Acta Oncologica 27 (1988) Fasc. 5

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EDTA CLEARANCE IN MONITORING CISPLATIN DOSE ESCALATION IN PATIENTS WITH BULKY METASTATIC GERM CELL TUMORS OF THE TESTIS

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Abstract

A fast cisplatin clearance may reduce exposure time of tumor cells to the drug, and thus impair the expected effects of dose escalation. This hypothesis was tested in 23 patients with bulky metastatic germ cell tumors of the testis, treated with etoposide, bleomycin and high-dose cisplatin (60 mg/m^2/24 h×4). The daily dose was retrospectively calculated in mg/l EDTA clearance/24 h. A daily dose of 60 mg/m^2 of cisplatin in a person with a body surface of 1.7 m^2 and EDTA clearance of 100 ml/min was equivalent to 0.69 mg cisplatin/l EDTA clearance/24 h. In the whole group, 10 patients had complete remission (CR), 10 partial response (PR) and 3 progressive disease (PD). The mean daily cisplatin dose ($\bar{X}$) in the whole group was 0.86 mg/l EDTA clearance/24 h (range 0.35–2.00). For patients with CR, $\bar{X} \pm$ SD was 1.00±0.46, for those with PR 0.80±0.44, and for those with PD only 0.61±0.07. A cisplatin dose over 0.86 mg/l EDTA clearance/24 h × 4 was obtained in 6/10 patients with CR versus 2/13 patients with PR + PD. Patients with PD received a significantly lower cisplatin dose than the whole group (0.61 versus 0.86 mg cisplatin/l EDTA clearance/24 h × 4.) The difference between the average toxicity grade after cisplatin dose over and below 0.69 mg/l EDTA clearance/24 h × 4 was significant only for leukocytes (WHO grade 2.17 versus 1.36). Thus, the effective escalated dose of cisplatin should preferably be calculated not per m^2 body surface but per 1 liter EDTA clearance. The 'ideal' escalated dose might be about 0.86–1.0 mg cisplatin/l EDTA clearance 24 h × 4.

Key words: Testis, neoplasms; germ cell tumors, bulky metastasis, cisplatin, dose escalation, EDTA clearance.

In patients with testicular cancer, the cytostatic effect of cis-diamminodichloroplatinum (cisplatin) has been shown to be dose dependant (11). Bulky disease is less responsive to the usual cisplatin schedules (8) and may therefore require escalation of the dose (6).

Cisplatin is mainly eliminated through the kidneys. This elimination is dependant on the protein-bound fraction of the drug, and its specific renal clearance. The life-span of therapeutic cisplatin concentrations in the plasma might be related to the clearance of the drug. A fast cisplatin clearance may reduce exposure time of tumor cells to the drug and thus impair the expected effect of dose escalation.

Cisplatin clearance is probably dependant on mechanisms similar to those which determine renal clearance of creatinine, EDTA and other substances with a similar excretion pathway. All these clearances are subject to wide individual variations. Renal handling of cisplatin is, however, known to include also mechanisms involved in tubular secretion (5). The importance of this cisplatin fraction in the renal handling of the drug has not yet been completely clarified.

The aim of our retrospective analysis was to determine whether the response rate of patients with bulky metastatic testicular germ cell tumors, receiving the same cisplatin dosage per m^2 of body surface per 24 h, had any relation to EDTA clearance rate, and to test whether the calculation of individual dosage per m^2 was a suitable tool for obtaining optimal therapeutic cisplatin dose.

Material and Methods

The retrospective analysis included 23 patients with bulky metastases from testicular germ cell tumors verified by current criteria (10).

The induction treatment comprised 6 chemotherapy cycles consisting of:

Presented at ECCO-4, Madrid, November 1–4, 1987.

- cisplatin 60 mg/m^2/24 h in 3% NaCl infusion days 1–4, with 3.5 l i.v. and 3.0 l p.o. hydration per day, chlorpromasine and/or methylprednisolon as antiemetics and both mannitol and furosemide induced diuresis.
- etoposide 120 mg/m^2/24 h i.v. days 1–5,
- bleomycin 10 mg/24 h i.m. days 1–5.

Assessement of treatment results, which was done following 6 courses, was performed according to the WHO criteria (4), including for complete remission normal physical examination, normal tumor marker levels (β-HCG, α-fetoprotein), normal chest radiogram and normal abdominal CT scan (or absence of malignant tissue in any resected residual postchemotherapy mass). In the whole group there were 10 complete remissions (CR), 10 partial responses (PR) and 3 patients with progressive disease (PD), patients classified as PD displaying at most a transitory minor response not exceeding 50% tumor mass reduction during the initial cycles.

