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Retinal Toxicity Associated With Cisplatin and Etoposide in Pediatric Patients

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Cisplatin is an effective chemotherapeutic agent used in the treatment of many pediatric solid tumors. Retinal toxicity is a side effect of the drug reported in adults, but is not well described in pediatric patients. We present the cases of two children treated with cisplatin and etoposide who experienced retinal toxicity documented by visual evoked response (VER) and electroretinogram (ERG). Significantly, both patients had abnormal renal function. The mechanism of visual toxicity induced by cisplatin is unknown but may result from central nervous system (CNS) accumulation of drug after repeated doses, especially with high-dose platinum (HDP) containing regimens. Because clearance of platinum is related to adequate renal-function, patients with any decrease in glomerular filtration rate (GFR) may have delayed platinum excretion. We propose that the patients at greatest risk of cisplatin-induced toxicity are those pretreated with nephrotoxic therapy or those with impairment of renal function from other causes. These patients should have prospective ophthalmologic evaluation especially when treated with HDP containing regimens. **Med. Pediatr. Oncol. 28:310–313.**

Key words: cisplatin; visual toxicity; children; renal function

INTRODUCTION

Cisplatin, a heavy metal coordination compound, is an effective antineoplastic agent employed in the treatment of many pediatric malignancies [1–4]. Well-known toxic effects of therapy with cisplatin include nephrotoxicity, ototoxicity, neurotoxicity, myelosuppression, and gastrointestinal toxicity [5–8]. Although less common, visual toxicity related to the use of cisplatin is well described in adults [9–14], but not in pediatric patients [15]. Cisplatin pharmacokinetics are complex, and changes in elimination of the drug are observed in patients with abnormal renal function [16]. Data from adult studies show a reduction in clearance of ultrafilterable (unbound) platinum with repeated courses of the drug [17], and a relationship between free platinum level and toxicity [18–20]. Unfortunately, increases of serum blood urea nitrogen (BUN), creatinine, and even creatinine clearance are not always predictive of cisplatin-induced renal impairment [19,21,22].

The following report describes two children who experienced retinal toxicity after repeated courses of cisplatin. We propose that this complication of therapy resulted from delayed excretion of ultrafilterable platinum in patients with impaired renal function that was not recognized by routine measurements of serum BUN and creatinine.

CASE REPORTS

Patient One

A 4-year-old girl presented to the hospital with a 16 cm retroperitoneal mass which markedly displaced the right kidney inferiorly and laterally. Serum alpha fetoprotein level was 14,810 ng/ml. Biopsy of the mass revealed a malignant mixed germ cell tumor. At the time of presentation, neurologic examination and vision were normal as were her fundi via direct ophthalmoscopy. The serum creatinine was 0.3 mg/dl prior to any therapy.

Her chemotherapy plan consisted of high-dose platinum (HDP) (40 mg/m^2/day) and etoposide (100 mg/m^2/day) both for 5 days with bleomycin (50 mg/m^2/day) on day 1. After completion of four courses of this therapy, her tumor was completely resected. Her serum creatinine remained stable at 0.3 mg/dl postoperatively. She received two more courses of the above chemotherapy regimen which increased the cumulative cisplatin dosage to 1,200 mg/m^2. Renal function, as measured by serum creatinine, was unchanged prior to and during her final course of therapy. Twelve days later, while hospitalized for fever and neutropenia, she complained of blurry vision and difficulty with depth perception. These visual problems began approximately 4 months after cisplatin therapy was

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initiated. The patient had no formal assessment of visual acuity during treatment with cisplatin. Magnetic resonance imaging of her head showed increased ventricular size but no evidence of metastatic disease or other focal abnormality. Notably, she now had evidence of renal insufficiency with a serum creatinine of 3.0 mg/dl, and ultrasound demonstrated right renal atrophy.

