Oncology and Translational Medicine
DOI 10.1007/s10330-021-0492-2

October 2021, Vol. 7, No. 5, P235–P238

CASE REPORT

A case of sorafenib-induced severe thrombocytopenia during treatment of unresectable hepatocellular carcinoma

Xiaoying Quan, Xiaoyan Chen, Lei Lei, Chunzhi Wu, Xiaoli Jia, Bin Ye (✉)

Department of Medical Oncology, the Sixth People's Hospital of Chengdu, Chengdu 610051, China

Abstract

An 81-year-old male with unresectable hepatocellular carcinoma underwent transarterial chemoembolization (TACE) combined with sorafenib. Platelet count was normal before and after TACE treatment, after which oral administration of sorafenib (400 mg po bid) was initiated. During this period, the patient experienced significant diarrhea, so the dosage was reduced to 200 mg po bid. Later, the patient showed obvious gingival bleeding with progressive exacerbation, and his blood routine examination showed a platelet count of 2×10^9 cells/L. The patient was clinically diagnosed with extreme severe thrombocytopenia. The patient was advised to stop taking sorafenib and was immediately treated with hemostasis, platelet transfusion, and suspended red blood cells. After the above treatment, the patient's symptoms improved, and he was discharged. Up to the date of follow-up, there was no further bleeding.

Received: 22 April 2021
Revised: 21 May 2021
Accepted: 23 June 2021

Key words: thrombocytopenia; sorafenib; hepatocellular carcinoma

An 81-year-old male patient presenting with "diagnosis of liver cancer more than one month, gingival bleeding for six days, and aggravation for one day" was admitted to our department on November 10, 2020. On September 8, 2020, the patient had undergone abdominal color ultrasonography and a large mass in the right lobe of the liver (maximum diameter approximately 9 cm) was suspected to be liver cancer. The patient sought further treatment and tumor marker results showed AFP was 8.45 ng/mL and CA199 was > 1000 U/mL. Abdominal enhanced computed tomography (CT) revealed a mixed low-density mass in the anterior right lobe and left medial lobe of the liver (approximately 10.3 cm long straight through), multiple similar enhanced nodules in the liver (maximum diameter, 2.4 cm), and tumor thrombus in the right anterior branch of the portal vein. On September 22, 2020, clinical diagnosis of liver cancer through "superselective hepatic arteriography, hepatic artery chemotherapy perfusion, and tumor supplying artery embolization" of the right femoral artery under local anesthesia was made. Intraoperative angiography showed a large, ill-defined, and irregular contrast agent staining of the mass shadow in the right lobe, with abundant pathological blood vessels and no early manifestation of portal vein branches. The patient was administered fluorouracil 1000 mg, epirubicin 50 mg chemotherapy infusion, tumor supplying artery iodized oil, and PVA embolization in the right and left hepatic arteries. The patient was discharged from the hospital after receiving protective liver function treatment. Later, on October 12, 2020, he began to take 400 mg po bid sorafenib (Bayer Medical & Healthcare Corporation, trade named Duojimei, German). On October 24, 2020, he developed diarrhea, which was not taken seriously and was treated. On October 28, 2020, he presented with worsening diarrhea and was administered antidiarrhea therapy. Considering drug-related side effects, the dose of sorafenib was reduced to 200 mg p.o. bid. However, on November 4, 2020, a small amount of gingival bleeding occurred in the patient, which could stop by itself. The patient did not receive further diagnosis and treatment, and continued sorafenib administration until November 10, 2020. The gingival bleeding worsened, and the skin of the limbs, head, and face was scattered in the petechiae, so he was admitted to our department at 19:04 on November 10, 2020.

Physical examination on admission: T 36.5°C, P 88 times/min, R 20 times/min, BP 140/81 mmHg, slightly

✉ Correspondence to: Bin Ye. Email:354539616@qq.com

poor nutrition, scattered petechias in the skin of the limbs, head and face without petechias. Double lung breathing sounds were thick, and no dry or wet rales were heard. Abdominal tenderness, no rebound pain, muscle tension, liver, spleen, and subcostal were not touched; the rest of the examination did not show positive signs. He had hypertension for more than ten years with the highest systolic blood pressure >180 mmHg, which was treated with oral nifedipine sustained-release tablets 10 mg po qd. No sign of diabetes, coronary heart disease, or other chronic diseases. No history of hepatitis, tuberculosis, or other infectious diseases. No history of blood transfusion or donations. No history of food or drug allergies. There was no significant family history.

