CASE REPORT

Hepatotoxicity Associated With Vismodegib

Prabhjot S Bedi,¹ Manoj P Rai,² Nishant Tageja,³ Heather Laird-Fick⁴¹Department of Internal Medicine, UPMC East, Monroeville, Pennsylvania, USA²Internal Medicine, Michigan State University / Sparrow Hospital, Lansing, Michigan, United States of America³Department of Hematology/Oncology, UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania, USA⁴Department of Internal Medicine, Michigan State University, Lansing, Michigan, USA

Correspondence to

Dr Manoj P Rai,
manojrai029@gmail.com

Accepted 27 January 2018

SUMMARY

An 82-year-old Caucasian woman with a history of basal cell carcinoma on vismodegib presented with nausea, vomiting and intermittent abdominal pain. Laboratory results were remarkable for the elevation of liver enzymes. Endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiogram (PTC) did not show evidence of intrahepatic or extrahepatic obstruction of the biliary tract. During PTC external biliary catheter was placed; however, bilirubin continued to rise. Further, laboratory work-up and imaging studies ruled out other possible aetiologies for hepatotoxicity such as infections, autoimmune hepatitis and other drugs known to be hepatotoxic thus leaving vismodegib the most likely cause of hepatotoxicity.

BACKGROUND

Basal cell carcinoma (BCC) accounts for 8 in 10 cases of skin cancer. Vismodegib (2-chloro-N-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl) benzamide; GDC-0449) was recently approved by Food and Drug Administration (FDA) for the treatment of recurrent, locally advanced or metastatic BCC. Both LiverTox and European Medicines Agency have listed hepatotoxicity as a potential adverse effect of vismodegib. However, neither the manufacturer nor FDA has issued any safety notifications related to hepatotoxicity.

CASE PRESENTATION

An 82-year-old Caucasian woman with a medical history significant for well-controlled hypertension, rate-controlled atrial fibrillation and right facial basal cell carcinoma recently started on vismodegib (GDC-0449) presented with nausea, vomiting and intermittent abdominal pain. Vismodegib was started 2 months prior to her presentation. There was no history of smoking, alcohol or illicit drug use. The patient's home medications included aspirin 81 mg daily, lisinopril 10 mg daily and metoprolol tartrate 25 mg two times per day. Review of systems was positive for chills, yellow discolouration of skin and constipation. Vitals were within normal limits, and physical examination was significant for conjunctival icterus, epigastric abdominal tenderness and generalised yellowish discolouration of the skin.

INVESTIGATIONS

On initial laboratory results, there was a remarkable elevation of aspartate transaminase (AST) 156 U/L, alanine transaminase (ALT) 204 U/L, alkaline phosphatase 232 U/L and total bilirubin of 17 mg/dL;

the laboratory results were closely followed during the hospitalisation (figures 1–3) with peak values rising up to: AST 194 U/L, ALT 209 U/L, total bilirubin 29 mg/dL and lipase 962 U/L (peak 3500 U/L). R factor was 2.64. The international normalised ratio was 3.2. Hepatitis A, hepatitis B (HBsAg) and hepatitis C were non-reactive; antismooth muscle antibodies, antimitochondrial antibodies and anti-nuclear antibody immunoglobulins were negative. Cytomegalovirus (CMV) IgM, Epstein-Barr virus (EBV) IgM and herpes simplex virus (HSV) IgM were also negative. Salicylate and acetaminophen levels were negative as well. Ultrasound of the abdomen showed cholecystolithiasis without cholecystitis, common bile duct of diameter 5 mm; CT without contrast showed mild pancreatitis without a fluid collection and cholelithiasis without any evidence of biliary ductal dilation. Endoscopic retrograde cholangiopancreatography (ERCP) was pursued which showed non-bleeding erythematous gastropathy and multiple duodenal ulcers with a clean base on the endoscopic portion. The ampulla was small, and multiple attempts at cannulation were unsuccessful. The ducts were injected and there was no evidence of dilation of either distal common bile duct or proximal pancreatic duct. Percutaneous transhepatic cholangiogram (PTC) was performed as well which showed normal bile ducts. Liver biopsy could not be performed since the patient refused it.

