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Beta-2-microglobulin excretion: An indicator of long term nephrotoxicity during *cis*-platinum treatment?

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Summary. *To evaluate the value of beta-2-microglobulin as an indicator of acute and long-term cis-platinum-induced nephrotoxicity, ^{51}Cr-EDTA clearance and serum concentration and urinary excretion of beta-2-microglobulin were measured in 18 patients treated with a regimen including cis-platinum. Before treatment all values were within the normal range. During treatment ^{51}Cr-EDTA clearance decreased from 108 to 90 ml/min/1.73 m^2 ($P < 0.02$). The decrease was irreversible, while a transient 2 to 5-fold increase in beta-2-microglobulin excretion in the urine was seen during treatment. Serum beta-2-microglobulin remained unchanged. The decrease in ^{51}Cr-EDTA clearance was not correlated to either the peak increase in the beta-2-microglobulin excretion or to the time of occurrence of the peak ($R = 0.3$). Thus, it is not possible to predict the long-term nephrotoxicity of cis-platinum by measuring the beta-2-microglobulin excretion during treatment.*

Introduction

The nephrotoxicity of *cis*-platinum is the dose-limiting factor in its clinical usage. In previous studies, it has been shown that the glomerular filtration rate (GFR) decreases during treatment [12] and that this decrease is sustained for at least 2 years [14]. As the major nephrotoxicity of *cis*-platinum presumably is due to tubular damage [3], it may not be optimum to monitor the function of the kidneys by means of an index of the GFR. Beta-2-microglobulin is filtered through the glomerular membrane and is reabsorbed and metabolized in the cells of the proximal tubules [2]. The concentration of beta-2-microglobulin in the urine therefore should be expected to increase as a consequence of significant tubular damage. The aim of the present study was to evaluate whether changes in serum concentration and urinary excretion of beta-2-microglobulin during *cis*-platinum treatment could be used as indices of tubular nephrotoxicity and to predict the long-term toxicity of the drug.

Materials and methods

Patients. In all, 18 patients (age range 18–38 years) with non-seminomatous germ cell tumors of the testis were included in the trial. During treatment seven patients died or relapsed, leaving 11 evaluable patients. None of the patients had a history or clinical or biochemical evidence of previous kidney disease. All were normotensive and none had previously received chemotherapy or been treated with drugs known to be nephrotoxic.

Regimen. The Einhorn regimen [4] included: Treatment with *cis*-platinum, vinblastine, and bleomycin (Fig. 1). *cis*-Platinum was given at a daily dose of 20 mg/m^2 by 15-min IV infusion for 5 consecutive days (days 1–5) every 3 weeks for six courses. On each day the administration of *cis*-platinum was preceded and followed by a hydration regimen with a total of 4 l isotonic fluids. The *cis*-platinum was given together with mannitol according to a slight modification of the Frick regimen [6].

Vinblastine was given at a dose of 6 mg/m^2 IV on days 1 and 2 of each of the six *cis*-platinum courses. Bleomycin was given as an IV bolus of 15 mg/m^2 on days 2, 9, and 16 of each of the first three *cis*-platinum courses, and at a dosage of 5 mg/m^2 on the same days of the last three courses. The total treatment period was 18 weeks.

Kidney function. Before the treatment and after the third and the sixth of the six *cis*-platinum courses ^{51}Cr-EDTA clearance was determined by means of a one-plasma-sample method [8]. The determination of ^{51}Cr-EDTA clearance was repeated 6 months after the termination of the treatment. Serum creatinine was measured at least once in connection with every

