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Case and Review

Sunitinib-Induced Acute Liver Failure

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Keywords

Tyrosine kinase inhibitors · Sunitinib · Acute liver failure

Abstract

Drug-induced liver injury is an uncommon but life-threatening entity. Sunitinib is a tyrosine kinase inhibitor used for advanced and imatinib-refractory gastrointestinal stromal tumors. It causes transient elevation in liver enzymes. The incidence of fatal acute liver failure is rare. Five cases of sunitinib-induced acute liver injury have been reported in the literature thus far. We present a case of fatal acute liver failure and cardiomyopathy within 2 weeks of sunitinib therapy initiation for advanced pancreatic neuroendocrine carcinoma. We believe our case is unique due to the rarity of its presentation. It highlights hepatotoxicity as a potentially fatal side effect of sunitinib therapy.

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Introduction

Sunitinib is a tyrosine kinase inhibitor (TKI). It has antitumor and anti-angiogenesis activity. It is approved for the treatment of renal cell carcinoma, gastrointestinal stromal tumors,

and pancreatic neuroendocrine tumors. It acts on different kinase receptors including platelet-derived growth factor receptors α and β , vascular endothelial growth factor receptors 1, 2, and 3, and the proto-oncogenes c-Kit and RET. Inhibition of these receptors will decrease cellular proliferation and tumor angiogenesis and can also lead to organ dysfunction, i.e., gastrointestinal upset, myelosuppression, cardiotoxicity, and hepatotoxicity. This primarily occurs due to the disruption of oxidative phosphorylation and adenosine triphosphate depletion. Elevation of liver enzymes occurs in 39% of patients while grade 3 and 4 hepatotoxicity occurs in 3% of patients [1]. Sunitinib-induced liver failure is a rare event. Herein, we present the unique case of a patient with a pancreatic neuroendocrine tumor who developed fatal acute liver failure and cardiomyopathy after receiving a first cycle of sunitinib.

Case Presentation

A 64-year-old Caucasian male with a history of end-stage renal disease on hemodialysis, stage IV high-grade pancreatic neuroendocrine carcinoma with metastases to the liver, spleen, and left adrenal gland, presented to the emergency department with right upper quadrant abdominal pain, nausea, and lethargy. He had been on octreotide 30 mg every 4 weeks for 1 year. Due to the progression of metastasis, the patient was started on sunitinib 50 mg once daily for 1 month prior to presentation. Sunitinib was discontinued 2 weeks before admission after the patient had developed severe fatigue, decreased oral intake, and dehydration. He was not on any other hepatotoxic medications or herbal remedies. His liver function tests were normal before starting sunitinib and after starting treatment up until that point.

Upon arrival in the emergency room, the patient was in sinus tachycardia at 120 beats per minute. Physical examination was positive for jaundice, disorientation to time, place, and person, and asterixis. The trend of liver function tests during the course of hospitalization is presented in Table 1. Acetaminophen concentration was undetectable. Viral hepatitis panel including HBsAg, HbC IgM antibody, HCV antibody, HAV antibody, EBV, CMV, and HSV PCR was negative. Antinuclear antibody, antimitochondrial antibody, anti-smooth muscle antibody, and antimicrosomal antibody assays were all negative. Ferritin was elevated at 17,535 ng/mL; his ceruloplasmin level was normal (32 mg/dL), and his ammonia level was 27 μ mol/L. Duplex ultrasound of the hepatic veins was unrevealing. A computed tomography scan of the abdomen and pelvis did not show any acute hepatobiliary pathology.

The patient was started on an N-acetylcysteine protocol for acute liver failure and was started on lactulose and rifaximin for suspected hepatic encephalopathy. He was deemed to not be a candidate for transplantation due to his stage IV cancer. Transthoracic echocardiography showed severe acute cardiomyopathy with an ejection fraction of 20–25%, severely decreased global left ventricular systolic dysfunction, and moderate pulmonary hypertension. Transthoracic echocardiography had been normal prior to sunitinib initiation.

On the second day of hospitalization, the patient's liver enzymes remained elevated. His coagulation profile worsened with elevation of international normalized ratio. He was persistently hypoglycemic with finger sticks <50 mg/dL. His mental status did not improve despite

three to four bowel movements per day. Despite aggressive supportive care, his liver failure was irreversible and he passed away on day 5 of hospitalization.

Discussion

Sunitinib is a TKI. It is FDA-approved for the treatment of gastrointestinal stromal tumor, pancreatic neuroendocrine tumor, and renal cell carcinoma.

