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Assessment of Renal Function during High-Dose *cis*-Platinum Therapy in Patients with Ovarian Carcinoma

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Summary. *Five courses of cis-dichlorodiammine platinum (II) (100 mg/m^2) were given to 22 patients with advanced stage III and IV ovarian cancer. Renal function was assessed by measurement of creatinine clearance, urinary osmolality and urinary B_2-microglobulin (B_2MG) in all patients, and by urinary alanine aminopeptidase (AAP) and N-acetyl-B-glucosaminidase (NAG) excretion in seven patients.*

Serum creatinine, creatinine clearance, urinary osmolality, and urinary B_2-microglobulin were within the reference ranges and did not change significantly after five courses of cis-platinum in any patient.

There was a significant increase in the urinary excretion of both enzymes (AAP and NAG) within 2 days of cis-platinum administration (NAG $P < 0.05$ and AAP $P < 0.07$). There was evidence of a cumulative effect during treatment for AAP ($P < 0.025$).

Introduction

cis-Dichlorodiammine platinum (II) (CDDP) is a useful chemotherapeutic agent, particularly against ovarian and testicular tumours [7, 8]. Nephrotoxicity was a great problem in the early studies with this drug, but the incidence of this declined markedly with the introduction of hydration and induced diuresis during administration of CDDP [2, 6, 12]. However, there may be nephrotoxic effects not detected by measurement of serum BUN and creatinine, which could possibly produce renal damage in the long term or predispose to renal failure if the patient is exposed later to additional nephrotoxic agents such as the aminoglycoside antibiotics or irradiation.

B_2-Microgloblin (B_2MG) is a low-molecular-weight protein filtered through the glomerulus and almost entirely reabsorbed in the proximal tubules. An increase in the urinary excretion of B_2MG in the presence of normal serum levels may indicate proximal tubular damage. The excretion of urinary enzymes has been suggested as a sensitive measure of tubular damage [13] caused, for example, by *cis*-platinum [3].

In this study patients with late-stage ovarian cancer were to receive five courses of high-dose CDDP alone. We were particularly interested in monitoring subtle changes of renal function, since patients in surgically confirmed complete remissions were to receive total abdominal radiotherapy. Renal function was therefore assessed by measuring creatinine clearance, urine osmolality, B_2MG, *N*-acetyl-β-glucosaminidase (NAG), and alanine aminopeptidase (AAP) excretion during treatment.

Patients and Methods

Chemotherapy. Twenty-two previously untreated patients with advanced ovarian carcinoma (stages III and IV) were treated with five courses of *cis*-dichlorodiammine platinum (II) 100 mg/m^2 given as a bolus at 3-weekly intervals. Each patient was admitted the day before treatment and given 3 l of saline (each with 10 mmol KCl added) IV over 24 h (day 1). On the second day each patient received 5 l of saline + 1 l of 10% mannitol over 24 h (day 2). The bolus of CDDP was given 1 h after the beginning of this second 24-h period.

Samples. Each patient fasted from 9 p.m. prior to day 1, and the early morning urine on day 1 was taken as a concentrated specimen for osmolality and B_2MG estimation. Urine from the 24-h day 1 period was collected for creatinine excretion and estimation of creatinine clearance.

In some patients concentrated early morning urine specimens were collected as described above an average of 34 h (range

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30–37 h) before, 38 h (range 35–42 h) after, and 62 h (range 59–65 h) after each injection of CDDP. The levels of AAP and NAG in these urine specimens were determined. Samples from 25 normal women of a variety of ages were measured as controls.

Assay Methods. Urines were concentrated by ultrafiltration and AAP was assayed by enzymatic hydrolysis of alanine-*p*-nitroanilide in phosphate buffer pH 7.6 by measuring the changes in absorbance at 405 nm due to the formation of *p*-nitroaniline [11].

N-Acetyl-*B*-glucosaminidase was assayed by measuring the change in absorbance at 410 nm due to the formation of *p*-nitrophenol following enzymatic hydrolysis of *p*-nitrophenol-*N*-acetyl-*B*-glucosaminide in citrate buffer pH 4.8 [14].

B_2-Microglobulin was measured by the Phadebas B_2-micro Test RIA kit from Pharmacia Diagnostics. Serum and urinary creatinine were measured on a Technicon SMA 12/60 and urinary osmolality on an Osmette precision osmometer.