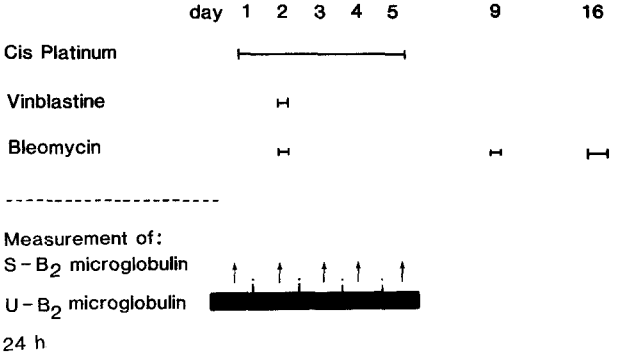

Fig. 1. The schedule of one chemotherapeutic treatment course, with indication of the serum and urine measurements. The course was repeated five times with 3-week intervals. The total treatment period was 126 days

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course. The concentration of albumin in the urine of the first four patients was analyzed for days 1–5 of each course. The analysis was performed according to a single radial immunodiffusion method [10]. As only traces of albumin were found, the albumin in the urine of the rest of the patients was estimated only by means of Hema-combistix daily on days 1–5 of each of the six treatment courses.

Beta-2-microglobulin assay. Beta-2-microglobulin was measured in serum and urine daily on days 1–5 (Fig. 1) during each of the six treatment courses. Samples of the urine and serum were stored at −20° C. All specimens (n = 1,100) were then analyzed blind in a consecutive run using the radioimmunoassay devised by Plesner [13]. The coefficient of variation determined on double measurements was 9%.

Results

Kidney function

At the termination of the treatment, ^{51}Cr-EDTA clearance had significantly decreased from an initial average of 108 ml/min/1.73 m^2 to 90 ml/min/1.73 m^2 ($P < 0.02$). No significant improvement was seen within the next 6 months after the termination of treatment (GFR = 92 ml/min/1.73 m^2). In none of the patients was any significant increase in serum creatinine or proteinuria observed before, during, or 6 months after termination of the treatment.

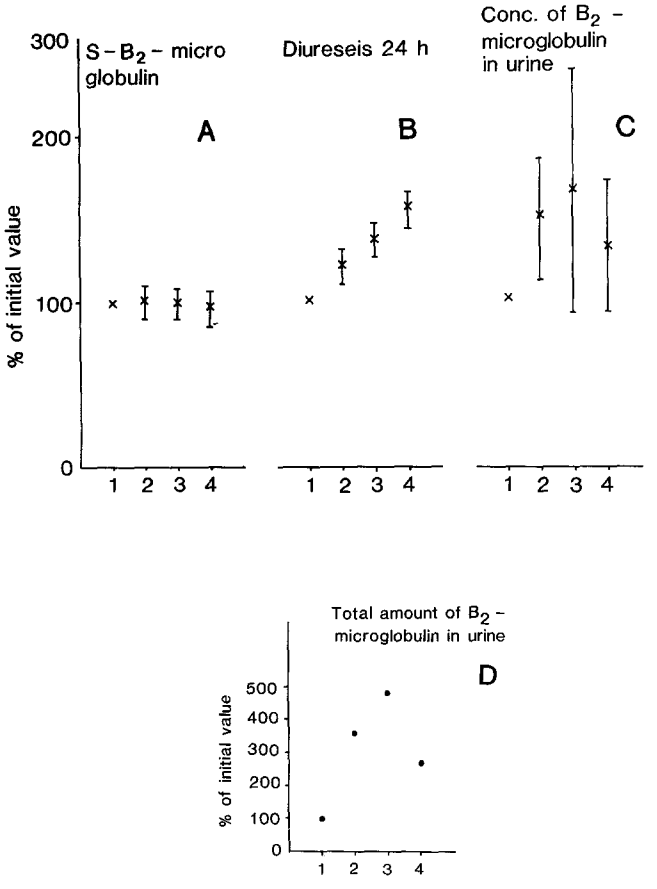

Fig. 2A–D. Cumulative in serum beta-2-microglobulin (**A**), 24-h diuresis (**B**), beta-2-microglobulin concentration in the 24-h urine (**C**), and total excretion in the 24-h urines during 5 days of treatment (**D**). The treatment was repeated every 3 weeks for a total of six cycles

Beta-2-microglobulin

Figure 2 shows the variation of beta-2-microglobulin in serum and urine during the 5 days of *cis*-platinum treatment. Before treatment, the mean serum beta-2-microglobulin was 142 ± 12 nmol/l (mean ± SD) (normal range 50–190 nmol/l). In Fig. 2A it can be seen that there were no significant changes in the serum concentration of beta-2-microglobulin ($P > 0.05$) during the 5 days of *cis*-platinum administration. Nor did the beta-2-microglobulin in serum change significantly from course to course.

