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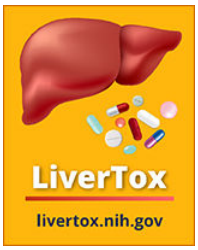


Sunitinib

Updated: June 27, 2018.

OVERVIEW

Introduction

Sunitinib is multi-specific tyrosine kinase receptor inhibitor that is used in the therapy of gastrointestinal stromal tumors and advanced renal cell carcinoma. Sunitinib therapy is associated with transient elevations in serum aminotransferase and bilirubin levels and rare instances of clinically apparent acute liver injury.

Background

Sunitinib (soo ni' ti nib) is an inhibitor of several tyrosine kinase receptors which are associated with tumor growth and angiogenesis. The tyrosine kinase receptors of cancer cells are often mutated and can cause unregulated cell growth and proliferation. Sunitinib is one of several tyrosine kinase receptor inhibitors that have been introduced into cancer chemotherapy and are specially directed at molecular abnormalities that occur in cancer cells. Inhibition of the receptor can lead to dramatic reversal of progression the cancer, although sometimes limited by the development of tumor resistance caused by mutations in the kinase. Sunitinib has special activity against the abnormal tyrosine kinase (cKit) that is found in gastrointestinal stromal tumors (GIST). Sunitinib also has activity against the receptors for platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF). Sunitinib received approval for use in the United States in 2006. Current indications are for unresectable or metastatic GIST with positive cKit (CD117), advanced renal cell carcinoma and advanced pancreatic neuroendocrine tumors. Sunitinib is also used in patients who are intolerant or become resistant to imatinib, the initial tyrosine kinase receptor inhibitor that has special activity against chronic myelogenous leukemia (CML) bearing the Philadelphia chromosome. Sunitinib is available in capsules of 12.5, 25 and 50 mg under the brand name Sutent. The typical dose of sunitinib is in cycles of 4 weeks, followed by a rest period of 2 weeks, using a starting dose of 37.5 or 50 mg daily and increasing or decreasing in 12.5 mg increments, with each cycle based upon tolerance and response. Side effects include fatigue, diarrhea, anorexia, skin discoloration, rash, hand-foot syndrome, edema, muscle cramps, arthralgias, headache, abdominal discomfort, anemia, cough, and pruritus. Uncommon side effects include heart failure, pancreatitis and renal failure.

Hepatotoxicity

In large clinical trials of sunitinib, elevations in serum aminotransferase levels were common, occurring in 39% of sunitinib vs 23% of placebo recipients. Values greater than 5 times the upper limit of normal (ULN) occurred in only 2% to 3% of sunitinib recipients (and 1% of controls). These abnormalities were usually asymptomatic. Dose adjustment or temporary discontinuation and restarting at a lower dose is recommended if enzyme levels are markedly elevated (ALT or AST persistently greater than 5 times ULN or bilirubin more than 3 times ULN).

Sunitinib therapy is also associated with a high rate of serum bilirubin elevations, generally in the mild-to-moderate range and not in association with ALT or AST elevations. These changes are probably due to interaction with hepatic UDP-glucuronyltransferase, the enzyme that is also responsible for bilirubin excretion.

More importantly, there have been several case reports of clinically apparent liver injury attributed to sunitinib therapy. The time to onset was after several cycles of therapy. The pattern of serum enzyme elevations was typically hepatocellular and the clinical presentation resembled acute hepatic necrosis. In some instances, the injury may have been due to hypotension, shock or ischemia rather than direct hepatotoxicity (Case 1). Regardless, the injury can be severe and several instances of acute liver failure and death have been reported. Immunoallergic features (rash, fever and eosinophilia) are not common.

Finally, sunitinib has also been reported to cause hyperammonemia and encephalopathy in rare patients with cancer treated with conventional or even low oral doses (Case 2). The time to onset was within 1 to 3 weeks, presenting with confusion and irritability with minimal elevations in serum enzymes and bilirubin and marked increases (4-10 times the ULN) in serum ammonia. Recovery is rapid once sunitinib is stopped and the syndrome can recur with re-exposure. Interesting, there appears to be little cross-reactivity to this complication with other tyrosine kinase inhibitors.

Likelihood score: B (highly likely cause of clinically apparent liver injury, including hyperammonemic syndrome).

