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CIS-platinum and the kidney. Renal function during treatment with cis-diammine-dichloro-platinum

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Summary

Cis-platinum or cis-diammine-dichloro-platinum (CDDP), a compound of platinum, has antineoplastic activity. An important side-effect of CDDP is its nephrotoxicity.

In chapter 1 the purpose of this thesis is formulated. An answer was sought to questions about incidence, character and prevention of CDDP-induced nephrotoxicity. The investigations were performed in patients with disseminated testicular cancer. All patients were treated similarly. This treatment consisted of a remission-induction phase of 4 courses. In each course of 3 weeks CDDP in a dosage of 20 mg/m² was administered on each of 5 consecutive days. This regimen also included vinblastine and bleomycin, drugs of which no nephrotoxicity has been reported. This remission-induction phase was followed by a maintenance therapy during one year, in which CDDP was given once every 6 weeks in a dosage of 50 mg/m².

In chapter 2 a review of the literature about CDDP-induced nephrotoxicity is given. In the initial phase of experimental acute renal failure a fall in renal plasma flow (RPF) occurred, usually accompanied by a reduction in glomerular filtration rate (GFR). In animals CDDP caused disturbances in renal function and morphologically tubulo-interstitial changes. The nephrotoxicity was dose related, its reversibility remained unclear. Reports on human nephrotoxicity are without conformity. Our observations obtained at various moments of treatment only partly agree with the experience of other authors. Finally, measures to prevent nephrotoxicity are discussed.

In chapter 3 renal function is evaluated in 24 patients during the remission-induction phase. GFR, effective renal plasma flow (ERPF), serum concentration of creatinine and beta-2-microglobulin were determined. At the end of the remission-induction phase median GFR and ERPF both were reduced 23% ($p < 0.01$). A nephrotoxic effect, hemodynamically induced and acting directly on the glomerular tuft is postulated on grounds of the relative change in ERPF and absolute change in filtration fraction ($FF = GFR/ERPF$) compared to pretreatment values. The reduction in GFR and ERPF remained unaltered in the 6 weeks after the remission-induction therapy. Serum creatinine and beta-2-microglobulin however did not rise. It is suggested that under the influence of chemotherapy with

CDDP the production of creatinine and beta-2-microglobulin is decreased. Thus, serum creatinine and beta-2-microglobulin are unsuitable as parameters for renal function.

Chapter 4 deals with the course in renal function before and after the remission-induction and maintenance therapy in 9 patients. The median GFR decreased during the remission-induction therapy from 146 to 118 ml/min. During the maintenance therapy no change in median GFR was found. It is concluded that neither cumulation nor reversibility in nephrotoxicity occurred. The median ERPF decreased over the total observation period from 705 to 514 ml/min. Median FF and serum creatinine were not changed significantly. It is suggested that intrarenal hemodynamic changes play a role in the nephrotoxicity of CDDP.

In chapter 5 the course in renal function in 8 patients during therapy and 1 year after its termination is described. The median GFR decreased in comparison with the pretreatment value 15.5% at the start of the maintenance therapy, 23% at the end of the maintenance therapy and 15.5% one year after termination of therapy. The comparable reduction in ERPF at those instants was 15.5, 19 and 23.5%, respectively. Indications for cumulative nephrotoxicity during therapy or improvement of renal function one year after treatment were not found. Serum levels of creatinine and beta-2-microglobulin did not express the changes in renal function.

Finally, in chapter 6 some concluding remarks about the questions posed in the first chapter are made and an outline for future research is given.