Results

The mean serum creatinine and creatinine clearance did not change significantly during treatment. Serial creatinine clearances in seven representative patients are shown in Fig. 1. Three of these began treatment

Table 1. Urinary excretion of NAG and AAP prior to administration of CDDP[a]

Patient	Age (years)	Course of treatment	NAG (IU/mmol creatinine)	AAP (IU/mmol creatinine)
OM	37	3	4.09	0.23
		4	6.46	0.31
MK	44	4	1.18	0.02
		5	1.05	0.11
DW	51	4	2.81	0.26
		5	5.45	0.35
WB	58	3	5.37	0.38
		4	5.39	0.55
		5	4.08	0.67
JA	59	2	2.36	0.11
		3	2.25	0.41
JF	59	2	1.63	0.08
QH	60	3	9.26	0.81
Reference range of 25 controls (ages 25–60 years)			0.36–1.59	0.01–0.24

[a] CDDP was administered in five courses at 3-weekly intervals. Urine samples were collected 34 h before each course of treatment

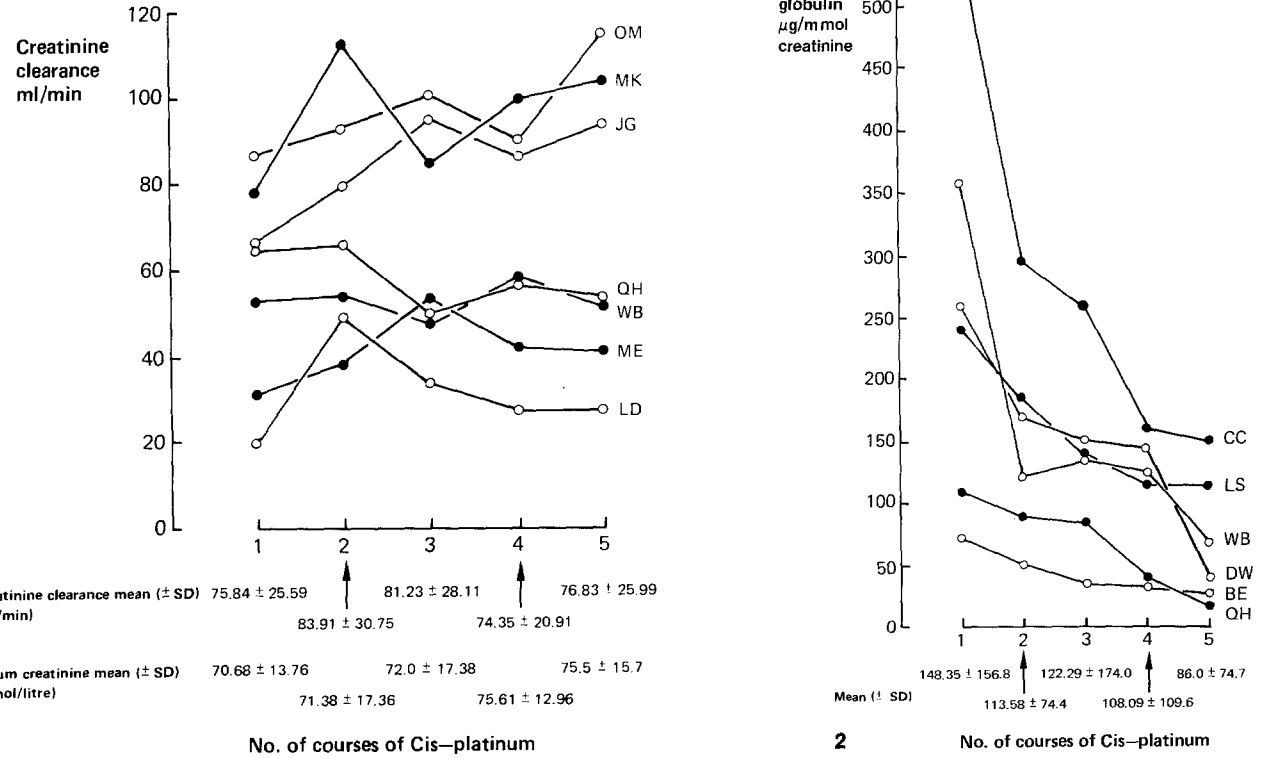

Fig. 1. Serial creatinine clearances on seven representative patients. The mean ($n = 22$) and standard deviation (SD) of creatinine clearance and serum creatinine are shown

Fig. 2. The pattern of B_2MG excretion on six representative patients. The mean ($n = 22$) and standard deviation (SD) are shown

Table 2. Changes in urinary excretion of NAG and AAP 34 h before and 38 h and 62 h after treatment with CDDP

Patient	Age (years)	Course of treatment	AAP (IU/mmol creatinine)			NAG (IU/mmol creatinine)		
			34 h before	38 h after	68 h after	34 h before	38 h after	68 h after
DW	51	4	0.26	0.42	0.46	2.81	9.23	5.08
		5	0.35	0.75	0.52	5.45	3.20	3.97
JA	59	2	0.11	0.14	0.18	2.36	6.75	9.01
		3	0.41	0.27	0.13	2.25	4.32	3.55
OM	37	3	0.23	0.51	0.20	4.09	4.95	4.75
		4	0.31	0.43	0.28	6.46	6.24	2.40
MK	44	4	0.02	0.12	0.01	1.18	4.96	3.57
		5	0.11	0.32	0.15	1.05	3.61	8.00
WB	58	3	0.38	1.48	0.80	5.37	8.93	11.12
		4	0.55	0.72	0.27	5.39	6.90	3.33
Reference range AAP < 0.24 IU/mmol creatinine						NAG < 1.59 IU/mmol creatinine		

with clearances below 60 ml/min but there was no overall decline in renal function initially.

