Seizure following chemotherapy (paclitaxel and cisplatin) in a patient of carcinoma cervix
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Abstract:
Cisplatin and paclitaxel both can cause peripheral neurotoxicity as an adverse effect; however, central nervous system neurotoxicity in the form of seizures is rare. We report a case of a 36-year-old female patient of metastatic carcinoma cervix, who developed seizure shortly after cisplatin infusion. Her laboratory investigations were within normal limits. Computed tomography scan and magnetic resonance imaging of the brain did not reveal brain primary metastasis or meningeal carcinomatosis. She had no complaints of fever, no signs and symptoms of infection, and no history of seizure nor was she on any medication predisposing to such an event. Excluding several causes, seizure was thought to be most likely related to the chemotherapy and cisplatin was the more likely agent in view of observed temporal relationship with the adverse event.

Key words:
Carcinoma, cervix, chemotherapy, seizure

Cisplatin, a commonly used antineoplastic agent, is associated with a variety of side effects such as nausea, vomiting, nephrotoxicity, ototoxicity, and neurotoxicity. The neurotoxicity usually manifests as an axonal sensory peripheral neuropathy. Central nervous system (CNS) neurotoxicity of cisplatin is rare, but seizures, hemiparesis, cortical blindness, aphasia, and coma attributed to cisplatin therapy have been reported.[1]

Paclitaxel, an antimicrotubule agent, has broad antitumor activities with adverse effects including myelosuppression and peripheral neurotoxicity. CNS toxicity is rare due to negligible penetration of the drug across an intact blood–brain barrier.[1]

We report a case of a 36-year-old woman, a diagnosed case of metastatic carcinoma cervix who developed seizure after administration of injection cisplatin.

Case Report
A 36-year-old woman who had received concurrent chemoradiation (initially diagnosed as FIGO Stage IIIB cervical cancer) came to our department for follow-up after treatment. Clinical examination showed no evidence of local disease. Ultrasonography revealed hepatomegaly with multiple hypoechoic areas of 2-6 cm in both lobes of the liver and multiple enlarged portocaval, para- and pre-aortic, and right iliac lymph nodes, which were suggestive of metastatic disease.

The patient was started on palliative chemotherapy consisting of day 1 injection paclitaxel 175 mg/m² and day 2 injection cisplatin 50 mg/m². The first day of chemotherapy went uneventful. Just after completion of day 2 injection cisplatin infusion, she developed generalized tonic–clonic seizure with up rolling of eyeballs, tongue biting. She was sedated with intravenous lorazepam and started on injection phenytoin. She had postictal confusion, slurring of speech, and drowsiness.

Neurology consultation favored a diagnosis of simple partial seizure with secondary generalization. Electroencephalography reported abnormal record with sharp wave and slowing pattern [Figure 1]. Contrast-enhanced computed tomography scan of the head was negative for any focal lesion. Contrast-enhanced magnetic resonance imaging (MRI) of the brain did not show any evidence of brain parenchymal or...
leptomeningeal disease or any feature suggestive of brain metastasis. Complete blood counts, liver function tests, renal function tests, blood sugar, serum electrolytes including serum calcium (8.5 mg/dl), sodium (144 mEq/L), potassium (4.3 mEq/L), chloride (102 mEq/L), and magnesium (2.4 mg/dl) were all within normal limits. Electrocardiography and two-dimensional echocardiogram were normal. Patient’s blood pressure remained in normal range before, during, and after chemotherapy. There was no complaint of fever and no signs of sepsis.

She remained on injection phenytoin for 8 days without any further episode of seizure. She was discharged on oral phenytoin. Three weeks later, although she had no neurological complaints, she was not able to receive the next cycle of chemotherapy on account of her poor general condition.

Discussion

Seizures in cancer patient may occur as a result of primary and metastatic brain tumors: paraneoplastic syndromes: treatment related such as radiation therapy, chemotherapy and biologic response modifiers: other drugs such as narcotics and antibiotics: radiological contrast media or as a result of infections or metabolic factors, etc. Seizures occur in <1% of patients treated with systemic chemotherapy. Implicated agents include methotrexate, cisplatin, L-asparaginase, 5-fluorouracil, busulfan, ifosfamide, cyclosporine, and paclitaxel.

