Cisplatin-induced encephalopathy and seizures

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Cisplatin induces mainly a peripheral sensory neuropathy, but occasionally may also induce an encephalopathy with or without seizures. We describe the clinical signs and symptoms of cisplatin encephalopathy. The clinical events in three patients that developed seizures and encephalopathy with focal signs are described. Two patients completely recovered, one patient developed a focal status epilepticus, refractory to antiepileptic treatment, and died due to ongoing seizures. Post-mortem examination of the central nervous system in this patient showed an ischemic lesion in the left temporal area and mild gliosis of the white matter. One patient was rechallenged with cisplatin after which he developed a second episode of encephalopathy. We conclude that physicians using cisplatin chemotherapy should be aware of this rare complication. ***Anti-Cancer Drugs*** **14:443–446 © 2003 Lippincott Williams & Wilkins.**

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Introduction

Cisplatin is an effective and widely used antineoplastic agent in the treatment of solid tumors. The most common side-effects are nausea, vomiting, nephrotoxicity, ototoxicity and neurotoxicity [1]. In general, neurotoxicity is limited to an axonal sensory neuropathy. Central nervous system (CNS) disorders such as seizures, cortical blindness, hemiparesis, aphasia and coma have been reported, but are rare [2]. We describe three patients with severe neurologic dysfunction following cisplatin-based chemotherapy. Post-mortem examination of the CNS was performed in one case.

Case reports

Case 1

A 20-year-old male presented with abdominal masses due to an undifferentiated carcinoma of unknown origin. The patient was treated with paclitaxel (75 mg/m^2, day 1, i.v.), bleomycin (30 mg, day 1, 8, 15, i.v.), etoposide (120 mg/m^2, day 1, 3, 5, i.v.) and cisplatin (20 mg/m^2, day 1–5, i.v.) every 3 weeks. Granulocyte colony stimulating factor (G-CSF) was given s.c. (5 μg/kg, day 6–15). Five days after the start of the fourth treatment cycle, the patient developed confusion, a focal seizure of the right arm and was subsequently unresponsive. Laboratory investigations revealed mild hypomagnesemia (0.53 mmol/l) and slightly elevated transaminases. Cerebral magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) examination were normal. The next day neurologic examination showed a comatose state, hyperreflexia, abnormal plantar reflexes and extension reactions of the arms after painful stimuli. Repeated examination of the CSF again gave normal results. Electroencephalogram (EEG) showed diffuse slow-wave activity. After 15 days the patient recovered completely. Six months later he was readmitted due to progression of disease. Chemotherapy was restarted, consisting of bleomycin (30 mg, day 1, 8, 15, i.v.), etoposide (100 mg/m^2, day 1–5, i.v.) and cisplatin (20 mg/m^2, day 1–5, i.v.). Two days later he again became confused and comatose. Laboratory results were normal, except for mild hypocalcemia (2.11 mmol/l). After 2 days he had recovered completely. No further chemotherapy was administered. Three months later the patient died from progressive disease.

Case 2

A 28-year-old woman, with a history of a fossa posterior neuroblastoma treated with resection, ventriculo-cardial CSF shunt and postoperative neuraxis radiation therapy at age 15, presented with diffuse neuroblastomal metastatic disease. Chemotherapy with etoposide (100 mg/m^2, day 1, 3, 5, i.v.), ifosfamide (1000 mg/m^2, day 1–5, i.v.) and cisplatin (20 mg/m^2, day 1–5, i.v.), every 4 weeks, was started. Eighteen days after the start of treatment, the patient developed fever, epileptic seizures, confusion, hemiparesis and coma. Laboratory investigations showed thrombocytopenia (62×10^9/l), leukopenia (1.41×10^9/l), neutropenia (0.43×10^9/l) and mild hypomagnesemia (0.69 mmol/l). Cerebral MRI and CSF examination gave normal results. Antibiotic and antiviral therapy was started. EEG showed diffuse slow-wave activity. Over the next days her condition gradually improved and after 2 weeks she had made a full recovery. Repeat cerebral MRI at that time was again normal; a second EEG showed improvement of the background rhythm with focal slowing over the right hemisphere. Tumor response

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evaluation showed tumor regression and chemotherapy was continued without further complications. Focal epileptic seizures recurred several times even after completion of chemotherapy, for which the patient was treated with phenytoin. Five years later, the patient is alive and free of seizures despite discontinuation of anticonvulsive medication. She has no evidence of malignant disease.

