CASE REPORT

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Acute Reversible Encephalopathy after Repeated Low-dose Cisplatin Infusions and Concomitant Radiotherapy for Cancer of the Tongue

Pia P. Vihinen, Kalevi M. Kätkä, Reijo K. Johansson, Tapani A. Vihinen and Eeva K. Salminen

From the Departments of Oncology and Radiotherapy (P. Vihinen, K. Kätkä, E. Salminen), Otorhinolaryngology (R. Johansson) and Internal Medicine (T. Vihinen), Turku University Hospital, Turku, Finland

Correspondence to: Pia P. Vihinen, Department of Oncology and Radiotherapy, Turku University Hospital, Kiinamyllynkatu 4-8, FIN-20520 Turku, Finland. Tel: +358 2 313 0000. Fax: +358 2 313 2809. E-mail: pia.vihinen@tyks.fi

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Cisplatin is a platinum-based cytotoxic agent that is therapeutically highly effective in the treatment of germ cell tumors, bladder cancer and head and neck cancer (1). In metastatic squamous cell carcinomas of the head and neck, cisplatin is used in combination with fluorouracil. Weekly cisplatin infusions (40–50 mg/m^2) can be used to enhance the effect of simultaneous irradiation therapy, i.e. in the treatment of gynecological cancers, non-small cell lung cancer or cancers of the head and neck.

The most common toxic effects of cisplatin are loss of hearing and peripheral neuropathy (2) and renal toxicity (3). Audiometry tests show ototoxicity in 75–100% of patients treated with cisplatin (4). Peripheral neurotoxicity is found as loss of vibration sense, paraesthesia and sensory ataxia (4). Cisplatin induces renal toxicity by causing tubular damage and reduction of glomerular filtration (4). Toxic effects of cisplatin on the central nervous system are rare, but have been described at total doses of 100–500 mg/m^2 ((5) and references therein). In this report, we describe a patient who developed acute reversible encephalopathy after neoadjuvant therapy with weekly cisplatin (50 mg/m^2, total dose 150 mg/m^2) and concomitant irradiation of the basal region of the tongue.

Case report. A 37-year-old male patient was diagnosed with stage I epidermoid carcinoma of the tongue (T2N0M0G2) in February 2002. No lymphadenopathy or signs of disseminated disease were detected on CT scans of the primary and regional areas. The patient was a non-smoker, did not use alcohol and had a previous history of familial hypercholesterolemia, which was treated with 20 mg simvastatin/day. The patient was not taking any other medication.

The patient was scheduled for treatment with preoperative radiotherapy of the tumor region (up to 62–64 Gy) and concomitant weekly cisplatin infusions (50 mg/m^2). Irradiation portals extended superiorly to the base of the skull and the floor of the sphenoid sinus. Anteriorly, the irradiation portals included the facial arch and the oral tongue, exceeding inferiorly to the supraglottic larynx. The upper neck was also irradiated. The radiotherapy was administered in 1.9 Gy daily fractions to a total mean dose of 47.10 Gy in the primary tumor and upper neck region. The field was reduced to encompass only the primary tumor with an additional 14.5 Gy boost and the posterior cervical region was boosted with electrons (20.07 Gy). The computed spinal cord dose was 35.9 Gy.

A percutaneous endoscopic gastrostoma was installed before the start of therapy and enteral nutrition was started after stomatitis related to a 30 Gy total irradiation dose. Supportive enteral nutrition led to mild diarrhea, which was treated with hydration fluids and loperamide. Six days after the third weekly cisplatin dose (total cumulative dose 240 mg; 150 mg/m^2) and 34 Gy total dose of irradiation therapy, the patient had a sudden bilateral sensory-neural hearing loss. In the same evening, he had a visual disturbance, but the physiological status of the eyes was normal. Within two days the patient became progressively confused and disorientated and finally went into coma. CSF tests were normal and there were no signs of infection. A CT scan of the brain was normal, but an MRI test showed symmetrical, periventricular atrophy of the white matter (see Fig. 1). Electroencephalography showed non-specific irregular activity, which was related to diffuse encephalopathy. Acyclovir (1 500 mg/day i.v.) was started on the basis of clinical symptoms, because the possibility of encephalitis could not be totally ruled out. However, PCR for herpes simplex virus in the CSF tested later on was found to be negative. Similarly, blood tests for cytomegalovirus antigen and Epstein-Barr virus antibodies were negative. No common respiratory infection virus antigens were found in the nasopharyngeal samples. The blood thiamine level was normal. The neurologic symptoms were thought to be associated with cisplatin-induced encephalopathy and high-dose steroid (16 mg dexamethasone i.v. daily) treatment was started. After 48 h of high-dose dexamethasone therapy, the patient became totally disorientated, aggressive and had delusions. Dexamethasone therapy was discontinued and anti-psychotic therapy was initiated.

