Treatment of portal hypertension in patients with HCC at the era of Baveno VII

Dominique Thabut, Masatoshi Kudo

PII: S0168-8278(22)03313-X
DOI: https://doi.org/10.1016/j.jhep.2022.11.019
Reference: JHEPAT 8960

To appear in: Journal of Hepatology

Received Date: 29 September 2021
Revised Date: 10 November 2022
Accepted Date: 15 November 2022

Please cite this article as: Thabut D, Kudo M, Treatment of portal hypertension in patients with HCC at the era of Baveno VII, Journal of Hepatology (2022), doi: https://doi.org/10.1016/j.jhep.2022.11.019.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier B.V. on behalf of European Association for the Study of the Liver.
Treatment of portal hypertension in patients with HCC at the era of Baveno VII

Dominique Thabut* and Masatoshi Kudo**

*all the authors share the first authorship

Affiliations:
1 Sorbonne Université, AP-HP, Sorbonne Université, Hôpital de la Pitié-Salpêtrière, service d’hépato-gastroentérologie, unité de soins intensifs d’hépatologie, Paris, France & Brain Liver Pitié-Salpêtrière (BLIPS) Study Group, INSERM UMR_S 938, Centre de recherche Saint-Antoine, Maladies métaboliques, biliaires et fibro-inflammatoire du foie, Institute of Cardiometabolism and Nutrition (ICAN), Paris, France

2 Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka-Sayama Osaka, Japan

Corresponding author:
Pr Dominique THABUT, MD, PhD
AP-HP, Sorbonne Université, Hôpital de la Pitié-Salpêtrière, service d’hépato-gastroentérologie, unité de soins intensifs d’hépatologie, Paris, France & Brain Liver Pitié-Salpêtrière (BLIPS) Study Group, INSERM UMR_S 938, Centre de recherche Saint-Antoine, Maladies métaboliques, biliaires et fibro-inflammatoire du foie, Institute of Cardiometabolism and Nutrition (ICAN), Paris, France

Tel: +33(0)1 42 17 57 55
Fax: +33(0)1 42 16 11 06
Mail: dominique.thabut@aphp.fr

Keywords: hepatocellular carcinoma, portal hypertension, cirrhosis, immunotherapy

Word count: 2498
Pages: 12
Table: 0
Figure: 1
Reference: 25

Disclosures:
Dominique Thabut declares having perceived consultant fees from MedDay Pharmaceuticals, Gore, Alfasigma, Gilead, Abbvie, Bayer.
Masatoshi Kudo declares the following conflicts of interest:
Lecture fee: Eisai Co., Bayer AG, MSD, BMS, EA Pharma, Eli Lilly and Company, Chugai Pharmaceutical
Grants: Eisai Co., Takeda Pharmaceutical Co. LTD, Otsuka, Taiho, EA Pharma, Gilead Sciences, Abbvie, Sumitomo Dainippon Pharma, Chugai, Ono Pharma;
Consulting/Advisory fees: Eisai, Ono, MSD, BMS, Roche, Eli Lilly and Company, Chugai Pharmaceutical Co.

Authors contributions: The two Authors have contributed in the same way to discussing and drafting this paper. The two Authors have shared all its statements.

Financial support: There was no financial support for this paper.
Summary

Portal hypertension (PHT) and hepatocellular carcinoma (HCC) often coexist, and their association impairs the prognosis of patients with cirrhosis. The interplay between those two complications is of major importance to propose adequate therapeutic options to patients with HCC, as well as to prevent and manage complications of portal hypertension. Recommendations on management of PHT have been deeply revised in last Baveno VII conference, redefining screening and extending indications of prophylaxis. PHT can preclude locoregional therapies, and TIPS placement can be discussed in HCC patients. New systemic therapies of HCC can influence the level of PHT and favor bleeding. In all patients, PHT complications should be prevented and treated adequately, especially if they present with advanced HCC. Those specific aspects will be discussed in the present review, taking into account the very recent data in HCC field.
Portal hypertension (PHT) and hepatocellular carcinoma (HCC) are major complications of cirrhosis. The management of patients with PHT has dramatically improved, with a better control of PHT and a significant increase of survival; this is paralleling (and maybe partly explaining, as patient’s life expectancy has increased), an augmentation of the incidence of HCC. Hence, PHT and HCC often cohabit now and must be managed together. During last Baveno VII conference[1], diagnosis and management of PHT was revised in deep, extending indications of non-invasive screening of PHT, and indications of medical therapy. Meanwhile, new systemic therapies of HCC, which can influence PHT, are emerging rapidly, and unraveling the management of HCC. Hence, in this review, we will focus on the clinical management PHT in cirrhotic patients with HCC, at the era of Baveno VII and in the perspective of new systemic therapies.