The pattern of B_2MG excretion for seven patients is shown in Fig. 2. There was an overall decline in excretion during treatment, with a mean value for 22 patients of 148.35 μg/mmol creatinine before treatment and 86.0 μg/mmol creatinine before the fifth course of CDDP. Mean urine osmolality was unchanged during treatment (initial mean 607.4 mmol/kg, final mean 608.3 mmol/kg, $n = 22$).

The upper limit of the control value for urinary NAG was 1.59 IU/mmol creatinine and that for AAP was 0.24 IU/mmol creatinine. There was a tendency for the levels to rise with age, but there was also marked variability from day to day within the control group. Urinary excretion of NAG and AAP before administration of the second to the fifth courses of CDDP for seven patients is also shown in Table 1. The pretreatment urinary NAG was raised in five of seven patients when measured after the first course of CDDP. Four of seven patients had at least one elevated pretreatment level of AAP.

The change in urinary NAG and AAP between the 34-h pretreatment values and 38- and 62-h posttreatment values is shown in Table 2 (5 patients). There was a tendency for the 38-h posttreatment level to be highest (NAG $P < 0.05$ AAP $P < 0.07$, paired t-test) with a decline at 62 h, but this was by no means universal. There is some evidence for cumulative toxicity in that there was a significant ($P < 0.025$, paired t-test) increase in consecutive pretreatment levels of AAP. This trend was not seen for NAG.

Discussion

With adequate hydration and diuresis the serum creatinine and creatinine clearance have not been found to be a good measure of the presumed minor degrees of renal impairment induced in this study by CDDP. In patients given CDDP without hydration or diuresis a rise in BUN or serum creatinine was seen in 26%–36% [5]. After the introduction of hydration and diuresis less than 5% were reported with a rise in these values after CDDP treatment [12]. The serum creatinine is an insensitive measure of renal function. When they measured creatinine clearance, both Dentino et al. [2] and Jones et al. [10] showed some fall in clearance after CDDP 20 mg/day for 5 days or 120 mg/m^2 as a bolus, respectively, even in well-hydrated patients. In the study reported here both pre- and post-CDDP hydration was used, and may have accounted for the lack of toxicity in terms of creatinine clearance. Great caution was used because patients were due to receive total abdominal radiation by the strip technique after five courses of CDDP. The degree of hydration does not appear to impair the overall response rate to CDDP, which was 76% in this study.

B_2-Microglobulin excretion was shown to rise after CDDP in the studies of Jones et as. [9], Cohen et al. [1] and Fleming et al. [43]. Jones et al. [10] showed that a rise in B_2MG excretion did not correlate with the fall in creatinine clearance that occurred in some patients. In the studies cited above, B_2MG excretion was assessed mainly before and shortly after CDDP administration. The excretion of

this protein increased in most patients within 5 days of treatment and then fell.

In some patients, however, excretion was still raised until the subsequent CDDP course. In our study B_2MG was measured immediately prior to the subsequent CDDP course only, and was found to fall with the number of courses given. The initial higher B_2MG levels may be attributable to raised serum levels and therefore increased filtered load. The lower levels with treatment may also reflect progressive lowering of serum B_2MG.

AAP is localised in the brush border membrane of the proximal tubules. NAG is a lysosomal enzyme; its highest activity is found in the proximal tubule but it is also located in the distal tubule. Both AAP and NAG are thought to be a sensitive measure of tubular damage. NAG excretion was raised in five of seven patients and AAP in four of seven prior to the subsequent course of CDDP, and AAP excretion gave some evidence for a cumulative nephrotoxic effect of CDDP. Jones et al. also showed rises in AAP and NAG excretion, particularly 36–48 h after CDDP, but again found that this did not correlate with a fall in creatinine clearance.

The importance of these rather subtle changes in renal function induced with CDDP is at present unknown. They occur without gross changes in the creatinine clearance, but each patient should be followed for as long as lack of recurrence will allow, in order to attempt to assess their importance. It is possible that the changes in urinary enzyme excretion may be transitory. Therefore, when this treatment protocol is used the drug seems to have negligible nephrotoxicity. The major dose-limiting factor for CDDP may be neurotoxicity.

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