In our study, the daily dose of cisplatin (60 mg/m^2) in a patient with a body surface of 1.7 m^2 was roughly equal to 100 mg. The mean normal EDTA clearance in healthy adults, according to reference values from our laboratory, is 100 ml/min which means 144 l/24 h. A total daily dose of X mg/m^2 cisplatin in a person with an EDTA clearance of Y l/24 h is equivalent to X/Y mg cisplatin/l EDTA clearance/24 h.

Toxicity was graded according to the WHO criteria (4).

Statistical tests included Student's t-test and Fisher's exact probability test. The aims of the statistical analyses (3, 9) were:

- to determine the mean daily cisplatin dose in mg/l EDTA clearance/24 h in the whole group of 23 patients, and the mean and median cisplatin doses per l EDTA clearance/24 h in patients with CR, PR and PD respectively.
- to determine the statistical significance of differences between mean values of daily cisplatin dose in mg/l EDTA clearance/24 h for patients with CR, PR and PD.
- to test the difference between the proportions of patients with CR and PR+PD after a dose of cisplatin/l EDTA clearance/24 h higher than the mean daily dose in the whole group.
- to test if the mean daily dose of cisplatin/l EDTA clearance/24 h administered to patients with PD was the same as the dose administered to the whole group (i.e. CR+PR+PD).

Results

The dose of 60 mg/m^2/24 h in a person with a body surface of 1.7 m^2, i.e. a dose of 100 mg cisplatin per day (i.e. the dose such patients actually received), in a person with EDTA clearance of 144 l/24 h was equivalent to 0.69 mg cisplatin/l EDTA clearance/24 h. The mean cisplatin dose in the whole group was 0.86 mg cisplatin/l EDTA clearance/24 h with a very wide range between 0.35 and 2.00 mg.

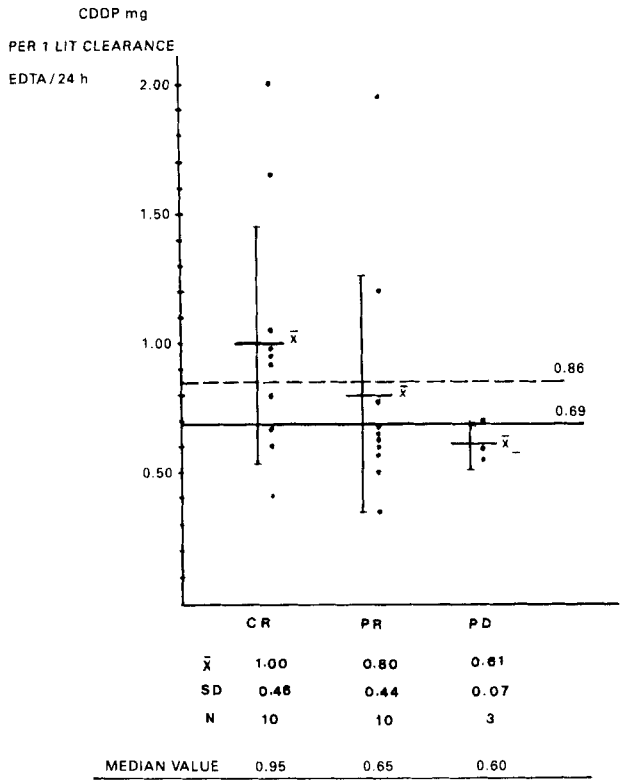

Figure. Response to treatment in relation to administered dose of cisplatin (CDDP) per l EDTA clearance/24 h. 0.86= mean cisplatin daily dose for whole group. 0,69= daily dose corresponding to 60 mg/m^2/24 h for a person with a body surface of 1.7 m^2 (calculated as 100 mg). CR = complete remission, PR = partial response, PD = progressive disease.

The results are presented in the Figure: 6/10 patients with CR received a daily dose of cisplatin per l EDTA clearance/24 h higher than the mean value for the whole group versus 2/13 patients with PR+PD; the difference with the Fisher's exact probability test is statistically significant (p=0.039 2-sided). Both mean and median values were highest in the CR group and lowest in the PD group. The differences between the 3 mean values were not statistically significant because of a large spread of the individual values, especially in the PR group. However, the cisplatin dose per l EDTA clearance/24 h in the PD group was significantly lower than in the whole group of patients (0.61 versus 0.86 mg, t=5.2, p<0.01).

Hematological and renal toxicities were roughly similar for patients receiving a dose of cisplatin above or below 0.69 mg/l EDTA clearance/24 h, and a significant difference was observed only for leukocytes. No grade II renal toxicity was observed. Hematological toxicity grade IV was noted in only one patient who received a cisplatin dose of 2.00 mg/l EDTA clearance/24 h (Table).

