Thematic Miniseries on HCV cure

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Antiviral therapy in the palliative setting of HCC (BCLC-B and -C)

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Summary

The potential impact of direct-acting antivirals (DAAs) in patients with Barcelona Clinic Liver Cancer (BCLC)-B/C stage hepatocellular carcinoma (HCC) is understudied. Patients with HCC have been systematically excluded from randomised controlled trials evaluating the effectiveness of DAAs. Thus, the benefits of DAAs in patients with HCC are less well defined. The presence of active HCC before the initiation of DAA treatment is reported to be a predictor of DAA failure, and studies in patients without HCC have demonstrated that improvements in cirrhosis complications were lower or absent after DAA failure. Even if viral eradication is achieved using DAAs, reversal of liver function impairment may take longer than the development of end-stage cancer status. Additionally, the impact of DAAs on HCC recurrence is still a controversial topic. Thus, the decision of whether to use DAAs should be made on a patient-by-patient basis, and each patient should be informed of all the potential risks and benefits associated with their usage. This document summarises the current data on the usage of DAAs in BCLC-B/C patients, discusses the concept of "the point of no return" in the setting of DAAs, and proposes tools for deciding the best option for each patient profile. If liver function improvement overlaps with symptomatic HCC progression, the benefits of DAAs could be minimised, worsened, or fully counterbalanced. If the BCLC stage is defined using only liver dysfunction, the decision to prioritise DAA treatment should be based on the option (or lack thereof) of liver transplantation and/or the HCC stage. We propose applying a shared decision-making approach, informing each patient of all the potential risks and benefits of the proposed medical intervention.

Keywords: HCC; DAA; BCLC-B; BCLC-C; BCLC-D; recurrence; liver function.

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Introduction

The treatment for advanced Barcelona Clinic Liver Cancer (BCLC)-C hepatocellular carcinoma (HCC) has evolved over time from the use of a single therapeutic drug to different treatment modalities.[1–7] The advent of new direct-acting antivirals (DAAs) has revolutionised the treatment of patients with HCV infection with very high rates (>90%) of sustained virologic response (SVR), very few contraindications, and low rates of adverse events. Nevertheless, the benefits of DAA treatment in BCLC-B/C/D patients are yet to be clearly identified, and it is crucial to avoid worsening the natural history of these patients.

Fig. 1 represents the natural history of patients with HCC and tumour-related symptoms, such as deterioration of Eastern Cooperative Oncology Group-performance status (ECOG-PS) and cirrhosis complications, with or without concomitant tumour progression.[8,9] An unmet issue is the identification of the 'reversibility time-point' wherein medical intervention could transform a decompensated patient into a compensated one, providing the possibility of administering onco-specific treatment. In this review, we aim to discuss the impact and applicability of antiviral therapy in BCLC-B and BCLC-C patients, considering not only the risk of developing hepatic decompensation but also tumour progression with or without liver decompensation (Fig. 2). Herein, we aim to underline the main issues, pitfalls, and drawbacks of using DAAs, beyond tolerance, in patients with intermediate/advanced HCC and HCV-related cirrhosis, which has never been a controversial topic in this field.

Studies for review in this article were retrieved from the PubMed database using the search terms 'hepatocellular carcinoma', 'liver cancer', and 'primary liver carcinoma', both individually and in combination with the terms 'direct-acting antivirals' and 'hepatitis C virus'. The search included literature published in English until August 2020.

Current data on DAA treatment in patients with compensated or decompensated cirrhosis

DAAs have been considered as an option to reduce complications in patients with cirrhosis, regardless of whether or not they present with HCC. They

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Keypoints

- In patients with BCLC-B/C, the benefits of DAAs are yet to be identified, and the possibility of modifying the natural history of these patients should be evaluated in prospective studies.
- If DAA treatment is administered at an irreversible time-point, the potential benefits of liver dysfunction improvement could be minimised because the time needed for liver function recovery will likely be longer than that needed for HCC progression.
- Given the lack of evidence on the benefits of DAA in the BCLC-B/C patient population, we suggest prioritising the treatment of cancer-related symptoms and liver decompensation rather than expecting an improvement in liver function through DAA therapy.
- If the only factor that can explain liver dysfunction in BCLC-B/C patients is the presence of hepatitis C infection, the decision to prioritise DAA treatment should be made on a patient-by-patient basis; moreover, each patient should be informed of all the potential benefits and risks of this treatment.
- If the BCLC stage is defined by cancer-related symptoms or tumour burden, DAA treatment will not modify BCLC staging. Thus, owing to the lack of evidence on the benefits of DAA in this population, existing data do not favour the administration of DAAs as a rule in BCLC-B/C patients.

