CASE REPORT

Tyrosine Kinase Inhibitors and Risk of Myocardial Infarction: Is there a Link?

Adnan M Hajjiah[1*], Osama Maadarani[2], Zuhair Bitar[2]

[1]Department of Pharmacy, General Ahmadi Hospital, Ahmadi, Kuwait
[2]Department of Internal Medicine, General Ahmadi Hospital, Ahmadi, Kuwait

ABSTRACT

Interstitial lung disease is one of the most chronic inflammatory conditions that progressively can affect pulmonary function and patient quality of life. Tyrosine kinase inhibitors are novel medicinal agents that play a role reducing disease progression. We report a case of an acute myocardial infarction that may have been associated with the use of nintedanib; a tyrosine kinase inhibitor.

Key Words: Tyrosine kinase inhibitors; Nintedanib; myocardial infarction; adverse drug reactions

Correspondence:

Adnan M Hajjiah, Department of Pharmacy, General Ahmadi Hospital, Ahmadi, Kuwait,

E-mail: ahajjiah@kockw.com, Tel: 0096566893218

INTRODUCTION

Nintedanib is a tyrosine kinase inhibitor used for the treatment of idiopathic pulmonary fibrosis and various cancers. It targets the platelet-derived growth factor receptors, vascular endothelial growth factors receptors and fibroblast growth factor receptors. It is usually well tolerated with adverse effects that include mainly gastrointestinal symptoms [1].

Tyrosine Kinase Inhibitors (TKI) is a class of drugs that disrupt the signal transduction pathways of protein kinases through a variety of mechanisms. This exercise will go through the medications that are currently on the market, their mechanisms of action, methods of administration, indications, contraindications, and side effects. Tyrosine Kinase Enzymes (TKs) are divided into three groups: Receptor Tyrosine Kinases (RTKs), Non-Receptor Tyrosine Kinases (NRTKs), and a small number of Dual-Specificity Kinases (DSKs) that may phosphorylate serine, threonine, and tyrosine residues. RTKs are transmembrane receptors that include VEGFR, PDGFR, the Insulin Receptor (InsR) family, and the ErbB receptor family, which includes EGFR and Human Epidermal Growth Factor Receptor (HER2)

TKI toxicity and effectiveness are frequently related, allowing on-target toxic effects to serve as indicators of effective pharmacological suppression for certain TKIs [2,3]. Skin rashes, for example, can be used to monitor the effects of particular TKIs that target EGFR and hypertension, as well as to assist monitor VEGFR inhibition in general. However, the combined negative effects of on-target and off-target toxicity can reduce a patient's quality of life and restrict the dose intensity of their drug, resulting in sub-therapeutic therapy.

Tyrosine Kinase Inhibitors (TKIs) have been created and clinically evaluated; TKIs have the ability to control new blood vessel creation by blocking selective tyrosine phosphorylation (activation) of a panel of cell surface angiogenic growth receptors [4-6]. TKIs have an effect on the growth factor receptors Vascular Endothelial Growth Factor Receptor (VEGFR), basic Fibroblast Growth Factor Receptor (bFGFR), Platelet-Derived Growth Factor Receptor (PDGFR), and Epidermal Growth Factor Receptor (EGFR). A number of TKIs have been authorised for clinical usage in advanced malignancies such as renal cell carcinoma, hepatocellular carcinoma, and certain lung cancers [7].

The limited efficacy of licenced TKIs appears to reflect tumours' capacity to respond through auxiliary vascular growth factors when just one or a few variables are predominantly impacted. As of yet, no TKIs have been produced that target all of the main vascular growth factor receptors. Surprisingly, a TKI side effect, hypothyroidism caused by sorafenib and sunitinib, may improve clinical prognosis in patients with renal cell carcinoma. This might be due to a decrease in thyroid hormones proangiogenic clinical contribution [8,9].