On ophthalmologic examination, visual acuity was 20/800 in each eye using Allen picture cards. Peripheral visual fields were only slightly constricted to finger confrontation. The anterior segment and fundus examination were normal except for mild diffuse optic nerve pallor in each eye. There was granular pigmentation of the retina. An electroretinogram (ERG) obtained 1 month after the onset of visual symptoms showed no discernible response to blue filtered and unfiltered flash in the scotopic state or to bright unfiltered flash in the photopic state or to flicker fusion stimuli. Visual evoked response (VER) demonstrated prolonged latencies and significantly attenuated amplitudes with a flash stimulus. Patterned stimulus generated no discernible visual evoked potential. One year later, her vision was remeasured at the same level, and the clinical examination was unchanged. ERG continued to show no recordable response. VER still showed delayed latencies, but the amplitudes to flash stimuli were normal. Patterned stimuli evoked recordable, but significantly abnormal responses. Two years after the onset of visual loss, visual acuity was 20/600 with Allen pictures and block "E." The optic nerves remained pallid and retinal pigmentation was still mildly granular.

The conclusion that the patient's visual abnormalities were more ascribable to retinal toxicity rather than optic nerve dysfunction is derived from the combined findings of ERG and VER. ERG measures electrical activity in the retina directly, independent of optic nerve function. As noted above, electrical activity in the retina was entirely extinguished. VER evaluates the ability of the optic nerve to stimulate electrical activity in the occipital cortex. Although the patient had prolonged latencies on VER, the amplitudes were attenuated initially, but normal on retesting. While these findings demonstrate some optic nerve dysfunction, as expected given that the optic nerve is comprised of axons from retinal ganglion cells, the fundamental electrical integrity of the optic nerve is preserved. Therefore, by combining the findings of ERG and VER, the patient's visual problems are consistent with dysfunction concentrated in the retina with relative sparing of the optic nerve.

Patient Two

A 7-year-old girl presented with several months history of abdominal pain and weight loss. Computed tomographic (CT) scan of the abdomen and chest revealed a 15 cm intrahepatic tumor with pulmonary metastases. The level of serum alpha fetoprotein was 656,000 ng/ml. Biopsy of the mass confirmed a diagnosis of hepatoblastoma. Her kidneys appeared normal on the initial CT scan with no evidence of tumor infiltration or obstruction. Serum creatinine prior to initiation of chemotherapy was 0.4 mg/dl.

The patient had minimal response to initial chemotherapy with carboplatinum, vincristine, and 5-fluorouracil (5-FU). Therapy was changed to HDP (40 mg/m^2/day) with etoposide (100 mg/m^2/day) both for 5 days. The serum creatinine prior to HDP was 0.5 mg/dl, and the kidneys remained normal by CT examination. During the fourth and final course of HDP and etoposide, the serum creatinine increased from 0.4 to 0.8 mg/dl. One week after this course (approximately 4 months after cisplatin therapy was started), she complained of blurry vision. The patient had no previous history of visual problems, and visual acuity was not assessed prior to starting treatment with cisplatin. Neurologic examination was normal; however, ophthalmologic examination showed her visual acuity to be 20/600, and she identified red objects as blue. Retinal examination demonstrated pale optic discs and granular peripheral pigmentation. As with patient one, ERG responses were nonrecordable under photopic, fusion, and scotopic testing conditions. VER testing revealed small, delayed responses from each eye with unfiltered light flashes. Follow-up examination 2 weeks later was unchanged.

Reevaluation 2 weeks after the final course of HDP and etoposide showed no improvement in her tumor, and now bilateral renal enlargement was noted. Significantly, her serum creatinine had increased to 5.6 mg/dl. Unfortunately, the patient's tumor remained unresectable, and she subsequently died from progressive disease.

DISCUSSION

As a chemotherapeutic agent, cisplatin has demonstrated activity against a variety of pediatric malignancies including germ cell tumors, osteosarcoma, neuroblastoma, and brain tumors [1–4]. This antineoplastic effect of cisplatin was first recognized in 1965 by Rosenberg et al. [23], who noted its cytotoxic effect on bacterial growth processes. Cisplatin is thought to exert its antitumor activity through disruption of DNA function via the formation of covalent interstrand crosslinks [24,25].