Renal toxicity was apparent. Serum creatinine enzyme levels were raised [184 μmol/L, normal values (NV) < 118 μmol/L]. The patient had hypomagnesemia (0.51 μmol/L, NV 0.7–1.1 μmol/L), mild hypocalemia (plasma-potassium level 3.2 mmol/L, NV 3.3–4.8 mmol/L) and hypocalcemia (plasma-calcium level 1.99 μmol/L, NV 2.17–2.47 μmol/L). Mild trombocytopenia (66×10^9/L, NV 150–400×10^9/L) and leucopenia (2.2×10^9/L, NV $3.7–10 \times 10^9$/L) were also registered. The patient suffered from metabolic alkalosis (blood pH 7.48, NV 7.35–7.43) resulting in hypoventilation and moderate hypercapnia (pCO2 7.7 kPa, NV 4.5–6 kPa) and was treated with magnesium, calcium and potassium supplementation together with hydration fluids. Simultaneously with the neutropenia, a pneumonic infiltrate was found on a thorax radiogram.

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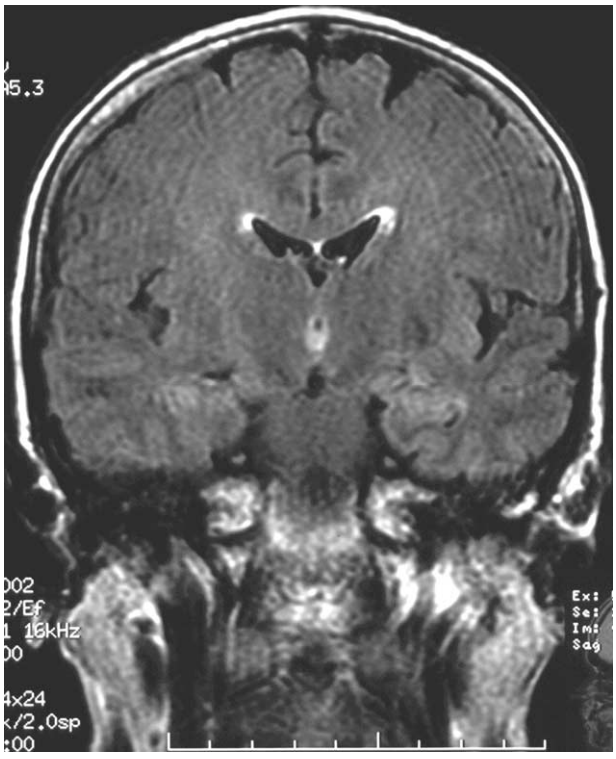

Fig. 1. Presence of symmetrical, periventricular white matter degeneration in whole brain MRI after cisplatin treatment. The patient received three weekly doses (50 mg/m^2) leading to a total cumulative dose of 150 mg/m^2.

Antibiotic therapy was started. Renal toxicity and most of the neurological disorders were relieved in 5 days, but the bilateral hearing loss remained despite carbogen gas treatment. Irradiation therapy was continued as scheduled after a break of two weeks. No further cisplatin infusions were given and the patient then underwent hemiglossectomy, neck dissection and microvascular reconstruction of the neck and mouth region as planned.

Discussion. Cisplatin shows negligible penetration over an intact blood–brain barrier and in rare cases central nervous system toxicity (6). The main neurological adverse effects of cisplatin include peripheral neuropathy (4), loss of hearing (4), cortical blindness, aphasia with seizures and mental disturbance (6). Cisplatin-induced ototoxicity produces high-frequency sensoryneural hearing loss, which is permanent and dose limiting (7). The mechanism of ototoxicity is poorly understood, but has been suggested to be related to binding of the drug to the plasma membranes of the outer hair cells rather than to the vascular supply of the inner ear (8).