have also been considered for the potential downstaging of patients with HCC from BCLC-D to C or from BCLC-C to B in cases where the BCLC stage is defined by liver decompenation. However, the benefits of DAAs in patients with HCC are less well defined; the impact of DAAs on HCC recurrence is a controversial topic because the randomised control trials (RCT) that evaluated the effectiveness of DAAs excluded patients with HCC.

Penner *et al.* reported that patients with a viable tumour, when starting DAA treatment, had a lower rate of SVR than patients with inactive or no HCC.[10] We believe that this lower rate of SVR is likely to be associated with a lower rate of improvement of cirrhosis complications in patients with HCC than in those without HCC. Table S1 summarises the publications[11–27] on the benefits of DAAs in patients with portal hypertension, liver decompensation, and fibrosis regression, as well as the percentage of patients with HCC included in the above-cited studies, which was limited.

It is already known that patients with HCC are at a risk of developing cirrhosis-related complications, and the results from Lens *et al.*'s[11] and Verna *et al.*'s[23] studies provide a reference for establishing the potential benefits of DAAs in the HCC population. Additionally, Belli *et al.*[28] reported a significantly lower probability of liver transplantation (LT) linked to improved liver function in patients treated with DAAs than in those not treated with DAAs. However, the indication for LT in patients with HCC goes beyond the rate of liver decompensation, which is reflected by the model for end-stage liver disease (MELD) score of patients with HCC included in Belli *et al.*'s[28] study.

DAA treatment was also suggested as an option for patients with BCLC-B for HCC downstaging prior to LT, when liver dysfunction limited the option of bridging treatment and downstaging. Although a recent study demonstrated a positive impact of DAAs on overall survival in patients successfully treated for early HCC, based on a significant reduction in the risk of decompensation,[29] it is not known whether these results will be reflected in patients with BCLC B/C stage.

Although there are several publications focused on the impact of DAA treatment on patients with HCC, only a few described outcomes in patients with BCLC-B/C stage. This could be for the following reasons: i) After the first publication on the unexpectedly high risk of developing HCC recurrence after DAA treatment,[30] the main concerns raised by the scientific community[31,32] were related to the inclusion of 6 BCLC-B patients (10% of the cohort) treated with trans-arterial chemoembolisation (TACE). These 6 patients were considered a major bias in the interpretation of the results and the key factor for the unexpectedly high risk of recurrence observed in the cohort. However, this was not the case since none of the TACE-treated patients developed HCC recurrence;[33] ii) There are no data regarding potential drug-drug interactions between DAAs and systemic treatments or immunotherapy in clinical practice because patients with HCC were excluded from RCTs evaluating DAA efficacy; iii) DAAs were prioritised for patients without HCC over those with HCC. Additionally, patients with early stages of HCC, those who were successfully treated for early stages of HCC, or those with active early HCC listed for LT were prioritised over those with intermediate or advanced HCC.

Improvements in cirrhosis complications using DAAs and their impact on BCLC-B and C patients

Rate of SVR in HCC patients

Patients with BCLC-B/C stage should have preserved liver function (Child-Pugh A or B7 without clinical ascites and/or encephalopathy) and all cirrhosis complications, such as variceal bleeding, should be under control. The limited published information[10,30,34–37] regarding DAA treatment in this population is described in Table S2. Chi *et al.*, Ogawa *et al.*, and Dang *et al.*[35,37] were the only cohorts that reported SVR (ranging from 77.8–100%) in BCLC-B/C/D patients. Beste *et al.*[38]

