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Case report
Prikaz slučaja
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SYSTEMIC TREATMENT OF HEPATOCELLULAR CARCINOMA IN A PATIENT WITH HEMOPHILIA A – A CASE REPORT

SISTEMSKA TERAPIJA HEPATOCELULARNOG KARCINOMA KOD PACIJENTA SA HEMOFILIJOM A – PRIKAZ SLUČAJA

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Summary

Introduction. Hepatocellular carcinoma is a serious problem for patients with hemophilia. Hepatitis C virus infection is the most common comorbidity in adult patients with inherited bleeding disorders, including hemophilia. **Case Report.** This is a case report of a 65-year-old male patient with hemophilia A and hepatocellular carcinoma. Sorafenib treatment was initiated at a dose of 400 mg/day, after a 50% dose reduction. In order to prevent bleeding episodes, prophylactic doses of replacement plasma-derived factor VIII concentrate (40 U/kg of body weight three times a week) were introduced. Our patient received a total of ten cycles of sorafenib therapy, in good general condition, without bleeding episodes. **Conclusion.** Differential chemotherapy is not contraindicated in patients with inherited bleeding disorders, provided that adequate hemostasis is achieved. In such cases, a multidisciplinary approach is necessary for the management of hemophilia during systemic cancer treatment.

Key words: Hemophilia A; Carcinoma, Hepatocellular; Sorafenib; Antineoplastic Agents; Factor VIII; Hemorrhage; Hemostasis; Diagnosis; Treatment Outcome; Drug-Related Side Effects and Adverse Reactions

Sažetak

Uvod. Hepatocelularni karcinom predstavlja ozbiljan problem za pacijente sa hemofilijom. Infekcija virusom hepatitisa C je najčešći komorbiditet kod odraslih pacijenata sa naslednim poremećajima krvarenja, uključujući hemofiliju. **Prikaz slučaja.** Predstavićemo slučaj iz naše ustanove, 65-godišnjeg pacijenta koji boluje od hemofilije A i hepatocelularnog karcinoma. Lečenje sorafenibom je započeto smanjenjem doze za 50% od 400 mg/dan. Da bi se sprečile epizode krvarenja, uključene su profilaktičke doze supstitucione terapije koncentratom faktora VIII iz plazme (40 U/kg telesne težine tri puta nedeljno). Naš pacijent je primio ukupno deset ciklusa sorafeniba, u dobrom opštem stanju, bez epizoda krvarenja. **Zaključak.** Diferentna onkološka terapija može da se sprovodi kod pacijenata sa nasledim poremećajima krvarenja, pod uslovom adekvatne korekcije hemostaze. U ovakvim slučajevima neophodan je multidisciplinarni pristup za lečenje hemofilije tokom sistemskog lečenja karcinoma.

Ključne reči: hemofilija A; hepatocelularni karcinom; sorafenib; antineoplastični lekovi; faktor koagulacije VIII; krvarenje; hemostaza; dijagnoza; ishod lečenja; nuspojave i neželjene reakcije izazvane lekovima

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men, the ninth in women, and the second most common cause of cancer-related death worldwide [1]. Up to 80% of HCC cases are associated with two viruses alone i.e., hepatitis C virus (HCV) and hepatitis B virus (HBV). Hepatitis C virus infection is the most common comorbidity in adult patients with inherited bleeding disorders, including hemophilia [2, 3]. According to Darby et al., in patients with hemophilia, the mortality is 16.7 times higher than in the general population for liver disease, and 5.6 times higher for liver cancer [4]. Therefore, HCC is a critical problem for hemophilia patients. The treatment of HCC depends on the stage of the disease. It includes surgical tumor resection, liver transplantation, chemoembolization, as well as systemic administration of sorafenib, a multikinase inhibitor. In the available literature, there are few reports on patients with hemophilia and HCC treated with sorafenib. We present a case from our clinical practice.

