Ototoxicity of cis-Diaminedichloroplatinum (II): Influence of Dose, Schedule and Mode of Administration

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Abstract—During and after 233 cycles of cis-diaminedichloroplatinum (II) (CDDP), 197 serial audiograms were obtained in 48 patients and compared with baseline audiograms. Use was made of three dose schedules (20 mg/m², 25–50 mg/m² and 70–120 mg/m²), two regimens (single-day or daily for 5 days) and three modes of administration (rapid infusion, 2- or 3-hr infusion, 24-hr infusion). Clinical hearing loss occurred in 12.5% and tinnitus in 25% of all patients. The incidence of audiographic changes (65% overall, 81% bilaterally) increased with increasing cumulative CDDP dose independent of treatment schedule. The incidence was correlated with the daily dose (P = 0.0037) and changes were more severe after single high doses. No difference was found between the single low dose and the daily for 5 days regimen. Rapid infusion of a single high dose was more ototoxic than a 24-hr infusion of the same dose (P = 0.0015). It is concluded that, compared with the single high-dose regimen, the daily low dose for 5 days is preferable in cases where the patient might be cured by a regimen including CDDP.

INTRODUCTION

cis-DIAMINEDICHLOOROPLATINUM II (CDDP) is one of the most effective anti-neoplastic agents. Since this drug is being used in chemotherapeutic regimens with curative potential, it is important to be aware of its long-term side effects. In 1971 hearing loss was first reported in a patient receiving CDDP in a dose of 4 mg/kg [1]. Few prospective studies on CDDP ototoxicity in relation to dose and treatment schedules have been done in man. In a randomized phase II study performed to compare five daily injections of 20 mg/m² of CDDP with a single high dose of 120 g/m² with mannitol-induced diuresis, the latter dose was the more toxic to both the kidney and the inner ear [2]. Recently, it has been suggested that audiometric abnormalities are correlated with the mode of CDDP administration, the highest incidence being associated with bolus injection [3]. Serial audiography indicated that CDDP ototoxicity is dose-related [3–6].

In the present study hearing acuity was assessed by serial audiography prior to each successive cycle of treatment with CDDP given according to three protocols differing as to dose or schedule. The results show correlation between daily dose and the occurrence of ototoxicity as well as an influence of infusion duration.

MATERIALS AND METHODS

Patients
Forty-eight patients with advanced cancer received CDDP as a single drug or in combination with other anti-neoplastic agents. The diagnosis included head and neck cancer (10 patients), ovarian cancer (10), testicular teratoma (9), cancer of the uterine cervix (7), lung cancer (4) and other types (8).

CDDP was administered every 3–6 weeks in several ways: (1) a single low dose (SLD) of 25–50 mg/m² (16 patients); (2) a single high dose (SHD) of 70–120 mg/m² (14 patients); or (3) a daily dose for 5 days (LD5) of 20 mg/m² day (15 patients); also, 3 patients received varying doses. The doses were given by rapid infusion (4–15 min), 2- or 3-hr infusion or 24-hr infusion.