Cisplatin pharmacokinetics are complex and not well documented in children. However, available studies show that removal of the drug from circulation is triphasic at 20–30 min, 60 min, and 24 hr. The initial phases of removal, $t_{1/2}\alpha$ and $t_{1/2}\beta$, reflect clearance of ultrafilterable platinum mainly by renal elimination [26]. $T_{1/2}\gamma$, the final phase of clearance at 24 hr, represents removal of protein bound platinum. Renal and biliary excretion, as well as protein catabolism, regulate this phase of clearance [26,27]. Renal clearance is an important route of cisplatin elimination, and reductions in glomerular filtration rate (GFR) are associated with elevated levels of ultrafilterable

platinum in plasma [16]. However, renal elimination of platinum exceeds creatinine clearance and represents a complex mechanism of both active secretion and reabsorption [28,29]. Unlike the relationship between plasma levels of carboplatin and GFR, creatinine clearance is not a good predictor of ultrafilterable platinum disposition. Because of this complex renal clearance mechanism, large changes in ultrafilterable platinum clearance can occur without a proportional change in creatinine clearance [19].

We propose that the retinal toxicity experienced by our patients is best explained by decreased renal clearance of unbound platinum. As Reece and colleagues [17] demonstrated, patients have reduced renal clearance of unbound platinum with repeated dosing, and it is known that certain cisplatin toxicities are related to free plasma platinum concentration [18–20]. Our patients were at risk for renal insufficiency due to prior treatment with nephrotoxic drugs, and in patient one, injury to one kidney during resection of her tumor. Although evidence of decreased renal function was not reflected, at least initially, by an increase in BUN or serum creatinine measurements, significant changes in platinum excretion can occur before an increase in serum creatinine is noted [21,22]. Patient two became symptomatic shortly after her last course of HDP, during which she had a distinct change in serum creatinine measurements. By the onset of visual symptoms, patient one had an elevated serum creatinine.

Ophthalmologic toxicities related to cisplatin therapy are more frequently reported in adults [9–14], possibly because abnormal renal function is more common among adult patients. Wilding et al. [14] substantiated the relationship of HDP to retinal toxicity by the prospective evaluation of three patients. Two patients developed blurred vision and color vision defects with associated changes in their ERGs. The authors also documented retinal toxicity in six of ten patients examined retrospectively. As with our pediatric patients, visual changes developed after three to four courses of therapy with HDP and were more frequent in patients who had received >600 mg/m^2 of cisplatin. No measurements of renal function in the affected patients before or at the onset of symptoms were provided. Berman and Mann [9], Pippitt et al. [10], and Diamond and colleagues [11] described patients who experienced cortical blindness after treatment with cisplatin. Although these patients had normal renal function as measured by BUN and serum creatinine pretreatment, at the onset of visual symptoms, there was no clear documentation of renal function. However, one patient had hypokalemia and hypomagnesemia, possible evidence for renal tubular dysfunction [10].

Although the mechanism of cisplatin-induced visual toxicity is not clear, there are similarities between platinum and other heavy metal-induced neuropathies [30]. Both lead and cisplatin are known to cause demyelination, and lead intoxication is frequently associated with visual abnormalities [31,32]. Unusually high central nervous system (CNS) accumulation of cisplatin may follow repeated dosing and thus lead to nerve demyelination and ophthalmologic toxicities [33]. This hypothesis is supported by the finding that cisplatin can have significant CNS penetration (40% of the plasma concentration in one pediatric report) [34]. Also, one of the adult patients who developed cortical blindness associated with cisplatin had a cerebrospinal fluid (CSF) cisplatin level virtually identical to that of the serum [11]. Because renal elimination is an important route of platinum excretion, even modest reduction in renal function and resultant delay in clearance of unbound platinum could lead to significant CNS levels. Clearly, most patients treated with cisplatin do not achieve such high CNS accumulation or develop visual symptoms. However, we believe the subset of patients at greatest risk for this toxicity are 1) patients pretreated with nephrotoxic therapy; 2) patients with potential for renal compromise secondary to tumor location; 3) patients with only one kidney; or 4) patients on HDP containing regimens.

With increased use of HDP regimens in pediatric malignancies, particularly in heavily pretreated patients, it is likely that further cases of ophthalmologic toxicity will occur. Prospective analysis of pediatric patients treated with cisplatin-based therapy is needed to determine the incidence of platinum-related visual abnormalities, particularly in the above-mentioned risk groups. Further studies to better define the mechanism of cisplatin-induced visual toxicity, as well as the pharmacokinetics of cisplatin in children, may provide methods of preventing this distressing complication of therapy.

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