

Case report

Hepatitis B virus treatment in hepatocellular carcinoma patients prolongs survival and reduces the risk of cancer recurrence

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Abstract

Chronic hepatitis B virus (HBV) infection and HBV-related liver disease are estimated to affect about 240 million people worldwide. Now that a vaccine is available, the number of new HBV infection cases has plummeted. Yet, there are still regions with very high incidence of HBV. Hepatocellular carcinoma (HCC) is the fourth to six most common malignancy in men and the ninth most common malignancy in women worldwide. 54% of all HCC cases are HBV-associated, making it the most common cause of cancer worldwide. Hepatitis B therapy prevents progression of chronic hepatitis to cirrhosis and HCC development, but even with the best HBV treatment, such patients are still at risk of HCC. Also in patients after transarterial chemoembolization (TACE), liver resection (hepatectomy) or liver transplant, suppression of hepatitis B virus (HBV) improves patient survival. In this paper we present current possibilities of HCC and HBV treatment, which lead to improved survival and quality of life.

Key words: HCC, HBV treatment, HCC treatment.

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Introduction

Chronic hepatitis B virus (HBV) infection is estimated to affect 240 million people worldwide [1, 2]. The natural course of infection leads to elimination of antigen S (HBsAg) in 92-95% of adults and only in 10% of children infected by perinatal transmission. Other patients develop chronic hepatitis and in rare cases extrahepatic manifestation of HBV infection [3, 4]. It is estimated that half of the patients with chronic hepatitis B will eventually develop cirrhosis over a 30-year-period and the annual incidence rate of hepatocellular carcinoma (HCC) in this group is 4%. Unfortunately, HBV-infected patients may develop HCC even without any previously confirmed liver lesions or cirrhosis and with confirmed HBsAg and HBeAg seroconversion [4]. The indications, contraindications

and recommendations on anti-HBV treatment are described in regularly updated guidelines published by the European Association for the Study of the Liver (EASL) [5], the American Association for the Study of Liver Diseases (AASLD) and Asian-Pacific guidelines updated for treatment in children [6, 7]. Eventually, though, it is the payer (commissioner) that sets the rules. The treatment should be prioritised in patients with known inflammatory/fibrotic lesions in the liver (confirmed by biopsy or elastography), extrahepatic manifestation of HBV infection, elevated alanine aminotransferase (ALT) and viral load above 2000 IU/ml. However, even with low ALT and HBV RNA, patients with cirrhosis or primary HCC make good candidates for antiviral treatment, which – in these circumstances – should be continued until the end of their lives. The primary goal of treatment is to achieve an unde-

tectable viral load, which in most patients improves their clinical presentation and histological liver status, thus decreasing the risk of cancer especially in individuals with cirrhosis. The optimum moment for treatment commencement in patients with chronic HBV infection, without liver damage and with a positive family history of HCC is a problem yet to be solved.

The treatment of hepatitis B includes a one-year regimen of pegylated interferon alpha (Peg-IFN α), and nucleoside/nucleotide analogues, such as entecavir, tenofovir, and older medications such as lamivudine are not recommended as first line chronic hepatitis B therapy due to the low barrier to resistance. Additionally, telbivudine and clevudine, unavailable in Poland, have been approved for use in hepatitis B treatment in some Asian countries.

Hepatocellular carcinoma epidemiology

In 2013, 559,000 new cases of HCC were diagnosed in men and 233,000 in women. The same year, 564,000 men and 254,000 women died due to HCC [1, 8].

The increasing HCC incidence worldwide is potentially associated with population ageing and increased exposure to carcinogenic factors. Geographically, increased HCC incidence has been reported in Central Europe, North America and the United Kingdom (especially in Chinese-speaking populations). At the same time, in Southern Europe, Japan and Hong Kong, the HCC incidence has declined, probably due to widespread hepatitis B vaccination programmes [2].

The well-established risk factors of HCC include cirrhosis (regardless of its aetiology), chronic HBV and/or hepatitis C virus (HCV) infection, schistosomiasis, NASH and metabolic liver disease. The risk increases with the presence of several risk factors and co-factors, e.g. cirrhosis, chronic HBV infection, alcohol abuse, and diabetes. At the same time, HCC is increasingly often diagnosed at early stages due to widespread screening, especially ultrasound-based screening in patients with liver disease [9].