CASE PRESENTATION

We present a case of 80 years old male patient with history of hypertension, diabetes mellitus since 20 years, ischemic heart disease, and long-standing interstitial lung disease. The patient is an ex-smoker and had multiple percutaneous coronary interventions with the latest four years ago. The patient was on dual antiplatelets for life along with high-intensity statin therapy. Nintedanib (tyrosine kinase inhibitor) 100 mg every 12 hours was part of his interstitial lung disease medications [10].

The patient presented to the emergency department complaining of chest pain. A diagnosis of acute myocardial infarction was confirmed by raising troponin level above 900+ and ST depression in the ECG. Therapeutic anticoagulation was commenced along with other anti-ischemic measures. According to the Naranjo, Adverse Drug Reactions (ADR) Probability Scale for assessing causality of an adverse event by a certain medication, a score of 3 was calculated confirming the reaction was possibly associated with the administration of the tyrosine kinase inhibitor nintedanib [11].

DISCUSSION

Tyrosine kinase inhibitors play a pivotal role in the treatment of multiple inflammatory conditions and various types of cancer. The association between tyrosine kinase inhibitors and myocardial infarction is well documented in the literature. Multiple pieces of evidence questioned the cardiovascular safety of tyrosine kinase inhibitor with cardiac toxicity varies in rate and severity with different tyrosine kinase inhibitors. The associated cardiovascular toxicity ranges from hypertension and acute coronary syndrome to conduction abnormalities and heart failure and has been reported with imatinib, dasatinib, sorafenib, lapatinib, warranting label warnings by healthcare regulatory institutions [9].

The mechanisms through which tyrosine kinase inhibitors exert their

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cardiotoxicity are not fully understood. They are thought to be by inhibition of different pathways. Electrical toxicity predisposing to corrected for heart rate (QTc) interval prolongation is one suggested theory which has been implicated with the use of vandetanib (Figure 1). Functional toxicity that leads to left ventricular dysfunction and decreased ejection fraction are adverse events associated with use of sunitinib and dasatinib. Another mechanism by which tyrosine kinase inhibitors are thought to cause cardiac toxicity is through impairment of mitochondrial function. Sorafenib directly affects mitochondrial function resulting in decreased oxidative phosphorylation. In addition, sorafenib association with an incidence of MI was 2.9% whereas ibrutinib use was associated with 1.4% incidence of cardiac ischemia. It is due to the fact that pathways inducing pathological proliferation of tumor cells are often responsible for regulating normal cells in the myocardium.

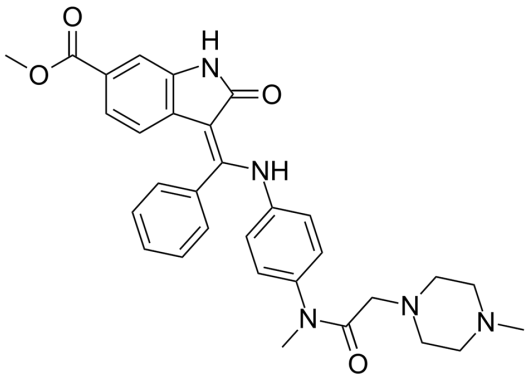

Figure 1: Chemical Structure of Nintedanib

Our case report is aligned with the incidence rates of tyrosine kinase inhibitors' cardiovascular toxicity illustrated in the literature. Incidence rates of MI with nintedanib is 3.03% per 100 patient-years in patients with higher cardiovascular risk. The development of atherosclerosis triggered by nintedanib is shown to be through inhibition of significant signalling pathways. Furthermore, nintedanib can affect instability of atherosclerotic plaques and plaque rupture through hindering of plaque healing. In addition, the findings of this case report needs more evidence to support the causality nature of this adverse effect with regard to tyrosine kinase inhibitors in general and nintedanib in particular.

CONCLUSION

Tyrosine kinase inhibitors pose a risk of cardiovascular toxicity in patients with pre-existing risk factors for cardiovascular disease. Treating healthcare professional needs to exercise extreme caution and monitoring when prescribing tyrosine kinase inhibitors in patients with existing cardiovascular risk factors to ensure optimal patient safety and reduce risk of cardiotoxicity.

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