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Case report

Hepatocellular carcinoma after direct-acting antivirals: an unresolved problem. Review of five cases

Agnieszka Joanna Bartosiewicz[1], Tomasz Mikuła[2]

[1]Student of the Medical University of Warsaw, Poland
[2]Medical University of Warsaw, Poland

Abstract

Aim of the study: To present the problem of hepatocellular carcinoma (HCC) occurring in patients treated with direct-acting antiviral (DAA) agents and to draw attention to the fact that HCC may develop even after successful therapy and in patients who were not previously diagnosed with it.

Material and methods: The inclusion criterion was confirmation of successful DAA treatment prior to HCC among hepatitis C virus (HCV)-infected patients with liver cirrhosis. The analysed group consisted of 5 patients.

Results: In three patients the emergence of hepatocellular carcinoma was very rapid. They developed sudden decompensation of liver function with its symptoms – ascites, oedema, coagulation dysfunction. Furthermore, they had liver encephalopathy and renal failure. One of the patients had cancer cell thrombosis. Two patients' status was stable, but they were disqualified from liver surgery due to large size of the focal lesions and their plurality.

Conclusions: DAAs, despite their high effectiveness in HCV treatment, still bear the risk of developing HCC. Patients after the therapy should remain under medical control for the early detection and treatment of the presumptive cancer.

Key words: risk factor, hepatocellular carcinoma, direct-acting antiviral.

Address for correspondence

Agnieszka Joanna Bartosiewicz, Medical University of Warsaw, 61 Żwirki i Wigury St., 02-091 Warsaw, Poland, e-mail: a.bartosiewicz@hotmail.com

Introduction

Direct-acting antivirals (DAAs), the new interferon-free therapy, have been revolutionary in the treatment of hepatitis C. Previously, the disease was treated with pegylated interferon (PegIFN) combined with ribavirin. The results were measured by sustained virological response – no hepatitis C virus (HCV) RNA in the patient's blood after 12 weeks of the therapy (SVR12), which was observed in about 50% of patients [1, 2]. The first new substances approved for hepatitis C treatment were: boceprevir and telaprevir (in May 2011) and sofosbuvir in combination with ribavirin (in 2013) [3]. In 2014 the combination of sofosbuvir and ledipasvir was also accepted. Soon the DAA therapy received the Food and Drug Administration's (FDA) Breakthrough Therapy Designation [4] as it had over a 90% sustained virological response rate [3].

Direct-acting antivirals comprise four groups of medical substances which are mixed together (also with ribavirin) depending on the genotype of the hepatitis C virus and accompanying liver cirrhosis or other diseases. The groups are:

1. NS3/4A protease inhibitors – glecaprevir, paritaprevir, voxilaprevir, grazoprevir,
2. Nucleoside and nucleotide NS5B polymerase inhibitors – sofosbuvir,
3. NS5A inhibitors – ombitasvir, pibrentasvir, daclatasvir, elbasvir, ledipasvir, velpatasvir,
4. Non-nucleoside NS5B polymerase inhibitors – dasabuvir.

As the new HCV treatment was spreading around the world, people from different countries began to notice the occurrence and recurrence of hepatocellular carcinoma (HCC) among patients who underwent the therapy. Several studies from different countries were made to announce that DAAs do not reduce and may

even increase the risk of HCC both in patients with a history of HCC and those who were not diagnosed with it before the treatment [5-10]. That led to more complex cohort research [11-13] which revealed that the risk of HCC is not increased, although it remains high in patients with a sustained virological response despite the eradication of the virus, which is the oncogenic factor. The patients who were most subject to the development of HCC were those with established liver cirrhosis before the direct-acting antiviral treatment [11]. The research is still being conducted to investigate how to predict and prevent the occurrence and recurrence of hepatocellular carcinoma [14].

Material and methods

Patients

A group of five patients was analysed, all of them with liver cirrhosis and chronic HCV infection in the past. None of these patients was previously diagnosed with hepatocellular carcinoma. They all underwent direct-acting antiviral therapy, which was successful (Table 1).

Assessments

The blood parameters were defined by standard laboratory techniques. The HCV RNA was measured by PCR methods. The cirrhosis was diagnosed by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), liver biopsy or FibroScan. The hepatocellular carcinoma was diagnosed by ultrasonography, CT, MRI and post-mortem examination in one case.