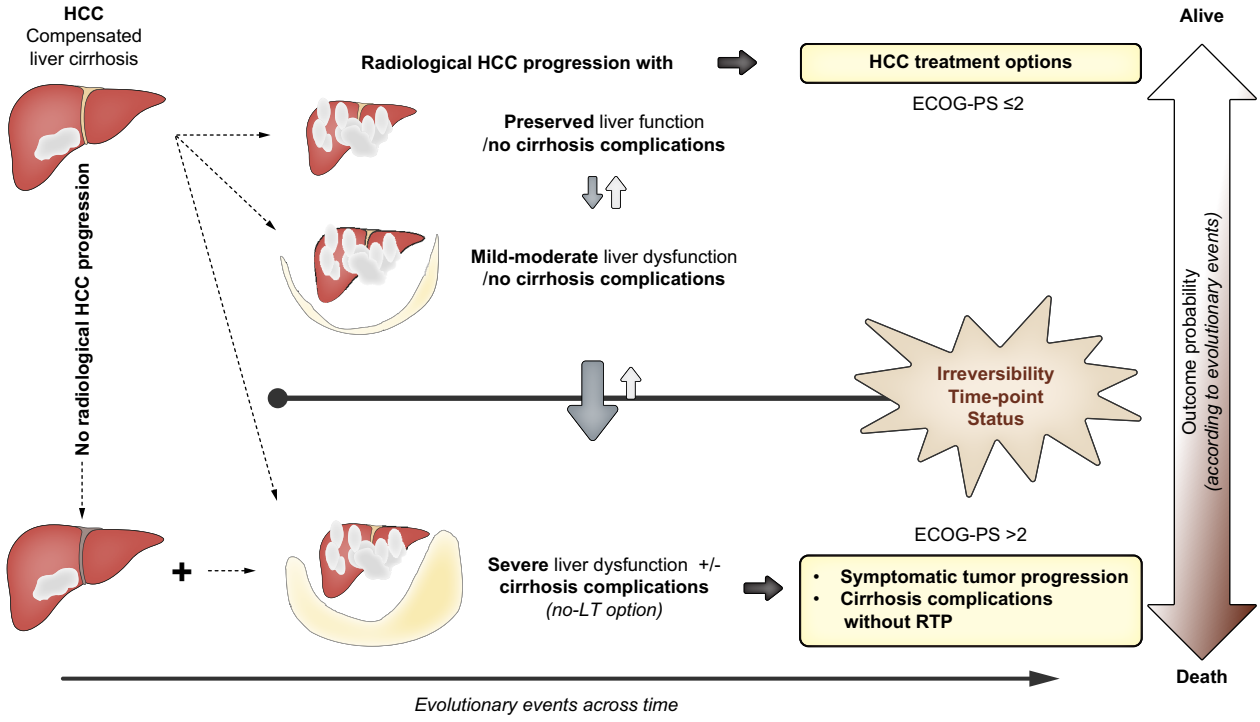

Fig. 1. HCC evolution according to the evolutionary event. Patient evolution will be conditioned by radiological progression and liver decompensation or a combination of both. Medical intervention could modulate the evolution of patients; however, if it is done when the patient is in the irreversibility time-point status, the chance of compensating the patient is extremely low or null. The outcome will be better or worse depending on the event which conditioned the evolution and the time at which the medical intervention is performed. ECOG-PS, Eastern Cooperative Oncology Group-performance status; HCC, hepatocellular carcinoma; LT, liver transplantation; RTP, radiological tumour progression.

analysed the SVR rate according to the last HCC treatment received before initiating DAA treatment. SVR was 70.0% (95% CI 63.6–75.7) in TACE-treated patients, while it decreased to 59.0% (95% CI 46.0–70.9) in those receiving sorafenib.

Chi *et al.*[35] reported on the largest cohort of BCLC-B patients (n = 70). SVR rates were similar in patients with BCLC-0/A and B HCC (95% and 97.8%, respectively), but decreased to 77.8% in BCLC-C patients. As expected, SVR was identified as the key independent risk factor for death, and multivariate analysis revealed that not achieving SVR was the only factor associated with poor recurrence-free survival.

