Case report

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

Monika Pazgan-Simon¹, Krzysztof A. Simon², Ewa Jarowicz³, Katarzyna Rotter¹, Anna Szmynek-Pasternak², Jolanta Zuwała-Jagiełło⁴

¹Department of Infectious Disease 1, Regional Specialistic Hospital, Wroclaw, Poland
²Department of Infectious Disease and Hepatology, Wroclaw Medical University, Wroclaw, Poland
³Department of Infectious Disease 2, Regional Specialistic Hospital, Wroclaw, Poland
⁴Department of Pharmaceutical Biochemistry, Wroclaw Medical University, Wroclaw, Poland

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.

Address for correspondence

Monika Pazgan-Simon, Department of Infectious Disease 1, Regional Specialistic Hospital, 5 Koszarowa St., 51-149 Wroclaw, Poland, e-mail: monika.pazgan.simon@gmail.com

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-
HBV treatment prolongs patients life

HBV treatment prolongs patients life...
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                  |
| HBcAg/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, HBcAg – hepatitis B core antigen, HBV – hepatitis B virus

analogs 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].
HBV treatment prolongs patients life

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 explanation (tumour less than 3 cm – met Milan criteria) has remained under the care of the Liver Transplant Clinic in Wroclaw. 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

| Parameter                                      | Value       |
|------------------------------------------------|-------------|
| 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
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 $3.5 \times 10^{-7}$ IU/ml. The patient was put on the priority waiting list for HBV treatment. Over that period, in a good general 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 uneventful. 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 decomposition (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 endominiloops (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 × 10^9/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.

References

1. Sangiovanni A, Colombo M. EASL Postgraduate course. Hepatocellular carcinoma – epidemiology. 2016
2. Balogh J, Victor D, Asham EH, et al. Hepatocellular carcinoma: a review. J Hepatocell Carcinoma 2016; 3: 341-353.
3. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012; 30: 2212-2219.
4. Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis 2003; 23: 47-58.
5. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012; 57: 167-185.
6. Clemente MG, Vairo P. An update on the strategies used for treatment of chronic hepatitis B in children. Exp Rev Gastroenterol Hepatol 2016; 10: 649-658.
7. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on management of hepatitis B: a 2015 update. Hepatol Int 2016; 10: 1-98.
8. Buendia MA, Neveuvt C. Hepatocellular Carcinoma. Cold Spring Harb Perspect Med 2015; 5: a021444.
9. Aubé C, Oberti F, Lonjon J, et al.; CHIC Group. EASL and AASLD recommendations for diagnosis of HCC to the test of daily practice. Liver Int 2017; 37: 1515-1525.
10. Siddique O, Yoo ER, Perumpali RB, et al. The importance of a multidisciplinary approach to hepatocellular carcinoma. J Multidiscip Healthc 2017; 10: 95-100.
11. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol 2008; 48 Suppl 1: S20-37.
12. Ridrujeo E. Does hepatitis B virus therapy reduce the risk of hepatocellular carcinoma? Expert Opin Drug Saf 2015; 14: 439-451.
13. Lampertico P, Vigano M, Di Constanzo GG, et al. Randomised study comparing 48 and 96 weeks peginterferon alfa 2a therapy in genotype D HBeAg negative chronic hepatitis B. Gut 2013; 62: 290-298.
14. Pol S, Lambertico P. First-line treatment of chronic hepatitis B with entecavir or tenofovir in real-life settings: from clinical trials to clinical practice. J Viral Hepat 2012; 19: 377-386.
15. Ke W, Liu L, Zhang Ch, et al. Comparison of efficacy and safety of tenofovir and entacavir in chronic hepatitis B virus infection: a systematic review and meta-analysis. PLoS One 2014; 9: e98865.
16. Aghdashi A, Ayres A, Yuen L, et al. Lamivudine resistance in patients with chronic hepatitis B: role of clinical and virological factors. J Gastroenterol Hepatol 2007; 22: 1078-1085.
17. Su TH, Tseng TC, Kao JK. HCC risk in patients with HBV-related cirrhosis receiving NA therapy: is HCC prevented or delayed? Hepatology 2017; doi10.1002/hep.29740
18. Zhonghu L, Zhao X, Jiang P, et al. HBV is a risk factor for poor patient prognosis after curative resection of hepatocellular carcinoma. Medicine 2016; 95: e4224.
19. Sakamoto K, Beppu T, Hayashi H, et al. Antiviral Therapy and Long-term Outcome for Hepatitis B Virus-related Hepatocellular Carcinoma after Curative Liver Resection in a Japanese Cohort. Anticancer Res 2015; 35: 1647-1655.
20. Bihl F, Russmann S, Gurtner V, et al. Hyperimmune anti-HBs plasma as alternative to commercial immunoglobulins for prevention of HBV recurrence after liver transplantation. BMC Gastroenterol 2010; 10: 71.
21. Ahn J, Cohen SM. Prevention of Hepatitis B recurrence in Liver Transplant Patients Using Oral Antiviral therapy without Long-Term Hepatitis B Immunoglobulin. Hepat Mon 2011; 11: 638-645.
22. Tanaka T, Renner EL, Selzner, et al. One year of hepatitis B immunoglobulin plus tenofovir therapy is safe and effective in preventing recurrent hepatitis B infection post liver transplantation. Can J Gastroenterol Hepatol 2014; 1: 41-44.
23. Zimmerman MA, Ghobrial RM, Tong MJ, et al. Antiviral prophylaxis and recurrence of hepatocellular carcinoma following liver transplantation in patients with hepatitis B. Transplant Proc 2007; 39: 3276-3280.
24. Hosaka T, Suzuki F, Kobayashi M, et al. HBcrAg is a predictor of post-treatment recurrence of hepatocellular carcinoma during antiviral therapy. Liver Int 2010; 30: 1461-1470.

25. Du Y, Su T, Ding Y, Cao G. Effects of Antiviral Therapy on the Recurrence of Hepatocellular Carcinoma After Curative Resection or Liver Transplantation. Hepat Mon 2012; 12 (10 HCC): e6031.

26. Peng JW, Lin GN, Xiao JJ, Jiang XM. Hepatitis B virus reactivation in hepatocellular carcinoma patients undergoing transcatheter arterial chemoembolization therapy. Asia Pac J Clin Oncol 2012; 8: 356-361.

27. Xu X, Huang P, Tian H, et al. Role of lamivudine with transarterial chemoembolization in the survival of patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2014; 29: 1273-1278.

28. Kubo S, Tanaka H, Takemura S, et al. Effects of lamivudine on outcome after liver resection for hepatocellular carcinoma in patients with active replication of hepatitis B virus. Hepatol Res 2007; 37: 94-100.

29. Li N, Lai EC, Shi J, et al. A comparative study of antiviral therapy after resection of hepatocellular carcinoma in the immune active phase of hepatitis B virus infection. Ann Surg Oncol 2010; 17: 179-185.