CASE REPORT

Successful twice interrupted therapy of HCV infection in patients with cirrhosis with hepatocellular carcinoma before and after liver transplantation

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SUMMARY

We are presenting the case study of the patient diagnosed at the age of 37 with liver cirrhosis due to genotype 1b hepatitis C virus infection. At the age of 46, he was diagnosed with hepatocellular carcinoma with subsequent resection of the tumour in May 2015. In December 2015, the treatment was started with ombitasvir, paritaprevir/ritonavir and dasabuvir (3D) with ribavirin (RBV) 1000 mg per day. After 24 days of this treatment, the patient received a deceased donor liver transplantation, followed by 18-day interruption of 3D therapy. Due to the anaemia, RBV dose was reduced to 600 mg per day for the rest of the treatment. At the 11th week of 3D+RBV treatment, there was another 8-day long discontinuation of therapy due to the postoperative wound infection. In total, the patient received 24 weeks of 3D+RBV treatment, achieving sustained virological response at week 24 post-treatment.

BACKGROUND

Hepatocellular carcinoma (HCC), representing more than 90% of primary liver cancers, is the fifth most common cancer, the third cause of cancer-related death and accounts for 7% of all cancers worldwide.¹ In developed countries, its major risk factor is chronic hepatitis C along with chronic hepatitis B.² Long-term follow-up studies have demonstrated that approximately 3%–8% of patients with cirrhosis related to hepatitis C virus (HCV) infection develop HCC per year.³

European guidelines recommend treating HCV infection prior to liver transplantation (LT) in patients with HCC.⁴ However, the unpredictability of organ availability may result in the necessity of LT during the HCV treatment. This particular situation was not investigated widely.

Here, we are presenting the case study of the patient who was diagnosed with liver cirrhosis, genotype 1b HCV infection (HCV G1b) and HCC and who underwent deceased donor LT with therapy including ombitasvir, paritaprevir/ritonavir, dasabuvir (3D) and ribavirin (RBV).

CASE PRESENTATION

We are presenting a case of a 48-year-old Caucasian male who was diagnosed with HCV G1b infection in 2004 at the age of 37, at the stage of compensated cirrhosis at the moment of diagnosis. The patient had also serological markers of previous hepatitis

B infection (HBs and HBe antigens were negative, while anti-HBc, anti-HBs and anti-HBe antibodies were positive), with no molecular signs of reactivation (serum hepatitis B virus-DNA was negative). Due to severe thrombocytopenia with platelet count of $60 \times 10^9/L$, he was disqualified from the treatment based on pegylated interferon alfa, and in 2006/2007 he received treatment with natural interferon alfa and RBV. At the moment of introduction of the treatment with natural interferon alfa and RBV, his platelet count was $65 \times 10^9/L$ and he had five points according to Child-Turcotte-Pugh (CTP) classification (bilirubin 1.8 mg/dL, albumin 3.6 g/dL, international normalised ratio (INR) 1.16, no ascites or encephalopathy). This therapy was ineffective—patient relapsed 24 weeks after termination of the treatment. In 2011, he experienced variceal bleeding. In November 2014, biochemical evaluation revealed elevated alfa-fetoprotein (AFP) level up to 114 ng/mL (normal range: less than 10.0 ng/mL). Abdominal ultrasonography revealed focal hyperechogenic lesion, measuring 11 × 8 mm, in the segment 3 of the liver, described as calcification or focal fibrosis. Four-phase contrast CT was not performed due to patient's decision to be discharged from hospital, against medical advice. In February 2015, patient was admitted again to our facility for endoscopic variceal ligation. Biochemical tests revealed the AFP level of 60.88 ng/mL. Four-phase contrast CT showed liver mass measuring 33 × 28 mm in segment 8 with typical radiological HCC appearance (enhanced density in arterial phase with washout in venous phase). According to Barcelona-Clinic Liver Cancer (BCLC) classification, the patient was at stage A. He was also at stage B with seven points according to CTP classification (bilirubin 1.19 mg/dL, albumin 2.7 g/dL, INR 1.12, no ascites or encephalopathy) and his Model for End-Stage Liver Disease score was 10 points.

