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Case Report
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Acute Liver Failure Induced by Sorafenib Combined with Diclofenac Sodium: A Case Report

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Abstract

Introduction: Drug-induced liver injury is one of the most common adverse drug reactions in clinical. Sorafenib is a widely used in hepatoma patients, while diclofenac sodium in patients suffering from cancer pain. Both of the two drugs showed mild and unfrequented liver damage. However, taking both drugs orally at the same time may cause severe liver function abnormity and there are few reports at present.

Case report: We'll expatiate on an unusual case of a patient with kidney cancer who takes sorafenib and diclofenac sodium simultaneously and suffered from severe and acute liver failure about nearly two months.

Conclusion: Sorafenib and diclofenac are likely to have some interactions. Clinically, the combination of the two should be carefully considered to reduce the potential risk of liver damage and avoid liver failure or even liver necrosis.

Keywords: Acute liver failure; Sorafenib; Diclofenac sodium

Abbreviations: CT: Computed Tomography; MRI: Magnetic Resonance Imaging; PT: Prothrombin Time Physical Therapy; APTT: Activated Partial Thromboplastin Time; ALT: Alanine Amino Transferase; AST: Aspartate Amino Transferase; UGT: Uridine Glucuronyl Transferases; T-Bil: Total Bilirubin; D-Bil: Direct Bilirubin; ID-Bil: Indirect Bilirubin.

Introduction

Sorafenib is a novel oral small-molecule tyrosine kinase receptor inhibitor and the first small-molecule targeted drug in the world to treat metastatic renal cancer. It mainly acts on vascular endothelial growth factor receptor and platelet derived growth factor receptor to inhibit tumour angiogenesis and tumour cell growth [1,2]. Liver failure caused by sorafenib is rarely reported at home and abroad.

Diclofenac sodium is a new type of non-steroidal anti-inflammatory drug [3]. Its active ingredient is diclofenac acid, which has anti-inflammatory and analgesic effects mainly by inhibiting the synthesis of prostaglandin. Drug-induced liver injury by diclofenac sodium occurs rarely.

Combined use of the two drugs may aggravate the degree of liver damage in a superposition manner, eventually leading to liver failure. There are few reports at present about this. Herein, we reported on an unusual case of a patient with kidney cancer who takes sorafenib and diclofenac sodium simultaneously and suffered from severe and acute liver failure about nearly two months.

Case Report

A 63-yr-old male whose neck pain occurred around April, 2017 without definite cause and gradually worsened. The CT examination of cervical in the beginning of September indicated compression of the 3-5 vertebral bodies, and solid was considered. Chest and abdomen CT and neck MRI considered multiple bone metastases, and solid was found in the lower pole of the right kidney. No contraindication was found, anterior cervical decompression and lesion removal was performed on September 22th 2017. Postoperative pathology indicated metastatic clear cell carcinoma, which was considered to be of renal origin. Because the patient refused to receive palliative radiotherapy, oral sorafenib was started in mid-October 2017 (the initial dose was 0.2 g pd, gradually increased to 0.4 g bid ten days later, and then reduced to 0.2 g bid by himself half a month before hospitalization). During the medication, the patient had no obvious neck pain but intermittent diarrhoea which could be improved after symptomatic treatment. After one month of targeted treatment, renal MRI and cervical CT showed that the right kidney and bone metastasis were basically stable. After two months, the patient was conscious of neck pain again, and the pain score was about 3-4. The patient refused to receive local radiotherapy, and self-intermittent oral diclofenac sodium 75 mg was used for pain control. Two days before admission, the patient appeared stained yellow skin and dark yellow urine. Laboratory tests in other hospital suggested significant increase in transaminase and bilirubin. The patient was admitted to our hospital on February 20th 2018 for further diagnosis and treatment. The initial diagnose then was right kidney cancer (stage IV) with bone metastasis. After admission, some tests were performed: PT: 19.1 s; APTT: 57.4 s; T-Bil: 195.5 umol/L; D-Bil: 117.2 umol/L; ID-Bil: 78.30 umol/L; ALT: 1640.8 U/L; AST: 1522.5 U/L. There was no abnormality in blood routine test, virus test and hepatitis test. Further examination on CT showed multiple metastases of the sternum, T9 vertebral body and accessories, L2 vertebral body and sacrum. The mass at the lower polar of right kidney was highly considered to be malignancy. The "sleeve sign" can be seen in the hepatic segment of inferior vena cava and portal vein branches when venous phase, which is consistent with liver function

damage. According to the comprehensive examination and consultation opinions of gastroenterologist, acute drug-induced liver injury and hepatocellular jaundice were considered. Hepatoprotective treatments such as isoglycyrrhizinate and glutathione were given, and sorafenib and diclofenac sodium were discontinued. Biochemical re-examination one week later indicated decreased aminotransferase (ALT: 463.3 U/L, AST: 266.1 U/L, T-Bil: 391.3 umol/L). Plasma exchange could not be performed due to abnormal coagulation function, then aminotransferase and bilirubin significantly decreased (ALT: 20 U/L; AST: 30 U/L; T-Bil: 58 umol/L) about more than forty days later.

