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INTRATHECAL CYTARABINE INDUCED HYDROCEPHALUS FOLLOWED BY SEIZURE

Raina Sebastian*[1], Dijo Wilson[1], K. Menaka[2] and T. Sivakumar[3]

[1]PharmD. Intern, Nandha College of Pharmacy.

[2]Assistant Professor, Nandha College of Pharmacy.

[3]Principal, Nandha College of Pharmacy, Erode, Tamil Nadu.

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***Corresponding Author**
Dr. Raina Sebastian
PharmD. Intern, Nandha College of Pharmacy.

ABSTRACT

Cytarabine (cytosine arabinose) is a nucleoside analogue that is approved by the FDA in June 1969 for the treatment of acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and Meningeal leukemia (ML). In addition, it is used for the treatment of Hodgkin's lymphoma, malignant meningitis, mantle cell lymphoma, myelodysplastic syndrome, and non-Hodgkin's lymphoma. Intrathecal use of Cytarabine can be associated with a mild chemical meningitis, It is more common with the liposomal, sustained-release preparation of Cytarabine (i.e., DepoCyt), and can recur with subsequent doses of the drug. Rarely, seizures, acute myelopathy and confessional syndromes can occur with Intrathecal usage. Acute cerebellar syndrome can be caused by high doses of cytarabine. Acute cerebellar syndrome include acute obstructive hydrocephalus (AOH) represents a life -threatening event in which clinical presentation is often non- specific but may include severe headache, vomiting and lethargy. The present study reports on the Acute obstructive hydrocephalus (AOH), developed in a patient with lymphoblastic leukemia during induction of chemotherapy period which was identified and confirmed on MRI scan when patient had an unexpected episode of abnormal movements and development of seizure disorder.

KEYWORDS: Cytarabine (cytosine arabinose) movements and development of seizure disorder.

INTRODUCTION

Cytarabine is an antimetabolite that requires phosphorylation by deoxycytidine kinase (DCK) within the cells to form the active derivative ara-CTP (ara-Cytidine-5′-triphosphate). The

anticancer activity of cytarabine is attributed to ara-CTP mediated direct inhibition of DNA polymerase and replacement of deoxycytidine triphosphate (dCTP) by ara-CTP within the DNA during replication. Together, these mechanisms interfere with DNA synthesis during the S-phase of the cell cycle resulting in cancer cell death.[3]

Cytarabine is mainly used for treatment of AML in combination with an anthracycline. In adults cytarabine is approved for use at low/intermediate dose (100 mg/m^2/day continuous i.v. infusion for 7 days or 100 mg/m^2 i.v. every 12 hours for 7 days) as well as high dose (3000 mg/m^2 i.v. infusion over 1–3 hours every 12 hours for 2–6 days) for induction therapy in combination with other approved chemotherapeutic agents. Cytarabine - induced cerebellar syndrome is common at high doses of cytarabine (total dose ≥36 g/m2), it rarely occurs at low doses (total dose <15 g/m^2).[3]

Cytarabine induced, acute obstructive hydrocephalus results from disturbed reabsorption of cerebrospinal fluid (CSF) caused by damage to the absorptive tissue. The most common causes in adults are infections of the central nervous system (CNS) and hemorrhages as a consequence of intracerebral bleeding or cranio-cerebral injury. On accumulation of CSF, the ventricles expand and may cause an increase in intracranial pressure, which can damage the surrounding brain tissue. In non-destructive hydrocephalus, decreased mental activity appears, including lethargy, apathy, impaired memory, and speech problems. Urinary and bowel incontinence can also occur.[6]

In this report, we describe the unusual case of a young patient with acute myeloid leukemia, who developed a non-destructive hydrocephalus followed with seizure during induction of chemotherapy.

CASE REPORT

A 7 year old Female child was presented with relapsed acute myeloid leukemia and also she was diagnosed with Hepatitis C. She was started with chemotherapy from second day onwards with Fluderabine (30mg IV OD), Cytarabine (200mg IV OD). Fourth day she was administered with intrathecal Cytarabine followed by the administration of Idorubicin (10mg IV OD) through Hick Mann line. On 6th day she showed abnormal movements and development of Seizure disorder, chemotherapy were end on that day itself. Patient shifted to ICU and movements were observed, she was referred for MRI. Her eyes were not opened, during the period immediately she was administered with Inj.Phenytoin, Inj. Levipill (250mg

IV BD) and Inj. Midazolam. MRI report was showed that she has intraventricular bleed with communicating hydrocephalus (Non-destructive hydrocephalus). Hydrocephalus induced the seizure disorder and started the therapy with Acetazolamide tablet. After few days patient's condition was improved, seizure symptoms got subsided.

