Intra-arterial Cisplatin–Associated Optic and Otic Toxicity

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• **Over a 22-month period, we investigated optic and otic toxicity accompanying intra-arterial cisplatin therapy. Baseline and serial neurologic and ophthalmologic examinations, visual evoked potentials, and brain-stem auditory evoked potentials were performed in six patients, aged 37 to 53 years. Patients received infraophthalmic intra-arterial cisplatin (60 mg/m²) every month for three to 10 treatments (mean, six treatments). Five of the six patients had progressive optic toxicity. In two patients, the visual evoked potential prolongation preceded acuity loss by at least 4 months. Two patients had evidence of otic toxicity by either brain-stem auditory evoked potential or click threshold and brain-stem auditory evoked potential. Intra-arterial cisplatin neurotoxicity may be significant in patients with already limited survival. Visual evoked potential and brain-stem auditory evoked potential should be used to monitor patients receiving potentially neurotoxic therapy.**

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Cisplatin (*cis*-dichlorodiammine platinum [II]) is used to treat both systemic and central nervous system (CNS) malignancies. It has a significant role in the treatment of testicular, ovarian, adrenal, lung, and bone tumors.[1] Cisplatin is also employed as an agent against neoplasms of the CNS. Some investigators have shown intra-arterial therapy to be efficacious in the treatment of malignant cerebral tumors.[2]

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The administration of cisplatin is limited by its toxic effects. Nephrotoxicity,[3-5] nausea, vomiting,[1,6,7] myelosuppression,[8,9] and peripheral neuropathy[10-12] occur frequently. Less commonly, systemic administration of cisplatin results in neurosensory hearing loss,[13-15] optic neuritis,[16] optic disc edema,[17] cortical blindness,[18] altered color vision,[19] papilledema,[16] encephalopathy,[20,21] and seizures.[22,23]

In patients with CNS neoplasms, intra-arterial therapy is employed in an attempt to produce increased drug levels at the tumor site and reduce or eliminate systemic toxicity.[24] Yet, intra-arterial cisplatin administration is known to produce visual system toxic effects[25,26] and may also yield neurosensory hearing loss.[27] With progression, these toxic effects can limit the use of cisplatin as an antineoplastic agent in the treatment of aggressive CNS neoplasms. We therefore elected to prospectively study patients receiving intra-arterial cisplatin therapy to document not only the onset and progression of optic and otic toxicity but also to determine whether the toxic effects were restricted to the treated side.

MATERIALS AND METHODS

Patient Population

Six patients with surgically proven oligodendroglioma (n = 1), anaplastic astrocytoma (n = 1), or glioblastoma multiforme (n = 4) received infraophthalmic intra-arterial cisplatin as a part of a Memorial Sloan-Kettering Cancer Center (New York, NY) treatment protocol from 1987 through 1989 (Table 1). Informed consent was obtained after the nature of the study had been fully explained. There were three men and three women, aged 37 to 53 years. Five patients were treated at the time of disease progression and one patient was treated at diagnosis. Radiation therapy (5500 to 6500 cGy) preceded cisplatin therapy by 2 to 7 months in two patients and 2 to 7 years in four patients. Two patients had previously received 200 mg/m² of carmustine (BCNU) intravenously.

Clinical Evaluation

The study monitored optic and otic toxicity accompanying intra-arterial cisplatin therapy. Clinical evaluation employed examinations that were readily available to the clinician and was not meant to represent an exhaustive study of the visual and auditory pathways. Clinical evaluation consisted of the neuro-ophthalmologic examination, visual evoked potential (VEP), and brain-stem auditory evoked potential (BAEP). The examinations were performed prior to each infusion. Clinical evaluation included Snellen acuity (hand-held chart with correction), perimetry by confrontation, pupillary reactivity, ocular motility, and ophthalmoscopy. A loss of acuity was defined as a progression of two or more lines on the Snellen chart. Ophthalmoscopy was performed by an ophthalmologist.