Cisplatin-related encephalopathy has been described when cisplatin is used as a single agent or in combination with other intravenous chemotherapy agents. Lyass et al. (9) have described a patient who developed a reversible, non-convulsive encephalopathy after cisplatin-based chemotherapy. Similarly, continuous low-dose cisplatin and 5-fluorouracil therapy can lead to acute encephalopathy when given together with intravenous hyperalimentation (10). Cisplatin-induced encephalopathy has also been demonstrated in connection with treatment of recurrent, previously irradiated oligodendrogliomas (11) and brain tumors (12). Nieto et al. (13) described acute encephalopathy in 5 out of 114 patients who received high-dose paclitaxel and cisplatin. However, two of these patients had also received prior whole-brain irradiation (13). These observations suggest that cisplatin-induced encephalopathy is rare in the case of an intact blood brain-barrier. However, the risk of CNS toxicity is probably increased when combination therapies or prior whole-brain irradiation is used.

The precise mechanism of cisplatin-induced CNS and neurotoxicity is unknown. Cisplatin binds RNA and DNA and thus interferes with DNA replication and synthesis. McKeage et al. (14) have recently shown that multiple doses of cisplatin are associated with a reduction in cell nucleoli size referring to a mechanism inhibiting rRNA synthesis. Meijer et al. (15) have shown that cisplatin can induce DNA platination, which leads to direct dorsal root ganglia neuropathy. Interestingly, the results of in vitro studies with neuroblastoma cells suggest that cisplatin-induced apoptosis is mediated by accumulation of p53 and Bax proapoptotic proteins and inhibited by anti-apoptotic bcl-2 protein expression (16). In vitro studies also show that neuroprotective antioxidants react against cisplatin-induced toxicity via inhibition of p53 accumulation (17).

Irradiation of brain tumors and extracranial neoplasms of the head and neck may be associated with toxicity leading to cognitive decline (18). In a recent review, Abayomi (18) describes the symptoms and pathogenesis of radiation-induced, vascular damage in the temporal lobe of the brain. Damage to the temporal lobe is mostly found after radiotherapy of cancers of the nasopharynx and paranasal sinuses, because of the anatomic relation-ships (18). In addition, the radiation-induced vascular damage typically has a late onset. In our case it is unlikely that the patient would have suffered from radiotherapy-induced injury to the brain, because of the acute onset of the neurotoxicity symptoms and low irradiation dose volumes involving the CNS.

Simvastatin, a hydroxymethyl glutamate coenzyme A (HMG-CoA) reductase inhibitor, is a commonly used cholesterol-lowering agent and was used by the patient in this report. Its toxic effects are rhabdomyolysis and hepatitis, which are increased by simultaneous use of potent inhibitors of cytochrome P450 3A4 enzyme (19). Simvastatin can activate nerve growth factor receptor Trk, and induce apoptosis in neuronal cells in vitro (20). However, no neuronal toxicity has been described in vivo even with high (40 mg) daily doses of simvastatin.

Nephrotoxicity is also a well-recognized adverse effect of cisplatin (3) and the role of reactive oxygen metabolites in its pathogenesis has been discussed recently (21). Its mechanism includes histologic changes in proximal tubules and alterations in enzymatic activity in the respiratory chain as well as disturbance of cellular calcium homeostasis (3). Baliga et al. (21) suggest that cisplatin-induced nephrotoxicity is associated with an increase in catalytic iron concentration, the upregulation of which is mediated by cytochrome P450. On the basis of these findings, the renal toxicity seen in our case might also be related to cisplatin-induced increase in reactive oxygen metabolites.

Hypomagnesemia is associated with renal toxicity in patients receiving cisplatin-containing chemotherapy (22) and it can also be related to encephalopathy caused by this treatment (6). Hypomagnesemia is possibly caused by direct injury to mechanisms of magnesium reabsorption in the renal distal tubule (22) and the detected hypomagnesemia in our case supports cisplatin-induced nephrotoxicity. The possibility of renal toxicity and neurotoxicity as well as electrolyte disturbances can be decreased by prehydration and mannitol diuresis, which have an essential role also in chemotherapy with low cisplatin doses.

In our case a relatively low cumulative (150 mg/m^2) cisplatin dose together with irradiation therapy led to severe, but mostly reversible toxicity, which was characterized by encephalopathy. Other causes of encephalopathy, i.e. brain metastases, CNS infection, and liver disease were ruled out by brain MRI, evaluation of CSF and blood testing. In most reported cases the patients made a full recovery from cisplatin-induced CNS disorders in less than three weeks (5). This was also seen in our case. Severe hearing loss remained, however. In conclusion, our findings suggest that the risk of induced encephalopathy should be considered when low-dose cisplatin therapy is combined with irradiation therapy in the treatment of cancer patients.