DISCUSSION

Central Cytarabine is primarily a cell cycle S phase–specific agent. When given intravenously, the drug is rapidly cleared from the blood by deamination in the liver, with a plasma half-life of 5 to 20 minutes. With these properties, continuous infusion is often the preferred route of administration. Cytarabine crosses the blood–brain barrier, achieving cerebrospinal fluid concentrations of 40% to 50% of those in the plasma. This feature allows for the treatment of CNS disease with systemic high-dose therapy.[1]

Cytarabine may be administered intrathecally and produces high concentrations that decline slowly because of the absence of cytidine deaminase in the CNS. It is often used in combination with other agents for synergistic activity. It also exhibits modest activity against lymphomas. The major side effect is myelosuppression. Bone marrow suppression with leukopenia, anemia, and thrombocytopenia are the most common serious adverse effects associated with cytarabine therapy.[1] Anaphylaxis, neuropathy, kidney disease, and infections have also been reported following treatment with cytarabine. The most common neuropathologic findings are cerebellar cortical atrophy and Purkinje cell loss. Symptoms usually resolve after discontinuation of Cytarabine.[2]

Neurotoxicity from Ara-C is usually noted in the context of high-dose IV therapy (≥ 3 g/m^2 every 12 hours × 4–6 days), and typically presents with a sub-acute pan cerebellar syndrome (Baker et al., 1991), and other symptoms include dysarthria, dysmetria, ataxia, and nystagmus and cerebral dysfunction.[2]

Monitoring parameters for cytarabine include bone marrow examination, platelet and leukocyte counts. Liver kidney function tests. Serum uric acid concentrations. Hematopoietic system should be checked in patients receiving drug intrathecally.[10]

In our case patient receiving Intrathecal Cytarabine on the 4th day of chemotherapy through Hickmann line. On 6th day of chemotherapy she showed abnormal movements and seizure disorders. Next day of seizure she has been performed for CT scan of head that shows

intraventricular bleed with communicating hydrocephalus (fig.1 a,b). After 16 days of seizure she has been performed CT scan of head and that shows hydrocephalus got normal.