The results of the auxiliary examination after admission showed that hepatitis B markers were negative. Blood routine indicated the white blood cell count was 7.86 × 10^9 cells/L, hemoglobin was 105 g/L, platelet count was 2 × 10^9 cells/L, C-reactive protein was 104.38 mg/L, and procalcitonin was 0.320 ng/mL. Liver function showed albumin was 33.4 g/L, alanine aminotransferase was 39 U/L, aspartate aminotransferase was 43 U/L, lactate dehydrogenase was 226 U/L, and á-hydroxybutyrate dehydrogenase was 176 U/L. Coagulation resulted prothrombin time was 14.8 s, partial prothrombin time was 55.4 s, fibrinogen was 6.19 g/L, and D-dimer was 1.30 mg/L. Tumor markers indicated AFP was 3.4 ng/mL and CA199 was 218.3 U/mL. Myocardial enzymology demonstrated hypersensitive troponin T was 28.59 ng/L and B-type natriuretic peptide precursor was 765.60 ng/L. Kidney function, electrolytes, and routine urine tests revealed no definite abnormalities. Contrast-enhanced head, chest, and abdominal CT (November 11, 2020) revealed postoperative changes in hepatocellular carcinoma (HCC) showing multiple nodules, masses, and lipiodol deposition in the liver, with the largest being approximately 10.2 cm × 6.6 cm. In the arterial phase of the enhanced scan, there was still significant enhancement, and the portal vein and venous phase decreased, suggesting that the tumor was still active, while contrast-enhanced scanning of the remaining sites showed no abnormal enhancement.

After admission, the patient was instructed to stop taking sorafenib immediately, and was administered tranexamic acid and phenolic sulfoethylamine to stop bleeding, platelet infusion, interleukin-11 elevated platelets, amino acid and fat milk for nutritional support, and blood pressure management. No gingival bleeding was observed after treatment. At 07:20 on October 11, 2020, the patient developed fever with a body temperature of 38.2°C, accompanied by chills without chills. Blood culture was performed, and the body temperature returned to normal after hypothermia treatment, and anti-infective treatment was administered cefazoxime sodium 2 g q12h. On October 11, 2020 solstice during November 13, 2020, the patient received five infusions of irradiated platelets. Routine blood examination (November 14, 2020) indicated a hemoglobin level of 56 g/L and a platelet count of 2 × 10^9 cells/L. The hematology department of our hospital considered secondary thrombocytopenic purpura in consultation and advised using terbium and gamma globulin to increase platelet count. A platelet matching antibody test negative. On November 14, 2020, the patient presented once with myelinolysis and weak positive occulted blood in stool. Considering severe anemia with gastrointestinal bleeding, he was prescribed fasting, pantoprazole for acid inhibition and hemostasis, infusion of suspended red blood cells to correct anemia, and recombinant human thrombopoietin and immunoglobulin to boost platelets. On November 18, 2020, routine blood analysis indicated a hemoglobin level of 37 g/L, and a platelet count of 67 × 10^9 cells/L. Due to continued positive fecal occlusion blood, acid suppression and hemostasis and transfusion of suspended red blood cells to correct anemia were maintained. On November 23, 2020, the patient had a good appetite, strong mental disposition, and no black stool. Routine blood examination showed a hemoglobin level of 72 g/L and a platelet count of 107 × 10^9 cells/L. After the above treatment, the patient's symptoms improved significantly and he was discharged to the hospital for rest on November 27, 2020.

Discussion

Primary HCC is a malignant tumor with high clinical morbidity and mortality. Due to its insipient onset, rapid progression, and difficulty in detection in the early stages, most patients are diagnosed in the middle and advanced stages, losing the opportunity for radical surgery, resulting in poor prognosis, with a median survival of only a few months [1]. Currently, transarterial chemoembolization (TACE) is an effective treatment for middle-to-advanced liver cancer that cannot be surgically resected, and its short-term efficacy has been clinically confirmed [2–3]. However, the long-term efficacy of TACE treatment is not ideal, because incomplete embolization of lesions causes ischemia and hypoxia in the tumor microenvironment, stimulates the secretion of large amounts of vascular endothelial growth factors by the remaining tumor cells, promotes tumor angiogenesis, and leads to tumor recurrence and metastasis. The development of sorafenib provides a new direction for the treatment of patients, as an oral multi-target molecular targeted drug that can inhibit the growth of tumor cells through the Raf/MEK/ERK pathway and block tumor angiogenesis [4]. Recently, some studies have confirmed that sorafenib can improve the prognosis of patients with advanced HCC and, combined with TACE, can significantly prolong the time

of disease progression and overall survival, which could benefit patients with advanced HCC [5–9].

Although TACE combined with sorafenib therapy has become a focus of intense research, its treatment-related toxicity is also under investigation. According to a number of studies [8–10], common adverse reactions to TACE treatment include fever, liver pain, nausea, and vomiting, while common adverse reactions of TACE combined with sorafenib treatment were mainly mild to moderate side effects including hand and foot skin syndrome, diarrhea, and fatigue. However, one study have shown [11] that myelosuppression was mainly mild to moderate in the TACE group alone, with seven cases of grade I/II leukopenia (12.5%), five of grade I/II thrombocytopenia (8.93%), and two of grade III thrombocytopenia (3.57%). In the TACE combined with sorafenib group, there were four cases of grade I/II leukopenia (7.14%), one of grade III leukopenia (1.79%), seven of grade I/II thrombocytopenia (12.5%), and one of grade III thrombocytopenia (1.79%). Another study reported [12] two patients (2.8%) with grade III thrombocytopenia from treatment with TACE alone, and ten patients (13.0%) with grade III thrombocytopenia who were treated with TACE combined with sorafenib. The above reports suggested that combination therapy did not significantly increase the probability of treatment-related side effects, and severe grade IV thrombocytopenia was not reported.

