Standard dose Cytarabine-Induced Encephalopathy in an Acute Myeloid Leukemia Patient: A Case Report

Mehrshad Ebrahimpour[1], Samin Ghorbani Moghadam[1], Mostafa Kamandi[2], Omid Arasteh[3*]

[1]Department of Pharmaceutical Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.
[2]Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences Mashhad Iran.
[3]Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

Received: 2024-08-09, Revised: 2024-08-24, Accepted: 2024-09-05, Published: 2024-09-30

Abstract

The mainstay of treatment for acute myeloid leukemia (AML), cytarabine, is known to induce encephalopathy, usually at high doses. During induction chemotherapy, a 38-year-old woman with non-M3 AML experienced encephalopathy following the administration of standard-dose cytarabine. The patient's mental state deteriorated, and she exhibited symptoms of physical weakness, confusion, and lethargy. There were no abnormalities in the brain parenchyma discovered by a CT scan. After a diagnosis of cytarabine-induced encephalopathy, cytarabine treatment was abruptly discontinued. Levetiracetam was used for managing seizures, intravenous hydration, and medication management, all of which were put into place as supportive measures. Over the next few days, the patient's mental state got better, and ten days later, she was fully conscious again. The encephalopathy and cytarabine were likely related, according to the Naranjo scale. Cytarabine was not reintroduced due to the patient's recovery and to prevent any potential problems. Rather, an alternate treatment regimen consisting of etoposide and mitoxantrone was initiated. This case emphasizes how crucial it is to take cytarabine-induced encephalopathy into account as a possible side effect when treating AML, even at lower doses of the medication. to minimize patient morbidity and ensure a successful treatment course, healthcare practitioners need to be on alert for signs and symptoms of this condition. Early detection and rapid cessation of cytarabine medication are critical steps in this regard.

J Pharm Care 2024; 12(3): 198-201.

Keywords: Cytarabine; Acute Myeloid Leukemia; Encephalopathy

Introduction

One of the most prevalent forms of acute leukemia is acute myeloid leukemia, which is correlated with malignant bone marrow disorders (1). AML can be categorized into various subtypes; however, a general distinction can be drawn between M3 and non-M3 classifications. The primary therapeutic approach for non-M3 AML is typically divided into two phases: induction and consolidation. The induction phase frequently employs the 3+7 regimen, while the consolidation phase often utilizes the HiDAC regimen (high-dose Ara-c). So, Cytarabine serves as the cornerstone of both induction and consolidation chemotherapy protocols. Furthermore, cytarabine remains a critical therapeutic intervention for M3 classifications of AML (2). Cytarabine, a medication belonging to the antimetabolite class that frequently causes adverse effects such as diarrhea, oral mucositis, vomiting, and neutropenia (3). However, cerebral adverse effects including encephalopathy, dysarthria and paraplegia are relatively rare with this agent at low doses and are typically observed at high doses (4). Nonetheless, in this case study, we look at a patient who received this medication in low doses and then suffered encephalopathy.

Case Presentation

The patient, an Iranian woman 38 years of age, obtained a diagnosis with AML (non-M3) based on bone marrow biopsy, and she received standard chemotherapy induction using a 7+3 regimen. (cytarabine 150 mg/m2/day continuous infusion for 7 days with daunorubicin 90 mg/m2 for 3 days) The initial stage of treatment proceeded well until day 5; when the first cycle was completed. At that point, the patient began to gradually deteriorate mentally, showing increased numbness, confusion, and lethargy.