REFERENCES

1. Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: an analysis of the literature. Ann Oncol 1998; 9: 13–21.
2. Kaplan RS, Wiernik PH. Neurotoxicity of antineoplastic drugs. Sem Oncol 1982; 9: 103–30.
3. Anand AJ, Bashey B. Newer insights into cisplatin nephrotoxicity. Ann Pharmacother 1993; 27: 1519–25.
4. McKeage MJ. Comparative adverse effect profiles of platinum drugs. Drug Saf 1995; 13: 228–44.
5. Verschraegen C, Conrad CA, Hong WK. Subacute encephalopathic toxicity of cisplatin. Lung Cancer 1995; 13: 305–9.
6. Gorman DJ, Kefford R, Stuart-Harris R. Focal encephalopathy after cisplatin therapy. Med J Aust 1989; 150: 399–401.
7. Schweitzer VG. Cisplatin-induced ototoxicity: the effect of pigmentation and inhibitory agents. Laryngoscope 1993; 103: 1–52.
8. Walker EM Jr, Fazekas-May MA, Bowen WR. Nephrotoxic and ototoxic agents. Clin Lab Med 1990; 10: 323–54.
9. Lyass O, Lossos A, Hubert A, et al. Cisplatin-induced non-convulsive encephalopathy. Anticancer Drugs 1998; 9: 100–4.
10. Kondo K, Fujiwara M, Murase M, et al. Severe acute metabolic acidosis and Wernicke's encephalopathy following chemotherapy with 5-fluorouracil and cisplatin: case report and review of the literature. Jpn J Clin Oncol 1996; 26: 234–6.
11. Cairncross G, Swinnen L, Bayer R, et al. Myeloablative chemotherapy for recurrent aggressive oligodendroglioma. Neuro-oncol 2000; 2: 114–9.
12. Hiesiger EM, Green SB, Shapiro WR, et al. Results of a randomized trial comparing intra-arterial cisplatin and intravenous PCNU for the treatment of primary brain tumors in adults: Brain Tumor Cooperative Group Trial 8420A. J Neurooncol 1995; 25: 143–54.
13. Nieto Y, Cagnoni PJ, Bearman SI, et al. Acute encephalopathy: a new toxicity associated with high-dose paclitaxel. Clin Cancer Res 1999; 5: 501–6.
14. McKeage MJ, Hsu T, Screnci D, et al. Nucleolar damage correlates with neurotoxicity induced by different platinum drugs. Br J Cancer 2001; 85: 1219–25.
15. Meijer C, de Vries EG, Marmiroli P, et al. Cisplatin-induced DNA-platination in experimental dorsal root ganglia neuropathy. Neurotoxicology 1999; 20: 883–7.
16. Park SA, Park HJ, Lee BI, et al. Bcl-2 blocks cisplatin-induced apoptosis by suppression of ERK-mediated p53 accumulation in B104 cells. Brain Res Mol Brain Res 2001; 93: 18–26.
17. Park SA, Choi KS, Bang JH, et al. Cisplatin-induced apoptotic cell death in mouse hybrid neurons is blocked by antioxidants through suppression of cisplatin-mediated accumulation of p53 but not of Fas/Fas ligand. J Neurochem 2000; 75: 946–53.
18. Abayomi O. Pathogenesis of cognitive decline following therapeutic irradiation for head and neck tumors. Acta Oncol 2002; 41: 346–51.
19. Kanathur N, Mathai MG, Byrd RP Jr, et al. Simvastatin-diltiazem drug interaction resulting in rhabdomyolysis and hepatitis. Tenn Med 2001; 94: 339–41.
20. Kumano T, Mutoh T, Nakagawa H, Kuriyama M. HMG-CoA reductase inhibitor induces a transient activation of high affinity nerve growth factor receptor, trk, and morphological differentiation with fatal outcome in PC12 cells. Brain Res 2000; 859: 169–72.
21. Baliga R, Ueda N, Walker PD, Shah SV. Oxidant mechanisms in toxic acute renal failure. Drug Metab Rev 1999; 31: 971–97.
22. Lajer H, Daugaard G. Cisplatin and hypomagnesemia. Cancer Treat Rev 1999; 25: 47–8.