Table

Toxicity grading

Parameter	Mean toxicity grade*	
	0.69 mg/l EDTA clearance/24 h	
	CDDP dose over	CDDP dose below
Hemoglobin	1.92	1.55
Leukocytes	2.17	1.36
Plastelets	1.17	1.55
Creatinine	0.58	0.27

* WHO criteria (3)

Discussion

In several series, dose escalation of cisplatin in patients with bulky germ cell tumor disease has been carried out with encouraging, but not univocal results (1, 7, 12). CR rates ranging from 17 to 88% have been reported. The different response in patients receiving a similar cisplatin dose per m^2/24 h may be due to several factors. One might be the time of tumor cell exposure to an effective cisplatin concentration, which would in turn be a function of the cisplatin renal excretion rate. At the start of this study, we presumed that the proportion of complete remissions could be related to the 'effective' cisplatin dose expressed as cisplatin dose/l EDTA clearance/24 h. This presumption would imply that patients with a fast EDTA clearance without further cisplatin dose escalation might be underdosed.

EDTA clearance was believed to be more suitable for this study than creatinine clearance. In fact, 25% of chromogenic substances determined as 'creatinine' are not creatinine at all, but different metabolites with renal excretion different from creatinine. The levels of these metabolites may vary in pathologic conditions, making creatinine clearance imprecise as a test for glomerular filtration (2).

Although the dose of cisplatin administered per m^2/24 h was the same in all our patients, the cisplatin dose per l EDTA clearance/24 h varied 6-fold. Larger doses of cisplatin per l EDTA clearance/24 h were more frequently associated with CR than lower doses. For patients with fast EDTA clearance (over 144 l/24 h) a dose escalation of cisplatin, based on EDTA clearance, seems warranted. The 'effective' dose of cisplatin, i.e. the dose calculated per l EDTA clearance/24 h seems to be an important, but probably not the only, factor determining response to treatment in bulky metastatic germ cell tumor disease. EDTA clearance might provide a better guideline for the cisplatin dosage than the body surface. Serial determinations of cisplatin serum concentrations might provide more data concerning this particular topic.

Our results suggest that a dose between the mean values in the whole group and in the CR group (0.86–1.00 mg cisplatin/l EDTA clearance/24 h), applied for 4 consecutive days, is an optimal dose for start of escalation, safe from toxicity point of view. Further dose escalation may be possible, but must be performed with great caution when the cisplatin dose approaches 2 mg/l EDTA clearance/24 h because of increasing risk of severe hematological toxicity. Furthermore, such dose escalation of cisplatin might lead to an increased amount of the drug undergoing tubular secretion. Thus, renal function should be closely monitored as the role of this fraction for cisplatin-associated renal functional impairment has not yet been clarified.

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REFERENCES

1. Daugaard G. and Rorth M.: High dose DDP and VP-16 in patients with poor prognosis germ cell cancer. Proc. Am. Soc. Clin. Oncol. 4 (1985), 99.
2. Hamburger J.: Semiologie nephrologique. *In*: Pathologie medicale—Nephrologie et Urologie, p. 45. Edited by J. Hamburger et al. Flammarion Medecine, Paris 1970.
3. Hill B.: Principles of medical statistics. Lancet. London 1981.
4. Miller A. B., Hoogstraten B., Staguet M. and Winkler A.: Reporting results of cancer treatment. Cancer 47 (1981), 207.
5. Nelson J. A., Santos G., and Herbert B.: Mechanisms for the renal secretion of cisplatin. Cancer Treat. Rep. 68 (1984), 849.
6. Ozols F. R., Corden B. J., Jacob J. et al.: High dose cisplatin in hypertonic saline. Ann. Intern. Med. 100 (1984), 19.
7. — Deisseroth A. D., Javadpour N. et al.: Treatment of poor prognosis nonseminomatous testicular cancer with a high dose platinum chemotherapy regimen. Cancer 51 (1983), 1803.
8. Peckham M. J., Barte A., McElwain T. J. et al.: Non seminoma germ cell tumors of the testis. Results of treatment and analysis of prognostic factors. Br. J. Urol. 53 (1981), 162.
9. Petrović F. and Mićović P.: Opşta demografska i zdravstvena statistika. VMŠ, Beograd 1971.
10. Pizzocaro G.: Primary secondary and salvage surgery in the management of germinal tissue tumors. Proc. II Germ Cell Tumor Conf., Leeds, August 1985.
11. Samson M. K., Rivkin S. E., Jones S. E. et al.: Dose response and dose survival advantage of high versus low dose cisplatin in disseminated testicular cancer. Cancer 53 (1984), 1029.
12. Trump D. L. and Hortvert L.: Etoposide and very high dose cisplatin salvage chemotherapy for patients with advanced germ cell neoplasias. Cancer Treat. Rep. 69 (1985), 259.