Mechanism of Injury

The clinical features of cases of severe acute liver injury due to sunitinib have suggested ischemic damage that may be related to hypotension and anoxia, rather than direct hepatic injury. Sunitinib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury may be related to production of a toxic intermediate. The cause of hyperammonemia due to sunitinib is unknown, but it appears to be idiosyncratic and may relate to inhibition of urea cycle enzymes by sunitinib.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) should lead to dose reduction or temporary cessation. In some situations, therapy can be restarted particularly with concurrent prednisone (10-20 mg daily). In patients with clinically apparent liver injury and jaundice, restarting therapy should be done with caution. There does not appear to be cross reactivity in risk for hepatic injury between sunitinib and other tyrosine kinase inhibitors and, in some situations, switching to another tyrosine kinase receptor inhibitor may be appropriate. Cases of acute liver failure have occurred in patients receiving sunitinib. In using this medication, other potentially hepatotoxic agents should be avoided.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

CASE REPORTS

Case 1. Severe acute liver injury during sunitinib therapy.

[Modified from: Mueller EW, Rockey ML, Rashkin MC. Sunitinib-related fulminant hepatic failure: case report and review of the literature. Pharmacotherapy 2008; 28: 1066-70. PubMed Citation]

A 75 year old woman with metastatic renal cell carcinoma developed severe diarrhea and dehydration after a fifth 4-week cycle of sunitinib and was found to be jaundiced. Her renal carcinoma had been diagnosed six months earlier, at which time she had undergone right nephrectomy. Metastases were identified in the inferior vena cava and lungs and she was started on sunitinib in 4 week courses, followed by a rest period of 2 weeks. She

had multiple side effects with chemotherapy including fatigue, arthralgias, dry mouth, thrombocytopenia, neutropenia, abdominal pain and diarrhea. Her liver tests were known to be normal before and during the first five cycles of sunitinib therapy (Table). Four days after the fifth cycle, she was brought to the hospital by her family because of dehydration and mental confusion following a 3 day history of diarrhea. She had no known liver disease, alcohol use or risk factors for viral hepatitis. Her past medical history included breast cancer treated with lumpectomy 7 years earlier as well as hypothyroidism, hypertension, chronic heart failure, gastroesophageal reflux disease, bladder surgery and carpal tunnel syndrome. Her other medications included letrozole, alendronate, irbesartan, docusate sodium, prochlorperazine, clonidine, lansoprazole, filgrastim and levothyroxine. On admission, she was tachypneic, but other vital signs were normal. Liver tests showed elevations in serum bilirubin (5.9 mg/dL) with marked elevations in serum aminotransferase levels (ALT 3332 U/L, AST 3872 U/L) and creatine kinase (21,729 U/L), with prolongation of the prothrombin time (INR 4.8) and elevation in serum ammonia (897 μg/dL). Serum blood urea nitrogen and creatinine were also elevated (84 and 2.7 mg/dL). Tests for hepatitis A, B and C were negative. Abdominal ultrasound showed no evidence of biliary obstruction. She was treated for suspected acute liver failure. With conservative medical management she began to improve, her mental status returning to normal within a few days and serum aminotransferase levels falling rapidly (Table). She was discharged after 7 days in the hospital and had normal liver tests when tested 1 month later.

Key Points

Medication:	Sunitinib (50 mg daily in 5 4-week cycles)
Pattern:	Hepatocellular (R=unable to calculate, no alkaline phosphatase results)
Severity:	4+ (jaundice, hospitalization and features of hepatic failure)
Latency:	~9 months
Recovery:	1 month
Other medications:	Stable doses of letrozole, alendronate, irbesartan, docusate sodium, prochlorperazine, clonidine, lansoprazole, filgrastim and levothyroxine

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	CPK (U/L)	Bilirubin (mg/dL)	Other
Pre	Pre	31-36		0.4-0.7	Values before and during five cycles
		Admitted for severe diarrhea and dehydration			
9 months	4 days	3332	21,729	5.9	INR 4.8, Ammonia 897 μg/dL
	5 days	2534	9981	6.4	
	6 days	2234	5824	6.4	
	7 days	1632		7.0	INR 1.7, Ammonia 85 μg/dL
	8 days	1060	656	5.9	
	9 days	618	329	4.6	
	10 days	465	198	4.6	INR 1.4
10 months	1 month	21		0.6	
15 months	6 months	33		0.5	
Normal Values		**<40**	**<250**	**<1.2**	