DIFFERENTIAL DIAGNOSIS

The various differentials considered in this case were acute hepatocellular injury due to acute viral hepatitis, autoimmune hepatitis, alcoholic liver disease, salicylate or acetaminophen-induced liver toxicity, ischaemic liver injury, Budd-Chiari syndrome and biliary tract obstruction. Based on her history, alcoholic liver disease was excluded. Imaging studies were negative for hepatic congestion ruling out Budd-Chiari

Figure 1 Graph on trend of aspartate aminotransferase over 21 days.

To cite: Bedi PS, Rai MP, Tageja N, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222969

Figure 2 Graph on trend of total bilirubin over 21 days.

syndrome. Infectious and autoimmune work-up was negative. Salicylate and acetaminophen levels were negative. The patient was haemodynamically stable, hence we ruled out possible ischaemic liver injury. There was no evidence of intrahepatic or extrahepatic obstruction of the biliary tract. During PTC, the patient also underwent external biliary catheter placement. Bilirubin continued to rise despite the drain placement making intrahepatic cholestasis a likely diagnosis. Thus, an intrahepatic process probably drug-induced cholestatic liver injury was thought to be the underlying pathophysiology for her clinical presentation. The only new medication to which patient had exposure was vismodegib (GDC-0449) making it the likely cause for patient's drug-induced cholestatic liver injury.

TREATMENT

She was started on ursodeoxycholic acid 300 mg two times per day, which was later increased to three times per day. She was also started on pantoprazole 40 mg two times per day given the multiple duodenal ulcers which were seen on ERCP.

OUTCOME AND FOLLOW-UP

On initiation of ursodeoxycholic acid, the patient's liver enzymes started to trend down, bilirubin peaked on day 12 and then trended down. She was followed up closely after discharge and serial laboratory results showed downward trend in bilirubin and liver enzymes.

DISCUSSION

Vismodegib (GDC-0449) is the first hedgehog signalling pathway inhibitor. Vismodegib acts by antagonising smoothened (SMO) thus aborting transmission of signals

Figure 3 Graph on trend of alanine aminotransferase over 21 days.

required for cell proliferation in BCC. It was approved by US FDA in January 2012. Its approval was for the treatment of locally advanced and metastatic BCC which recurred after surgery or for patients who are not suitable candidates for surgery and radiation.¹⁻⁴ Vismodegib is administered as 150 mg once daily based on its pharmacokinetic properties observed in phase I trial.⁵ Even though it is a substrate of CYP2C9 and CYP3A4 pathways; concurrent administration of either CYP3A4 inducers or inhibitors do not affect its metabolism. The drug and its metabolites are primarily eliminated by the liver, with 82% of drug excreted in the faeces and 4.4% recovered in the urine. Elimination half-life is about 4 days after the continuous dosing and 12 days after a single dose.

The initial interrogation by the National Cancer Institute (NCI) designated comprehensive cancer centres did not show reports of hepatotoxicity. This likely occurred due to the evaluation of a small number of patients (n=15) in only two comprehensive cancer centres. The first case of vismodegib-induced hepatotoxicity was reported in 2011. Since then there has been an increase in its incidence.^{6,7} Ventarola and Silverstein reported 15 cases of hepatotoxicity. In 4 out of the 15 cases (26.67%), vismodegib was noted as the sole responsible agent associated with hepatotoxicity.⁶ Ash and Jolly reported a case of acute liver injury due to the interaction between vismodegib, aspirin and naproxen, so concomitant use of hepatotoxic drugs with vismodegib can easily increase the susceptibility.⁸ Three cases of vismodegib associated severe liver dysfunction were published by the Australian Therapeutic Goods Administration.⁷ Ninety four patients with vismodegib-induced liver dysfunction were reported on FDA Adverse Events Reporting System and 35 of them were found to have severe liver.⁷ LiverTox as also listed hepatotoxicity as its adverse effect.⁹ The mechanism for vismodegib-induced hepatotoxicity is unclear. Factors that can increase susceptibility for hepatotoxicity are underlying non-alcoholic steatohepatitis, medication use, alcohol consumption and chronic liver disease.¹⁰

