Rapid Virological Response After Early Treatment with a Combined Therapy of Ledipasvir and Sofosbuvir in HCV Genotype 4 After Living Donor Liver Transplantation in a HCC Downstaged Patient: Case Report and Review of the Literature

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Conflict of interest: None declared

Patient: Male, 54
Final Diagnosis: HCC with portal vein
Symptoms: Liver failure
Medication: —
Clinical Procedure: Hepatitis c treatment • hcc tratment
Specialty: Transplantology

Objective: Unusual clinical course

Background: Hepatitis C virus (HCV) genotype 4 (GT-4) is widespread in the Middle East, where it is responsible for the majority of HCV infections. It shows moderate treatment response rates when compared to other genotypes in the current era of interferon-based regimens. However, in the era of direct acting antiviral (DAA) drugs, its response is at least as good as observed for HCV genotypes 1–3.

Case Report: We present a case of a 44-year-old patient with HCV cirrhosis. Since 2007, he has been treated for HCV infection with multiple ineffective regimens of interferon (INF) and ribavirin. A liver biopsy in 2010 revealed stage 5-6/6 indicating cirrhosis, which was later complicated by the occurrence of portal vein thrombosis and a large hepatocellular carcinoma (HCC) (maximum diameter 9 cm).

The patient was successfully treated with sorafenib, transcatheter arterial chemoembolization (TACE), and radiofrequency ablation. After four TACE procedures, the patient’s AFP (alpha-fetoprotein) decreased remarkably and almost normalized. The HCC disappeared radiologically as shown by triple phase CT, MRI with contrast, and PET-CT. He successfully underwent a living donor liver transplantation. Four weeks post liver transplantation he started treatment with sorafenib, and switched from tacrolimus to Rapamune (sirolimus) as immunosuppressant therapy. Ten weeks after liver transplantation, HCV treatment was introduced along with ledipasvir and sofosbuvir due to his increasing liver enzyme levels. A rapid viral response was achieved after 14 days. In total, the patient received 12 weeks of this treatment.

Conclusions: This case study might be of significance in informing early management and personalized treatment of patients with recurrent HCV GT-4 infections after liver transplantation, even in complex clinical surroundings.

MeSH Keywords: Carcinoma, Hepatocellular • Chemoembolization, Therapeutic • Hepatitis C • Liver Transplantation

Abbreviations: HCV – Hepatitis C; GT-4 – genotype 4; SVR – sustained viral response; HCC –hepatocellular carcinoma

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Background

End-stage liver disease as a result of hepatitis C virus (HCV) infection is a very common indication for liver transplantation, and accounts for approximately 40% of all indications for liver transplantation. There are several subtypes of HCV genotypes, and treatment strategies tend to differ depending on the genotype. Worldwide, there are approximately 180 million people infected with HCV. Of these patients, about 20% will develop liver cirrhosis and 4% per year will develop hepatocellular carcinoma (HCC) after decompensation [1].

HCV genotype 4 (GT-4) is very common in the Middle Eastern region, especially in Egypt, where it is responsible for more than 80% of all HCV infections. It is the cause of approximately 35 million cases of chronic HCV infections worldwide [2]. HCV infection is still considered a potential threat for HCC development and patient death.

Tada et al. showed that the eradication of HCV decreased not only liver-related deaths but also liver-unrelated mortality in patients with chronic HCV infection. In addition, Tada et al. were able to show that the eradication of HCV reduced the incidence of HCC [3]. In previous studies, ledipasvir and sofosbuvir achieved excellent sustained viral response (SVR) rates in HCV GT-1 and -2. Similarly, several reports evaluated the SVR rates in HCV GT-4 infected patients with excellent SVR rates.

In this case study, we discuss the case of a preoperatively downstaged HCC patient who was treated for his HCV infection with ledipasvir and sofosbuvir (an interferon/ribavirin-free (IRF) regimen). Rapid virological response was attained 14 days after introducing this dual therapy.

