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"

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Saudi Food and Drug Authority (SFDA) – Safety Signal of Dabrafenib and the Risk of Disseminated Intravascular Coagulopathy (DIC)

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

Introduction

Dabrafenib is an antineoplastic drug indicated for treatment of melanoma and non-small cell lung cancer (NSCLC). It inhibits some mutated forms of the protein kinase B-raf selectively (BRAF). Dabrafenib inhibits tumor cell growth by inhibiting BRAF [1]. Disseminated Intravascular Coagulopathy (DIC) is characterized by the widespread activation of coagulation resulting in the intravascular formation of fibrin and ultimately thrombotic occlusion of small and midsize vessels. DIC can also compromise the blood supply to organs and, in conjunction with hemodynamic and metabolic derangements, may contribute to the failure of multiple organs [2]. The aim of this review is to evaluate the risk of DIC associated with the use of Dabrafenib and to suggest regulatory recommendations if required.

Methodology

Signal Detection team at the National Pharmacovigilance Center (NPC) of Saudi Food and Drug Authority (SFDA) performed a comprehensive signal review using its national database as well as the World Health Organization (WHO) database (VigiBase), to retrieve related information for assessing the causality between Dabrafenib and the risk of DIC [3]. We used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [4].

Results

Case Review: There were 21 individual case safety reports (ICSRs) for the combined drug/adverse drug reaction as of April 2022 [3]. Applying WHO causality assessment tool on 13 cases with completeness score (0.5) revealed two DIC cases possibly related to Dabrafenib [4].

Data Mining: Information component (IC), a tool developed by WHO-UMC to measure the reporting ratio, is used to estimate the disproportionality of the observed and expected reporting rates for drug/adverse drug reaction pairs. Positive IC values indicate a positive statistical association, whereas negative values indicate no statistical association. The results of (IC= 2.4) revealed that the drug/ADR combination has a positive statistical association. In other words, DIC has been observed more than expected with Dabrafenib compared to other medications in the database [3].

Literature: two published case reports highlighted the risk of DIC in association with Dabrafenib:

A 61-year-old Japanese woman was treated with the combination therapy of dabrafenib and trametinib for BRAF V600E-mutated melanoma. On day 25 her complete blood cell counts revealed leukocytopenia (white blood cell count, 1.8 * 103/mcL) and thrombocytopenia (platelets, 86 * 103/mcL). blood coagulation test revealed striking elevation of total fibrin degradation product of 148.1 mcg/mL and plasma D-dimer level of 125.5 mcg/mL, although the D-dimer level was 0.7 mcg/mL 4 days before. DIC was suspected. DIC score was at least 4 points. Her condition gradually improved after the cessation of combination therapy [5].

A 23-year-old man was treated with dabrafenib (300 mg/day) plus trametinib (2 mg/day) therapy for metastatic malignant melanoma. On day 28, a blood coagulation test revealed a remarkable increase of fibrin degradation product (FDP; 99.9 mcg/mL), D-dimer (52.8 mcg/mL) and plasmin-a2–plasmin inhibitor complex (PIC; 11.7 mcg/mL). Thrombin–antithrombin III complex (TAT; 5.2 ng/mL) and fibrinogen (426 mg/dL) were also increased. Disseminated intravascular coagulation (DIC) score was 3 points. remarkable elevation of FDP, D-dimer and PIC, and elevation of TAT were observed despite no evidence of thrombosis, indicating development of coagulopathy with widespread intravascular activation of coagulation and subsequent fibrinolysis [6].

Conclusion

The weighted cumulative evidence identified from the reported cases, data mining and literature are sufficient to support a causal association between Dabrafenib and the risk of DIC. Health regulators and health care professionals must be aware of this potential risk and it is advisable to monitor any signs or symptoms in treated patients.

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:

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