During the 5 days of hydration there was a significant increase in diuresis ($P < 0.001$) (Fig. 2B). This was paralleled by a marked increase ($P < 0.01$) in both the concentration and the total amount of beta-2-microglobulin in the urine (Fig. 2C and D).

A 2- to 5-fold increase in beta-2-microglobulin excretion in the urine was observed in all patients. In the main, this marked variation was attributable to the results recorded in two patients. They experienced an excessive increase in beta-2-microglobulin excretion during the first two treatment courses. During the last four courses their results followed the trend of the other patients.

The decrease in ^{51}Cr-EDTA clearance was not correlated to either the peak increase in the beta-2-microglobulin excretion or to the time of occurrence of the peak (R = 0.3).

Discussion

The initial pathologic change in the kidney after *cis*-platinum treatment is tubular necrosis affecting primarily the distal convoluted tubules, while neither glomerular nor vascular lesions have been reported [7, 9]. Beta-2-microglobulin is produced by the nucleated cells and is rapidly eliminated by glomerular filtration, followed by 99.9% reabsorption in the proximal tubule cells, where it is catabolized [2]. The results of the present study are consistent with these ideas. Before and during treatment the serum levels of beta-2-microglobulin were within the normal range and no significant changes within or between treatment courses were seen. In contrast, a significant and irreversible decrease in GFR, as evaluated by ^{51}Cr-EDTA, was seen.

If the production of beta-2-microglobulin were constant, the serum level of beta-2-microglobulin would be determined by the glomerular filtration rate, and the serum level of beta-2-microglobulin could be expected to rise during the trial as the GFR decreased. This was not the case, and a decrease in the production or a leakage in the microvascular bed with extravascular catabolism of beta-2-microglobulin can be postulated.

In a variety of solid tumors an increase in serum beta-2-microglobulin concentration is seen, caused by a stimulation of the immunocytes by the tumor products. When the patients responded to treatment the serum beta-2-microglobulin normalized. This is not a familiar finding in testicular cancer [2], and a leakage in the microvascular bed can be postulated. In a comparable group of patients undergoing the same treatment we have not been able to show any increase in the transcapillary escape rate [15]. We conclude that no disease- or treatment-induced damage to the microvascular

bed could be identified, so we were not able to explain the above-mentioned discrepancies.

In a similar trial, Meijer et al. [12] also found an irreversible decrease in GFR, while they also found an unchanged *s*-beta-2-microglobulin level during *cis*-platinum treatment. They thought that this discrepancy could be explained by a decrease in the production in beta-2-microglobulin during treatment.

By measuring the albumin and beta-2-microglobulin in the urine it is possible to distinguish between glomerular and tubular damage. In this study we observed a 2- to 5-fold increase in the excretion of beta-2-microglobulin in the urine, while no increase was seen in the albumin excretion. The excretion returned to normal within each treatment course, indicating a selective transient damage to the tubular cells of the kidney during *cis*-platinum treatment. This is consistent with the pathologic findings and in agreement with the findings of other groups [1, 5, 11].

No correlation was established between long-term toxicity reflected in decreasing ^{51}Cr-EDTA clearance and acute tubular damage reflected in increasing beta-2-microglobulin excretion in the urine.

Therefore, we conclude that there is transient tubular damage during *cis*-platinum treatment, but that there is no correlation between acute and chronic toxicity. Consequently, measurements of beta-2-microglobulin excretion in the urine cannot predict the long-term decrease in kidney function during *cis*-platinum treatment.

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