Prenner *et al.*[10] evaluated 137 patients with a history of HCC. Most patients had Child-Pugh A disease (81%), and 108 of these were treated with TACE or radioembolisation; however, only 21.9% (n = 30) of the cohort had BCLC-B/C stage. According to their data, the SVR rate was conditioned by the presence of HCC (lower probability of SVR in patients with HCC than in those without HCC); a DAA failure rate of 21% was reported in patients with HCC compared to 12% in patients without HCC (p = 0.009). Additionally, the rate of SVR was also related to the presence of a viable tumour in patients with HCC. Twenty-seven patients with HCC and failed primary treatment had BCLC-A HCC (59%), followed by stage B (29%), stage 0 (7%), and stage C (4%). In contrast, Owaga *et al.* suggested that SVR was reduced in patients with active but not inactive HCC after DAA treatment. However, only 12.5% of the patients had BCLC-B HCC, and only 5% had BCLC-C/D HCC.

According to the data of Prenner *et al.*[10] and Verna *et al.*,[23] the expected MELD score for BCLC B/C patients was around 10 points (which was similar to that reported by Belli *et al.* in the ELITA registry[28]), and the expected SVR rate was approximately 90%. However, as mentioned before, these cohorts comprised patients with early stage HCC.

HCC recurrence and/or progression in BCLC-B/C patients treated with DAAs

Heterogeneity in the baseline characteristics of patients (prior to DAA treatment and during follow-up) and the radiological schedule of different patients across different cohorts (and within the same cohort) limit the interpretation of studies evaluating the efficacy of DAAs in patients with BCLC-B/C stage.[39] Additionally, the reported information is sometimes only focused on patients who achieved SVR. In this regard, a meta-analysis of individual patient data, which included more than 1,000 patients with HCC and complete response, showed that only 7.1% of patients had

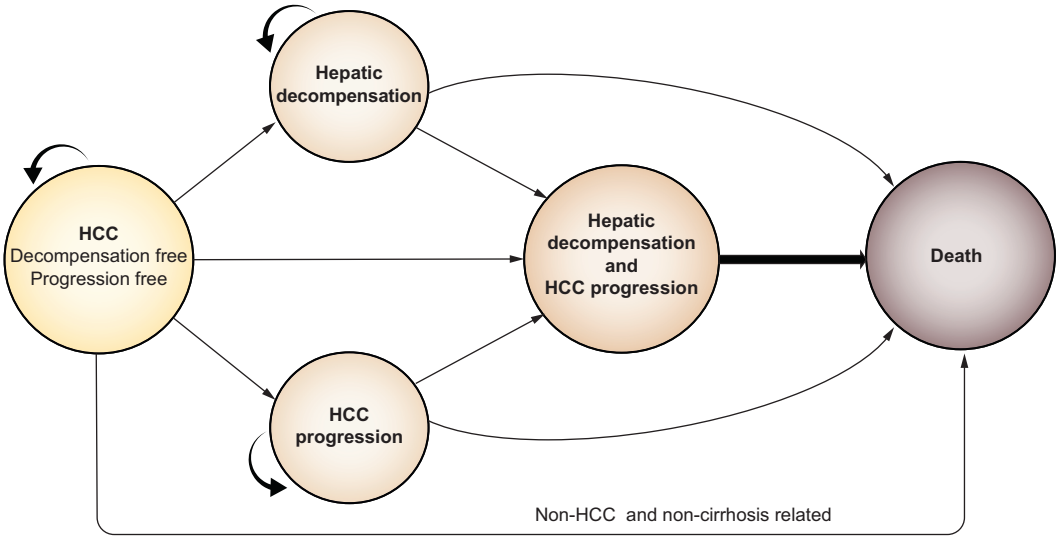

Fig. 2. Competing risk factors in survival analyses for HCC outcomes. This figure represents the probability of developing hepatic decompensation, tumour progression or events not related to HCC or liver decompensation, which will define the outcome of patients with HCC. However, this outcome is also conditioned by the probability of modifying the natural history of hepatic decompensation and/or tumour progression at each stage of HCC. The combination of these factors will condition the clinical decision making in the setting of HCC. HCC, hepatocellular carcinoma.