Hepatocellular carcinoma development in patients with chronic hepatitis B

Chronic inflammation and necrosis is the key factor predisposing patients to develop HCC. In HBV-infected individuals it is viral load which determines the severity of inflammation, fibrosis, cirrhosis and eventually HCC development [4, 10, 11]. High viral load, cirrhosis, detected HBeAg, genotype "C" HBV, and elevated serum HBsAg levels were found to correlate with HCC development. The common character-

istics of all HBV-infected patients with HCC included: detection of HBV DNA in tumour cells; cellular oncogene activation due to HBV DNA integration to host genome; some degree of genetic instability induced by HBV DNA integration and/or regulatory effect of HBx protein and the associated long non-coding RNA (lncRNA); as well as HBV protein-induced chronic immune response [4].

Role of hepatitis B virus infection in hepatocellular carcinoma prevention

The only potentially curative treatments in HCC involve either resection of hepatic tissue with the tumour (subtotal hepatectomy, lobectomy, ablation) or liver transplant. However, as HCC is usually diagnosed at advanced stages only < 20-30% of patients (only 10% in Poland) are eligible for surgery, which can be performed in very early (< 2 cm) or early HCC according to Barcelona Clinic Liver Cancer (BCLC). If only one lobe is affected, with normal liver function and absence of portal hypertension, it should be resected with a 1 cm surgical margin. In more advanced cases (1 tumour less than 5 cm or 3 less than 3 cm) without large vessel involvement, liver transplant should be performed, which gives > 75% chance of 5-year survival according to the Milan criteria [2]. For other patients, palliative surgery may be an available option HCC prevention should definitely start with causal treatment of HBV-infected patients, that is, inhibition of carcinogenesis by suppressing HBV replication to the lowest possible, optimally undetectable, level. Such management may reverse inflammation and fibrosis, thus preventing complications of cirrhosis. The published data, along with our experience, confirm that the optimum moment for treatment commencement is as soon as chronic hepatitis has been confirmed. However, even patients with cirrhosis (including decompensated cirrhosis) may benefit from antiviral treatment [12].

Patients with chronic hepatitis B should be initially treated with Peg-IFN α , due to its immunomodulatory, anti-oncogenic, and antifibrotic effects, exerted regardless of its antiviral effect [13]. Nevertheless, many patients after effective treatment with Peg-IFN α (approx. 30%) still have detectable serum levels of HBsAg, despite undetected HBV RNA, so there still remains some risk of progression to cirrhosis and subsequent HCC development. Due to numerous adverse effects, peginterferon is not recommended in treatment of patients with cirrhosis.

In cases where interferon is ineffective or contraindicated, nucleos(t)ide analogues should be used, with the most effective being highly potent nucleoside

Table 1. Indications for antiviral treatment following cancer treatment in patients with hepatocellular carcinoma

Marker/tissue type	Effect on survival	Risk of HCC recurrence
HBeAg/serum	Worsens	Early
HBcrAg/serum		Independent marker of recurrence
High HBV RNA/tumour tissue	Worsens	High
Viral load below < 10 ⁴ IU/ml/serum	Improves	Lower

HCC – hepatocellular carcinoma, HBeAg – hepatitis B e antigen, HBcrAg – hepatitis B cr antigen, HBV – hepatitis B virus

analogues with a high genetic barrier, such as entecavir (ETV), tenofovir (TDF) and the newest, tenofovir alafenamide (TAF). Nucleoside analogue treatment inhibits progression of liver disease to cirrhosis, which increases the patient's chance for effective treatment (due to better liver function) should they develop HCC. However, once HCC is diagnosed, the treatment should be continued until the end of the patient's life. Six-year tenofovir treatment was demonstrated to permanently suppress the virus, significantly reducing fibrosis and cirrhosis in 96% of patients. 74% of patients with significant fibrosis at baseline were free of cirrhosis at 5 years. Incidence of HCC in patients treated with tenofovir in studies 102/103 was lower than predicted using the REACH-B risk estimation model, both in patients with and without cirrhosis [14, 15].

Entecavir was equally effective in this regard in patients with chronic hepatitis B. In the Virgil study with over 3-year follow-up, sustained virological response (SVR) to entecavir was associated with risk of decompensation, HCC or death reduced by 71% as compared to patients in whom SVR was not achieved.