Case Report

A 65-year-old male patient with hemophilia A was admitted to the Regional Center for tooth extraction. As part of the preoperative preparation, impairment of the liver function was observed. Additional serological tests were performed and HCV was diagnosed. After assessment by an infectologist, a regular follow up was indicated. Furthermore, abdominal computed tomography was performed **(Figure 1)** and tumor lesions in the segment (S)5 and S6 of the liver, ranging in size from 60

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Abbreviations

HCC – hepatocellular carcinoma
HCV – hepatitis C virus
S – segment
MRI – magnetic resonance imaging

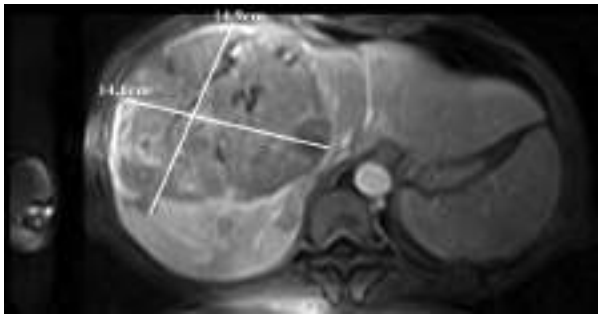

Figure 1. Abdominal MRI at the time of HCC diagnosis (August 2019)
Slika 1. *Magnetna rezonancija abdomena u momentu postavljanja dijagnoze (avgust 2019.)*

to150 mm, were found. Tumor marker alpha-fetoprotein (AFP) was elevated (over 100 ng/ml).

Esophagogastroduodenoscopy and total colonoscopy were performed and showed no pathological findings. Abdominal magnetic resonance imaging (MRI) was performed and expansive liver lesion was found in S8 (131 x 145 x 137 mm in size), with typical HCC characteristics. Also, there was a suspicious involvement of the peritoneum, infiltration of the diaphragm, compression and probably infiltration of the main liver vessels. Retroperitoneal lymphadenomegaly and signs of portal hypertension were also reported. The functional liver status, according to Child-Pugh score (class A) was 5. According to the Barcelona Clinic Liver Cancer Criteria, the patient was stage C. The case was presented to a multidisciplinary team of our institute, where it was decided to continue the treatment with tyrosine kinase inhibitor - sorafenib. Sorafenib treatment was initiated at a dose of 400 mg/day, after a 50% dose reduction. In order to prevent bleeding episodes, prophylactic doses of replacement plasma-derived factor VIII concentrate (40 U/kg of body weight three times a week) were introduced, according to guidelines for managing hemophilia patients that were previously established [5]. Our patient received ten cycles of sorafenib therapy and he was in a good general condition, without bleeding episodes. After every two cycles a complete restaging was performed **(Figure 2)** and MRI of the abdomen showed a stable disease. The functional liver status, according to the Child-Pugh score, was 5. After a total of ten cycles, radiological and clinical progression of the disease was noted.

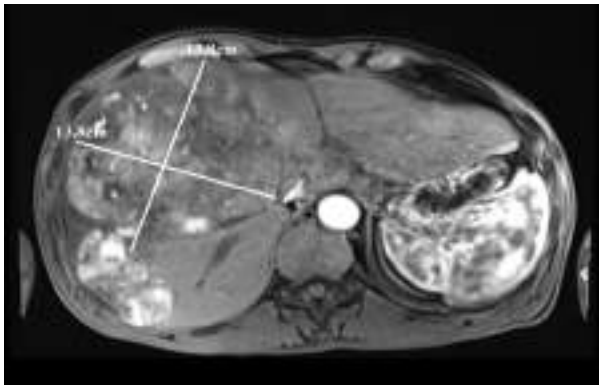

Figure 2. Abdominal MRI after sixth cycles of sorafenib therapy (June 2020)
Slika 2. *Magnetna rezonancija abdomena nakon šest ciklsa sorafeniba (jun 2020.)*

Discussion

Sorafenib is a multikinase inhibitor which blocks the growth of tumor cells by inhibition of several pathways which interfere with angiogenesis. It has been shown to antagonize the angiogenic effect of vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) on their receptors VEGFR2 and PDGFR, respectively. Anti-angiogenic drugs show a great spectrum of both thrombotic and hemorrhagic complications. The most common adverse reactions are diarrhea, fatigue, alopecia, infection, hand-foot skin reaction, and rash. Among the most important serious adverse reactions is hemorrhage with an incidence of 2 – 3% in treated patients, ranging from frequent and mild to rare severe hemorrhages [6, 7]. To our knowledge, only one case report discussed the use of sorafenib in the treatment of HCC in patients with hemophilia [8]. In that case report the patient received only two cycles of sorafenib.

Our experience suggests that hemostasis correction is critical in patients receiving sorafenib, to prevent bleeding complications associated with the use of this drug. Prophylactic treatment with factor VIII concentrates is associated with a better long-term outcome when compared to on-demand treatment.

Conclusion

Differential chemotherapy is not contraindicated in patients with inherited bleeding disorders, provided that adequate hemostasis is achieved. In such cases, a multidisciplinary approach is necessary for the management of hemophilia during systemic cancer treatment.

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