multifocal HCC and <0.5% of the cohort had extrahepatic spread or vascular invasion, with the most frequent treatment being ablation (47.3%), followed by resection (31%) and chemoembolisation (15.3%).[40] Similar to the findings of previous meta-analyses,[41,42] the heterogeneity between studies/patients was very high, and it was not possible to reach a robust conclusion. However, when the individual data were matched with a cohort of patients with HCC who did not receive DAAs, all patients with multifocal HCC and/or extrahepatic spread and/or vascular invasion were excluded, as it was impossible to match them with controls. These studies reveal the limitations of the information available on BCLC-B/C-D patients who never received interferon or in whom HCV was not considered a factor in treatment decisions. Despite the fact that Singal *et al.* analysed the impact of DAAs[43,44] on overall survival in patients with HCC, BCLC-B/C patients were underrepresented in that cohort and in the meta-analysis conducted by Waziry *et al.*[42] The percentage of patients with HCC at BCLC-B/C in each study is presented in Table S3. According to the current data, there is no clear evidence that DAAs have a beneficial impact on outcomes in patients with BCLC-B/C stage. Thus, we cannot offer a robust opinion about this specific population in our review.

How do we apply the current data to clinical decision making?

Clinical decision making is a balance between the risks and benefits of a specific treatment (Fig. 2). Costs are also considered for evaluating cost-

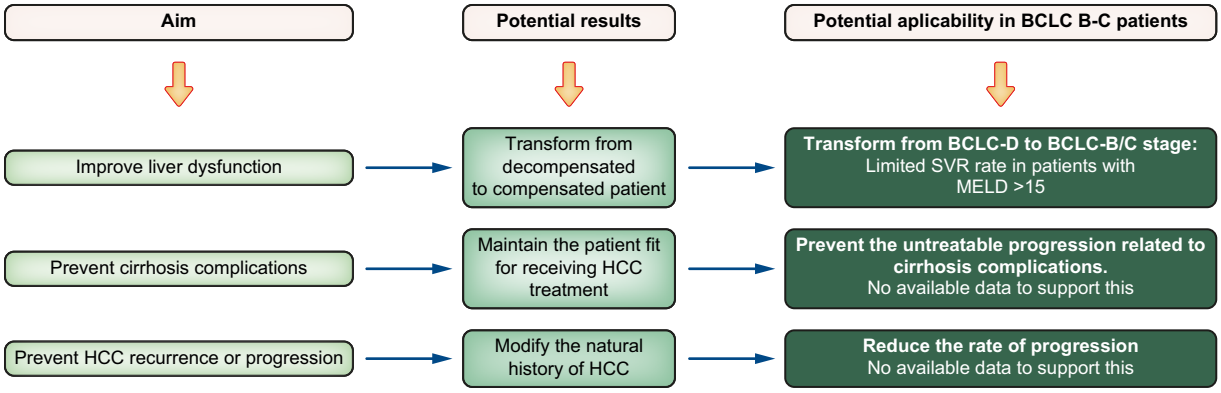

Fig. 3. Current information for defining the risks/benefits of DAA treatment in patients with BCLC-B/C stage. This figure describes the aim, potential benefits, and current data of DAA in BCLC-B/C patients. BCLC, Barcelona Clinic Liver Cancer; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; SVR, sustained virologic response.