Discussion

It has been reported in the literature that the most common adverse reactions of sorafenib are gastrointestinal reactions, such as nausea, vomiting and diarrhoea, followed by hand-foot syndrome, hypertension, hair loss, rash and fatigue [4]. Sorafenib occasionally causes abnormal

Liver function with elevated ALT, and usually appears after 30 days of the medication [5]. In China, sorafenib-induced liver dysfunction is reported to be of low grade 1-2, which can be recovered by symptomatic treatment, drug reduction or drug withdrawal [6]. In this case, sorafenib was taken orally for nearly four months, and acute liver failure (grade-4) occurred about two months after the combined treatment with diclofenac sodium. The course was short and the onset was urgent, which was improved after long-term liver protection treatment, which was extremely rare in clinical practice, probably due to the combined effect of the two drugs.

Diclofenac sodium oral absorption is complete, mainly through liver metabolism, clinical widely used in pain and inflammation caused by osteoarthritis, rheumatoid arthritis. The main adverse reactions of diclofenac sodium will be damage of digestive system, nervous system and urinary system [7]. Neurological manifestations include headache, vertigo, and hypersomnia and so on, while urinary system damage can cause acute renal failure performing edema, oliguria or electrolyte disorders. Gastrointestinal reactions are the most common among digestive system injuries, mainly including stomach discomfort, poor appetite and nausea but fewly ulcers, bleed and perforation. Drug-induced hepatitis, transient elevation of ALT and AST, jaundice and erythra occur rarely.

Drug-induced liver injury is one of the most common adverse drug reactions, which may lead to liver failure or even death. From this case, the degree of liver damage in patient is severe, but hepatitis virus test is negative, and there're no obvious intrahepatic metastases and no alcoholism. So without regard to viral hepatitis, alcoholic hepatitis, liver metastasis stem from kidney and other factors may lead to liver damage, drug-induced liver injury attributed to the concurrent-use of sorafenib and diclofenac sodium is correct. Sorafenib and diclofenac sodium both can cause abnormal liver function, and there may be interactions between them. The mechanism by which sorafenib causes liver dysfunction has not been fully elucidated, the metabolism of sorafenib in the liver requires the involvement of hepatocyte pigment P450 and urea glycoside diphosphate UGT transferase, and the competitive inhibition of UGT enzyme may affect the metabolism of bilirubin. Abnormalities in liver function may also be associated with non-specific injury of sorafenib to liver cells [8]. Liver injury caused by diclofenac sodium is an idiosyncratic reaction, with complex mechanism and no correlation with pharmacological effect, prominent individual differences, low incidence, and difficult to predict [9]. Most studies have shown that diclofenac sodium is mainly metabolized by cellular metabolic enzymes CYP2C9 and CYP3A4 in the liver, 95% of which is catalysed by CYP2C9 to generate 4-hydroxydiclofenac, and a small amount of which is catalysed by CYP3A4 to generate 5-hydroxydiclofenac with high chemical activity. 5-hydroxydiclofenac can directly bind to macromolecular proteins in liver cells, then form complex and induce immune response, leading to liver cell damage. Genetic polymorphisms of CYP3A4 may be an important factor leading to drug-induced liver injury in diclofenac sodium sensitive population [10].