Comment

While the patient was considered to have acute liver failure due to sunitinib induced liver injury, a more likely cause was acute ischemia or shock causing centrolobular acute hepatic necrosis and attendant liver failure, coagulopathy and confusion. The clinical phenotype of the presentation and course was that of acute hepatic necrosis, with rapid rise and rapid fall in serum aminotransferase levels, accompanied with increase in creatine kinase and early appearance of coagulopathy, encephalopathy and renal dysfunction. Acute liver failure due to medications typically has a more insidious onset with hepatic failure arising in the setting of deep jaundice and recovery being slow and protracted. While sunitinib therapy is associated with a high rate of minor serum aminotransferase elevations (in up to 61%), these abnormalities are rarely severe (~2%), and are usually asymptomatic and rapidly resolve either spontaneously or with dose adjustment.

Case 2. Hyperammonemia and coma during sunitinib therapy.

[Modified from case 2 in: Lee NR, Yhim HY, Yim CY, Kwak JY, Song EK. Sunitinib-induced hyperammonemic encephalopathy in gastrointestinal stromal tumors. Ann Pharmacother 2011; 45: e56. PubMed Citation]

A 68 year old woman with metastatic gastrointestinal stomal tumors (GIST) of the cecum developed confusion and irritability 10 days after starting sunitinib (50 mg daily) and required emergency hospitalization. She had been treated with imatinib for 3 years, but had developed disease progression despite dose increases. She had no history of liver disease or risk factors for viral hepatitis and denied taking other medications except for lansoprazole (30 mg daily) and tramadol (40 mg daily). Laboratory tests showed minimal elevations in serum ALT (53 U/L) and AST (44 U/L) with normal serum bilirubin (0.7 mg/dL), but marked elevations in serum ammonia (Table). CT scans of the brain showed no abnormalities. Sunitinib was stopped and she was treated with hypdration and lactulose. She improved rapidly with ammonia levels decreasing within 24 hours and she was discharged four days later. However, she presented with a similar severe episode of confusion within a week, having restarted sunitinib immediately after discharge. Again she improved within 24 hours of stopping sunitinib for the second time and was discharged 4 days later. She did not restart sunitinib and had no further episodes of hyperammonemia.

Key Points

Medication:	Sunitinib (50 mg daily of 10 days)
Pattern:	Minimal enzyme elevations
Severity:	4+ (encephalopathy)
Latency:	10 days initially, 7 days on re-exposure
Recovery:	4 days
Other medications:	Lansoprazole and tramadol

Laboratory Values

Time After Starting	Time After Stopping	Ammonia (µg/dL)	Bilirubin (mg/dL)	Other
Pre	Pre		0.4	No known liver disease
0	Sunitinib (50 mg daily) started for metastatic GIST			
10 days	0	389	1.7	Admission for confusion
11 days	1	116	1.7	Clinically improved
14 days	4 days	Discharged and sunitinib restarted		
21 (7) days	11 (0) days	210	1.5	Re-admitted for confusion

Table continued from previous page.

Time After Starting	Time After Stopping	Ammonia (µg/dL)	Bilirubin (mg/dL)	Other
(8) days	(1) day	59	1.5	
(11) days	(4) days	Discharged		
Normal Values		**<45**	**<1.2**	

*Values parenthesis represent days after restarting or restopping sunitinib.

Comment

Hyperammonemic coma is a rare but distinctive syndrome that has been linked to therapy with valproic acid and with various cancer chemotherapeutic regimens. Patients are typically dehydrated and present with irritability, stupor and confusion progressing to frank coma. Routine liver tests are usually normal or minimally abnormal, but ammonia levels are high. The syndrome reverses rapidly once the causative medication is stopped, but it can be severe and fatalities have been reported. The cause of the syndrome is not known, but probably relates to inhibition of mitochondrial or urea cycle enzyme function rather than frank hepatic failure.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Sunitinib – Sutent®

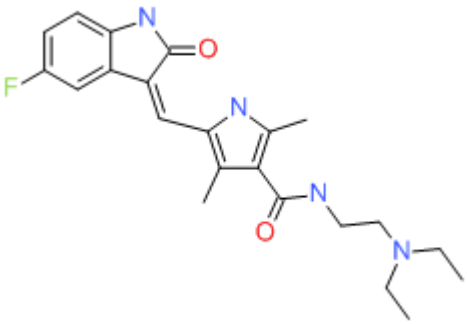
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Sunitinib	557795-19-4	C22-H27-F-N4-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 27 June 2018

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of tyrosine kinase receptor inhibitors such as sunitinib).

