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CASE REPORT

Hepatic Toxicity Induced by Sunitinib Malate: A Rare Case Report

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ABSTRACT

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Introduction: Sunitinib malate, an oral multi-targeted tyrosine kinase inhibitor (TKI), is prescribed for metastatic renal cell carcinoma (mRCC) and gastrointestinal stromal tumors (GIST) following imatinib failure. While effective, Sunitinib is associated with various adverse effects, including rare but severe hepatic toxicity. This report discusses a case of acute liver injury attributed to Sunitinib, emphasizing the importance of monitoring liver function in patients undergoing this treatment.

Case Report: A 49-year-old male with GIST on Sunitinib therapy presented with progressive breathlessness, edema, and jaundice over several weeks. Despite normal vital signs, physical examination revealed pallor, jaundice, and pitting edema. Laboratory tests indicated liver dysfunction, and after excluding other causes, Sunitinib-induced acute liver injury was diagnosed. The patient received supportive care, including blood transfusions, and was subsequently discharged.

Conclusion: This case highlights the rare yet significant risk of acute liver injury associated with Sunitinib. Clinicians should monitor liver function vigilantly during Sunitinib therapy. Further research is required to elucidate the mechanisms of Sunitinib-induced hepatotoxicity and to enhance patient safety.

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Introduction

Sunitinib malate is a widely used multi-targeted tyrosine kinase inhibitor (TKI) effective in treating metastatic renal cell carcinoma (mRCC), gastrointestinal stromal tumors (GIST), and pancreatic neuroendocrine tumors (Iacovelli et al., 2014). By inhibiting key receptors such as vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs), Sunitinib disrupts tumor growth and angiogenesis. Despite its efficacy, Sunitinib is associated with various adverse effects, including a potentially severe form of hepatotoxicity. Understanding these risks within the broader context of anticancer therapy provides essential insights into managing and mitigating such adverse effects.

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The spectrum of anticancer drugs includes several classes, each with distinct mechanisms and associated risks. Tyrosine kinase inhibitors (TKIs) such as Sorafenib and Imatinib, along with traditional chemotherapeutics like Methotrexate and Doxorubicin, frequently present hepatotoxic risks. For instance, Sorafenib can induce hepatocellular injury and cholestasis, while Methotrexate is linked to dose-dependent liver fibrosis (Ibrahim et al., 2013; Martino 2023). Other agents, such as Lapatinib and Trastuzumab, also pose risks of liver injury, although their primary adverse effects may differ (Yardley, 2013; Guillen SS., 2016). These variations highlight the complex nature of drug-induced liver injury and underscore the importance of vigilant monitoring in cancer therapy.

Case Details

A 49-year-old male patient with a history of gastrointestinal stromal tumor (GIST) and a Whipple's procedure performed three years ago, currently on Sunitinib malate 50 mg orally, presented to the emergency department on May 22, 2024. He reported experiencing breathlessness for the past two days, edema for three days, and jaundice characterized by yellowing of the skin and sclera for two months. Additional symptoms included fatigue and loose stools over the previous month. On clinical examination, his vital signs were normal; however, pallor, jaundice, and pitting edema were noted.

Laboratory tests showed elevated serum aminotransferases and bilirubin levels, indicating liver dysfunction. Further imaging and assessments were performed to evaluate liver involvement and exclude other potential causes of liver injury.

The patient received supportive care, including blood transfusions, and continued Sunitinib therapy under close liver function monitoring. The patient was stabilized and discharged with follow-up plans for reassessment of liver function.

Discussion

Sunitinib, an FDA-approved TKI, is employed for treating GIST, pancreatic neuroendocrine tumors, and renal cell carcinoma (Iacovelli et al., 2014; Teo et al., 2015). Despite the general safety profile of TKIs compared to traditional chemotherapeutics, they are associated with significant adverse effects, including hepatotoxicity. Approximately 40% of patients on TKIs experience elevated liver enzymes, with severe hepatotoxicity in about 3% (Ibrahim et al., 2013; Iacovelli et al., 2014). Sunitinib's hepatotoxicity is linked to its broad-spectrum kinase inhibition, leading to mitochondrial dysfunction and oxidative stress (Paech et al., 2017; Teo et al., 2015).

Comparatively, hepatotoxicity mechanisms differ among various drugs:

Acetaminophen causes liver damage primarily through the formation of N-acetyl-p-benzoquinone imine (NAPQI), which depletes glutathione and leads to oxidative stress (Lee, 2012). This mechanism is distinct from Sunitinib's oxidative stress mediated by mitochondrial injury.

Isoniazid induces hepatotoxicity via covalent binding of its metabolites to hepatic proteins, a mechanism somewhat similar to Sunitinib's reactive metabolite-induced damage (Metushi I et al., 2016).

Methotrexate causes dose-dependent hepatocellular damage and fibrosis, highlighting a more predictable dose-response relationship compared to Sunitinib's idiosyncratic toxicity (Martino 2023).

Halothane leads to acute liver failure through an immune-mediated reaction to trifluoroacetylated liver proteins, differing from Sunitinib's oxidative and mitochondrial damage (Habibollahi P 2011).

In addition to hepatotoxicity, Sunitinib can cause cardiotoxicity, gastrointestinal symptoms, and myelosuppression, reflecting a broad range of potential adverse effects similar to those seen with other anticancer agents (Greineder et al., 2011; Schmidinger et al., 2009).

Based on WHO-UMC criteria, the causality assessment for this case is likely "Probable": The adverse reaction is likely related to the drug, given its temporal relationship, consistency with known side effects, and lack of alternative explanations for the liver injury. A definitive assessment would require further clinical details, including the outcome post-discontinuation of Sunitinib and any rechallenge data. (The Uppsala Monitoring Center, 2024).

Conclusion

This case underscores the rare but severe adverse effects associated with Sunitinib, particularly acute liver failure. It highlights the necessity for careful monitoring of liver function in patients receiving Sunitinib therapy. Further research is essential to elucidate the mechanisms behind Sunitinib-induced hepatotoxicity and to develop effective strategies for managing these risks.

Conflict of Interest

Authors declered no conflict of interest.

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