Case Report

We treated a 44-year-old patient with a history of HCV GT-4 infection since 2007. He received multiple ineffective regimens of interferon (INF) and ribavirin. A liver biopsy in 2010 revealed stage 5–6/6 with impending liver cirrhosis. Until 2013, he was treated with INF-based regimens. In September 2014, he had increased AFP (alpha-fetoprotein) levels up to 75 ng/mL, and a triple-phase CT was negative for focal lesions. In December 2014, he presented in Iraq with variceal bleeding and a work-up showed highly elevated AFP levels (1,000 ng/mL). On April 1, 2015, a triple-phase CT showed a huge liver mass in segment 8 with typical radiological HCC behavior. Shortly thereafter, the patient presented with portal vein thrombosis. The HCC was located in segment 8 of the liver and considered to be outside of the Milan transplantation criteria. A review of the previous CT by four radiologists confirmed previous findings that indicated no focal lesions.

A multidisciplinary board decided to treat the patient with drug-eluting doxorubicin beads (TACE) four times followed by radio-frequency ablation, and sorafenib (Nexavar), a multikinase inhibitor, was given at 400 mg twice daily, starting immediately. The HCC decreased after four TACE procedures and AFP levels normalized after two months. Repeated abdomen CT, MRI, and PET-CT revealed a complete disappearance of the HCC in segment 8, and the patient’s AFP had dropped to a normal level.

The patient condition was again discussed at a multidisciplinary transplant board meeting, and after careful evaluation, the decision was made to provide the patient with a liver transplantation. He received a living donor liver transplantation of the right lobe from his younger brother. The histopathological examination of the explanted liver revealed an invasion of a small portal vein branch in segment 8. Lymph nodes were not involved. The liver transplantation was uneventful, and three weeks later, the patient was discharged.

Four weeks after transplantation, the patient was switched from Prograf (tacrolimus) to Rapamune (sirolimus) 2 mg daily, targeting a blood drug level of 6–8 ng/mL; in addition, sorafenib therapy was reintroduced. After eight weeks, the patient was started on ledipasvir 400 mg and sofosbuvir 90 mg (a interferon/ribavirin-free regimen). After three months, the patient developed a biliary stricture and was treated with the placement of a biodegradable stent via endoscopic retrograde cholangiopancreatography/percutaneous transthepatic cholangiography (ERCP/PTC). Rapid virological response was attained 14 days after initiation of the dual ledipasvir-sofosbuvir therapy, followed by a sustained virological response three months later.

Discussion

HCC management in cases of cirrhosis depends on the tumor characteristics, liver disease stage, and the underlying liver disease. HCV infection is the main etiological cause of HCC worldwide. Carcinogenesis might arise indirectly from long-standing liver inflammation and fibrosis. It may also result directly from viral proteins and their interaction with the intracellular apparatus of the host [4,5].

HCC is one of the leading causes of cancer-related deaths in the world. It has been anticipated that the rate of HCV-related HCC will decline considerably after the extensive implementation of DAAs, but there remains a persistent risk for HCC even among some patients with advanced fibrosis who have achieved SVR [6]. Consequently, Pinzone et al. suggested a continuous surveillance of patients with cirrhosis after achieving SVR in order to identify HCC early and treat it opportunely [7].
Regardless of the fact that it may not be relevant for HCV infections with GT-4, there have been several studies highlighting the safety and the effective application of interferon/ribavirin-free anti-HCV therapies. Recently, several studies assessed the efficacy and safety of combination therapy with ledipasvir and sofosbuvir with or without interferon/ribavirin. Lewitz et al. suggested that dual therapy with sofosbuvir and ledipasvir, including or excluding ribavirin, has the potential to cure nearly all patients with HCV GT-1, irrespective of previous treatment or the occurrence of compensated cirrhosis [8].