Results

Baseline characteristics

In the group of five patients with HCV infection there were genotypes 1b and 3. Among them two were treated with sofosbuvir, ledipasvir and ribavirin, one with sofosbuvir and ribavirin, one with sofosbuvir and ledipasvir, and one with sofosbuvir, ribavirin and interferon. All patients had liver cirrhosis before the beginning of the therapy. None of them was diagnosed with hepatocellular carcinoma before the direct-acting antiviral treatment. Two patients had an alpha-fetoprotein (AFP) level within the normal limits and one patient had an AFP level above the normal limits (23.3-25.1 IU/ml), which increased to 66.9 IU/ml one year before the DAA therapy (during this year ultrasonography was performed twice and showed no focal lesions). Three patients had no focal lesions in USG, one patient had minor hyperechogenic changes (stable for 2 years) and one patient had hyperechogenic focal lesions slowly progressing throughout 3 years before the treatment with 27 mm maximum diameter. On the Child-Turcotte-Pugh (CTP) scale three patients had class A (one with 5, two with 6 points) and two patients had class B (7 and 8 points). One patient had a history of alcohol, benzodiazepine and narcotic abuse.

Treatment response of direct-acting antiviral therapy

Four patients who finished the direct-acting antiviral therapy reached a sustained virological response after 12 weeks of the treatment. The viraemia was undetectable until the day of admittance to the hospital. One patient who was undergoing the therapy had his viraemia tested during the therapy and it was also undetectable.

Monitoring

All five patients were undergoing ultrasonography regularly every 1 to 2 years beginning from 3 to 10 years before the therapy. Three patients also had the AFP level checked every 1 to 2 years.

Three patients had no focal lesions in every ultrasonography examination after the DAA treatment. One patient had stable minor hyperechogenic changes for the last 2 years before the HCC diagnosis. One patient had hyperechogenic focal lesions slowly progressing throughout three years with 27 mm maximum diameter in the last examination before HCC diagnosis.

Two patients had AFP levels within the normal limits and one patient's AFP level increased to 66.9 IU/ml one year before the DAA therapy and was stable until sudden liver function decompensation. In this patient ultrasonography examination was performed twice after the AFP level increase and revealed no focal lesions.

Table 1. Basic characteristics of the patients

Characteristic	Patients
Number of patients	5
Patients' age [years]	56-66
Gender	all male
Finishing of DAA therapy	4 patients: 6 months – 2 years before HCC diagnosis 1 patient: during the therapy
HCV viraemia	undetectable in all patients
CTP scale	3 patients: class A (one 5, two 6 points) 2 patients: class B (7 and 8 points)

The reason for admittance to the hospital

One patient was admitted to the hospital due to liver function decompensation. The complaints were sudden ascites, icterus and lower legs' oedema with liver encephalopathy and succeeding renal failure. Three patients were admitted owing to the newly detected focal lesions in the liver with no symptoms of liver function decompensation. The changes varied from 27 to 133 mm in diameter and were not present in the previous ultrasonography examinations. One patient was admitted to the hospital for the diagnostic process of portal venous thrombosis, with increasing ascites, icterus, liver encephalopathy and renal failure. In four patients the new focal lesions or symptoms succeeded suddenly after 6 months to 2 years from finishing the therapy. One patient was undergoing the therapy when the symptoms of liver function decompensation appeared. All the previous AFP and ultrasonography examinations were either correct or stable.

Diagnosing

In the diagnostic process of hepatocellular carcinoma three patients' AFP levels were increased (89.9; 188 and > 10000 IU/ml). In two of these patients the marker Ca 19.9 was also above the normal limits – 828 and 135.4 U/ml.

All patients had ultrasonography examination which revealed the area of blurred lesions sized from 42 to 133 mm in three patients and plural hypo- and hyperechogenic changes from 12 to 40 mm in diameter. All lesions were newly detected and were also confirmed in MRI or CT. Three patients were classified as BCLC (Barcelona Clinic Liver Cancer) B and two as BCLC C.

Progression

Three patients developed succeeding liver encephalopathy and renal failure. Three patients had blood coagulation dysfunction, and one of them also experienced severe bleeding from a ruptured anal varicose vein. One patient had progressive portal venous thrombosis (38 × 16 mm). Three patients have died due to advanced liver failure and its complications. Two patients' status was stable; however, they were disqualified from liver surgery owing to the large size of the lesions and their plurality. One patient's hepatocellular carcinoma was diagnosed only in post-mortem examination which revealed portal venous thrombosis caused by cancer cells.