Clinically significant portal hypertension (CSPH, defined by HVPG>10 mmHg) is predictive of HCC occurrence independently of the severity of the underlying cirrhosis[2]. The prevalence of PHT in patients with HCC depends on the severity of cirrhosis, and probably the stage of HCC. In patients with early-HCC, PHT ranged from 35% to 52%. In patients with advanced HCC, the presence of PHT is almost never stated in clinical trials[3]. However, its prevalence is probably higher than in resectable HCC, because of a more severe liver disease, and a potential portal invasion. Of concern, the presence of HCC is independently associated with mortality in case of PHT-related bleeding[4]. A higher level of PHT could be the culprit there: indeed, HCC increases HVPG through the presence of arteriovenous shunting and modifications of liver architecture; moreover, HCC can be associated with vascular invasion of the portal and/or its branches and contributes to increase PHT. This is why evaluation of PHT is mandatory to indicate an adequate prophylaxis of acute variceal bleeding (AVB).

**Screening, surveillance and prophylaxis of PHT in the era of Baveno VII consensus in patients with HCC (Figure 1).**

Until recently, screening of PHT in cirrhotic patients (without HCC) paralleled with screening of high-risk varices, i.e. medium/large EV[5]. Upper endoscopy was indicated at the diagnosis of cirrhosis in all patients but those with favorable Baveno VI criteria (platelets count>150000/mm3 and LSM<20 kPa). A recent landmark trial showed that treating CSPH by beta-blockers significantly decreased the occurrence of cirrhosis decompensation (mainly ascites)[6]. Thus, Baveno VII consensus introduced the idea of targeting CSPH instead of varices, consequently decreasing dramatically the indications of upper endoscopy, and then start primary prophylaxis by beta-blockers regardless of EV status. HVPG not being performed in routine practice, LSM measurement is now the tool of choice to rule in or rule out CSPH, its value combined sometimes with that of platelets count. Algorithm of screening of CSPH and indications of endoscopy in non-HCC patients are depicted in **Supplementary Figure 1.** Regarding
secondary prophylaxis after AVB, there is now a place of choice for TIPS placement, in its preemptive indication, as soon as possible after AVB (Within 72 hours, the better being within 24 hours), in selected high-risk patients[1]. The question here is whether those new recommendations apply to patients with HCC (Figure 1).

Question 1: can we avoid upper endoscopy in patients with favorable Baveno VI or VII criteria?

The presence of liver tumors may interfere with the elastometry results, with higher values than expected[7]. In that regard, the risk of false negatives when using its index for the detection of high-risk EV is very low. However, platelets level may also be impacted by HCC, in the sense of increasing their absolute number[8], hence decreasing the sensitivity for the detection of high-risk EV. Consequently, waiting for clinical studies, we think that Baveno VI and VII criteria do not seem accurate to rule out high-risk EV, and that screening endoscopy is indicated in patients with HCC, platelets>150000/mm3 and LSM<15/20 kPa.

Question 2: can we avoid upper endoscopy in patients with LSM over 25 kPa?

The first consideration here is that HVPG is probably not a perfect estimate of the degree of PHT in patients with HCC, because vascular invasion also increases PHT[9]. On the other hand, LSM can be increased because of HCC, and the presence of CSPH in patients with LSM>25 kPa overestimated[7]. Despite this, the only risk when considering patients with LSM>25 kPa is that of ruling in CSPH in patients without.

The rationale of treating all patients with CSPH with beta-blockers is to decrease significantly cirrhosis decompensation[6]. Moreover, beta-blocker use has been suggested to be associated with a significantly decreased risk of HCC in patients with cirrhosis [10], and a lower liver cancer mortality rate[11]. Consequently, the risk/benefit of treating the patients with beta-blockers is clearly in favor of treatment.