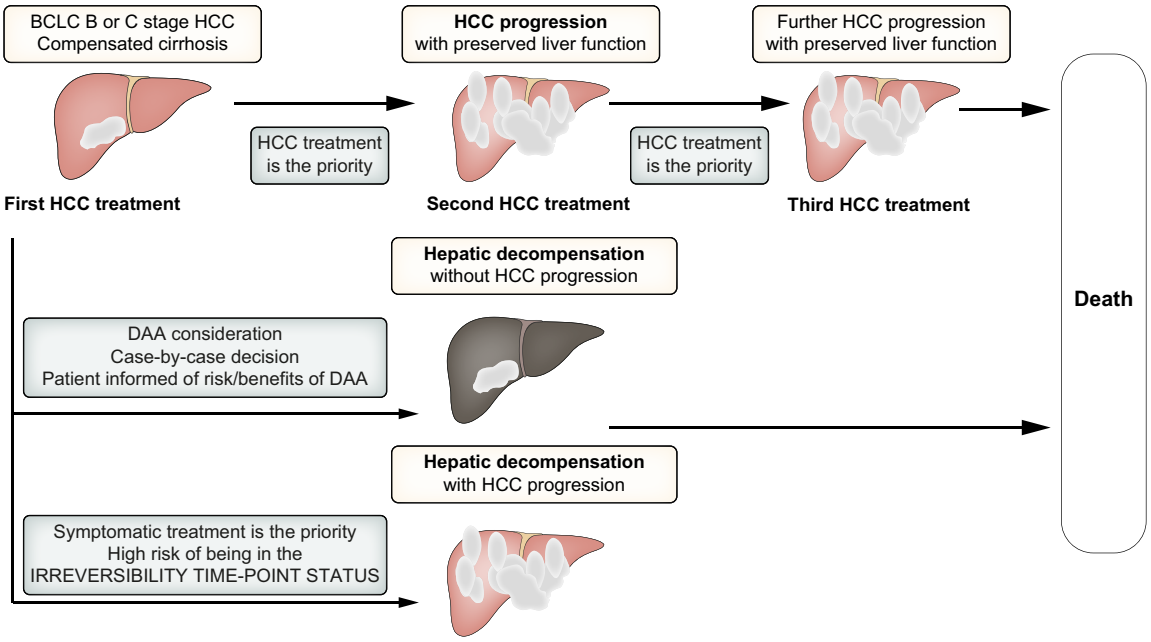

Fig. 4. Treatment prioritisation according to BCLC-B/C patient evolution. This figure describes the different evolution of BCLC/B-C patients after receiving their first HCC treatment and the author's proposal of treatment prioritisation according to the prevalent risk factors (HCC progression without liver decompensation or liver decompensation with/without HCC progression) considering DAAs as one of the potential medical interventions in the analysis. BCLC, Barcelona Clinic Liver Cancer; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma.

effectiveness. For clinical decision making, we need to consider data from all patients, not only those who achieve an SVR, because the latter is an evolutionary event associated with a good outcome, which is unknown before initiating DAA treatment. If we put aside the hypothetical risk of increased recurrence or occurrence, DAA treatment at early stages is very well tolerated; however, in patients with HCC, it is not possible to exclude this factor from the equation of benefits/risks. Thus, we propose considering the following aims before personalising any decision (Fig. 3):

Downstaging BCLC-D HCC to BCLC-B/C stage:
To define this point, we need to identify factors that characterise the BCLC-D stage.

i. If the BCLC-D stage is defined by cancer-related symptoms or tumour burden, DAA treatment may not achieve the expected outcome; the expected median survival will not change and will range from 3 to 6 months. In our opinion, ***prioritising DAA treatment is not the optimal option.***

ii. If the BCLC-D stage is defined by liver dysfunction, and the patient has a multifocal HCC without extrahepatic spread or vascular invasion, it is essential to know whether the patient is a candidate for HCC downstaging. The spectrum of this population should be carefully evaluated:

ii.i. ***Patients with multifocal HCC, without extrahepatic spread or vascular invasion, and without (non-HCC) contraindications for LT***: These patients are potential candidates for HCC downstaging depending on liver dysfunction. If liver dysfunction is the only factor limiting the consideration of LT:

ii.i.i. The reported SVR rate ranges from 100% to 59% in BCLC-B patients with complete response; however, if the tumour is viable (as is the case in patients who are candidates for HCC downstaging), the risk of DAA failure is higher than in patients with inactive tumours.[10]

ii.i.ii. The expected SVR rate in patients with decompensated cirrhosis is lower than in patients with compensated cirrhosis. Although 47% of the 250 patients evaluated by Curry *et al.* had improved Child-Pugh scores over baseline, 42% showed no change, and 11% had worsened Child-Pugh scores. In the same study, 114 of those patients had an MELD score of <15, 51% had an improved MELD score, 22% had no change, and 27% had a worse MELD score.[16]

ii.i.iii. Thus, the probability of achieving SVR varies according to baseline liver function, and it is also defined by the presence of active or inactive tumours. The benefits of DAA treatment are observed in around 50% of patients with liver dysfunction, although the risk of recurrence/progression also affects around 50% of patients irrespective of DAA efficacy.