Discussion

Hepatocellular carcinoma is a frequently occurring tumour, especially in developing countries [15]. The most frequent cause of this cancer (44%) is liver cirrhosis caused by chronic hepatitis C infection. Direct-acting antivirals are definitely a disruptive achievement in medicine. They changed the sustained virological response (SVR) from about 50% (when using PegIFN combined with ribavirin) [1, 2] to over 90% [3]. These statistics should lead to reducing the incidence of hepatocellular carcinoma, but it is still controversial whether it is true or not.

In the group of five analysed patients who developed HCC during or shortly after successful DAA therapy the disease spread very quickly, with a tumour growing even 133 mm in one year. They were not diagnosed with hepatocellular carcinoma before the treatment and they were undergoing regular ultrasonography examinations and alpha-fetoprotein blood tests regularly every 1 to 2 years. In three patients the first symptom of the developing disease was sudden decompensation of liver function. These patients died in a few months after the diagnosis. One of these patients developed cancer cell thrombosis. The two remaining patients had no symptoms of HCC development; they were diagnosed owing to the regular ultrasonography examinations.

Literature review

In 2016 Italian studies [5] demonstrated that DAAs do not reduce the risk of emergence of hepatocellular carcinoma. The patients may develop HCC in the short term after the therapy even if it was successful. The cancer was detected in people who were previously diagnosed with HCC as well as patients with no HCC history. Patients who underwent DAA therapy and were previously treated with HCC were most subject to its return.

The studies from Spain [8] showed even an increased rick of hepatocellular carcinoma in patients with previous HCC who received the new therapy. This was a small study with only 58 patients, but it was the beginning of the controversial problem.

The researchers from Austria [6] also noticed the high risk of hepatocellular carcinoma both in patients with previously diagnosed HCC and those with no signs of cancer before. Similar results were obtained by researchers from Portugal [7] who analysed only those patients who were not diagnosed with HCC before the treatment and compared *de novo* HCC among patients after interferon-based and direct-acting antiviral-based therapies. The Italians took into

consideration the benefit of DAA therapy in patients with a history of HCC, since they observed surprisingly high recurrence of cancer among them in their study [10]. Egyptian cohort studies [9] compared two groups of patients with hepatocellular carcinoma history – those who were DAA-exposed and those who were not receiving this treatment. They pointed to the possible role of DAAs in the recurrence of HCC. All these studies drew attention to the possible problem and started a more complex discussion on that topic.

The studies from the USA [11] with over 20 000 analysed patients showed no evidence of increased risk of cancer among those treated with direct-acting antivirals. However, they suggested ongoing HCC surveillance, due to the fact that in patients with a sustained virological response the risk of hepatocellular carcinoma remained high despite the treatment. Similar results were obtained by researchers from France [12] who analysed over 6 000 patients treated with DAAs and also did not observe higher HCC recurrence. The Australians analysed 41 single studies involving almost 14 000 patients trying to compare the risk of HCC in patients treated with interferon-based therapy and direct-acting antiviral therapy and also did not find evidence of higher HCC occurrence or recurrence in patients receiving DAAs [16].

Researchers from Japan tried to discover the mechanism of early emerging HCC after DAAs [17]. They suggested that it is connected to NK cells and that higher pre-treatment NKG2D expression and FIB-4 score are important factors in the development of hepatocellular carcinoma after the treatment. The results were similar to those of other Japanese scientists [18] who claimed that NK cells have an important role in the elimination of hepatitis C virus in both interferon-based therapy and direct-acting antiviral treatment. Thus their exhaustion leads to less effective cytotoxicity and cytokine production, which results in a lower antitumor response. Researchers from Germany [19], apart from NK cells, also pointed to the role of continuous activation and impaired function of virus-specific T cells. Italian studies [20] showed that the occurrence or recurrence of hepatocellular carcinoma is associated with the serum level of inflammatory cytokines before direct-acting antiviral treatment. These pharmaceuticals may modify the cytokines, promoting the development of cancer. Moreover, the sharp decrease of viraemia can dysregulate the antitumor response.

Conclusions

The question whether direct-acting antiviral agents have impact on HCC development has not been answered yet. Researchers are still trying to obtain unambiguous information. However, the studies from many countries show that the risk of hepatocellular carcinoma after DAA therapy remains high. HCC may emerge even after the permanent elimination of the oncogenic factor, which is hepatitis C virus. The disease may be sudden, unexpected and it can have a very rapid course. That means that patients, as well as doctors, should not depart from regular imaging examinations in patients with a sustained virological response. Computed tomography and magnetic resonance imaging are the most valid examinations for cirrhotic patients, since ultrasonography may not always reveal the presence of hepatocellular carcinoma.

Disclosure

Authors report no conflict of interest.

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