Pattern reversal VEPs (Nicolet CA 1000) were obtained prior to each treatment. The VEP was recorded as follows: O_z referenced to C_z, 1 Hz to 250 Hz filtering, two repeats of 100 sweeps at 1.88 Hz, 1-m viewing distance, 80 cd/m² luminance, 100% contrast, 15-degree field. In a control population for the pattern VEP, a check size of 0.25 degrees produced a response with a mean latency of 107 milliseconds and 3 SDs represented a latency of 119 milliseconds. For 0.50-degree and 2-degree check sizes, mean P-100 latency was 100 milliseconds, with 3 SDs equal to a latency of 112 milliseconds. A change in latency of 8 milliseconds or more within an individual patient was considered to be significant.[28]

Brain-stem auditory evoked potentials (Nicolet CA 1000) were measured at 65 dB above click threshold by standard clinical methods (ears referenced to C_z, 150 Hz to 3000 Hz filtering, two repeats of 2000 sweeps at 11.1 Hz, rarefaction clicks). Normal average values and 3 SDs for latencies were as follows: wave I, 1.8 ± 0.5 milliseconds; wave III, 3.9 ± 0.7 milliseconds; and wave V, 5.7 ± 0.8 milliseconds. A change of a 0.5-millisecond latency for an individual patient was considered to be significant on the basis of laboratory norms.

Treatment

Prior to each treatment, serum urea nitrogen and creatinine were determined to verify normal renal function. Patients received 1 L of 0.45% sodium chloride 12 to 24 hours prior to cisplatin administration. The internal carotid artery was cannulated ipsilateral to the tumor site via a transfemoral approach under fluoroscopic guidance. The tip of the catheter was positioned inferior to the ophthalmic artery and monitored under fluoroscopy throughout the infusion. Heparin, 3000 IU, was administered intravenously. Cisplatin, 60 mg/m^2, was dissolved in 175 mL of 0.45% sodium chloride and infused over a 20-minute period. Blood pressure, heart rate, respirations, and temperature were assessed prior to and during drug administration. Treatments were performed monthly and ranged from three to 10 treatments, with a mean of six treatments.

RESULTS

Otic Toxicity

Prior to drug administration, all patients had normal click thresholds and BAEPs. Two of the six patients developed evidence of otic toxicity during treatment with cisplatin (Table 1). One patient had prolongation in BAEP while the second patient developed abnormalities in both BAEP and click threshold.

In patient 4 the latency of wave V on BAEP increased from 5.78 to 6.30 milliseconds ipsilateral to the treated side. No significant increase in latency occurred contralateral to the treated side. This change in latency occurred over a treatment course of seven cycles. No deterioration in click threshold was noted.

Patient 5 had evidence of hearing loss on both BAEP and audiogram following six cycles of cisplatin administration. On the treated side, latency of wave V increased from 5.80 to 6.52 milliseconds. The BAEP latencies did not change significantly contralateral to the side of treatment but click threshold increased bilaterally. Click threshold increased from 30 to 60 dB on the treated side and click threshold increased from 35 to 50 dB contralateral to the treated side. Increased click threshold was noted 3 months prior to prolongation in BAEP.

Optic Toxicity

None of the six patients experienced changes in perimetry, pupillary function, ocular motility, or funduscopic examination with cisplatin administration. No patient developed papilledema. Yet, progressive optic toxicity was documented by loss of visual acuity and/or increased VEP latency (Table 1). Neither single modality documented all instances of the onset of cisplatin optic toxicity (Table 2).

Table 1.—Patient Demographics With Cisplatin Optic and Otic Toxicity*

Patient/ Age, y/Sex	Pathologic Findings	Prior WBRT	Prior Carmustine	Cisplatin Infusions	Evidence of Toxicity		
					VA	VEP	BAEP
1/37/M	Oligodendroglioma	Yes	No	10	NL	NL	NL
2/45/F	Glioblastoma	Yes	Yes	3	DT	DT	NL
3/41/M	Glioblastoma	Yes	Yes	4	DT	NL	NL
4/39/M	Glioblastoma	Yes	No	7	NL	DT	DT
5/53/F	Glioblastoma	Yes	No	6	DT	NL	DT
6/41/F	Astrocytoma	Yes	No	5	DT	DT	NL

*WBRT indicates whole brain radiation therapy; VA, visual acuity; VEP, visual evoked potential; BAEP, brainstem auditory evoked potential; NL, normal; and DT, deterioration.