Case 3

A 60-year-old woman presented with inoperable stage T3N2cMx sinus piriformis carcinoma. The intended treatment consisted of chemotherapy with weekly courses of cisplatin (70 mg/m^2) and paclitaxel (90 mg/m^2), within a clinical trial, followed by radiation therapy after 6 courses. Five days after the fifth administration of cisplatin and paclitaxel the patient was admitted for asthenia, fever and pain in the left loin. Laboratory investigations revealed neutropenia (0.26×10^9/l), severe hypomagnesemia (0.28 mmol/l), moderate hypokalemia (3.1 mmol/l) and mild hypocalcemia (2.16 mmol/l). Creatinine clearance was 44 ml/min. Neurologic examination was normal. Antibiotic treatment with imipenem was started. The next day the patient developed confusion and a grand mal seizure, followed by aphasia, hemiparesis and right homonymous hemianopia. She was treated with i.v. phenytoin and acyclovir, and imipenem was replaced by meropenem. Cerebral MRI and computed tomography (CT) were normal, except for wide ventricles and sulci. Examination of the CSF including microbiological investigations gave normal results. EEG showed continuous left occipital-temporal region focal epileptic activity, consistent with partial status epilepticus. Her neurological condition did not improve and she required intubation for respiratory failure for 5 days, 16 days after the onset of neurologic symptoms. Physical examination of the cervical lymph nodes and direct laryngoscopy showed partial response to chemotherapy. Repeated neurologic examination including MRI, EEG and CSF examination after 4 weeks showed no new findings; in particular, no evidence of metastases. Focal and generalized seizures occurred at several occasions during hospitalization. The patient showed temporary neurologic improvement. However, 52 days after hospitalization seizures recurred, not responding to treatment with five different antiepileptic drugs. EEG confirmed a generalized status epilepticus. The patient died 64 days after hospitalization. Post-mortem examination of the CNS showed an ischemic lesion in the left temporal area and mild gliosis of the white matter, without evidence of metastases.

Discussion

All three cases presented with focal deficits and seizures following i.v. administration of cisplatin. Despite repeated examinations during life no other causes for the neurologic symptoms were found. Two patients showed complete recovery; one of them developed another episode with neurological deficits after rechallenge with cisplatin. The outcome was fatal in the third patient, at least partially due to ongoing focal seizures.

Two types of CNS disorders have been reported after cisplatin chemotherapy. The first consists of the posterior leuko-encephalopathy syndrome, with a usually typical combination of cortical blindness, seizures, decreased level of consciousness and hypertension [1,3–10]. These patients have typical neuroradiological abnormalities especially on T2-weighted MRI imaging, with predominant involvement of the occipital lobes. This occurs usually immediately at the end or shortly after the end of the cisplatin administration; despite the severe clinical symptoms and signs, most patients make a full recovery.

In other patients focal neurological deficits or decreased level of consciousness, with or without seizures, were reported [11–16]. In this second type of CNS disorders, symptoms start between a few hours and 3 months after the last cisplatin exposure, and are not related to the (cumulative) cisplatin dose. CT, MRI and CSF examination are normal; the EEG shows generalized slowing sometimes with epileptic discharges. In most cases the symptoms disappear without permanent neurological deficits. Fever, neutropenia, hypomagnesemia, hyponatremia, hypokalemia and renal dysfunction are described as contributory factors. Many of these were present in patients 2 and 3; if present they should be treated immediately [4,12,17]. Hypomagnesemia, which is known to lower the seizure threshold, was found in all patients [11]. Since its initial description in 1979 [1], at least 26 patients with seizures after cisplatin-based chemotherapy have been described, either with or without clinical signs of the posterior leuko-encephalopathy syndrome (Table 1). Status epilepticus has been reported twice [7,16]. Patient 3 is the only documented patient in whom status epilepticus lasted for more than 2 weeks and in which it recurred.

Five cases of post-mortem examination in patients with cisplatin-associated encephalopathy have been reported. Three showed no CNS abnormalities [11,16,18]; one a multifocal necrotizing leuko-encephalopathy [19]. The fifth showed severe nerve cell loss, gliosis and spongy changes in the bilateral occipital cortex, and demyelination in the subcortical white matter of the occipital cortex, Goll's tract and dorsal root ganglia [3].

Post-mortem CNS examination in patient 3 revealed an ischemic lesion in the left temporal area and mild gliosis of the white matter, but no evidence of metastases. This patient had no history of trauma, coagulopathy, vasculitis, arrhythmia or thrombosis explaining the cause of the ischemic lesion. There have been several reports with

Table 1 Cisplatin-induced encephalopathy with seizures; review of the literature[a]