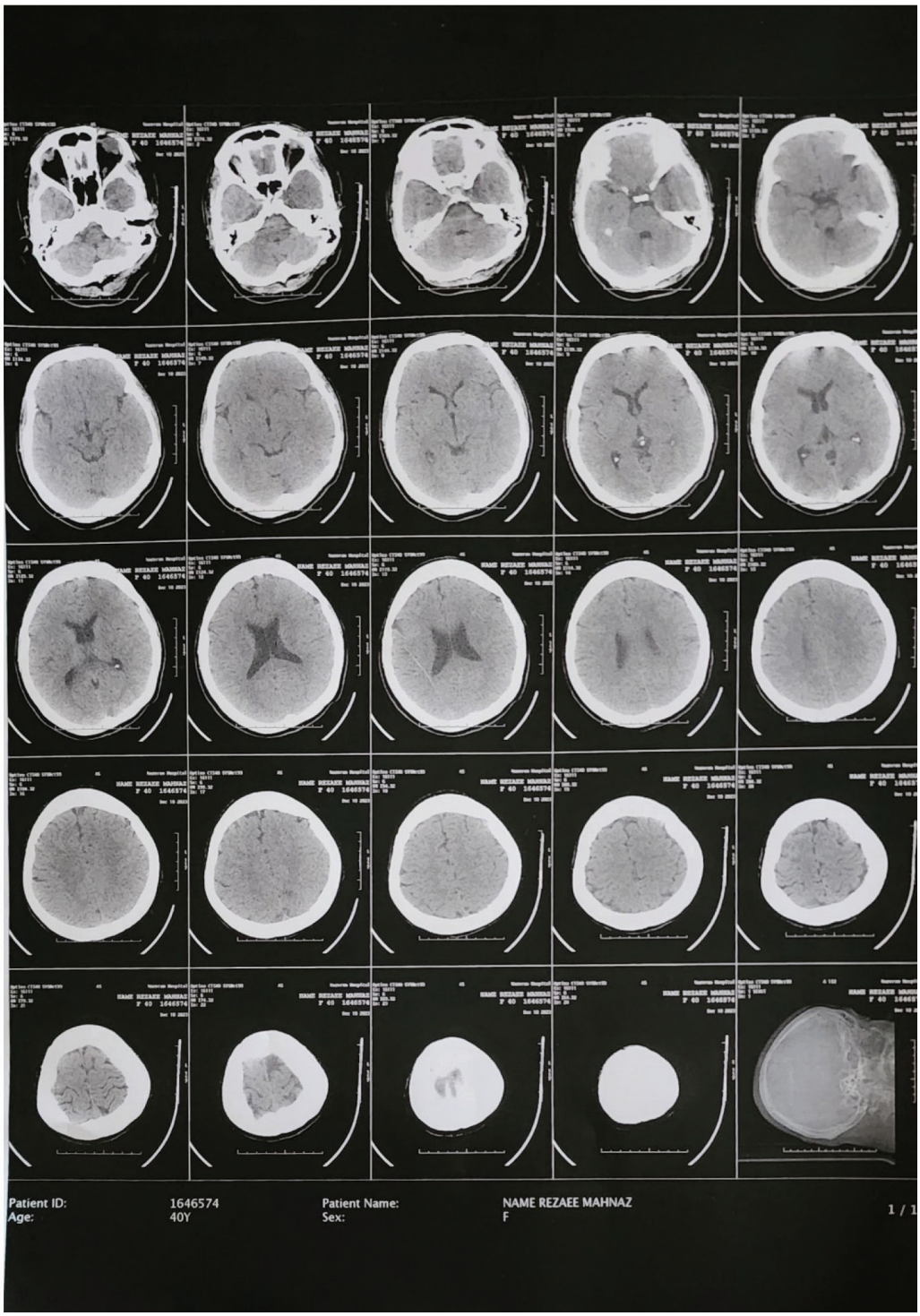
Corresponding Author: Dr Omid Arasteh
Address: Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.
Email: ArastehO@mums.ac.ir

Clinical Findings and Diagnostic Workup

Upon physical examination, the patient exhibited significant disorientation and drowsiness, making it challenging for her to follow commands and respond to basic questions. At that time, her Glasgow Coma Scale (GCS) was approximately six to eight. A neurological assessment indicated general weakness and impaired level of consciousness

In order to expeditiously rule out alternative etiologies such as intracranial hemorrhage contributing to the patient's rapidly deteriorating mental status, a cranial computed tomography (CT) scan was requisitioned. The examination yielded unremarkable findings, with no evidence of structural abnormalities within the brain parenchyma.

Picture1. Brain CT-Scan of patient; No pathological findings.



Treatment and Course

Considering the clinical presentation, the temporal association with cytarabine administration, and the exclusion of alternative etiologies, the patient received a diagnosis of cytarabine-induced encephalopathy. Consequently, cytarabine was discontinued immediately. The treatment plan shifted to supportive measures, including intravenous hydration to maintain electrolyte balance and close monitoring of her vital signs. Additionally, parenteral haloperidol and biperiden was given to patient in order to treat her agitation. Patient also received levetiracetam as a treatment for her seizure. Thankfully, the patient's mental status showed gradual improvement over the following days and patient was fully consciousness after 10 days.

According to Naranjo scale of adverse drug reactions, this adverse reaction is probably caused by cytarabine (score=5) (5). Concerning patient's condition, the physician did not re-challenge of cytarabin administration again; Furthermore, a new regimen including mitoxantrone and etoposide was initiated for her.

Table 1. Naranjo scale and scores of the studied patient.

