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Single Case

Clearance of Hepatitis C Virus following Immune Checkpoint Inhibitor Therapy for Hepatocellular Carcinoma: Case Report

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Abstract
Introduction: Patients with advanced hepatocellular carcinoma (HCC) have limited treatment options in the context of decompensated cirrhosis. HCC occurs in patients with hepatitis C virus (HCV) infection and cirrhosis at 1–4% per year. Direct-acting antiviral (DAA) efficacy is decreased in the presence of HCC. We present a case where immunotherapy may have resulted in HCV clearance, when DAA therapy had been ineffective. We hypothesise that immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway can reverse T-cell exhaustion and aid in the clearance of chronic HCV. ***Case Presentation:*** This case study describes a male in his 40 s identified by a re-engagement initiative for HCV, who had been unaware of his diagnosis. On further investigation he was found to have compensated for liver cirrhosis and HCC. He was treated with HCV DAA therapy (sofosbuvir/velpatasvir) and then systemic immunotherapy for HCC with atezolizumab and bevacizumab, in an attempt to downstage the disease. Hepatitis C therapy did not achieve sustained virological response, with viral relapse after the end of treatment. This, combined with ongoing alcohol use, resulted in hepatic decompensation and cessation of immunotherapy after the fifth cycle. The HCV RNA subsequently became undetectable without further DAA re-treatment. ***Conclusion:*** To our knowledge, this is the first case of HCV clearance after DAA relapse and the timing of this event after immunotherapy suggests a causal link. We hypothesise that this may be due to the reversal of antiviral T-cell exhaustion. This would therefore support further investigation into other chronic viral infections that create tumour associated with immunosuppressive microenvironments.

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Introduction

Liver cancer is the third most common cause of cancer death globally and has a rising incidence in Western countries [1]. Patients with advanced hepatocellular carcinoma (HCC) have limited treatment options in the context of decompensated cirrhosis. Prognosis depends on tumour burden, liver synthetic function and patient performance status. Systemic therapies are the mainstay of palliative treatment and can prolong survival, where liver function and performance status allow.

The rate of HCC occurrence in those with hepatitis C virus (HCV) infection and cirrhosis is 1–4% per year [2]. In those with advanced HCC, viral clearance as a result of direct-acting antiviral (DAA) therapy may be beneficial in maintaining or improving hepatic function and lengthening the opportunity for systemic therapy. However, the efficacy of DAA therapy for HCV infection is reduced in the presence of HCC [3].

The advent of immunotherapy has allowed improved survival for patients with advanced HCC. The phase III IMbrave-150 study found that the combination of anti-programmed death-ligand (PD-L1) inhibitor atezolizumab and vascular endothelial growth factor inhibitor bevacizumab had superior median overall and progression-free survival as first line therapy compared to the multi-targeted tyrosine kinase inhibitor sorafenib [4].

We present a case where immunotherapy may have resulted in HCV clearance, when DAA therapy had been ineffective. We hypothesise that immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 pathway can reverse T-cell exhaustion and aid in the clearance of chronic HCV. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539646).

Case Report

This 42-year-old male was identified by our HCV operational delivery network (ODN) re-engagement initiative in April 2020. He had previously tested positive for HCV RNA but was unaware of the diagnosis until notification by the ODN. On assessment, he was drinking around 210 units of alcohol weekly and had no clinical signs of decompensated chronic liver disease. He had no previous history of intravenous drug use, was HIV negative and had normal renal function. Further testing confirmed hepatitis C genotype 3a infection, viral load 41,687 IU/mL, with bilirubin 22 μmol/L, albumin 40 g/L, ALT 63 μmol/L, AST 73 μmol/L, AFP 6.8 ng/mL. FibroScan showed median elasticity 12.7 kPa (IQR 1.0), in keeping with cirrhosis. He planned to engage with alcohol support services to reduce his intake and, due to being treatment naïve, started HCV DAA treatment with Epclusa (sofosbuvir/velpatasvir) for 12 weeks in January 2021.

Following his diagnosis, before starting treatment for his HCV, an ultrasound of the liver demonstrated a focal lesion in the right lobe. MRI confirmed a hypervascular tumour within segments 6 and 7, measuring 4.5 cm, with radiological features of HCC and invasion into the right posterior portal vein and right hepatic vein. There were no signs of portal hypertension. Staging CT confirmed the absence of distant metastases.

His Barcelona clinic liver cancer stage, with a single lesion, Child-Pugh class A5 and good performance status was early stage (A). Surgery was considered; however, indocyanine green clearance assessment of liver function was unfavourable for resection. Endoscopy demonstrated grade 1 oesophageal varices. The multidisciplinary team recommended a strategy of attempted tumour "downstaging" by systemic immunotherapy with atezolizumab and bevacizumab, alongside DAA therapy, with a plan to reassess for sufficient improvement in

liver function to allow resection. Immunotherapy commenced in February 2021 for 6 planned cycles.

In March 2021, end-of-treatment HCV RNA was undetectable. The patient continued to have 4 cycles of atezolizumab and bevacizumab, with his last fourth dose occurring in late May. There was a subsequent viral relapse with viral load in June of 51,286 IU/mL. This coincided with a return to harmful levels of alcohol. Despite imaging evidence of good tumour response, his 5th cycle of immunotherapy was held due to abnormal liver function (ALT 105, AST 230, bilirubin 64) which may have been due to viral relapse, alcohol relapse, immunotherapy hepatitis or a combination thereof. Both further systemic HCC therapy and second-line DAA therapy with Vosevi (sofosbuvir/velpatasvir/voxilaprevir) were contraindicated due to hepatic decompensation (Child-Pugh B cirrhosis).

Despite no further antiviral treatment, in July 2021 his HCV RNA became undetectable. Unfortunately, he did not attend further oncology clinic appointments due to alcohol dependence. He was admitted to hospital in February 2022 with tense ascites and HCV RNA remained undetectable on two separate blood tests, confirming sustained virological response more than 24 weeks after therapy. There has been a progression of his disease and, following the best supportive care, the patient passed away at home.

Discussion

To our knowledge, this is the first case of HCV clearance after DAA relapse and the timing of this event after immunotherapy suggests a causal link. This would support further investigation of immunotherapy, including checkpoint inhibitors, in the curative treatment of chronic viral hepatitis.

ICIs overcome natural homoeostatic immune mechanisms and tumour associated immunosuppressive microenvironments to enhance immune activation [5]. The combination of atezolizumab and bevacizumab has established efficacy as a first line therapy, producing a median overall survival of 19.2 months versus 13.4 months with sorafenib [4]. The blockade of inhibitory checkpoint molecules can produce a range of adverse reactions, including hepatitis, which is common in the context of viral hepatitis infection.

In common with HCC, chronic HCV infection produces an immune-tolerant environment within the liver. T-cell exhaustion and viral escape mutations have been identified as the main mechanisms for persistent viral replication [6]. Exhausted HCV-specific CD8+ T cells express inhibitory receptors such as CTLA-4 and PD-1 [7]. HCV-specific CD4+ T cells express typical markers such as PD-1 in the acute phase of infection, but their signatures decline with chronicity [8]. Blockade of PD-1 signalling has been shown to improve virus-specific T-cell response and immune control in the context of viral infections in mice [9].

Initial theoretical concerns regarding viral reactivation of HCV in the treatment of HCC with ICIs leading to toxicity and reduced efficacy have been disproven with no evidence of reactivation when using Nivolumab in patients with advanced HCC [10]. However, active HCV infection can worsen liver function, precluding some individuals from systemic therapy. Indeed, some cohort studies in the DAA era suggest HCV clearance is a more important determinant of long-term survival than HCC response to systemic therapy [11]. In this centre, our practice is to treat hepatitis C in all patients who have a palliative therapy option for their HCC. In addition, we give DAA therapy to patients with small tumours and decompensated liver disease. In these patients, survival is predominantly determined by their liver function. They have approximately 50% chance of recompensating if they achieve HCV clearance, opening the door to a range of HCC treatments including systemic therapy.

Current Clinical Context and Conclusion

If immunotherapy can reverse antiviral T-cell exhaustion, this supports further investigation in other chronic viral infections to achieve clearance, particularly in hepatitis B. It is of interest that HBsAg positive patients experience checkpoint inhibitor hepatitis more frequently than HBsAg negative patients, despite viral suppression on nucleotide therapy treatment [12]. A number of clinical trials have shown a modest decline in HBsAg levels with PDL-1 inhibition and several more are underway combining checkpoint inhibitors with therapeutic vaccination and other treatments [13].

A recent study suggests immunotherapy with atezolizumab and bevacizumab is safe and of equivalent efficacy in Child-Pugh B liver disease as compensated for cirrhosis [14]. In patients with genotype 3 infection treated with Epclusa with ribavirin cure is achieved in 80% of those with decompensated cirrhosis and in 78% of those with HCC [15]. We postulate that in such hard-to-treat HCV cases, concomitant therapy with checkpoint inhibitor-based regimens may increase the chance of achieving both hepatitis C cure and tumour response. The potential subsequent re-compensation may lengthen the opportunity or broaden the modalities for further HCC treatment. Patients most likely to benefit are those with mild decompensation and no other risk factors for liver disease, since they would be expected to experience the largest decline in MELD (Model for End-Stage Liver Disease) score with HCV clearance and to tolerate immunotherapy safely.

In conclusion, the role of checkpoint inhibitors in release of antiviral T-cell exhaustion for chronic viral infections merits further exploration. Alongside this, further research into the concomitant effects of immunotherapy on HCV cure in hard-to-treat patients (DAA relapse, HCC, decompensated liver disease) should be conducted. Despite the substantial advances in HCV and HCC therapy, late diagnosis, and barriers to engagement with care (such as alcohol dependence) remain major obstacles for many patients.

Statement of Ethics

The patient's identity has been kept anonymous throughout the report. The age of the patient, date of diagnosis, and duration of HCV infection have also been altered for further anonymity. Verbal consent was obtained from the patient for publication. A joint meeting with the patient and an interpreter was organised to obtain written consent. Sadly, the patient passed away before this was possible to happen. The verbal consent procedure was approved by the lead of the hepatology department. The patient does not have next of kin in the UK. He is survived by his parents overseas, to whom he never disclosed his hepatitis C diagnosis. Therefore, it would be inappropriate to seek consent from this party. The study protocol was approved by the hepatology department at the Royal Free hospital. This retrospective review of patient data did not require ethical approval in accordance with local/guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Wilson H wrote the manuscript. Bryce K critically reviewed, revised, and designed the manuscript. Macdonald D critically reviewed the manuscript. All authors reviewed and approved of the final version.

Data Availability Statement

All data generated or analysed during this study are included in this article. Any further data are not available due to ethical reasons. Further enquiries can be directed to the corresponding author.

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