Lamivudine is the least effective, although it is the most popular due to its affordable price. Unfortunately, with lamivudine treatment and to a lesser extent also with entecavir treatment, the odds of YMDD mutations in hepatitis B virus polymerase gene increases with therapy duration, which in turns elevates the risk of HCC [16].

Regardless of anti-HBV treatment used, it should be noted that effective antiviral treatment only decreases the risk of cancer in individuals with end-stage cirrhosis [17].

Effect of anti-hepatitis B virus treatment after hepatocellular carcinoma resection on cancer recurrence and patient survival

Treatment of HBV infection in patients after radical HCC treatment poses a challenge. It is thought

that the risk of HCC recurrence is linked to high HBV RNA at baseline and an active inflammatory process. Nucleoside analogues are recommended as well tolerated and safe, since treatment with interferon alfa poses a risk, potentially leading to decompensation, which significantly shortens patient survival [18, 19].

The Asian Pacific Association for the Study of the Liver (APASL) recommends NA-based antiviral treatment in all patients with HCC and HBV RNA > 2000 IU/ml, both pre- and postoperatively [6].

A clinical control study showed that postoperative use of lamivudine in patients with chronic HBV infection decreased the risk of HCC recurrence to 40.6% vs. 49.7% in an untreated population, and decreased the HCC-associated mortality to 24.6% vs. 36.4%, respectively in a 5-year follow-up (Table 1).

Pre-transplant and post-transplant management

Clinical research shows that effective anti-HBV treatment reducing viral load to undetectable levels at least 3 months before liver transplant prevents HBV reactivation following the procedure. Standard treatment in such cases involves using anti-HBs immunoglobulin combined with entecavir or tenofovir, which prevents recurrence in 98%. No clear guidelines have been developed regarding the immunoglobulin dosage scheme. However, serum HBsAb level should be kept at the level of 100 IU/ml or more [20, 21].

However, due to the high cost of immunoglobulin and its relative unavailability, attempts are being made to either shorten immunoglobulin treatment duration or reduce its dose, or even use one or two nucleoside analogues without immunoglobulin. The key issues for HCC recurrence prevention appear to be the suppression of hepatitis B core-related antigen (HBcrAg), which combines the antigenic reactivity resulting from denatured precore protein (HBeAg), nucleocapsid or hepatitis B core antigen (HBcAg) and an artificial 22-kDa core-related protein (p22cr), as well as inhibition of covalently closed circular DNA (cccDNA). In order to prevent HCC recurrence, highly potent nucleoside analogues with a high genetic barrier should be used, such as entecavir and tenofovir. Their use improves liver condition and overall patient survival [22, 23].

Within the last 10 years, a number of reports have been published assessing different strategies of preventing recurrent HBV infection. All of them have been very effective, with the reported HBsAg recurrence rate below 3%. The most effective treatment modalities feasible in Poland include immunoglobulin and ETV administered before liver transplantation [24]

and ETV in monotherapy administered postoperatively, as reported by You *et al.* in 2013, or tenofovir, emtricitabine and immunoglobulin administered preoperatively, and nucleoside analogues administered postoperatively. Zimmerman *et al.* [23] analysed 101 patients with HCC/HBV after orthotopic liver transplantation, who received antiviral prophylaxis with lamivudine (150 mg/day) and anti-HBV immunoglobulin (pre-1998 cohort: 10,000 U IV in a single dose during the anhepatic phase, followed by 10,000 U each day for 7 days, and 10,000 U each month; post-1998 cohort: 10,000 U IV in a single dose during the anhepatic phase, followed by 2,000 U each day for 6 days, and 1560 U IM each month). Highly elevated (> 500 ng/ml) AFP levels at baseline, presence of vascular invasion by explant and HBV recurrence were independent predictors of HCC recurrence-free survival. The risk of death was lower in patients receiving this treatment.

Post-resection management

Patients with cirrhosis should be treated before tumour resection [24]. Patients with chronic liver disease without previous treatment indications should be started on anti-HBV treatment as soon as possible after HCC diagnosis and should continue this treatment after surgery. In treated patients with chronic hepatitis B, lower rates of HCC recurrence were demonstrated at 1 year and 3 years, as compared to untreated ones. Anti-HBV treatment decreases the risk of HCC recurrence by approximately 30% [25].