Banding has never shown its superiority to beta-blockers in primary prophylaxis, and may be risky in HCC patients, because of an increased risk of bleeding in patients with HCC[12], especially in patients under bevacizumab. For all those reasons, we advise to favor beta-blockers vs banding in primary prophylaxis for HCC patients.

Hence, waiting for clinical studies, we think that upper endoscopy can be avoided in HCC patients with LSM over 25 kPa, and that those patients should be treated with beta-blockers, regardless their EV status.

Question 3: How should PHT be monitored in patients with HCC?
Except for patients with LSM > 25 kPa under beta-blockers, regular endoscopies at a rhythm of each 2/3 years[1, 5] are advised. Moreover, PHT can progress faster, because of occurrence of vascular invasion, or worsening of liver disease due to HCC and its therapies[9]. Thus, in our expert opinion, monitoring of PHT should include regular endoscopies in all patients but those with LSM over 25kPa under beta-blockers in primary prevention, within a smaller delay than for patients without HCC (one year seems reasonable).

**Question 4: how should primary prophylaxis of PHT-related decompensation be conducted in patients with HCC?**

Which beta-blocker should be used remains an open question. Many studies were performed with propranolol. However, carvedilol has shown to have a significantly higher effect on PHT decrease, and is now recommended at first choice, except in decompensated cirrhosis[1]. Waiting for clinical studies, we think that carvedilol is the treatment of choice in primary prevention of PHT-related decompensation in patients with HCC.

**Question 5: how should secondary prophylaxis after AVB be conducted in patients with HCC? Is TIPS contra-indicated?**

Secondary prophylaxis includes a combination of beta blockers and banding[1]. Rebleeding prophylaxis improves outcomes in patients with HCC[13]. Hence, even if a fear of post-banding bleeding, combination therapy remains the rule in HCC patients requiring secondary prophylaxis.

The prognosis of AVB in cirrhotic patients has largely improved in the past 10 years, especially because of the widespread of TIPS indications. The presence of HCC may preclude TIPS placement because of the fear of liver failure and HCC spread[14]. We described recently our experience of TIPS placement patients with HCC and AVB: each time TIPS was feasible, outside HCC route. We never observed any HCC spread, nor liver failure[15]. Waiting for more clinical data, we think that TIPS indications should be discussed in patients with HCC, and that HCC is not a contra-indication to TIPS, if feasible technically.

**TIPS in patients with HCC requiring locoregional therapies**

CSPH impacts the choice of HCC treatment. CSPH is a well identified predictive factor for liver decompensation and death after liver resection (LR). Currently, optimal surgical candidacy for resection is based on a multiparametric evaluation including compensated Child-Pugh class A liver function with MELD score < 10, to be matched with grade of PHT, acceptable remaining parenchyma and the possibility of a laparoscopic/minimally invasive approach. CSPH is also associated with decreased overall survival after ablation and transarterial chemoembolization (TACE). Moreover, most
of HCC locoregional treatments are contraindicated in case of refractory ascites or decompensated cirrhosis due to the risk of liver failure. In that case, liver transplantation (LT) remains the only treatment for well selected patients (In Milan criteria worldwide or AFP score <3 in France).

TIPS could allow to access HCC treatments that are discarded because of PHT levels/ascites: pre-operative TIPS before LR, and before ablation in small HCC, especially when a laparoscopic approach is discussed, is an attractive option. Before external radiation therapy, selective internal radiation therapy, or TACE, TIPS can be indicated, mainly in a perspective of downstaging before LT. Here, consequences of TIPS may be different regarding the type of locoregional therapy. There is a concern regarding the potential increased risk of liver failure after TACE, and a decrease in efficacy of HCC treatments[16]. On the opposite, radioembolization appears to be safe after TIPS in a recent series of 39 patients [17], suggesting that tolerance may be better in those patients, and that radioembolization should be preferred to TACE, when possible. In our recent study, TIPS allowed access to curative treatment in all patients, and was not associated with worsening of liver function or tumor spreading[15]. All patients were eventually transplanted for their HCC, and are still alive. Hence, we now consider TIPS in selected patients with CSPH, in order to allow minimally invasive treatments such as ablation or radiotherapy of HCC, either in order to bridge patients to LT, or to allow curative treatment.