DeLeve LD. Erlotinib. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents published; erlotinib has been linked to several cases of clinically apparent liver injury, 2 of which were fatal).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-54.

(Textbook of pharmacology and therapeutics).

Deeks ED, Keating GM. Sunitinib. Drugs 2006; 66: 2255-66; discussion 2267-8. PubMed PMID: 17137406.

(Review of structure, pharmacology, mechanism of action, clinical efficacy and safety of sunitinib; no mention of hepatotoxicity or ALT elevations during therapy).

Adams VR, Leggas M. Sunitinib malate for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. Clin Ther 2007; 29: 1338-53. PubMed PMID: 17825686.

(Systematic review of the literature of clinical efficacy and tolerability of sunitinib; ALT or AST elevations occurred in 39% of sunitinib vs 23% of placebo recipients, values >5 times ULN in 2% vs 1% and bilirubin elevations in 16% vs 8%).

Goodman VL, Rock EP, Dagher R, Ramchandani RP, Abraham S, Gobburu JV, Booth BP, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. Clin Cancer Res 2007; 13: 1367-73. PubMed PMID: 17332278.

(Summary of the FDA review of sunitinib in support of its approval in the United States; ALT or AST elevations occurred in 39% of sunitinib and 23% of placebo recipients and were greater than 5 times ULN in 2% vs 1%; no mention of clinically apparent liver injury).

Mueller EW, Rockey ML, Rashkin MC. Sunitinib-related fulminant hepatic failure: case report and review of the literature. Pharmacotherapy 2008; 28: 1066-70. PubMed PMID: 18657022.

(75 year old woman with metastatic renal cancer developed diarrhea and dehydration after a fifth cycle of sunitinib and was found to be jaundiced on admission [bilirubin 5.9 mg/dL, ALT 3332 U/L, INR 4.8] with hepatic failure, but rapid clinical improvement and resolution within the next 6 months: Case 1).

Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, Hariharan S, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009; 10: 757-63. PubMed PMID: 19615940.

(Summary of results from expanded access to sunitinib for renal cell carcinoma in 4564 patients enrolled in 52 countries; common side effects were fatigue and diarrhea, nausea, stomatitis, anorexia, hand-foot syndrome, hypertension and dyspepsia; rates of serum ALT elevations not reported, but among 63 [1.4%] deaths attributed to treatment related adverse events, 4 [0.1%] were due to hepatic failure; no details given).

Weise AM, Liu CY, Shields AF. Fatal liver failure in a patient on acetaminophen treated with sunitinib malate and levothyroxine. Ann Pharmacother 2009; 43: 761-6. PubMed PMID: 19336648.

(57 year old woman with metastatic gastrointestinal stromal tumors resistant to imatinib therapy developed jaundice on day 4 of a 9th cycle of sunitinib [bilirubin 2.8 mg/dL, ALT 1588 U/L, Alk P 81 U/L, INR 2.17], with progressive liver failure and death 4 days later, autopsy showing marked centrolobular necrosis).

Gomez-Abuin G, Karam AA, Mezzadri NA, Bas CA. Acalculous cholecystitis in a patient with metastatic renal cell carcinoma treated with sunitinib. Clin Genitourin Cancer 2009; 7: 62-3. PubMed PMID: 19213671.

(62 year old woman with metastatic renal carcinoma developed acute acalculous cholecystitis during 4th week of first cycle of sunitinib [bilirubin "slightly" increased, ALT and Alk P values not given], resolving with conservative management, and the patient was able to restart sunitinib without recurrence).

O'Reilly EM, Niedzwiecki D, Hall M, Hollis D, Bekaii-Saab T, Pluard T, Douglas K, et al; Cancer and Leukemia Group B. A Cancer and Leukemia Group B phase II study of sunitinib malate in patients with previously treated metastatic pancreatic adenocarcinoma (CALGB 80603). Oncologist 2010; 15: 1310-9. PubMed PMID: 21148613.

(Trial of sunitinib in 77 patients with previously treated metastatic pancreatic cancer found median survival of less than 4 months and toxicity to be common; ALT or AST elevations occurred in 7%, but there was no mention of clinically apparent liver injury).