Bourlière et al. showed that ledipasvir and sofosbuvir plus ribavirin for 12 weeks and ledipasvir and sofosbuvir for 24 weeks offered equally high SVR-12 rates in prior non-responders with HCV GT-1 and compensated cirrhosis [9]. Mizokami et al. suggested that in Japanese patients, ledipasvir and sofosbuvir might be a significant treatment option for HCV GT-1 [10]. Kohli et al. underlined the safety of 12 weeks of interferon-free treatment with ledipasvir and sofosbuvir and documented that toleration was good in patients with HCV GT-4. Their results showed 100% SVR for all patients who received the study drugs for three months. This was the first report of an interferon- and ribavirin-free treatment with the combination therapy of sofosbuvir and ledipasvir for patients with HCV GT-4 [11].

Our patient’s case presents a downstaging strategy based on a multimodality approach that was highly effective in the treatment of a rapidly growing HCC in segment 8. The disappearance of the tumor after four TACE procedures encouraged the transplant board members to recommend the liver transplantation. Moreover, AFP levels declined to normal range.

Green et al. showed that HCC treatment with DEB-TACE has a good possibility of shrinking the HCC in order to meet the Milan criteria [12]. Obed et al. showed that patients who underwent a previous TACE treatment without tumor progression had good survival rates after liver transplantation [13]. According to Obed et al., the selection of patients for liver transplantation based on tumor progression results in good survival, and they concluded that the evaluation of HCC patients should not only be based on tumor size and number of foci, but also on tumor progression and growth behavior under TACE therapy [13].

Cholongitas et al. concluded that mammalian targets of rapamycin inhibitors are associated with lower rates of HCC recurrence after liver transplantation [14]. We started our patient on therapy with sorafenib after four weeks, and therapy with Rapamune after two months, with the aim of delaying or even avoiding an early HCC recurrence. Antiviral therapy after liver transplantation is a complex issue because of possible side effects and inferior efficacy in patients that are liver transplant recipients, as well as due to drug interactions with immunosuppressants.

Rapamune (sirolimus) is an immunosuppressant with inhibiting effects on epithelial healing and biliary cell restoration capability. These effects may have a negative impact on the healing of biliary anastomosis after liver transplantation with prolonged cold conservation. Early repeat of ERCP after liver transplantation has been linked to Rapamune-based immunosuppression [15–17]. In general, anastomotic strictures (AS) are very common after living donor liver transplantation. The development of AS is associated with multiple recipient factors like cold ischemia time, type of anastomosis, single or multiple duct anastomosis, the surgeon’s skills, and donor factors like sex, weight, age, and liver steatosis [18–22].

Several groups assessed the evidence of HCC downstaging prior to liver transplantation in patients with HCC initially staged outside the Milan criteria. Gordon-Weeks et al. showed that overall and disease-free survival rates in liver recipients following downstaging therapy were comparable to those in patients within the Milan criteria [23]. Liver transplant recipients who meet the UCSF or Milan criteria after an application for successful preoperative downstaging therapy in living donor liver transplant can achieve the same results and outcomes when compared to conventional Milan criteria patients [24–26].

In our opinion, patients with HCC beyond the Milan criteria should be offered downstaging therapies. Patients who are effectively downsized to the Milan criteria have to be qualified for liver transplantation like those who initially met the Milan criteria.

In summary, we presented a case of a patient with a relapsing HCV GT-4 infection after liver transplantation, who showed a rapid sustained viral response after having been efficiently treated with ledipasvir and sofosbuvir while neither ribavirin nor interferon were used. Furthermore, we assumed that the early eradication of HCV with the use of sorafenib and Rapamune may have had a good impact on the disease-free survival of our patient.

As far as we know, this is the first report mentioning the successful use of ledipasvir and sofosbuvir in a case with a recurrent HCV GT-4 infection after living donor liver transplantation.

Conclusions

The combination therapy with ledipasvir and sofosbuvir (interferon/ribavirin-free regimen) may be a valuable and safe approach for the therapy of HCV GT-4 infections, especially for recurrent HCV GT-4 infections after living donor liver transplantation in HCC-downstaged patients.

Conflict of Interest

The authors declare no conflict of interest.
Obed A. et al.: Rapid virological response after early treatment with a combined therapy of ledipasvir.
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