Hepatitis B management after transarterial chemoembolization in patients with inoperable hepatocellular carcinoma

Transarterial chemoembolization (TACE) promotes reactivation of hepatitis B in patients with detectable anti-HBc antibodies and undetectable HBsAg, so they need antiviral treatment, regardless of treatment received for cirrhosis, even if HBV RNA was no longer detectable preoperatively [26].

Xu *et al.* demonstrated increased duration to HCC progression in patients treated with lamivudine after HCC surgery, as compared to subjects not receiving nucleoside analogues after cancer treatment (8.2 vs. 4.3 months, respectively; $p = 0.005$), as well as better 1-year (83% vs. 60%, respectively), 2-year (69% vs. 48%, respectively) and 5-year survival (58% vs. 48%, respectively). Lamivudine treatment and low AFP levels were found to significantly affect patient survival [27].

Hepatitis B management in hepatocellular carcinoma patients after tumour resection or radiofrequency ablation

Kubo *et al.* demonstrated longer survival of HBV-infected patients after HCC resection or radiofrequency ablation (RFA) with LAM as compared to untreated ones [28]. Li *et al.* had similar findings, yet nucleoside analogue therapy did not affect the risk of HCC recurrence in the discussed studies [29] (Table 2).

Three cases from our practice collectively summarised in Table 3 exemplify effective anti-HBV treatment.

Patient 1

A 56-year-old man, white-collar worker, after liver transplant received in 2004 due to HBV-associated cirrhosis and HCC diagnosed only after liver explantation (tumour less than 3 cm – met Milan criteria) has remained under the care of the Liver Transplant Clinic in Wrocław. The patient was diagnosed with cirrhosis in June 2003. As soon as HBV infection was confirmed (detected HBsAg, detected HBeAg, detected HBV RNA, AFP 6 mg/ml), treatment with lamivudine 100 mg once daily was started. Six months later, HBV RNA in serum was not detected. In March 2004, the patient received a liver transplant. In the perioperative period as well as after the transplant, the patient was not administered anti-HBs immunoglobulin. However, treatment with lamivudine was continued (after transplant, the anti-HBc total was detected, while HBsAg and HBV RNA were not detected). Unfortunately, the same patient was diagnosed with HCV (genotype 1b) in 2010. Liver biopsy was performed in 2012, which demonstrated G2, S1, Ishak 1, BANFF G0, RAI 1/9. Due to active HCV replication (regardless of lamivudine treatment), he was started on 6-month anti-HCV treatment with sofosbuvir, ledipasvir and ribavirin in June 2015 and a sustained virological response at 24 weeks (SVR24) was achieved. Currently, 12 years following the liver transplant, the liver is still in good condition, and lamivudine treatment has been continued until now.

Table 2. Hepatitis B virus-related parameters affecting risk of hepatocellular carcinoma recurrence and patient survival

HBV RNA > 10 ⁻⁴ IU/ml at time of surgery
HBeAg and/or anti-HBcAg detected in tumour tissue
High ALT or Ishak fibrosis score > 6
High inflammatory marker expression in peritumour tissues.

HBV – hepatitis B virus, HBeAg – hepatitis B e antigen, HBcAg – hepatitis B c antigen, ALT – alanine aminotransferase

Table 3. Patient characteristics

Factor	Patient 1	Patient 2	Patient 3
Age	56	63	72
Sex	Male	Male	Male
Age at hepatitis B diagnosis	40	35	60
Liver disease staging	Child-Pugh A	Child-Pugh A	Child-Pugh A
HBV RNA at baseline	Detected	3.5 x 10 ⁷ IU/ml	5.1 x 10 ⁸ IU/ml (09.2012)
ALT at baseline	46 IU/l	100 IU/l	121 IU/l
HBsAg	Detected	Detected	Detected
HBeAg	Not detected	Not detected	Not detected
HBV treatment	Zeffix 100 mg	Baraclude 0.5	Zeffix 100 mg
HBV treatment commencement date	2003	2014	2005-2008; 2012-2014
HBV treatment efficacy	HBV RNA not detected	HBV RNA not detected	HBV RNA not detected after 1 year on the second HBV treatment
HCC diagnosis	10.2003	07.2015	8.2012
AFP	-	52.26	14.4
HCC grading (BCLC)	A	B	B
HCC treatment	Transplant	TACE	no
Survival after HCC diagnosis	The patient is still alive (12 years)	9 months	26 months