Cirrhosis complications	ECOG-PS deterioration	Radiological HCC progression	Patient profile	Management suggestion	DAA consideration in BCLC- B/C
No	No	No	Compensated, asymptomatic and SD, PR or RC	Regular clinical, laboratory and radiological control	No
No	No	Yes	Compensated, asymptomatic/mild symptoms and radiological progression	HCC treatment options according to BCLC stage	No
Yes	No	Yes	Decompensated cirrhosis with radiological progression	Cirrhosis complications resolved before considering HCC treatment	Patient by Patient considering risk/benefits and LT option in BCLC-B who achieve the downstaging criteria
Yes	Yes	No	Decompensated cirrhosis without radiological progression	Cirrhosis complications resolved	
No	Yes	No	Compensated, symptoms not related to radiological progression	Re-staging and ruling out confounding factors	No
Yes	Yes	Yes	Symptomatic tumor progression	Symptomatic treatment	No

Fig. 5. Proposal to guide DAA treatment in BCLC-B/C patients. The figure describes the author's management proposal based on patient profile (presence or absence of cirrhosis complications, ECOG-PS and radiological status of HCC) and the potential role of DAAs in each clinical condition. BCLC, Barcelona Clinic Liver Cancer; DAA, direct-acting antiviral; ECOG-PS, Eastern Cooperative Oncology Group-performance status; HCC, hepatocellular carcinoma.

ii.ii. ***Patients in whom transplantation is contraindicated owing to non-HCC related comorbidities:*** These patients do not have tumour-related symptoms and their liver dysfunction is the only factor characterising the BCLC-D stage.

In the field of HCC, MELD purgatory would not be detrimental for LT candidates as the MELD score is independent from liver dysfunction if patients have BCLC-0/A HCC. However, LT is not indicated in patients with BCLC-D HCC, owing to either tumour burden beyond the criteria for LT or comorbidities.

In both scenarios, we propose prioritising symptomatic treatment to improve liver dysfunction; if the only factor that can explain liver dysfunction is the presence of HCV, the decision of whether to initiate DAA therapy should be made on a patient-by-patient basis, and each patient should be informed of all the potential risks and benefits.

Preventing untreatable progression due to cirrhosis complications in BCLC-B/C patients

It is well-known that the risk of hepatic decompensation may affect the number of treatments with TACE for patients with intermediate HCC and the possibility of being subsequently treated with first- or second-line systemic therapy after progression (Fig. 4). Sieghart *et al.*,[45] using the assessment for retreatment with TACE score (ART score), reported that a Child-Pugh score of 7 or >8 points predicted worse outcomes in BCLC-B patients after TACE. According to Sieghart *et al.*,[45] 21% and 22% of the patients in the training and validation cohorts, respectively, presented worse outcomes after TACE. The median survival in these cohorts was 8.6 months (95% CI 6.5–10.7) and 6.4 months (95% CI 1.1–11.7), respectively. Thus, the point of 'no return'[46] (a patient who develops symptomatic tumour progression before resolving cirrhosis complications), which in this manuscript is referred to as the '*irreversibility time-point status*', is one of the main issues in the management of patients with liver cancer. Indeed, the window of intervention before reaching the irreversibility time-point for BCLC-C and D patients is extremely small but should be considered during clinical decision making.

This is particularly relevant now, as several systemic therapeutic options are available.[47] Moreover, in patients with advanced HCC treated with sorafenib, the outcome and overall survival were challenged by the high rates of anticipated discontinuation caused by tumour progression, liver decompensation, and some adverse effects.[48,49]

Hence, considering the data shown above regarding early improvements in disease severity (Child-Pugh and MELD scores) and long-term preservation of liver function in most HCV patients treated with DAAs, one could speculate that DAAs would confer a similar benefit in patients with active BCLC-B/C stage HCC by reducing the risk of decompensation-related treatment discontinuation. Thus, given the lack of suitable evidence, a similar

statement, that ***the decision should be made on a patient-by-patient basis, and each patient should be informed of all the potential risks of DAA failure and HCC progression*** is applicable here.

The importance of the effect of DAAs on the risk of hepatic decompensation in patients with HCC leads to several general reflections concerning the peculiarity of HCC. It is well known that cirrhosis underlies HCC in most patients, and the functional impairment of the liver has a significant impact on prognosis, irrespective of the tumour stage. Thus, liver function is one of the determinants of HCC prognosis since it is reflected in the BCLC staging classification as well as in other integrated prognostic scores. Moreover, there is increasing evidence demonstrating that hepatic decompensation during follow-up affects the chances of receiving HCC treatment and ultimately affects survival. Although from a theoretical point of view the transition from one stage to another could be modulated by medical intervention, such as DAA treatment, the real impact of that intervention could be conditioned by factors other than liver dysfunction, such as HCC progression without liver decompensation (Fig. 4). Thus, if we consider DAA treatment at the irreversibility time-point, the interventions will no longer have an impact, or could even be associated with a worse outcome than the natural course of the disease.