Management of PHT in patients with advanced HCC- particular setting of patients under tyrosine kinase inhibitors (TKIs) and atezolizumab-bevacizumab.

**Question 1: how should PHT be screened before systemic therapy in patients with advanced HCC? How should PHT be monitored?**

During the last decades, tyrosine kinase inhibitors (TKIs) were the standard of treatment for advanced HCC. Sorafenib and Lenvatinib were used in first line treatment while regorafenib, ramucirumab and cabozantinib in second line[3, 14]. All of these TKIs target the VEGFR and may impact PHT. However, whereas a higher rate of treatment-emergent ascites with TKIs was observed, no effect on bleeding was noted. The effect of the new combination atezolizumab plus bevacizumab on PHT remains to be studied. Bevacizumab is an antibody directed against VEGF. Atezolizumab is an immune checkpoint inhibitor (ICI-anti-PDL1) aiming to restore anti-tumor immunity. In the IMbrave 150 study, bleeding events were more frequently observed with the combination Bevacizumab/ Atezolizumab than with Sorafenib (25.2% vs 17.3%), including 7% and 4.5% of gastrointestinal bleeding respectively, and 2.4% and 0.6% of PHT-related AVB[18], and this in well selected patients (patients were excluded in case of PHT-related bleeding within 6 months before therapy and benefitted from optimal PHT prophylaxis).
increased bleeding risk under Bevacizumab ranged from 9%[19] to 26%[20] in the two previous phase 2 studies, depending on PHT prophylaxis. In our recent study in a selected population of patients under atezolizumab/bevacizumab, history of AVB was significantly associated with a higher risk of bleeding [21]; this was not confirmed in another series, where anticoagulation was less often prescribed [22]. In HIMALAYA trial, no bleeding event was observed in high dose tremelimumab/durvalumab (STRIDE regimen) arm[23]. No bleeding event is also observed in Nivolumab[24] or Pembrolizumab associated with lenvatinib [25] regimens. These data suggest that ICI monotherapy or ICI combination immunotherapy does not increase bleeding risk; bleeding risk is especially increased in combination immunotherapy containing bevacizumab, suggesting that inhibition of wound healing effect as well as increased PHT induced by bevacizumab led to AVB.

Portal invasion is another issue which could precipitate PHT-related events. Subanalysis of IMbrave 150 study, showed that HCC patients with portal vein invasion showed high ABV events (14%) as compared with 1% in patients without, suggesting that complete obstruction of main portal vein increases pressure in varices. This event occurring often, there is a need for frequent PHT monitoring.

Altogether, we think that a strict work-up of PHT before starting treatment with atezolizumab-bevacizumab in all patients who are not already under primary prophylaxis is mandatory, and beta-blockers started when needed. Surveillance should be performed regularly, probably at a periodicity higher than that recommended in patients without systemic therapy (endoscopies at 6-month intervals could be suggested). Whether those recommendations will be necessary with new immune checkpoints without bevacizumab regimens remains to be determined. In our opinion, in patients with a history of AVB, those new regimes may be favored.

Question 2: How to handle banding in patients under systemic therapies?

Banding is indicated in primary prophylaxis in case of contra-indication/intolerance to beta-blockers, and in secondary prophylaxis. There is no fear of higher bleeding rate under TKIs or ICI therapy without bevacizumab. The question is that of banding in patients under bevacizumab, which could delay post-banding ulcer healing as well as bleeding control. Because of this, a 4- week interval is usually recommended after surgery before starting bevacizumab, which can be reduced to 7 to 14 days for less invasive procedures. Banding sessions are generally performed at 2-week intervals, and usually 3 to 4 sessions are necessary to eradicate varices.

We do not recommend to delay too much systemic therapy after banding, because of the fear of HCC progression, and consider that a delay of 2 weeks after first banding is reasonable to start therapy.

In case of bleeding under atezolizumab/bevacizumab, we advise to stop bevacizumab and keep atezolizumab in monotherapy. However, this assertion should be tempered by 2 points: (1) there might be an indication for TIPS instead of combination therapy in those patients, even outside the criteria of
preemptive TIPS; (2) the forecoming availability of other regimens without bevacizumab will certainly help in that matter.

