron (▲, μg/dl); **b** ferritin (□, μg/ml); **c** reticulocyte count (■, cells/1000 red blood cells); **d** SGPT (●, units/l). **e** A paradigmatic case controlled for 15 days concerning these variables; the values are expressed as an increase in the post-treatment values/pretreatment values. The numbers shown on the *abscissa* represent days. ↓, cisplatin administration

As far as Fe and FER are concerned, the time-courses of the variables were quite different. The serum iron levels were clearly increased soon after the cisplatin administration (in many patients a twofold increase was found after only 24 h).

The elevation of serum iron concentrations was progressive during the first 4 days, reaching a peak at the time of the last cisplatin administration (Fig. 1a). This was followed by a slow decrease, which reached pretreatment values during the 2nd week after the start of therapy.

No changes in FER serum levels occurred before the 2nd or 3rd day. A progressive increase was subsequently observed, reaching a plateau on the 7th or 8th day (as shown in Fig. 1b), with very slow regression to the basal conditions after 2 weeks. A two-way analysis of variance performed on the first 10 days of observation showed that the changes were significant ($P<0.001$) for both Fe and FER.

Table 1. Mean values of variables evaluated in 18 patients receiving 36 courses of cisplatin (200 mg/m²/course)

Variables	Fe	FER	TRF	UIBC	HPT	RBC	Hb	Ht	RET	BIL	SGPT
Before treatment											
Mean	61.3	61.0	294.7	273.3	240.5	3.90	11.63	35.18	19.75	0.60	19.08
SD	20.3	56.8	103.8	47.5	121.4	0.59	1.64	9.59	11.80	0.20	11.20
1st week											
Mean	177.6*	495.3*	282.3	160.5*	253.7	4.30+	12.89+	37.72+	2.92*	1.10+	102.83*
SD	90.3	386.1	68.2	61.8	147.6	0.68	2.21	4.21	2.10	0.50	101.10
4th week											
Mean	65.4	170.4	287.3	261.6	211.8	3.76	11.26	34.68	18.13	0.60	23.41
SD	20.7	165.8	97.6	51.4	76.5	0.45	1.20	3.81	10.90	0.30	12.50

Abbreviations and units are defined in Materials and methods except for RBC (million/mmc), and RET (number/1000 RBC)
* = $P<0.001$; + = $P<0.05$. No statistical differences were found between pretreatment levels and those observed after 4 weeks

A dramatic fall in the RET count was observed during the 1 week of treatment (Fig. 1 c). A return to previous values within 2 weeks after chemotherapy was also evident.

No statistical changes were found for HPT and TRF (Table 1).

The increase of Fe in the serum significantly reduces the UIBC, a value calculated as the difference between TIBC and plasma iron ($P<0.001$).

SGPT concentrations were substantially modified during this type of treatment. In fact, Fig. 1 d shows an increase in these levels 2–3 days after treatment (peak on the 6th or 7th day), followed by a rapid recovery. The variations in the SGPT serum concentrations followed iron and preceded the FER changes.

Between the 2nd and the 4th weeks of treatment (21.2 ± 5 days) the Hb values decreased (11.5 ± 1.47 g/dl). These minimum values were significantly different (Student's paired t-test: $P<0.001$) from the pretreatment values.

A >2 g/dl decrease in the Hb concentration (9 ± 1 g/dl) was found in 41.7% of courses (11/18 patients). In the remaining cases a less pronounced Hb reduction was observed. Figure 1 e shows the behavior of the four variables in a single paradigmatic case.

Discussion

Few studies have evaluated early serum iron changes in patients receiving specific cytotoxic agents [2, 5, 9, 18]. Increased plasma iron levels have recently been observed in lung cancer patients receiving standard-dose cisplatin (120 mg/m^2 every 3 weeks) and vindesine (2 mg/m^2 weekly) [10]. These changes, however, occurred late after repeated chemotherapy (two courses in most cases), with return to the approximate pretreatment values a few months after chemotherapy was discontinued.