TKIs are known to be less toxic compared to other chemotherapeutic agents, but they have a narrow therapeutic window. Hepatotoxicity is common with TKIs, but fulminant liver failure is a rare complication. A meta-analysis on the side effects of sunitinib showed elevated liver enzymes in 40% of 5,658 patients. Grade 3 and 4 hepatotoxicity, on the basis of Drug-Induced Liver Injury Network assessment, occurred in 3% of patients, and no fatal hepatotoxicity was reported [2]. Hepatotoxicity does not depend on the type or stage of tumor that is treated with sunitinib [3].

Sunitinib causes time- and concentration-dependent cellular injury [4]. The time to onset is variable. It was observed to be 1–3 weeks in few case reports, while some mentioned incidence of hepatotoxicity after several months into treatment [5]. A dose >50 mg/day is associated with hepatotoxicity [5]. The exact mechanism of sunitinib-induced organ dysfunction is not known. It inhibits complex one of the electron transport chain in mitochondria. This results in the accumulation of reactive oxygen species within the mitochondria which can subsequently interfere with glycolysis by inhibiting adenosine monophosphate kinase. Reactive intermediate metabolites formed by hepatic metabolism of the TKI by cytochrome CYP3A4 also contribute to cellular toxicity [6]. The low incidence and occurrence of hepatotoxicity even at therapeutic doses favors type B (idiosyncratic) drug reaction [7]. However, dose-dependent cellular injury also favors type A (intrinsic) drug reaction. The pattern of liver injury in patients receiving TKIs is typically hepatocellular. However, cholestatic patterns have also been described in the literature, particularly with pazopanib [3, 4]. Hyperbilirubinemia, however, is secondary to interaction with UDP-glucuronyltransferase. The pathogenesis behind ammonia elevation remains incompletely understood.

Cardiac dysfunction is caused by the inhibition of oxidative phosphorylation, which compromises myocardial energy consumption. Acute cardiomyopathy is seen in 10% of patients on sunitinib [8]. Systolic function is known to be affected more than diastolic function. Cases of acute decompensated heart failure with sunitinib use have been reported [9]. It remains unclear whether the risk of hepatotoxicity increases in patients with baseline abnormal liver function tests. It is also unknown whether the risk of cardiotoxicity increases in patients with underlying cardiac disease.

Our patient had acute liver failure and cardiomyopathy after sunitinib initiation. The pattern of liver enzyme elevation as well as the absence of hypotension, signs of volume overload, or signs of right-sided heart failure on examination goes against congestive hepatopathy. The characteristic findings of ischemic hepatitis with an increase in lactate dehydrogenase and an alanine transaminase/lactate dehydrogenase ratio <1.5 were not also observed in our case either [10]. Therefore, based on a Naranjo adverse drug reaction probability index of 6 and a

Roussel Uclaf Causality Assessment Method score of 6, sunitinib was deemed the most likely cause of drug-induced liver injury in our case.

The definitive management of organ dysfunction includes withholding of sunitinib along with supportive care. This case emphasizes that overt liver failure and systolic cardiac dysfunction are infrequent but major complications of sunitinib therapy. We recommend periodic monitoring of baseline liver function and cardiac function status for patients on sunitinib therapy, especially within the first year of treatment.

Statement of Ethics

Written informed consent was received from the patient and family members to publish this case report. Ethical approval to undertake this study was granted by Staten Island University Hospital. The guidelines followed for this report were HIPAA-compliant. The study adhered to the tenets of the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

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Author Contributions

A. Aqsa and S. Droubi: literature review, manuscript writing. S. Amarnath: final review of the manuscript. H. Al-Moussawi and J. Abergel: supervision. The final version of the manuscript was read and approved by all authors.

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Table 1. Trend of liver function tests during the course of hospitalization

	Platelet count, ×10 ³ /μL	INR	Total bilirubin, mg/dL	ALP, U/L	AST, U/L	ALT, U/L	Ammonia, μmol/L	Albumin, g/dL
Day 0	147	3.06	2.8	5,858	5,036	2,351,351		4.2
Day 1	118	4.18	3.9	633	3,447	20,352,035	27	3.7
Day 2	77	6.05	4.1	6,969	2,146	1,643,643		3.9
Day 3	57	7.15	4.6	700	1,803	1,469,469		3.8
Day 4				72	1,746	1,371		3.6