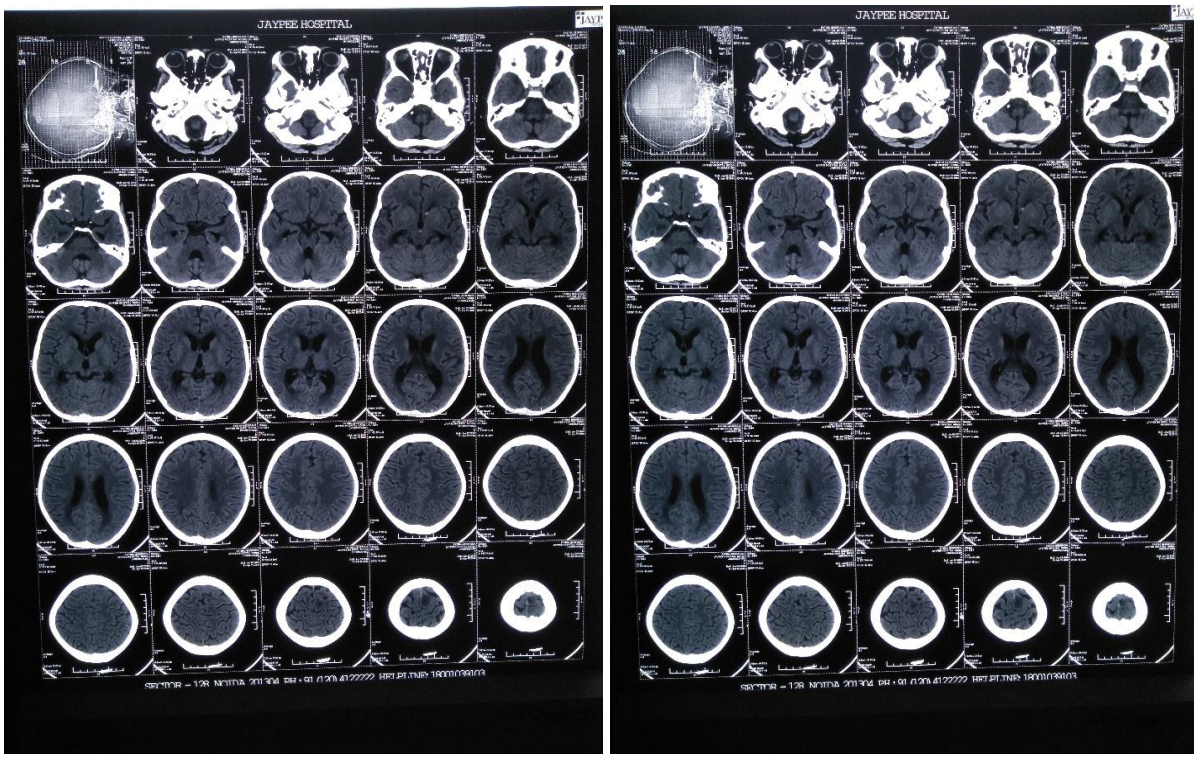

Fig.1a fig.1b

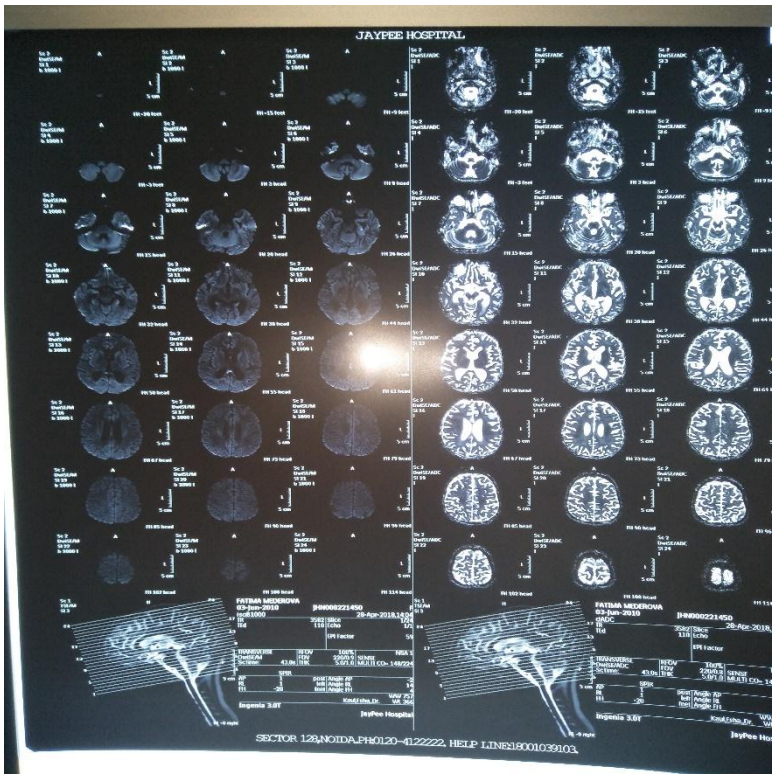

Fig.2.

CONCLUSION

Clinicians should be aware of the possibility of developing acute obstructive hydrocephalus in all acute myeloid leukemia cases when intrathecal cytarabine is given. The symptom of lethargy and abnormal movements should alert clinicians to immediately rule out the presence of acute obstructive hydrocephalus. If suspecting, necessary differential diagnosis should be done to confirm its presence and prevent its complications and further worsening by managing it at right time.

REFERENCES

1. Karl K. Kwok, James N. Gibson, in Pharmacology and Therapeutics for Dentistry (Seventh Edition), 2017.
2. Riccardo Soffietti, ... Roberta Rudà, in Handbook of Clinical Neurology, 2014.
3. Sipan Keshishyan, ... Sidhartha D. Ray, in Side Effects of Drugs Annual, 2015.
4. Department of pediatrics, Kyoto Prefectural University of Medicine, Kawaramachi, Hirokoji, Kamikyoku, Kyoto, 602 Japan 5. Piccin A, Tripodi M, Cassibba V, Cavattoni I, Primerano M, et al. (2014) Acute Obstructive Hydrocephalus during Chemotherapy inT-Lymphoblastic Lymphoma. J Clin Diagn Res., 2: 110. doi: 10.4172/2376-0311.1000110.
5. Kalina Ramadanova, Hansjörg Hoff, Nicola Gökbuget, Ulrike Reuner, Susanne Hamann, et al. Toxic non-resorptive internal hydrocephalus as a result of hemorrhagic ventriculitis during induction chemotherapy of Bcr-Abl positive acute lymphoblastic leukaemia. Annals of Hematology.
6. High-Dose Cytarabine Neurotoxicity: MR Findings during the Acute Phase.
7. David J. Vaughn, 1 Jeffrey G. Jarvik, 2 David Hackney, 2 Sara Peters, 3 and Edward A. Stadtmauer1.
8. High-dose cytarabine-associated cerebellar toxicity: A case report Delcey Reachel Varghese**1**, Dawnwin Joseph**1**, Raghuveer Prabhu**2**, Anila K N**1** Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Amrita University, Kochi, Kerala, India, 2Department of Medical Oncology and Haematology, Amrita Institute of Medical Sciences and Research Center, Amrita University, Kochi, Kerala, India.
9. The Toxicity of Cytarabine Jesper Stentofi Department of Internal Medicine and Haematology B, Aalborg Hospital South, Aalborg, Denmark.
10. IBMmicromedex.comDrugref.