Since vinca alkaloids have been reported to have a substantial effect on serum iron levels early in treatment [2], the study reported by Graw et al. [10] could have evaluated the effects of the subsequent courses of vindesine rather than those of cisplatin; there are no known delayed effects of cisplatin on iron metabolism [19]. In the present study, we attempted to define the cisplatin-related iron modifications together with any clinical implications these might have.

To our knowledge, this is the first report concerning very early changes of iron and some other Fe-related variables in patients receiving only very high-dose cisplatin (200 mg/m^2 total dose) [11].

Our data show highly significant increases of serum iron levels ($P<0.001$), occurring early (approximately 24–48 h after the first cisplatin dose) and rapidly reaching the highest levels (fourfold increase on average on day 5 of treatment). A rapid fall follows the discontinuation of therapy, suggesting a direct relationship between the drug administration and its effects on iron.

How can these alterations be interpreted?

Any increase in dietary intake seems to be exclude, since the diet was standard and nausea and vomiting limited the food ingestion. Decreased excretion should be considered. In fact, increased serum levels of both BIL and of SGPT was observed, suggesting some degree of liver involvement with a possible reduction of iron excretion through bile efflux [11].

A relationship exists between liver diseases and iron increases [4], but the question to be answered is whether or not this increase is due to cisplatin-induced hepatic toxicity.

Our data show that the total BIL levels rarely exceeded 2 mg/dl and that SGPT rose about 2 days after iron changes. Alkaline phosphatase remained unmodified (data not shown). If SGPT, BIL, and alkaline phosphatase represent suitable indexes of hepatic toxicity [16] their time-courses, unlike those of iron, could reasonably be thought to exclude the possibility that iron changes initially depend on cisplatin-related hepatic injury.

In agreement with other reports [8], a hemolytic phenomenon could also be excluded, since the mean values for HPT were statistically unaffected during the first week of treatment (Table 1).

Of the Fe proteins, transferrin showed no modifications (UIBC, instead was significantly lowered). Ferritin presented a great increase (up to 30 times in some patients) but with a 2- to 3-day delay compared with the iron changes. Its time-course was similar to that of SGPT.

Of more than 30 variables observed, only the RET modifications varied with iron concentrations, although inversely (R ranged between -0.70 and -0.80). The reduction in reticulocytes was kinetically similar to that in iron increases.

Since the RET count represents a reliable erythropoietic index, the shift in both Fe and RET strongly suggests a lack of iron uptake by the erythroid precursors.

On the 7th day, at the same time as the RET decreased and the iron increased, a slight but significant ($P<0.05$) increase in Hb was observed. This paradoxical phenomenon could probably be explained by dehydration of the patient at the end of a vigorous hydration program.

Between the 2nd and the 4th weeks of treatment, a significant reduction in Hb values was observed ($P<0.001$). These modifications generally returned to the original values after the 4th week of therapy, the patients needing blood transfusions during 25% of courses.

An erythropoietin deficiency syndrome related to a nephrotoxic effect has been suggested as a possible cause of the anemia affecting patients receiving prolonged courses of cisplatin [8, 19]. However, a strict correlation between erythropoietin serum values and reticulocyte counts was not observed [17, 19]. A recent study demonstrates that cisplatin-induced anemia is not mediated through erythropoietin [7]. In the present report, serum creatinine levels were transiently higher than 2 mg/dl in only 8% of courses, with no close relationship to the iron changes. Therefore, at present, the data do not indicate a nephrotoxic-induced erythropoietin deficiency as a possible cause of impaired iron utilization. Evidence of a blocking effect of cisplatin in the biosynthesis of porphyrins and haem has been reported [1]. The recently suggested lead mobilization during cisplatin chemotherapy [9], with its possible role in erythropoiesis inhibition, is the latest exciting finding.

The progressive kidney iron deposit described in rats receiving weekly doses of cisplatin [13] could be a possible delayed effect of repeated cisplatin-induced increases in serum iron levels in humans [14]. In light of this new information, further studies are needed to clarify the mechanism(s) of these phenomena and their clinical implications, especially for anemia in patients with defective iron utilization by erythroid precursors.

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