Question	Yes	No	Don't Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	**+1**
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	**+2**
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	**+1**
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	**0**
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	**0**
6. Did the reaction reappear when a placebo was given?	-1	+1	0	**0**
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	**0**
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	**0**
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	**0**
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	**+1**

Discussion

One well-known side effect of cytarabine is encephalopathy (6). However, a high dose of this agent has been utilized in the majority of documented cases of cytarabine-induced encephalopathy (6-8). Rubin et al., identified several potential predictors for cytarabine-induced encephalopathy, including elevated serum creatinine (≥1.2 mg/dL), advanced age (≥40 years), and elevated alkaline phosphatase (ALP) exceeding three times the upper limit of normal. However, it is noteworthy that these risk factors were established within the context of high-dose cytarabine regimens (9). Different studies suggest a potential correlation between impaired renal function and cytarabine-induced encephalopathy in AML patients. (10-12) Elevated serum creatinine levels, a sign of kidney dysfunction, were also observed in some of the individuals with high-dose cytarabine-induced encephalopathy that have been documented. The findings emphasize how critical it is to keep an eye on kidney function when taking cytarabine for patients to prevent cerebral damage (8, 13). The patient presented in this case report received a standard-dose cytarabine treatment and lacked any of the aforementioned risk factors in particular, renal insufficiency.

Although the precise mechanism of cytarabine neurotoxicity is not known, an autopsy demonstrated that glial cells proliferated erratically and Purkinje cells in the cerebellum died out. Furthermore, cytarabine may result in patchy losses in the cerebellum's granular and molecular layers, but it hardly ever damages the deep nuclei (14).

The urgency of promptly diagnosing and treating cytarabine-induced encephalopathy as a potential adverse reaction during the treatment of acute myeloid leukemia (AML) is emphasized by this case report. It highlights how important it is for healthcare providers to be on alert for symptoms of the condition and to act quickly to discontinue cytarabine therapy in order to reduce patient morbidity and ensure an effective course of treatment. In order to prevent more neurological problems and enhance the overall well-being of the patient receiving AML treatment, early detection and action are crucial.

Conflict of interest

The author claims they have no financial or other conflicts of interest.

Conflict of interest:

The author claims they have no financial or other conflicts of interest.

References

1. Chaurasiya PS, Lamsal DK, Khatri A, et al. Prevalence of acute myeloid leukemia and its associated risk factors at a tertiary care center: a retrospective cross-sectional study. Ann Med Surg (Lond). 2023;85(10):4794-8.
2. [Available from: Vakiti A, Mewawalla P. Acute Myeloid Leukemia. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507875/.
3. Lopes LM, Nucci M, Portugal RD. Toxicity and outcome of adults with acute myeloid leukemia receiving consolidation with high-dose cytarabine. Hematol Transfus Cell Ther. 2024;46(4):397-401..
4. Sainz de la Maza Cantero S, Jiménez Martín A, de Felipe Mimbrera A, Corral Corral Í. Cerebellar toxicity due to cytarabine: A series of 4 cases. Neurologia. 2016;31(7):491-2.
5. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.
6. Lenfant C, Greiner N, Duprez T. Cytarabine-Induced Encephalitis. J Belg Soc Radiol. 2021;105(1):46.
7. Jolson HM, Bosco L, Bufton MG, et al. Clustering of adverse drug events: analysis of risk factors for cerebellar toxicity with high-dose cytarabine. J Natl Cancer Inst. 1992;84(7):500-5.
8. Newey CR, Chandrasekaran PN, Mohebbi MR. Posterior reversible encephalopathy syndrome after high-dose cytarabine in acute myelogenous leukemia. Neurology India. 2017;65(1):220.
9. Rubin EH, Andersen JW, Berg DT, Schiffer CA, Mayer RJ, Stone RM. Risk factors for high-dose cytarabine neurotoxicity: an analysis of a cancer and leukemia group B trial in patients with acute myeloid leukemia. J Clin Oncol. 1992;10(6):948-53.
10. Herbst J, Grommes C, Schaff L. NCMP-14. Neurotoxicity after a single cycle of intravenous cytarabine. Neuro-Oncology. 2022;24(Suppl 7):vii193-vii4.
11. Lindner LH, Ostermann H, Hiddemann W, et al. AraU accumulation in patients with renal insufficiency as a potential mechanism for cytarabine neurotoxicity. Int J Hematol. 2008;88(4):381-6.
12. Smith GA, Damon LE, Rugo HS, Ries CA, Linker CA. High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. J Clin Oncol. 1997;15(2):833-9.
13. Hasle H. Cerebellar toxicity during cytarabine therapy associated with renal insufficiency. Cancer Chemother Pharmacol. 1990;27(1):76-8.
14. Tran PN, Kong XT. Cytarabine Induced Acute Cerebellar Syndrome during Hyper-CVAD Treatment for B-Cell Acute Lymphoblastic Leukemia. Case Rep Neurol. 2017 May 9;9(1):114-120.

PLEASE CITE THIS PAPER AS:

Ebrahimpour M, Ghorbani Moghadam S, Kamandi M, Arasteh O. Standard dose Cytarabine-Induced Encephalopathy in an Acute Myeloid Leukemia Patient: A Case Report. J Pharm Care 2024; 12(3): 198-201.