The patient in our study was elderly with unresectable liver cancer who was treated with TACE combined with sorafenib. No fever, abdominal pain, abnormal liver function, bone marrow depression, or other complications were found after TACE treatment. The patient began to take sorafenib orally 22 days after the operation, and diarrhea and bleeding gums occurred more than ten days after beginning oral sorafenib administration, resulting in a platelet count of 2×10^9 cells/L. Therefore, we analyzed patients with thrombocytopenia that were closely associated with sorafenib. On the one hand, the peak of chemotherapy-related side effects mainly occurred on the seventh to fourteenth day of chemotherapy, while no myelosuppression was observed in these patients after TACE. The dose of TACE chemotherapy drugs was much lower than in normal intravenous chemotherapy. On the other hand, a separate study showed serious adverse reactions of sorafenib mainly included hand-foot syndrome, fatigue, diarrhea, and hypertension [13]. However, myelosuppression usually presents as grade I/II white blood cells and neutropenia, while there was no severe thrombocytopenia [14]. The reason for thrombocytopenia may be related to the anti-tumor mechanism of sorafenib, which inhibits vascular endothelial growth factor receptor and platelet-derived growth factor receptor, and can act against tumor angiogenesis. Therefore, sorafenib is associated with adverse reactions after recognition and binding to the corresponding receptors in normal tissues and organs of the body.

Conclusion

The patient in this study developed severe thrombocytopenia after oral administration of sorafenib. Clinicians must therefore closely monitor routine blood tests and blood coagulation indices of patients being treated with sorafenib and be alert to bleeding caused by thrombocytopenia to ensure the safety of medication.

Conflicts of interest

The authors indicated no potential conflicts of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, *et al*. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2018, 68: 394–424.
2. Raoul JL, Forner A, Bolondi L, *et al*. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treat Rev, 2019, 728–736.
3. Ogasawara S, Ooka Y, Koroki K, *et al*. Switching to systemic therapy after locoregional treatment failure: Definition and best timing. Clin Mol Hepatol, 2020, 26: 155–162.
4. Ahmed A, Abdelgalil, Hamad M, *et al*. Sorafenib. Profiles Drug Subst Excip Relat Methodol, 2019, 44: 239–266.
5. Cai R, Song R, Pang P, *et al*. Transcatheter arterial chemoembolization plus sorafenib versus transcatheter arterial chemoembolization alone to treat advanced hepatocellular carcinoma: a meta-analysis. BMC Cancer, 2017, 17: 714.
6. Li L, Zhao WZ, Wang MM, *et al*. Transarterial chemoembolization plus sorafenib for the management of unresectable hepatocellular carcinoma: a systematic review and meta-analysis. BMC Gastroenterol, 2018, 18: 138.
7. Kok VC, Chen Y, Chen YY, *et al*. Sorafenib with transarterial chemoembolization achieves improved survival vs. sorafenib alone in advanced hepatocellular carcinoma: a nationwide population-based cohort study. Cancers, 2019, 11: 985.
8. Cheng Z, He L, Guo Y, *et al*. The combination therapy of transarterial chemoembolisation and sorafenib is the preferred palliative treatment for advanced hepatocellular carcinoma patients: a meta-analysis. World J Surg Oncol, 2020, 18: 243.
9. Li H, Li S, Geng J, *et al*. Efficacy evaluation of the combination therapy of sorafenib and transarterial chemoembolization for unresectable HCC: a systematic review and meta-analysis of comparative studies. Ann Transl Med, 2020, 8: 540.
10. Ren B, Wang W, Shen J, *et al*. Transarterial chemoembolization (TACE) combined with sorafenib versus TACE alone for unresectable hepatocellular carcinoma: a propensity score matching study. J Cancer, 2019, 10: 1189–1196.
11. Wu FX, Chen J, Bai T, *et al*. The safety and efficacy of transarterial chemoembolization combined with sorafenib and sorafenib mono-therapy in patients with BCLC stage B/C hepatocellular carcinoma. BMC Cancer, 2017, 17: 645.
12. Masatoshi K, Kazuomi U, Masafumil, *et al*. Randomised, multicentre

prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial, Gut, 2019, 69: 1492–1501.
13. Li Y, Gao ZH, Qu XJ. The adverse effects of sorafenib in patients with advanced cancers. Basic Clin Pharmacol, 2015, 116: 216–221.
14. Ziogas DC, Papadatos-Pastos D, Thillai K, *et al*. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: age is not a problem. Eur J Gastroenterol Hepatol, 2017, 29: 48–55.

DOI 10.1007/s10330-021-0492-2
Cite this article as: Quan XY, Chen XY, Lei L, *et al*. A case of sorafenib-induced severe thrombocytopenia during treatment of unresectable hepatocellular carcinoma. Oncol Transl Med, 2021, 7: 235–238.