Table 2.—Visual Acuity (VA) vs Visual Evoked Potential (VEP) in Detection of Cisplatin Optic Toxicity

Patient	Treatment Hemisphere	VA Change		VEP Change		VA vs VEP Sensitivity
		OS	OD	OS	OD	
1	Right	No	No	No	No	VA = VEP
2	Left	Yes	Yes	Yes	Yes	VA = VEP
3	Right	Yes	Yes	No	No	VA > VEP
4	Left	No	No	Yes	Yes	VA < VEP
5	Right	Yes	Yes	No	No	VA > VEP
6	Right	No	Yes	Yes	Yes	VA < VEP

Although patient 2 suffered bilateral loss of acuity and increased VEP latency following three cycles of cisplatin therapy, optic toxicity initially occurred on the treated side. The time course of visual acuity deterioration paralleled VEP prolongation. On the treated side, acuity deteriorated from 20/20 to 20/50 and VEP latency increased from 113 to 152 milliseconds with 0.25-degree check size and from 105 to 151 milliseconds with 0.50-degree check size. On the contralateral side, visual acuity worsened from 20/20 to 20/70. The VEP latency increased from 120 to 134 milliseconds with 0.25-degree check size and from 108 to 126 milliseconds with 0.50-degree check size.

Following four cycles of cisplatin therapy, patient 3 experienced bilateral loss of visual acuity. The deterioration was equal in both magnitude and time course, resulting in an acuity change from 20/20 to 20/40 bilaterally. No prolongations in VEP were noted.

Patient 4 completed seven cycles of cisplatin and experienced no loss of visual acuity. Yet, the patient suffered prolongation of VEP initially on the treated side and then subsequently contralateral to the treated side. On the treated side, VEP duration increased from 107 to 140 milliseconds (0.25-degree check size) and from 101 to 125 milliseconds (0.50-degree check size). Contralateral to the treated side, the VEP was prolonged from 110 to 121 milliseconds (0.25-degree check size) and from 100 to 115 milliseconds (0.50-degree check size).

Patient 5 experienced bilateral loss of visual acuity following six cycles of cisplatin administration. Visual acuity loss occurred initially on the treated side. Visual acuity deteriorated from 20/25 to 20/30 on the treated side and from 20/25 to 20/40 contralateral to the treated side. No prolongation in VEP was found.

Prior to cisplatin therapy, patient 6 suffered from chronic bilateral retinal disease of unknown cause. Since VEP check sizes of 0.25 degrees and 0.50 degrees were small and unreliable in this patient, a 2-degree check size was employed. Deterioration in both visual acuity and VEP was documented over a course of five cycles of cisplatin. Ipsilateral to the treated side, visual acuity deteriorated from 20/100 to 20/200. The VEP latency was prolonged from 99 to 122 milliseconds (2-degree check size). The flash latency was unchanged. The prolongation in VEP latency occurred 1 month prior to visual acuity loss. Contralateral to the treated side, baseline visual acuity consisted of finger counting and was not altered by cisplatin administration. Baseline VEPs were absent on the contralateral side. The flash latency, however, subsequently increased from 120 to 160 milliseconds during cisplatin therapy.

COMMENT

Otic toxicity is a well-documented

complication of systemic cisplatin therapy. Damage occurs within the organ of Corti and the stria vascularis.[29,30] Otic toxicity that occurs with intravenous administration has been shown to be dose dependent,[31-33] present bilaterally with high-dose bolus administration,[13] and occurs with increased incidence in the elderly[34] and in patients with prior otologic disease.[14] Initial hearing loss has been shown to occur with ultrahigh frequencies of 9000 Hz and above with doses ranging from 20 to 225 mg/m^2 via intravenous administration. Progressive hearing loss of lower frequencies also occurs with repeated doses.[13,14] Irreversible bilateral deafness has been associated with intracarotid and vertebral artery cisplatin administration.[27]

Two of the six patients who received intra-arterial cisplatin therapy in our study developed subsequent otic toxicity (Table 1). The toxic effects appeared to involve both central and peripheral auditory pathways. Patient 4 did not experience any change in click threshold but suffered clinically occult prolongation of BAEP in wave V on the treated side suggesting brain-stem involvement. In contrast, patient 5 reported progressive bilateral hearing loss during treatment with intra-arterial cisplatin therapy. This was documented by a loss of click threshold sensitivity as well as a central latency delay of wave V on the treated side. The BAEP prolongation in this patient may be a consequence of the peripheral hearing loss, since the change in BAEP latency was detected 3 months following deterioration of click threshold.