TREATMENT

According to current BCLC treatment strategy, patient was a candidate for LT. However, due to difficult to predict time of waiting for liver donor, on 7 May 2015, the resection of liver tumour was performed and patient was put on the LT waiting list. On 15 December 2015, the treatment with 3D+RBV 1000 mg per day was started. At the moment of introduction of the 3D+RBV treatment, his platelet count was $60 \times 10^9/L$ and he

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had six points according to CTP classification (bilirubin 1.46 mg/dL, albumin 2.9 g/dL, INR 1.21, no ascites or encephalopathy). After 24 days of treatment with directly acting antivirals (DAAs), the patient received a deceased donor LT. The histopathological examination of the explanted liver revealed additional tumour of 18 mm (well-differentiated HCC) that was not revealed by CT performed before the surgery. The site after previously resected tumour was free of cancerous infiltrations. Postoperative period was complicated by perihepatic haematoma, evacuated during laparotomy on the sixth day post-transplantation and by biliary duct anastomosis leak treated with the placement of a stent via endoscopic retrograde cholangiopancreatography on the seventh day post-transplantation. In the immunosuppressive treatment, the patient received tacrolimus and prednisone. 3D+RBV treatment was stopped on the day of transplantation and recommenced after 18 days, on the day of discharge from hospital. Before the DAAs treatment resumption, the dose adjustment of tacrolimus was not introduced, which resulted in the elevation of tacrolimus concentration in blood from 15.1 ng/mL up to 60 ng/mL. Tacrolimus was stopped for 2 weeks and reintroduced at the dose of 0.5 mg per week after having achieved therapeutic level. On the day of surgery, patient was screened for other infections: hepatitis B reactivation, HIV, cytomegalovirus, toxoplasmosis, urinary tract infection, respiratory infection, which all proved to be negative. Three weeks post-transplantation, on the visit at the outpatient's clinic, laboratory examinations revealed haemoglobin drop to 8.5 g/dL. It was decided to reduce RBV dose to 600 mg per day. RBV was continued at this dose until the end of the treatment. At the 11th week of DAAs treatment, patient was hospitalised due to the postoperative wound infection. This resulted in another temporary discontinuation of HCV treatment for 8 days. The patient did not receive any growth factors to treat therapy-associated anaemia or leucopenia. Further course of treatment was uneventful.

OUTCOME AND FOLLOW-UP

In total, the patient received 24 weeks of 3D+RBV treatment. HCV RNA was negative at the 12th week of treatment, at the end and 24 weeks after termination of DAAs treatment (sustained virological response (SVR) 24). No signs of hepatitis B reactivation were observed during and after DAAs treatment.

To the best of our knowledge, this is the first report mentioning the successful peritransplantation treatment with 3D+RBV in the subject with HCV-related HCC.

DISCUSSION

According to the current European Association for the Study of the Liver (EASL) guidelines in patients with compensated liver cirrhosis and HCC awaiting LT, antiviral treatment should be initiated as soon as possible in order to complete a full treatment course before the transplantation. Treatment options in this case for HCV G1b are the same as for patients without HCC and include sofosbuvir (SOF) with ledipasvir (LDV), SOF with velpatasvir (VEL), SOF with daclatasvir (DCV), 3D without RBV and grazoprevir (GZR) with elbasvir (EBR).⁴ At the time when the treatment of our patient was started, the only available option in our facility was 3D and contemporary guidelines recommended adding RBV in patients with cirrhosis.⁵

There are no extensive clinical trials investigating efficacy of DAAs treatments in patients diagnosed with HCC, but there are case reports of successful HCV treatment with different DAAs regimens, including 3D+RBV in patients with HCC. In 2016, Bulgarian authors described, for the first time in the literature,

two cases with HCV-related cirrhosis and completely destroyed early HCC, treated successfully with interferon-free therapy. Their two patients received 3D+RBV treatment.⁶

EASL guidelines advise to avoid regimens containing a protease inhibitor for HCV treatment post-LT due to significant interactions with immunosuppressive agents.⁴ However, the efficacy of 24-week 3D+RBV treatment in liver transplant recipients with recurrence of HCV G1 infection was confirmed in CORAL-I clinical trial with 34 patients. SVR 12 rate was 97% (33/34). Treatment was generally well tolerated: 6% of patients reported severe adverse events, 17% had anaemia, one patient discontinued therapy after week 18 due to adverse events (however, this patient achieved SVR 12). Authors concluded that interactions between 3D+RBV and immunosuppressive agents were manageable.⁷ Similarly, our patient required RBV dose reduction due to anaemia, but apart from that, he tolerated the treatment well and lower dose of RBV did not have the negative impact on SVR. What is more, after correction of tacrolimus dosage to 0.5 mg per week, further course of immunosuppressive treatment was uneventful and well tolerated.