Question 3: In case of cruric portal thrombosis, should anticoagulation be stopped before Bevacizumab?

Curative anticoagulation is often prescribed because of cruric portal thrombosis, to limit its extension. Portal thrombosis increases portal hypertension, and is by itself favoring AVB[14]. For some physicians curative anticoagulants could be a potential contraindication for atezolizumab/bevacizumab, because patients with curative anticoagulation were excluded from the IMBRAVE 150 trial[18]. On the opposite, we believe that stopping anticoagulation in those patients would probably increase portal pressure. Indeed, except for patients under bevacizumab, there is no evidence that anticoagulation increases bleeding, which is related to PHT and portal thrombosis, and not mucosa injury. In addition, for the particular subgroup of patients under bevacizumab, and in patients with other tumours, anticoagulant therapy, including new oral direct-oral anticoagulants, are not contra-indicated. Hence, we recommend to pursue any kind of anticoagulant. In patients who experienced banding, we would suggest to prefer low-molecular-weight heparin, to facilitate management of bleeding if necessary.

In conclusion, the combination of PHT and HCC is associated with poorer prognosis in patients with cirrhosis. Screening and treatment of PHT is of major importance in patients with HCC, in order to prevent PHT complications. Upper endoscopy remains to be performed except in patients with CSPH treated with beta-blockers. TIPS represents an appealing option in patients with HCC, and should always be discussed when needed. In the treatment of atezolizumab plus bevacizumab as a first line for advanced HCC, regular screening before treatment is mandatory, and primary prophylaxis should be started before systemic therapy, preferring beta-blockers. The risk of bleeding is not increased in patients under ICI alone, and banding must be performed cautiously in those patients.
References


Figure 1: Indications of screening and treatment of PHT in patients with cirrhosis at the era of Baveno VII in HCC patients.

Screening endoscopy is indicated in patients with LSM below 25 kPa. Beta-blockers are to be prescribed to patients with LSM over 25 kPa, in the absence of contra-indication/intolerance, without endoscopy. Endoscopy is indicated in patients with contra-indication/intolerance to beta-blockers and LSM over 25 kPa.

Supplementary Figure 1: Indications of screening and treatment of PHT in patients with cirrhosis at the era of Baveno VII in non-HCC patients.

CSPH can be ruled out in patients with LSM<15 kPa associated with platelets count>150000/mm3 ("Favorable Baveno VII criteria"). Patients with favorable Baveno VI/VII criteria should be monitored by regular LSM and platelets assessment. Patients with LSM>25 kPa are at high probability to display CSPH (alcohol, metabolic except obese pts, HBV and HCV patients): they should be treated by beta-blockers (carvedilol preferently), EV banding indications now being restricted to patients with intolerance/contra-indications to beta-blockers. Screening endoscopy is indicated in patients within the grey zone of LSM between 20-25 kPa, and below 20 kPa if platelets count is below 150000/mm3.

Platelets: plt; liver elastography: LSM; clinically significant portal hypertension: CSPH, esophageal varices: EV.
Figure 1: patients with HCC

- **5 kPa**: No PHT
- **10 kPa**: No ACLD
- **15 kPa**: 
  - + plt>150000, risk of false negative of CSPH
  - + plt>150000, risk of false negative of high-risk EV
- **20 kPa**: Assume CSPH (viral metabolic except obese, alcohol-related cirrhosis)
- **25 kPa**: 
  - Screening endoscopy
  - No Endoscopy, carvedilol*

*if contra-indication/intolerance, endoscopy & banding if needed
Supplementary Figure 1: patients without HCC

- 5 kPa: No PHT
- 10 kPa: No cACLD
- 15 kPa: cACLD
- 20 kPa: + plt > 150,000, No CSPH
- 25 kPa: + plt > 150,000, No high-risk EV

Assume CSPH (viral metabolic except obese, alcohol-related cirrhosis)

No Endoscopy, regular plt & LSM

Screening endoscopy if plt < 150,000/mm²

*if contra-indication/intolerance, endoscopy & banding if needed