SFDA SAFETY SIGNAL

"A signal is defined by the SFDA as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature"

30-4-2023

Saudi Food and Drug Authority (SFDA) – Safety Signal of Cytarabine and the Risk of Tumour lysis syndrome

*The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of **Tumour lysis syndrome** associated with the use of **Cytarabine**. The signal has been originated as a result of routine pharmacovigilance monitoring activities.*

Introduction

Cytarabine may be used alone or in combination with other antineoplastic agents. It is indicated alone or in combination for induction of remission and/or maintenance in patients with acute myeloid leukaemia, acute non-lymphoblastic leukaemias, acute lymphoblastic leukaemias, acute lymphocytic leukaemia, erythroleukaemia, blast crises of chronic myeloid leukaemia, diffuse histiocytic lymphomas (non-Hodgkin's lymphomas of high malignancy), meningeal leukaemia and meningeal neoplasms. Clinicians should refer to the current literature on combination therapy before initiating treatment. [1] Tumor lysis syndrome (TLS) is a constellation of metabolic abnormalities resulting from the rapid release of intracellular metabolites when massive lysis of tumor cells occurs. This process of tumor cell lysis is accompanied by significant metabolic derangements, most notably hyperkalemia, hyperphosphatemia, hyperuricemia from nucleic acid degradation, and hypocalcemia. TLS poses a life-threatening risk of organ failure, particularly kidney injury in patients with cancer. Kidney injury results from uric acid and calcium phosphate deposition in the kidneys. Acute kidney injury (AKI) in the setting of tumor lysis can evolve rapidly and can be prevented with clinical vigilance. [2] The aim of this review is to evaluate the risk of Tumour lysis syndrome associated with the use of Cytarabine and to suggest regulatory recommendations if required.

Methodology

Signal Detection team at SFDA performed a signal review using National Pharmacovigilance Center (NPC) database, and World Health Organization (WHO) database, VigiBase, with literature screening to retrieve all related information to assess the causality between Tumour lysis syndrome and Cytarabine use. The search conducted on February 2023.

Results

Case Review: Signal detection team at SFDA have searched Saudi national database and WHO database to find individual case safety reports (ICSRs). While the Saudi National database resulted in

single ICSR, the WHO database resulted in 244 global case-reports. [3] The authors selected the cases with completeness score of 0.73 and above (30 cases) to apply the WHO-UMC causality assessment criteria on them, which resulted in more than half of them are possibly linked to Cytarabine (1 probable + 19 possible + 7 not assessable + 3 unlikely = 30 ICSRs). [4]

Datamining: The disproportionality of the observed and the expected reporting rate for drug/adverse drug reaction pair is estimated using information component (IC), a tool developed by WHO-UMC to measure the reporting ratio. Positive IC reflects higher statistical association while negative values indicates less statistical association, considering the null value equal to zero. The results of (IC= 5.3) revealed a strong positive statistical association for the drug/ADR combination. [3]

Literature: On February 2023, the author searched for eligible publications using the terms "Cytarabine" and "Tumor lysis syndrome" which resultein in a published case-report in 2015 describes a 13-year-old boy developed tumour lysis syndrome (TLS), respiratory failure, uric acid nephropathy and renal failure following treatment with intrathecal cytarabine.

Conclusion

The weighted cumulative evidence identified from assessed cases, literature and data mining are sufficient to suggest causal association between Cytarabine and Tumour lysis syndrome. Health care professionals and health regulators must be aware of the potential risk in drug recipients.

Report Adverse Drug Events (ADRs) to the SFDA

The SFDA urges both healthcare professionals and patients to continue reporting adverse drug reactions (ADRs) resulted from using any medications to the SFDA either online, by regular mail or by fax, using the following contact information:

National Pharmacovigilance Center (NPC)
Saudi Food and Drug Authority-Drug sector
4904 northern ring branch rd
Hittin District
Riyadh 13513 – 7148
Kingdom of Saudi Arabia
Toll free number: 19999
Email: NPC.Drug@sfda.gov.sa

References:

1- Saudi Drug Information (2021). Cytarabine 100 mg/ml Injection SPC. Retrieved from: https://sdi.sfda.gov.sa/Home/Result?drugId=10000 [Accessed 14/02/2023].
2- Cairo MS, Coiffier B, Reiter A, Younes A; TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Br J Haematol. 2010 May;149(4):578-86. doi: 10.1111/j.1365-2141.2010.08143.x. Epub 2010 Mar 16. PMID: 20331465.
3- Vigilyze.who-umc.org. 2023. [online] Available at: https://vigilyze.who-umc.org/ [Accessed 14/02/2023].
4- World Health Organization WHO (2013). WHO-UMC system for standardised case causality assessment. Available at https://www.who.int/publications/m/item/WHO-causality-assessment [Accessed 14/02/2023].
5- Simangan, L. R. (2015). Tumor lysis syndrome and it's complications: case report. Reactions, 1550, 72-9.