Drug interactions can change drug absorption, distribution, metabolism and excretion, and affect the incubation period, clinical phenotype, course and outcome of drug-induced liver injury, which is the cause that cannot be ignored to increase the risk of drug-induced liver injury in clinical practice. Sorafenib can inhibit the activity of cell metabolic enzymes CYP2C8, CYP2B6, CYP2C9, CYP2C19 and CYP2D6, while diclofenac is mainly catalysed by CYP2C9 in the liver, so the combination of diclofenac and sorafenib may slow down the metabolism of diclofenac and increase its blood concentration. Studies have shown that drug dose is also an important factor affecting the occurrence and development of idiosyncratic liver injury and the degree of liver injury caused by high-dose drug is more serious and the prognosis is worse [11]. The weak induction effect of Sorafenib on cell metabolic enzyme CYP3A4 [12], and the inhibiting to the activity of CYP2C9 may increase the amount of 5-hydroxydiclofenac, the active metabolite generated by diclofenac through the CYP3A4 metabolic pathway, and accumulate in the liver, leading to the aggravation of liver damage. In addition, sorafenib and diclofenac bind to plasma proteins at a rate of more than 99% [13,14]. If both of them compete for the similar binding sites, it may increase the free components of either of them and increase the risk of adverse reactions. To sum up, sorafenib and diclofenac are likely to have some interaction, but the research data on the interaction is limited. Clinically, the combination of the two should be carefully considered to reduce the potential risk of liver damage and avoid liver failure or even liver necrosis.

Conclusion

Theoretically, there are interactions between sorafenib and diclofenac sodium within the mechanism, because of which severe and acute liver function damage may occur and it needs hepatoprotective treatment for longer time. The combination of the two drugs should be avoided clinically. Furthermore, mastering the types of drugs commonly causing liver damage, avoiding the combination of two or more drugs that may cause liver damage, and reducing the occurrence of serious adverse reactions will be very necessary.

Standard cancer pain treatment is an important link to improve the quality of life in cancer patients. The "three-step analgesic scheme" recommended by World Health Organization (WHO) is widely used, including the non-steroid anti-inflammatory drug, the weak opioids and strong opioids. Their adverse reaction may be central nervous system toxicity or gastrointestinal reactions such as constipation, nausea, and vomiting. Local palliative radiotherapy is also an effective and safe method to treat cancer bone pain, which is helpful to improve the quality of life of patients. In clinical, strengthening the education of patients understanding drug toxicology also should not be overlooked.

References

1. Yun-Feng Lu, Yu-Fei F, Xin H, Kai-Shun B (2007) Sorafenib: Pharmacology and clinical studies. Chinese Journal of New Drugs 16: 88-91.
2. Choueiri TK, Garcia JA, Elson P, Khasawneh M, Usman S, et al. (2007) Clinical factors associated with outcome in patients with metastatic clear-cell renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. Cancer 110: 543-550.
3. Small RE (1989) Diclofenac sodium. Clin Pharm 8: 545-558.
4. Rini BI (2006) Sorafenib. Expert Opin Pharmacother 7: 453-461.
5. Ying L, Yue-Xiang C (2012) Liver damage due to abuse of sorafenib. Adverse Drug Reactions Journal 14:168-169.
6. Tang B, Chi Z, Sheng X, Cui C, Si L, et al. (2015) Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma. National Medical Journal of China 95: 2459-2461.
7. Yun-Lang Z, Xiang-Mei R (2015) Clinical application and adverse reactions of diclofenac sodium. World Latest Medicine Information 15: 38-39.
8. Jun W (2016) Pathogenesis and treatment principle of adverse reactions of anti-angiogenetic drugs. Medical Recapitulate 22: 3154-3157.
9. Jun-Jun M, Zheng J, Ming-Kang Z, Wei-Min C (2014) Research progress on the correlation between drug-induced liver damage and HLA gene polymorphism. Chinese Pharmaceutical Journal 49: 806-811.
10. Ji-Wei X, Lian-Qun F (2017) Research progress of drug-induced liver injury. World Latest Medicine Information 17: 33-34.
11. Wang G, Liu Y, Hou XF, Song J, Qiu HH, et al. (2017) Discussion on influence factors, mechanism and traditional Chinese medicine pathogenesis of idiosyncratic drug-induced liver injury. China Journal of Chinese Materia Medica 42: 3036-3043.
12. Jian-Long Z, Hui Z, Yue Y, Wen-Zhe L, Zhong-Hui W, et al. (2014) Sorafenib on clinical application and drug interaction. The Chinese Journal of Clinical Pharmacology 30: 958-961.
13. Lin-Hua Y, Guo-Hong Q, Jia-Liang T, Long-Bao C (2017) Pharmaceutical care on patients treated with targeted drug for advanced renal cell carcinoma. Pharmaceutical and Clinical Research 25: 416-420.
14. Mei-Xia Z, Ying-Ying Z (2013) Review of adverse reactions to diclofenac-containing anti-inflammatory drugs. Strait Pharmaceutical Journal 25: 294-296.