Matsumoto K, Sawaki A, Mizuno N, Hara K, Hijioka S, Niwa Y, Tajika M, et al. Clinical efficacy and safety of sunitinib after imatinib failure in Japanese patients with gastrointestinal stromal tumor. Jpn J Clin Oncol 2011; 41: 57-62. PubMed PMID: 20858619.

(Among 18 patients with advance GIST tumors who were switched to sunitinib after failure of imatinib, some degree of "liver dysfunction" occurred in 26 [72%] and was grade 3-4 in 4, but details were not given).

Lee NR, Yhim HY, Yim CY, Kwak JY, Song EK. Sunitinib-induced hyperammonemic encephalopathy in gastrointestinal stromal tumors. Ann Pharmacother 2011; 45: e56. PubMed PMID: 21954449.

(58 year old man and 68 year old woman developed confusion 17 and 10 days after starting sunitinib for GIST [ammonia 210 and 389 µg/dL, bilirubin 1.9 and 0.7 mg/dL, ALT 50 and 53 U/L], with rapid improvement upon stopping and rapid recurrence on restarting; both patients had previously tolerated imatinib: Case 2).

Powles T, Sarwar N, Jones R, Wilson P, Boleti E, Protheroe A, Crabb SJ, et al. An indirect comparison of the toxicity of sunitinib and pazopanib in metastatic clear cell renal cancer. Eur J Cancer 2012; 48: 3171-6. PubMed PMID: 22766517.

(Among 77 patients given either sunitinib or pazopanib for 12 weeks before nephrectomy of renal cell cancer, raised "liver function" occurred in 9 patients [26%] on pazopanib, but none on sunitinib).

Ibrahim EM, Kazkaz GA, Abouelkhair KM, Bayer AM, Elmasri OA. Sunitinib adverse events in metastatic renal cell carcinoma: a meta-analysis. Int J Clin Oncol 2012; 18: 1060-9. PubMed PMID: 23179639.

(Systematic review of adverse events reported in clinical trials of sunitinib in 5658 patients wtih renal cell cancer found serum liver enzyme elevations in 40% of patients, but elevations >5 times ULN in only 3%).

Mermershtain W, Lazarev I, Shani-Shrem N, Ariad S. Fatal liver failure in a patient treated with sunitinib for renal cell carcinoma. Clin Genitourin Cancer 2013; 11: 70-2. PubMed PMID: 23063577.

(62 year old man with emphysema developed weakness and jaundice within 3 weeks of starting sunitinib for unresectable renal cell carcinoma [bilirubin 6.1 rising to 15.7 mg/dL, ALT 31 to 3086 U/L, LDH to 23,949 U/L, Alk P 124 U/L, INR 1.62], with progressive hypoxia, coma and death within a few days).

Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug Saf 2013; 36: 491-503. PubMed PMID: 23620168.

(Review of the hepatotoxicity of 18 tyrosine kinase inhibitors approved for use in cancer in the US as of 2013; aminotransferase elevations occurred in 40-60% of patients in registration trials of sunitinib, and were above 5 times ULN in 2-5% and at least one case of severe liver injury has been reported since its approval [Weise 2009]).

Shea YF, Chiu WY, Mok MY, Hung IF, Yau CC. Sunitinib-induced hyperammonaemia in a patient with pancreatic neuroendocrine tumour. J Clin Pharm Ther 2013; 38: 327-9. PubMed PMID: 23586819.

(61 year old man with pancreatic neuroendocrine tumor metastatic to liver developed stupor and somnolence 2 weeks after starting sunitinib [bilirubin and INR normal, ALT 43 U/L, Alk P 196 U/L, ammonia 147 μM], resolving within 24 hours of stopping sunitinib).

Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013; 369: 722-31. PubMed PMID: 23964934.

(Among 1110 patients with metastatic renal cell cancer treated with either pazopanib or sunitinib, overall survival was similar, but pazopanib patients had higher rates of side effects including hand-foot syndrome [50% vs 29% and ALT elevations [60% vs 43%; 17% vs 4% over 5 times ULN], and bilirubin [36% vs 27%]; no mention of clinically apparent liver injury).

Motzer RJ, Johnson T, Choueiri TK, Deen KC, Xue Z, Pandite LN, Carpenter C, Xu CF. Hyperbilirubinemia in pazopanib- or sunitinib-treated patients in COMPARZ is associated with UGT1A1 polymorphisms. Ann Oncol 2013; 24: 2927-8. PubMed PMID: 24107802.