Infraophthalmic, intra-arterial cisplatin administration has been associated with ipsilateral retrobulbar neuritis,[25] ipsilateral retinal pigmentation, cavernous sinus disease,[35] retinal necrosis,[26] and bilateral visual impairment.[2] Supraophthalmic administration of cisplatin can result in ipsilateral retinal infarcts,[26] ipsilateral optic nerve degeneration,[36] and ipsilateral as well as bilateral Marcus-Gunn pupils.[37]

Following infraophthalmic cisplatin therapy in our patient group, optic toxicity consisted of visual acuity loss and/or VEP prolongation. None of our patients developed abnormalities of visual fields, pupillary function, ocular motility, or ophthalmoscopic examination. Refractive error alone cannot account for the observed optic toxicity. For example, patient 4 experienced VEP prolongation but no loss of visual acuity. In patient 2 who suffered both VEP prolongation and visual acuity loss, the loss of visual acuity that may be secondary to refractive error is insufficient to account for VEP prolongation.[38] Clinical examination and evoked potentials were complementary in documenting the onset of optic toxicity (Table 2). In two patients, VEP prolongation preceded visual acuity loss. In two other patients, visual acuity testing detected toxic effects prior to increased VEP latencies. In addition, visual acuity examination and VEP concurrently detected optic toxicity in one patient bilaterally and in another individual unilaterally.

Optic toxicity following intra-arterial cisplatin administration does not appear to be dependent on the method of administration. Both infraophthalmic and supraophthalmic artery administration result in optic toxicity.[25,26] In addition, disease is not restricted to the side of treatment.[2,37] In our study, four of five patients initially suffered optic toxicity on the treated side. Yet, with subsequent treatments, all patients experienced bilateral optic toxicity. The optic toxicity was always bilateral by either visual acuity or VEP documentation. In patients 2 and 4, the optic toxic effects were worse on the treated side. Prolongation of VEP latencies on the untreated side occurred subsequent to prolongation of VEP latencies on the treated side but it is unclear whether this represents a cumulative dose effect or differences in the temporal course of the cisplatin toxicity.

Consistent with the findings of others,[2] the incidence or severity of optic toxicity was not dependent on the cumulative dose of cisplatin (Table 1). For example, the individual with 10 treatments suffered no toxic effects. In addition, the cumulative dose in the remaining individuals was not related to the progression of visual acuity loss or increase in VEP latencies. The mechanism of neuronal injury following intracarotid cisplatin administration is not well defined. Although a single administration of intra-arterial cisplatin (28 mg/m^2) in dogs results in a clinical neurologic deficit as well as cortical edema, hemorrhagic necrosis, and blood-brain barrier disruption ipsilateral to the treated side,[39] toxic effects may be secondary to an idiosyncratic effect of the drug in humans, since disease may result following one or multiple treatments at a dose of 60 mg/m^2.

Prior radiation therapy or intravenous carmustine administration did not appear to be acutely responsible for the optic toxic effects that we observed (Table 1). All patients received whole-brain radiation therapy and two patients received intravenous carmustine prior to treatment with cisplatin. With the exception of one individual, all patients entered the study with essentially normal visual acuity and VEP examinations. Patient 6 suffered from bilateral retinal disease since birth. Treatment with radiation therapy may have worsened this patient's visual acuity and VEP latencies. Yet, it is likely that this individual suffered further optic toxicity during therapy with intra-arterial cisplatin since this patient's visual acuity had remained unchanged for years prior to receiving cisplatin.

In experimental models as well as in human trials, cisplatin can be efficacious as a CNS antineoplastic agent.[2,40] Intra-arterial administration is a more attractive modality, since increased drug levels are applied to the tumor site and the risk of systemic toxic effects is lessened.[24] In our patient population, time to tumor progression during intra-arterial cisplatin therapy varied from 2 to 13 months, with a mean of 6.2 months. Yet, otic and optic toxic effects may initially develop on the treated side and progress to bilateral involvement with subsequent treatments. This toxicity can be an unacceptable result of intra-arterial cisplatin therapy and may lessen a patient's overall quality of life. The development of significant otic and optic toxicity should limit further intra-arterial cisplatin administration unless therapy has proven to be beneficial and the consequences of toxicity are acceptable to the patient. Otic and optic toxicity associated with intra-arterial cisplatin therapy can be promptly detected and accurately followed through the combined use of visual acuity and evoked potential monitoring. The ability to document otic and optic morbidity with cisplatin administration can assist in preparing an effective treatment protocol for an individual patient. We recommend the use of visual acuity, VEP, and BAEP to monitor patients receiving potentially neurotoxic therapy.

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