

CASE REPORT

High-dose cytarabine-associated cerebellar toxicity: A case report

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ABSTRACT

High-dose arabinoside cytarabine is used as an effective regimen for post-remission acute leukemia and refractory leukemia treatment. Most commonly used regimen is 3 g/m² IV over 1-3 h q12 h for a total of 8-12 doses. Major toxic effects associated with cytarabine are related to bone marrow, gastrointestinal tract, and nervous system. Acute cerebellar toxicity with ataxia and dysarthria is well-known adverse effect during high-dose cytarabine therapy. This case report describes about a patient with acute myeloid leukemia on high-dose cytarabine who developed ataxia and left-sided nystagmus as cerebellar toxicity. These symptoms persisted till 2 days after the termination of high-dose cytarabine the gradually improved with steroids. Patient's good response to methyl prednisolone illustrates immune-mediated mechanism of neurotoxicity.

KEY WORDS: High-dose Arabinoside Cytarabine; Acute Myeloid Leukemia; Neurotoxicity

INTRODUCTION


Cytarabine is a pyrimidine analog which enters into the cells through a carrier process and then converted to its active compound, aracytidine triphosphate.^[1] Decreased DNA synthesis and repair resulting from the inhibition of DNA polymerase is its primary action when cytarabine incorporated into DNA. The incorporation into DNA correlates direct proportionally with the degree of cytotoxicity. This proportionality highlights to the idea that DNA incorporation is responsible for toxicity and drug activity. Cytarabine blocks progression from the G₁ to the S phase, thus act specifically in the S phase of the cell cycle.^[2] A well-known complication of high-dose cytarabine is neurotoxicity. The pathophysiology of neurotoxicity is not known; however, it is hypothesized as an immune-mediated mechanism.^[3]

CASE REPORT

A 44-year-old male patient diagnosed with acute myeloid leukemia 5 years and was under chemotherapy with 3+7 regimen. In view of elevated urea and creatinine, the patient was given adequate intravenous fluids simultaneously. Gastroconsultation was suggested due to complaints of severe vomiting and abdominal pain. Endoscopy showed hemorrhagic gastritis due to chemotherapy. Ultrasonography abdomen revealed mild ascites and bilateral renal parenchymal disease. During the consolidation phase, the patient was started with high-dose cytarabine. Cytarabine was withheld on the 5th day of chemotherapy, as the patient had ataxia and left-sided nystagmus due to cerebellar toxicity. Methylprednisolone 125 mg IV once daily was prescribed for 3 days for persistent ataxia beyond 48-72 h. The patient had a gradual improvement.

DISCUSSION

Mechanism of cerebellar toxicity is thought to be inhibition of cytarabine-dependent neurotrophic signals in the brain. The incidence of cerebellar toxicity with high-dose arabinoside

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cytarabine (HIDAC) is ~10%.^[4] It can be diagnosed in a way that the MRI brain reveals cerebellar atrophy and reversible white matter changes. The cerebrospinal fluid is usually normal. Authors suggested that the direct toxic effect of cytarabine on axonal and myelin metabolism of peripheral nerves assumed to be the cause of peripheral neuropathy, but some of them suggested vasculitis as the cause.^[3,5] It was reported in published reports about the acute phase of HIDAC neurotoxicity that ancillary diagnostic evaluation has often not been helpful. Electroencephalography revealing diffuse slow waves and an elevated cerebrospinal fluid protein are found to be non-specific findings. Computed tomography of the brain is appeared normal during the acute phase of toxicity. An excellent response to methylprednisolone suggested HIDAC-induced immune-mediated neuropathy occurred due to either by nerve damage with resultant exposure or modification of peripheral nerve antigen or by an effect on reconstituting immune cells,^[3] and same observation was obtained in this case report also. The unremarkable cortical pathology confirmed the reversibility of the syndrome. The cerebellum was spared radiographically despite pronounced symptoms and a loss of Purkinje cells with reactive gliosis - the typical pathologic findings in high-dose cytosine arabinoside-related cerebellar injury.^[6] In some studies like Jolson *et al.*, they highlighted certain risk factors for high-dose cytarabine-induced cerebellar toxicity, *i.e.*, age >50 years, total dose ≥ 20 g/m², type of leukemia, disease stage, severe hyperbilirubinemia (>3 mg/dl), abnormal pre-treatment liver function, and decreased creatinine clearance (<60 ml/min). Using St. Luke's Screening assessment for cerebellar toxicity with high-dose cytarabine (Ara-C),^[7] we can assess following criteria such as confused or somnolent, slurred speech, nystagmus (rhythmic eye beats with gaze), ataxic or unsteady gait, arm tremor (extend forward palms up), and also patient signature (assess deterioration of fine motor coordination).

CONCLUSION

From this case report, we highlight the excellent response of methylprednisolone on high-dose cytarabine cerebellar toxicity that suggests an immune-mediated mechanism of neurotoxicity.

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