European guidelines recommend HCV treatment before LT in patients with HCC.⁴ Such strategy prevents liver graft infection. However, the time period between listing and transplantation may be unpredictable, which may result in the interruption of treatment before the recommended course is completed. In recently published Spanish study, the authors describe 15 cases of patients with the interruption of DAAs treatment around LT.⁸ Ten of those patients were diagnosed with HCC prior to LT. Interruption in treatment ranged from 2 to 55 days. Almost all patients received SOF-based regimens but in contrary to our patient, none was treated with 3D+RBV regimen. Fourteen patients completing 12 weeks of follow-up achieved SVR.⁸ In ALLY-1 study on SOF+DCV+RBV in advanced liver cirrhosis, three patients with HCC underwent LT after 1–71 days of treatment. They received 12 weeks of post-transplantation treatment extension beginning 1–3 days post-transplantation which resulted in SVR achievement in all three cases.⁹ Pooled data from SOLAR I and SOLAR-II studies showed four cases of patients who received LT during SOF+LDV+RBV treatment. All these patients achieved SVR 12.¹⁰

Our patient had one more interruption in 3D+RBV treatment, at the 11th week of treatment, due to postoperative wound infection. There are no studies on efficacy of 3D+RBV regimen temporarily interrupted due to LT or for other reasons. But the case of our patient shows that, although not recommended, temporary interruptions in 3D+RBV therapy may not result in treatment failure.

Learning points

- ▶ Ribavirin (RBV) dose reduction and two interruptions of hepatitis C virus (HCV) treatment with 3D+RBV did not have negative influence on sustained virological response in patient with HCV-related hepatocellular carcinoma treated with liver transplantation. However, we presented only one case, and further investigation in other patients is required to validate our finding.
- ▶ It is important to seek to obtain the negative viral load prior to the liver transplantation in order to prevent graft reinfection, although due to unpredictability of organ availability, patient might be transplanted before the virus has been cleared.

Our patient required RBV dose reduction to 600 mg/day due to anaemia. However, it did not compromise the SVR. Similar results were obtained in recently published observational study of 35 liver transplant recipients with recurrent HCV genotype 1 infection, who obtained 3D±RBV treatment. Anaemia was observed in 29 of those patients (83.9%), with 21 (60%) requiring RBV dose reduction or discontinuation. All patients achieved SVR 12.¹¹

Contributors ASP collected the data, drafted and revised the paper. KR collected the data and revised the paper. KS revised the paper.

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REFERENCES

- de Oliveira Andrade LJ, D'Oliveira A, Melo RC, *et al.* Association between hepatitis C and hepatocellular carcinoma. *J Glob Infect Dis* 2009;1:33–7.
- Parkin DM, Bray F, Ferlay J, *et al.* Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
- Ioannou GN, Splan MF, Weiss NS, *et al.* Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2007;5:938–45.
- European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2016. *J Hepatol* 2017;66:153–94.
- European Association for Study of Liver. EASL recommendations on treatment of hepatitis C 2015. *J Hepatol* 2015;63:199–236.
- Krastev Z, Jelev D, Antonov K, *et al.* Ombitasvir, paritaprevir, ritonavir, dasabuvir and ribavirin in cirrhosis after complete destruction of hepatocellular carcinoma. *World J Gastroenterol* 2016;22:2630–5.
- Mantry PS, Kwo PY, Coakley E, *et al.* High sustained virologic response rates in liver transplant recipients with recurrent HCV genotype 1 infection receiving ABT-450/r/ombitasvir plus dasabuvir plus ribavirin. *Hepatology* 2014;60:298A–9.
- Carrillo CF, Crespo G, de la Revilla J, *et al.* Successful continuation of HCV treatment following liver transplantation. *Transplantation* 2016.
- Poordad F, Schiff ER, Vierling JM, *et al.* Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology* 2016;63:1493–505.
- Müllhaupt B, Kwo P, Agarwal K, *et al.* High efficacy of ledipasvir/sofosbuvir plus ribavirin among patients with decompensated cirrhosis who underwent liver transplant during participation in the Solar-1 and -2 studies. *J Hepatol* 2016;64:S749.
- Tronina O, Durlak M, Wawrzynowicz-Syczewska M, *et al.* Real-World safety and efficacy of ombitasvir/paritaprevir/ritonavir/±dasabuvir±ribavirin (OBV/PTV/r/±DSV±RBV) therapy in recurrent hepatitis C virus (HCV) genotype 1 infection post-liver transplant: AMBER-CEE study. *Ann Transplant* 2017;22:199–207.

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