(Among 1110 patients with renal cell cancer treated with tyrosine kinase inhibitors, bilirubin elevations ≥1.5 times ULN occurred in 16% on pazopanib vs 9% on sunitinib, and the accumulated rate of the elevations was higher in patients who were homozygous for the UGT1A1 polymorphisms of Gilbert syndrome).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 [6%] were attributed to antineoplastic agents including 9 to kinase inhibitors including imatinib [n=5], lapatinib [n=2] and regorafinib [n=1], but none were attributed to sunitinib).

Karczmarek-Borowska B, Sałek-Zań A. Hepatotoxicity of molecular targeted therapy. Contemp Oncol (Pozn) 2015; 19: 87-92. PubMed PMID: 26034384.

(Review of hepatotoxicity of modern molecular targeted therapies including monoclonal antibodies, protein kinase inhibitors and proteosome inhibitors; sunitinib has an increased risk of liver injury).

Reichardt P, Kang YK, Rutkowski P, Schuette J, Rosen LS, Seddon B, Yalcin S, et al. Clinical outcomes of patients with advanced gastrointestinal stromal tumors: safety and efficacy in a worldwide treatment-use trial of sunitinib. Cancer 2015; 121: 1405-13. PubMed PMID: 25641662.

(Among 1124 patients with refractory GIST treated with sunitinib in an open label worldwide treatment program, ALT elevations above 5 times ULN occurred in 2%; no mention of clinically apparent liver injury or liver failure).

Komatsu Y, Ohki E, Ueno N, Yoshida A, Toyoshima Y, Ueda E, Houzawa H, et al. Safety, efficacy and prognostic analyses of sunitinib in the post-marketing surveillance study of Japanese patients with gastrointestinal stromal tumor. Jpn J Clin Oncol 2015; 45: 1016-22. PubMed PMID: 26373318.

(Review of the reported hepatotoxicity of molecular targeted therapies for cancer including sunitinib and 6 other kinase inibitors).

Eichelberg C, Vervenne WL, De Santis M, Fischer von Weikersthal L, Goebell PJ, Lerchenmüller C, Zimmermann U, et al. SWITCH: a randomised, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib versus sunitinib-sorafenib in the treatment of metastatic renal cell cancer. Eur Urol 2015; 68: 837-47. PubMed PMID: 25952317.

(Among 365 patients with metastatic renal cell carcinoma who were switched from sorafenib to sunitinib or vice versa, response rates were similar in the two groups; ALT elevations and hepatotoxicity were not mentioned).

Shantakumar S, Nordstrom BL, Djousse L, Hall SA, Gagnon DR, Fraeman KH, van Herk-Sukel M, et al. Occurrence of hepatotoxicity with pazopanib and other anti-VEGF treatments for renal cell carcinoma: an observational study utilizing a distributed database network. Cancer Chemother Pharmacol 2016; 78: 559-66. PubMed PMID: 27438066.

(Review of hepatotoxicity associated with anti-VEGF treatments of renal cell cancer from two large US health care databases, highest rates of ALT elevations were found with first line treatment with pazopanib [n=180] and slightly lower rates for sorafenib [n=160], sunitinib [n=721] and bevacizumab [n=83], but clinically apparent injury with jaundice was rare [1 case with sorafenib, 2 with sunitinib]).

Guillen SS, Meijer M, de Jongh FE. Lethal acute liver failure in a patient treated with sunitinib. BMJ Case Rep 2016; 2016. PubMed PMID: 26933184.

(79 year old man with metastatic renal cell cancer developed acute liver and kidney injury after the 8th six week cycle of sunitinib [bilirubin [5.4 mg/dL, ALT 1844 U/L, Alk P 78 U/L, LDH 3386 U/L, prothrombin time 28 sec], with progressive liver failure and death 4 days later).

Bunchorntavakul C, Reddy KR. Drug hepatotoxicity: newer agents. Clin Liver Dis 2017; 21: 115-34. PubMed PMID: 27842767.

(Overview of hepatotoxicity of newer agents including tyrosine kinase inhibitors such as imatinib, bosutinib, nilotinib, ponatinib, sorafenib and sunitinib, all of which have been implicated in causing ALT and AST elevations [in 23-50% of patients] as well as clinically apparent liver injury).