HBV – hepatitis B virus, ALT – alanine aminotransferase, HBsAg – hepatitis B s antigen, HBeAg – hepatitis B e antigen, AFP – α -fetoprotein, HCC – hepatocellular carcinoma

Patient 2

A 66-year-old man, blue-collar worker, reported HBV infection 28 years earlier (detected while in compulsory military service). He disregarded the problem so he had neither been treated nor monitored until July 2014, when due to unspecific dyspeptic symptoms abdominal ultrasound was performed, which indicated cirrhosis. At the same time, numerous undetermined focal lesions were detected in the liver, which were later characterised in 4-phase CT scan as “most likely being regenerative nodules”. Targeted liver biopsy demonstrated chronic hepatitis (G2, S3), no sign of malignancy, with AFP of 15 ng/ml and HBV RNA of 3.5 x 10⁷ IU/ml. The patient was put on the priority waiting list for HBV treatment. Over that period, in a general good condition, he remained under the care of the local liver clinic. The antiviral treatment was only started in July 2015, due to commissioning issues and lack of sufficient financing, and the patient received entecavir 0.5 mg PO. This led to a viral load decrease to only 149 IU/ml at 12 weeks. At the same time, the contrast-enhanced 4-phase CT scan revealed that the lesions previously thought to be regenerative nodules were actually malignant, verified in the biopsy as HCC. Transarterial chemoembolization of the biggest lesion was performed with doxorubicin-eluting microspheres (DEB-TACE), which was unevent-

ful. In December 2015, the follow-up laboratory test showed a serum AFP level increase to 200 ng, and the follow-up CT scan confirmed HCC progression. In March 2016, the patient was hospitalised in our department with liver decompensation (Child-Pugh C). During the same hospitalisation, severe thrombosis of the portal vein and inferior vena cava as macrovascular invasion of HCC was diagnosed. Entecavir treatment was continued. The patient was disqualified from sorafenib therapy because of the low platelet count. His total survival since the diagnosis of inoperable HCC is 12 months.

Patient 3

A 72-year-old ex-sailor with HBV-associated cirrhosis diagnosed in the mid-1990s (Child-Pugh A) (detected HBsAg, not detected HBeAg, detected HBV RNA) was treated with lamivudine 100 mg/day between December 2005 and August 2008, according to NHF (National Health Fund) guidelines at that time. Afterwards, the patient was monitored on a regular basis with abdominal ultrasound performed every 12 months. Due to portal hypertension secondary to end-stage cirrhosis, and severe oesophageal varices, the patient was treated as an inpatient a number of times at our department, undergoing oesophageal varices ligation with endomino loops (3-8 loops per procedure).

In September 2012, due to active HBV replication (5.1×10^8 IU/ml), having found no DNA polymerase gene mutation in the patient, he was re-started on lamivudine 100 mg/ day. The next ultrasound scan revealed 2 focal lesions in segments 4 and 6, sized 2-3 cm each, typical of HCC. The diagnosis was confirmed with 4-phase contrast-enhanced CT (as per EORTC guidelines) and histology assessment (targeted core needle biopsy). At the time of HCC diagnosis, the patient had Child-Pugh grade B liver disease and BCLC grade C HCC. He was ineligible for surgery or sorafenib treatment, due to severe thrombocytopenia below 30×10^6 /ml, so treatment with lamivudine was immediately re-started. One year later, HBV RNA was not detected and it remained so until the patient's death in October 2014, 26 months after the diagnosis of primary hepatocellular carcinoma.

Conclusions

Historically (before the availability of nucleoside analogues and effective, radical anti-HCC treatments), the mean survival of such patients from diagnosis did not exceed 6 months. The presented literature data and case reports demonstrate the beneficial effect of antiviral treatment with nucleoside analogues of intermediate potency, such as lamivudine that was used historically, while currently highly potent ANs are the first choice, used in combination with (or without) surgery (liver transplant, resection, embolisation, thermal ablation), for delaying HCC progression in HBV-positive patients, improving the condition of liver parenchyma and delaying the time until decompensated cirrhosis, which improves patient survival. Analogues in patients with cirrhosis and or suspicion of HCC should be introduced as soon as possible. Regular screening with ultrasound performed by an experienced radiologist every 6 months, and confirmation with contrast CT of any suspicion is needed for early detection and is crucial for curative therapy (which was not the case in the presented cases).

Disclosure

The authors report no conflict of interest.

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