Common Terminology Criteria for Adverse Events (CTCAE) is used for grading drug-related toxicity. It is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4) and death (Grade 5).¹¹ According to CTCAE, our patient had Grade 3 adverse event which is defined as severe or medically significant but not immediately life-threatening reaction requiring hospitalisation or prolongation of existing hospitalisation.

Unexpected, serious adverse drug reactions can be reported to the FDA using the medical-watch system either through filling out a paper or by calling 1-800-FDA-0178.

Although rare, this case illustrates that vismodegib can be directly related to hepatotoxicity, and can indirectly decrease the threshold for hepatotoxicity when combined with other hepatotoxins. FDA should consider enlistment of hepatotoxicity as

Learning points

- ▶ Hepatotoxicity can be a potentially serious adverse effect of vismodegib.
- ▶ Vismodegib should be used in patients with the severe liver disease only if benefits outweigh its risks.
- ▶ Concomitant use of hepatotoxic medications with vismodegib should be avoided.
- ▶ Food and Drug Administration should consider enlistment of hepatotoxicity as one of its serious adverse effects.

one of the serious adverse effects. We believe that vismodegib should be used in patients with severe liver disease only if benefits outweigh its risks, also concomitant use of hepatotoxic medications should be avoided.

Contributors PSB contributed mainly to the case description, he also prepared the graphs and was also responsible for obtaining the consent. MPR contributed to the summary, background, discussion and learning points. NT provided recommendations on improving the case, later revised the manuscript. HL-F: revised the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Proctor AE, Thompson LA, O'Bryant CL. Vismodegib: an inhibitor of the Hedgehog signaling pathway in the treatment of basal cell carcinoma. *Ann Pharmacother* 2014;48:99–106.
- 2 Cirrone F, Harris CS. Vismodegib and the hedgehog pathway: a new treatment for basal cell carcinoma. *Clin Ther* 2012;34:2039–50.
- 3 Sandhiya S, Melvin G, Kumar SS, et al. The dawn of hedgehog inhibitors: Vismodegib. *J Pharmacol Pharmacother* 2013;4:4–7.
- 4 Lyons TG, O'Kane GM, Kelly CM. Efficacy and safety of vismodegib : a new therapeutic agent in the treatment of basal cell carcinoma. *Expert Opin Drug Saf* 2014;13:1125–32.
- 5 Sekulic A, Migden MR, Basset-Seguin N, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. *BMC Cancer* 2017;17:332.
- 6 Ventarola DJ, Silverstein DI. Vismodegib-associated hepatotoxicity: a potential side effect detected in postmarketing surveillance. *J Am Acad Dermatol* 2014;71:397–8.
- 7 Edwards BJ, Raisch DW, Saraykar SS, et al. Hepatotoxicity with Vismodegib: An MD Anderson Cancer Center and Research on Adverse Drug Events and Reports Project. *Drugs R D* 2017;17:211–8.
- 8 Ash MM, Jolly PS. Cholestatic hepatic injury associated with vismodegib, aspirin, and naproxen use: a case study and review of vismodegib safety. *Int J Dermatol* 2015;54:370–4.
- 9 United States National Library of Medicine. Search Livertox Database [Internet]. <https://livertox.nlm.nih.gov> (cited 2017 Sep 16).
- 10 Navarro VJ, Senior JR. Drug-related hepatotoxicity. *N Engl J Med* 2006;354:731–9.
- 11 Schwab M, ed. CTCAE. In: *Encyclopedia of Cancer*. Heidelberg, Berlin: Springer, 2008:778.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow