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Case Report

Is there Synergy Between Direct Acting Antivirals (DAA) and Immunotherapy? Two Cases of Complete Hepatocellular Carcinoma Regression Due to Direct-Acting Antiviral Treatment in Combination with Check-Point Inhibition (CPI)

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Abstract

Hepatocellular carcinoma (HCC) is the second cause of worldwide mortality among cancer patients with over 800 deaths annually. The major cases of HCC associated with hepatitis B and C viruses. Direct-acting antiviral agents (DAA) has become a breakthrough in the treatment of HCV infection. Short-term oral DAA administration results in more than 95% of effective virus elimination. However, the impact of DAA- on HCC has not been thoroughly studied. HCC is the second cause of mortality among cancer patients with the incidence rate being increased worldwide including Russia. About one half of patients with HCC commonly receive Sorafenib or Lenvatinib as first-line or regorafenib, cabosantinib or ramucirumab as second-line-therapy. Immune CPI have been an outstanding advance in the treatment of HCC for the last five years. The combination of Atezolizumab and Bevacizumab appears to be standard therapy for HCC as it was shown to increase the overall survival rate compared with Sorafenib alone [1]. The combined therapy based on CPI is preferable in all HCC stages. It was also shown that durvalumab combined with tremelimumab resulted in better overall survival compared with sorafenib alone, at the same time atezolizumab in combination with cabozantinib demonstrated better progression-free survival. In addition, pembrolizumab as monotherapy and nivolumab combined with ipilimumab managed to win a outbreaking FDA approval as second-line HCC chemotherapy [2,3]. Development of DAA appears to be a breakthrough in the HCV treatment. Short-term oral DAA administration results in more than 95% of effective virus elimination. The impact of DAA on the HCC has not been carefully studied. It can be attributed to the fact that two different categories of CHC patients were commonly included in the CPI-clinical trials: those without previous antiviral therapy (AVT) or those who had previously had effective AVT if the interval between the end of AVT and the start of CPI was not less than four weeks.

Keywords: *Direct Acting Antivirals (DAA); Check-Point Inhibition (CPI); Hepatocellular Carcinoma (HCC); Antiviral Therapy (AVT)*

Introduction

We present two observations of complete regression of HCC as a result of immunotherapy while taking DAA.

Two case reports of complete HCC regression due to effective DAA treatment in combination with CPI are presented.

Case Reports

Case Report 1

M. was a 79-year-old woman who was diagnosed CHC (genotype 1-b) in 2003.

The patient did not receive AVT. In 2014 she first presented with a hepatic tumor mass. Subsequent histology samples revealed no tumor growth. In February 2017 abdominal MRT showed tumor progression and liver cirrhosis. In March 2017 biopsy performed in Blokhin Cancer Research Centre confirmed HCC Chest CT showed metastasis to lungs. From April 2017 the patient started Sorafenib 800 mg daily. Twenty-one days after the start of therapy, the patient complained of a rash on her hands and feet, and the dose of Sorafenib was reduced to 600 mg per day. But the side effects associated with taking Sorafenib have not disappeared. The patient complained of diarrhea G1 and high blood pressure G2. The administration of Sorafenib was discontinued, and the prescribed symptomatic therapy led to a complete regression of toxic effects. However, with the subsequent use of Sorafenib at a dose of 400 mg per day, a rash appeared and covered more than 50% of the skin. Blood pressure rose to 210/100 mmHg. In June 2017 Sorafenib was completely withdrawn because of intolerable toxicity. Sorafenib administration lasted for a total of 9 weeks.

In August 2017 the patient started with Pembrolizumab in the dose of 200 mg as part of a clinical trial of the second line therapy for advanced HCC (Figure 1).

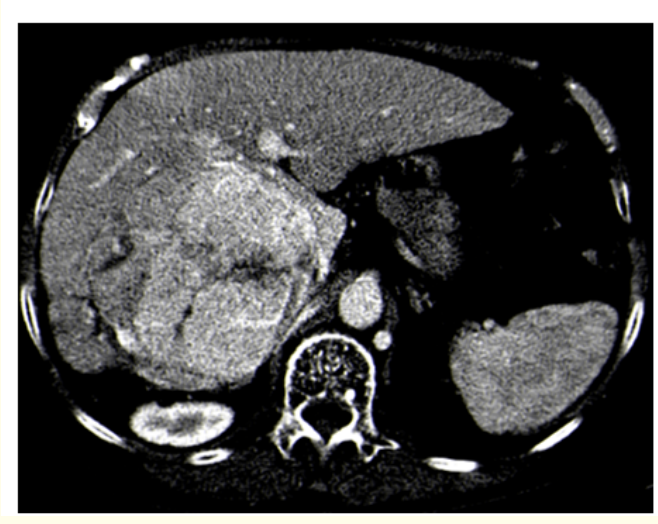

Figure 1: *Abdominal computer tomography from 21.08.2017.*

The patient's status at the start of pembrolizumab therapy was T3aN0M1, stage 4 (metastasis to the lungs). Alphafetoprotein was 24,7 IU/ml; platelets - 121*109/l, ALT (1.7ULN) and AST (2.5 ULN). As serum HCV RNA was IU detected, AVT was not performed following the requirements to the clinical study protocol. After the 5th Pembrolizumab administration (week 12) the patient developed rash (2nd grade of severity) accompanied by itch and the treatment was interrupted for 1 week. Local steroid therapy led to the resolution of symptoms. After the 6th administration (week 19) rash (3rd grade of severity) reappeared. The was withheld and - prednisolone 1 mg/kg was prescribed. After 7 days the symptoms regressed up to those of the 1st grade. Pembrolizumab was resumed from January 2018. In August 2018 after the 18th dose (week 54) CT showed the primary tumor progression (+21% of the tumor process according to RECIST [Response Evaluation Criteria in Solid Tumours] 1.1 criteria) (Figure 2).

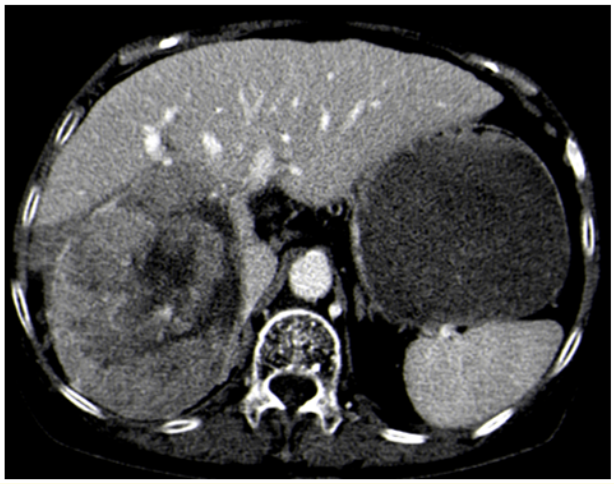

Figure 2: *Abdominal computer tomography from 03.12.2018.*

The treatment was continued as no clinical deterioration followed. In November 2018 the enhanced ALT (3.4ULN) and AST (5.3ULN) activity necessitated HCV RNA study (6*10 IU/ml). The lack of experience in immunotherapy in patients with viral hepatitis in 2018 made us associate increase of transaminase activity with either immune-mediated hepatitis or the worsening of viral hepatitis. The decision was made to begin AVT with sofosbuvir (400 mg) and velpatasvir (100 mg) daily in December 2018. Sustained biochemical and virological responses were achieved. In January 2019 CT showed the tumor debulking (-13% according to RECIST 1.1 and -48% according to mRECIST). The effect was achieved after 6 weeks (Figure 3). In September 2019 the final dose of pembrolizumab was administered (cycle 35). The positive tumor response has been observed up to the day of the present report (complete regression according to mRECIST). No clinically significant toxic effect has been reported. A study performed in January 2022 showed that tumor size remained unchanged, AFP was within normal limits, HCV RNA was not detected. 54.3 months have passed since the time the diagnosis was established and 49.2 months since the beginning of pembrolizumab therapy. The follow up period has been 64,8 months.

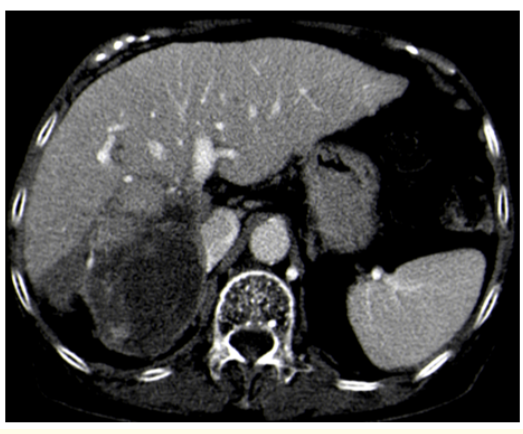

Figure 3: *Abdominal computer tomography from 03.12.2018 tumor size mRecisct 2,8 x 1.5 sm.*

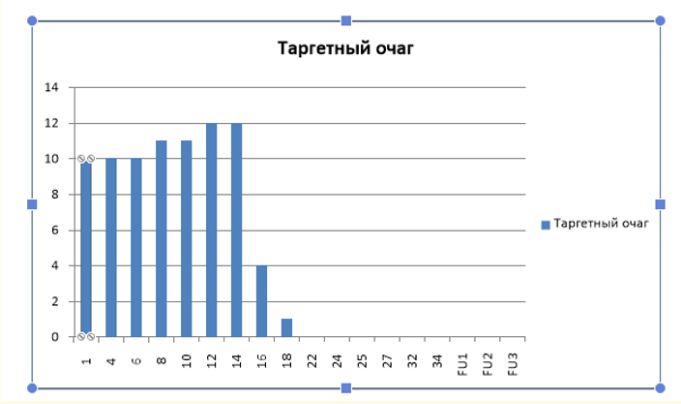

Figure 4: *Growth dynamics by cycle of anticancer therapy.*

Case Report 2

The 43-year old male patient who was diagnosed chronic hepatitis C (genotype 1-b) in 2014. He did not receive any AVT for the disease.

In January 2021 abdominal MRT first revealed hypervascular bilobar liver mass with satellite lesions up to 1 cm accompanied by the portal vein trunk and branches thrombosis (Figure 5).

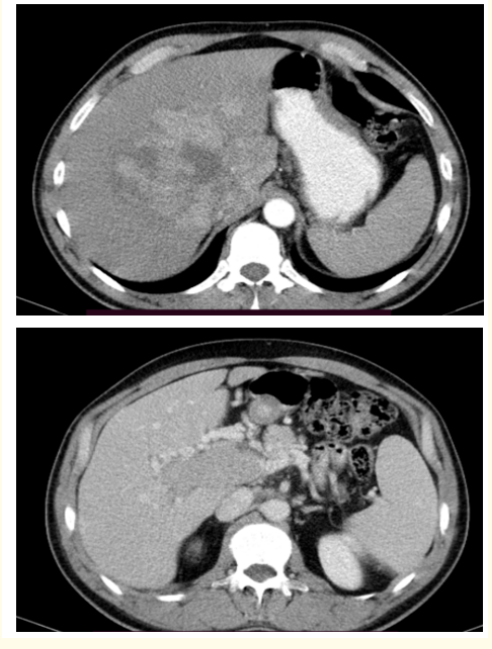

Figure 5: *Abdominal computer tomography from before the start of therapy from 16.01.2021, the main node is 12.7 x 10.5 cm and the tumor thrombus in the lumen of the portal vein trunk is up to 2.7 cm.*

Liver biopsy confirmed HCC and liver cirrhosis. The patient's status was established as BCLC-C (portal vein thrombosis), T4N0M0, stage III. AFP before treatment was 45 IU/ml. The increased activity of ALT (72 IU/l) and AST (63 IU/l) was observed. HCV RNA was 6*10 IU/ml. In February 2021 first-line therapy with Atezolizumab (1200 mg) and Bevacizumab (15 mg/kg) intravenously was started. In March 2021 the increased ALT (156 IU/l) and AST (123 IU/l) were seen. Glecaprevir (300 mg) and Pibrentasvir (120 mg) combination daily for 12 weeks was started. By antitumor medicine administration 6 the process had been stabilized (according to RECIST 1.1 criteria). After administration 9 the patient developed eruption on the penis, accompanied by itch and ulceration (Figure 6).

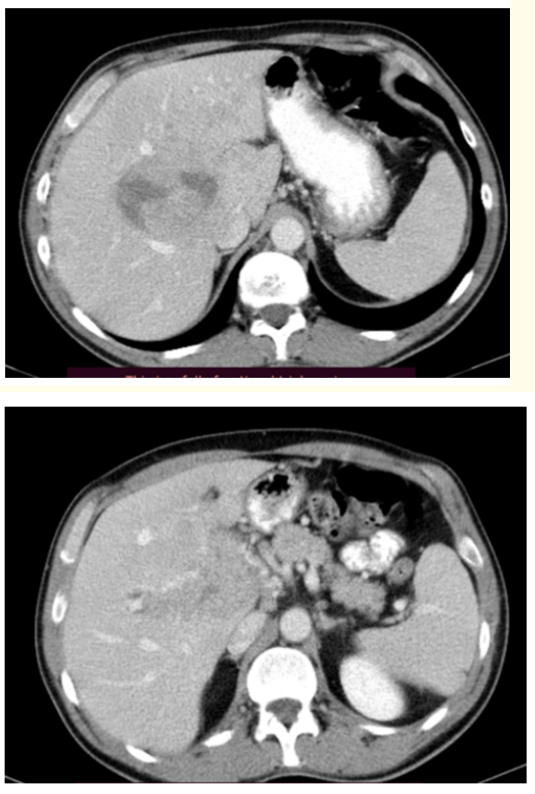

Figure 6: *Abdominal computer tomography from before the start of therapy from 03.08.2021, the main node is 10,5 x 8,5 cm and the tumor thrombus in the lumen of the portal vein trunk is up to 3.5 cm.*

Local and specified therapy for toxic dermatitis and herpes-associated genital infections resulted in positive effect. Thus, the treatment was interrupted for two weeks. A dramatic decrease of tumor size was seen on CT scan after 12 administrations (-57% according to RECIST 1.1 and -85% according to mRECIST 1.1) (Figure 7). Normal AFP (2 IU/ml) was first observed. PCR test showed minimal levels of HCV viremia and treatment was continued. In January 2022 a repeated CT showed a significant decrease of tumor size (-63% according to RECIST 1.1 and -100% according to mRECIST 1.1). A total antitumor course Included 19 dose administrations. In March 2022 the final Atezolizumab and Bevacizumab doses were administered. The objective response to therapy remained unchanged (-63% according to RECIST 1.1 and -100% according to mRECIST 1.1). No toxic manifestations were seen. The patient did not receive any therapy.

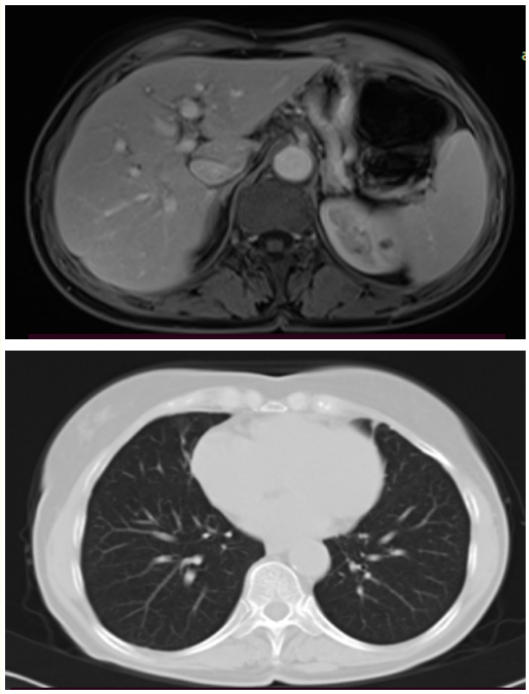

Figure 7: *Abdominal computer tomography from before the start of therapy from after 04.05.2022 the end of therapy, complete regression of the tumor is preserved.*

The final examination made in June 2022 showed no changes in tumor size, indicating a complete tumor regression. AFP was within normal limits. 21 months have passed since the time the diagnosis was confirmed and 20 months since the time of initial treatment.

The follow up period has been 20 months.

Discussion

We present two cases of complete reversible HCC in patients with previous cirrhosis caused by CHC, who received CPI after DAA therapy was added to anticancer therapy. The effect observed seems to be astonishing and obviously can be considered to be a matter of accident. At the same time it can be explained in terms of pathogenesis. Thus, a question may arise: is effective antiviral therapy able to enhance CPI effect on the disease?

Cases of spontaneous HCC regression while taking DAA seem to be of special interest. Three similar cases have been reported elsewhere.

The first case of spontaneous HCC regression in a 57-year old woman diagnosed with liver cirrhosis due to CHC was reported by investigators from the USA [4].

A local 26 mm mass in liver (according to LI -RADS 5 criteria) was revealed, with the increased serum AFP activity (218 ng/ml). After 1-month therapy with Sofosbuvir and Simeprevir the mass reduced in size to 6x5 mm with AFP activity being decreased up to 22 ng/ml. Thereafter a report about DAA-associated spontaneous regression of histologically confirmed HCC with lung metastasis in a patient who was a liver transplant recipient followed [5]. Sorafenib therapy in that patient was not effective but the tumor (including lung metastasis) regressed after 24 weeks Sofosbuvir and Ribavirin added for recurrent hepatitis C. In addition, the patient took low doses of everolimus (1 mg daily).

Mahmoud., *et al*. (2016) reported a complete regression of a small size HCC due to 48 -week Sofosbuvir and Ribavirin therapy in a 59-year old patient with compensated cirrhosis [6]. Sofosbuvir was one of the agents that present in all reported cases of HCC spontaneous regression. Pharmacologically active form of Sofosbuvir (GS-461203) acts as a chain terminator, inhibiting RNA-dependent RNA polymerase NS5B HCV that results in significant decrease of viral load. Antiviral effect of Ribavirin is achieved due to inhibition of

mitogen-activated protein kinase p38 (MARK) phosphorylation pathways.

Those mechanisms can be responsible for antitumour effect of the above agents.

Unfortunately, we have not been able to find a report of a complete or partial HCC regression possibly attributed to modern DAA. Sofosbuvir has been recommended up to the present time for CHC as one of the components of AVT. As far as Ribavirin is concerned, its role in modern AVT regimes is even less significant and hepatologists are unlikely to prescribe it in the near future.

A number of reports suggesting that HCV elimination with DAA should be as effective as IFN therapy in inhibiting HCC have been published [7-9]. Therefore, DAA can change and even enhance HCV-induced immune response and hence, influence on antitumour immunity. However, the specific mechanism by which virus elimination due to DAA reduces the risk of CHC development is still obscure.

S Li., *et al*. (2022) studied the DAA impact on the immune response in patients with CHC previously infected with HCV. The investigators compared immune responses to 19 tumor antigen-associated peptides as well as immune cells profiles before and 24 weeks after the start of DAA. As a result, they concluded that the underlying mechanism of antitumor effect is connected with inhibition of protein PD-1 expression caused by profile F decrease or elimination. DAA tended to change CHC patients' immune responses, diminishing the frequency of PD-1 expressing CD4+ and CD8+ T-cells [10]. Ramadan., *et al*. (2021) showed that in HCV-induced liver diseases (irrespective of their severity) alterations in signaling pathways PI3K/AKT and JAK/STAT were observed after DAA administration. In CHC patients who received DAA increased p-AKT and pSTAT5 regulation and decreased p-STAT3, HIF-1a and COX-2 regulation were observed. Moreover, increased CD3+, CD8+ and CD4+ percentage as well as Cd4FoxP3+/CD25+, CD8+/PD-1and CD19+/PDL-1 decrease were noted in CHC patients after DAA administration. Active oxygen forms (ROS) as well as IL-1B, IL-6, IL-8 and TNF-a decreased significantly in HCV patients following DAA treatment [11]. According to the prospective study, conducted by L. Szereday., *et al*. (2020) DAA not only inhibited HCV replication but altered adaptive and immune responses contributing to the restoration of exhausted adaptive immune responses and thus, resulting in persistent immune responses [12]. Sustained viral response was associated with the increased number of peripheral blood CD3+ and CD8+ cytotoxic T-lymphocytes and decreased number of light NK-cells. After effective treatment with DAA decreased TIM-3, CD4+ expression by T cells, light NK and NKT cells was observed. PD-L1 expression by NK -cells and regulatory T-cells, as well as that of galectine-9 by NK-cells and monocytes were significantly reduced.

In the framework of our discussion concerning modern DAA impact on the HCC course and outcome, the results obtained by Lockart., *et al*. (2021) seem to be of interest. The investigators showed that survival of HCV-associated HCC patients improved significantly in the era of DAA (2015-2019) in comparison with period of 2008-2014. At the same time overall survival rate of HBV-associated HCC patients as well as all-cause HCC patients has not changed [13]. No improvement in the survival of all-cause HCC patients observed so far is an indirect evidence of the fact that the effects reported were not due to the overall improvement in the HCC therapy. The authors suggest

that improved HCV-associated HCC survival is connected with slow fibrosis progression and decreased decompensation risk as well as with extra-hepatic causes (i.e. those not due to neoplasms). There exist other large cohort studies demonstrating that HCV eradication improves HCC patients' survival. Unfortunately, those reports did not study DAA impact on the characteristics of the tumor process.

Conclusion

The role of modern antiviral agents in HCC regression has not been elucidated.

To better understand their impact on tumor, voluminous clinical, molecular and genetic investigations on a large scale are needed.

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