Author [Reference]	Tumor type	Age/sex	Co-treatment	Cumulative cisplatin dose (mg/m^2)	Neurologic symptoms		Duration	Brain imaging (MRI/CT/isotope)	EEG	CSF	Autopsy
					Encephalopathy	Seizures					
Berman [1]	germ cell tumor	30M	VBL, BLEO	100	cortical blindness, headache	GMS	3 days	nl	diffuse slowing	nl.cisplatin level	NP
Nomura [3]	ovarian	61F	VP-16	325	headache, hemiparesis, confusion, cortical blindness	FS	1 month	NR	NR	NR	–[b]
Van Gelder [4]	germ cell tumor (2)	17–25 2M		700 885	cortical blindness, hemiparesis	GMS (1) FS (2)	5 days–<1 month	nl (2)	NR	NR	NP
Young [5]	germ cell tumor	21F	VBL, BLEO	200	cortical blindness	GMS	8 days	occipital and frontal cortical abnormalities	paroxysmal discharge occipital cortex	nl	NP
Highley [6]	neuroblastoma (3)	6–93F		640 (2) 880 (1)	headache, apraxia deteriorated vision, aphasia, cortical blindness	GMS (2) FS (1)	5–10 days	nl (2) ≥ 3 low-density lesions (1)	nl (1) bilateral abnormalities (1)	nl (2)	NP
Philip [7]	ACUP	59F	HU	225	confusion, headache, deteriorated vision	SE	14 days	few small ill-defined abnormalities	NR	NR	NP
Cattaneo [8]	ACUP	38F	VP-16	480	cortical blindness, headache	GMS	4 days	nl	NR	NR	NP
Hitchins [9]	germ cell tumor	22M	VBL, BLEO	500	confusion, desorientation, tunnel vision, aggression	GMS	21 days	nl	diffuse slowing	nl	NP
Wiltshaw [10]	ovarian carcinoma	NR		≥ 300	blurred vision	SNS	<6 months	NR	NR	NR	NP
Bellin [11]	ovarian carcinoma	34F	DOX	320		GMS	2 × seizure	nl	NR	nl	CNS nl
Brauers [12]	germ cell tumor	50M	IFOS, VP-16	300		GMS	<21 days	nl	nl	NR	NP
Clamon [13]	head/neck cancer	34F	DOX	90	confusion	SNS	1 day	nl	NR	NR	NP
Gorman [14]	germ cell tumor (2)	13–21M–1F	VBL, BLEO	200 300	aphasia, hemiparesis	GMS (1) FS (2)	1 h–2 days	nl (2)	NR	NR	NP
Schindler [15]	ovarian carcinoma	48F		NR		GMS FS	NR	NR	NR	NR	CNS nl
Mead [16]	germ cell tumor (4)	23–66 3M + 5F	VBL, BLEO VP-16 (1)	160 (1) 240 (2)	hemiparesis, aphasia	GMS (8) FS (4)	NR	nl (2) cerebral atrophia (1)	nl (1) focus posterio-temporal area (2)	NR	NP
	ovarian		DOX, CTX (5)	320 (2)		SE (1)					
			VBL, BLEO	400 (2) 500 (1)							
Present	head/neck	20–60 1M + 2F	TAX (1)	350	confusion, aphasia,	GMS (2)	14–64 days (death)	nl (2)	diffuse slowing, focus	nl (3)	(1)[c]
	cancer (1)		TAX, BLEO,	400	hemiparesis, coma,	FS (2)		white matter changes	occipito-temporal area (1)		NP (2)
	CUP (1)		VP-16 (1)	200	hyperreflexia	SE (1)		right parietal lobe (1)	diffuse slowing (2)		

[a]In parentheses: number of patients, (A)CUP: (adeno)carcinoma of unknown primary, VP-16: etoposide, VBL: vinblastine, BLEO: bleomycin, HU: hydroxurea, DOX: doxorubicine, IFOS: ifosfamide, CTX: cyclophosphamide, TAX: paclitaxel, FS: focal seizure, GMS: grand mal seizure, SE: status epilepticus, SNS: seizure not specified, NR: not reported, nl: normal, NP: not performed.
[b]Nerve cell loss, changes in occipital cortex and demyelination. Cisplatin found in occipital cortex, spinal cord and cauda equina.
[c]Diffuse metastases in various organs, no cerebral metastases, ischaemic lesion in the left temporal area, mild gliosis of the white matter.

regard to vascular toxicity of cisplatin, including cerebrovascular ischemic events [20]. The mechanism of this vascular toxicity is unknown and may include hypomagnesemia or altered platelet aggregation.

Our findings support the hypothesis that cisplatin-associated encephalopathy may be caused by vascular events that are not seen in cerebral imaging, but can be identified in post-mortem examination. Other mechanisms that have been suggested in the literature to cause cisplatin-associated encephalopathy are toxic encephalopathy, e.g. heavy metal toxicity and demyelinization.

In all cases there was a temporal, and therefore probably causal, relationship between the neurologic symptoms and the cisplatin treatment. Patients 1 and 3 were also treated with paclitaxel for which central neurotoxicity (but without seizures) has been reported [21]. However, in patient 1, symptoms recurred at the time of rechallenge with cisplatin, providing further evidence for a causal relationship. High-dose ifosfamide is also a known cause of encephalopathy [22]. However, this causes a rather typical clinical syndrome of somnolence, agitation and hallucinations which occurs typically 1–5 days after the start of treatment. None of the other concurrent medications has been related to either focal or diffuse encephalopathies.

In conclusion, physicians should be aware that encephalopathy and seizures in cancer patients treated with cisplatin are not necessarily due to CNS involvement by the tumor, but could be caused by the cisplatin treatment. In that case, the neurological signs and symptoms are usually transient and reversible with adequate treatment of the seizures and cessation of cisplatin therapy.

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