Neurotoxicity associated with cisplatin is most commonly a peripheral sensory neuropathy because platinum agents have more propensities to enter the dorsal root ganglia and peripheral nerves compared to the brain, where there is poor penetration of the blood–brain barrier. More commonly toxicity is related to hypomagnesemia, hypocalcemia, and hypokalemia. Preexisting renal disease and hypertension may exacerbate the process.[11]

The first known case of transient cortical blindness and seizures associated with cisplatin in a patient of testicular embryonal cell carcinoma was reported in 1977.[12] Another case of transient cortical blindness in a patient of ovarian germ cell tumor with the same agent was reported in 2006.[13] There have also been case reports of posterior reversible encephalopathy syndrome (PRES) with cisplatin.[14] Our patient did not have clinicoradiological picture of PRES.

Our patient had received five cycles of weekly injection cisplatin (40 mg/m²) concurrently with radiotherapy without any neurotoxicity. Manchana et al.[15] and Vieillot et al.[16] reported encephalopathy with cisplatin and carboplatin only after multiple cycles of chemotherapy. CNS toxicity was observed immediately at the end or shortly after the end of the cisplatin administration, often when the total dose was >200 mg/m². This probably explains the seizure in our patient as she had exceeded this cumulative dose.

Both acute and late-onset encephalopathy have been reported with paclitaxel; however, some of these reported cases had underlying brain metastasis, history of previous radiotherapy to the brain, previous brain surgery, or some form of disruption of blood–brain barrier. There are also reports of seizure shortly after starting infusion of paclitaxel, and in one case, the patient developed hypersensitivity signs such as chest tightness and flushing within 5 min of infusion, followed by generalized tonic–clonic seizure. Paclitaxel infusion had been uneventful in our patient. Cremophor (solvent vehicle for paclitaxel) is also known to be a neurotoxic agent having procoagulatory effects which may lead to thrombotic-embolic effects.[17] Our patient’s brain MRI did not show any CNS infarct.

A diagnosis of chemotherapy-induced seizure was made (WHO-UMC causality assessment system-Probable/Likely causality) considering (1) the development of encephalopathy shortly after chemotherapy (cisplatin) infusion; (2) exclusion of other physical or metabolic factors that may cause seizures such as hyper/hypoglycemia, azotemia, hepatic failure, electrolyte imbalance, sepsis, no previous history of seizure, leptomeningeal carcinomatosis, and brain metastasis, (3) no present concomitant administration of other drug or analgesic, and (4) response to withdrawal.

Cisplatin appears to be the more likely agent in view of observed temporal relationship between this chemotherapeutic agent and the subsequent seizure. We cannot entirely rule out paclitaxel as a causative factor.

Conclusion

Seizures induced by chemotherapeutic agents are rare; however, it is important to recognize such cases to maximize treatment after exclusion of other possible causes.

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Conflicts of Interest
There are no conflicts of interest.

References

1. Flowers A. Seizures and syncope in the cancer patient. In: Levine A, editor. Cancer in the Nervous System. 2nd ed. New York: Oxford University Press; 2002. p. 438-53.
2. Ziske CG, Schöttker B, Gorschützer M, Mey U, Kleinschmidt R, Schlegel U, et al. Acute transient encephalopathy after paclitaxel infusion: Report of three cases. Ann Oncol 2002;13:629-31.
3. Berman IJ, Mann MP. Seizures and transient cortical blindness associated with cis-platinum (II) diamminedichloride (PDD) therapy in a thirty-year-old man. Cancer 1980;45:764-6.

4. Manchana T, Sirisabaya N, Lertkhachonsuk R, Tresukosol D. Transient cortical blindness during chemotherapy (PVB) for ovarian germ cell tumor. J Med Assoc Thai 2006;89:1265-8.

5. Hinchey J, Chaves C, Appignani B, Breen J, Pao L, Wang A, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334:494-500.

6. Vieillot S, Pouessel D, de Champfleur NM, Becht C, Culine S. Reversible posterior leukoencephalopathy syndrome after carboplatin therapy. Ann Oncol 2007;18:608-9.

7. Cronk M, Abraham R, Perrin L. Case report of a generalized seizure related to paclitaxel infusion. J Natl Cancer Inst 2004;96:487.