Accordingly, we think that time taken to develop hepatic decompensation, decompensation-free survival, and the type of decompensation should be considered as a safety measure in studies on HCC and should be included in other outcomes in trial designs of systemic or locoregional therapies, such as time taken for recurrence and recurrence-free survival in the early stages and time to progression or progression-free survival in the advanced stages.

Preventing tumour progression

There is currently no data available to support the use of DAAs solely for the treatment or prevention of HCC recurrence or progression.

In summary, our proposal for considering DAA treatment in the setting of BCLC-B/C is described in Fig. 5. Given the complexity of the disease (particularly in the presence of chronic liver disease) and the large number of potentially useful anti-cancer therapies, it is not surprising that the expertise of many physicians is required to provide optimal care to patients with HCC. In this regard, the risk of decompensation (or worsening of residual liver function) and tumour progression are the competitive risk factors that drive disease evolution in patients with HCC. For this reason, it is crucial to share decision making with patients.

Conclusion

Owing to the lack of studies evaluating the impact of DAA treatment in BCLC-B/C patients, we propose making decisions on a patient-by-patient basis, and applying a shared decision-making approach, informing each patient of all the potential risks and benefits of the proposed medical intervention.

Abbreviations

BCLC, Barcelona Clinic Liver Cancer; DAAs, direct-acting antivirals; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; RCT, randomised controlled trial; SVR, sustained virologic response; TACE, trans-arterial chemoembolization.

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Conflict of interest

Giuseppe Cabibbo: Consultancy fees from Bayer, Ipsen. María Reig: Consultancy fees from Bayer, BMS, Roche, Ipsen, AstraZeneca, and Lilly; lecture fees from Bayer, BMS, Gilead, Lilly, and Roche; and research grants from Bayer and Ipsen.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Both authors contributed equally to the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.01.046.

References

Author names in bold designate shared co-first authorship

[1] Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Canc Inst 2008;100:698–711. https://doi.org/10.1093/jnci/djn134.

[2] Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet (London, England) 2018. https://doi.org/10.1016/S0140-6736(18)30207-1.

[3] Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2016:S0140–S6736.

[4] Abou-Alfa, Ghassan K, Meyer T, Cheng A-L, El-Khoueiry AB, Rimassa L, et al. Cabozantinib (C) versus placebo (P) in patients (pts) with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib: results from the randomized phase III CELESTIAL trial. J Clin Oncol 2018;36. abstr 207.

[5] Zhu AX, Kang Y-K, Yen C-J, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282–296. https://doi.org/10.1016/S1470-2045(18)30937-9.

[6] Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894–1905. https://doi.org/10.1056/NEJMoa1915745.

[7] Bruix J, Reig M, Rimola J, Forner A, Burrel M, Vilana R, et al. Clinical decision making and research in hepatocellular carcinoma: pivotal role of imaging techniques. Hepatology 2011;54. https://doi.org/10.1002/hep.24670.
[8] Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018. https://doi.org/10.1016/j.jhep.2018.03.019.
[9] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet (London, England) 2018;391:1301–1314. https://doi.org/10.1016/S0140-6736(18)30010-2.
[10] Prenner SB, VanWagner LB, Flamm SL, Salem R, Lewandowski RJ, Kulik L. Hepatocellular carcinoma decreases the chance of successful hepatitis C virus therapy with direct-acting antivirals. J Hepatol 2017;66. https://doi.org/10.1016/j.jhep.2017.01.020.
[11] Lens S, Baiges A, Alvarado E, LLop E, Martinez J, Fortea JI, et al. Clinical outcome and hemodynamic changes following HCV eradication with oral antiviral therapy in patients with clinically significant portal hypertension. J Hepatol 2020. https://doi.org/10.1016/j.jhep.2020.05.050.
[12] Mandorfer M, Kozbial K, Schwabl P, Chromy D, Semmler G, Stättermayer AF, et al. Changes in hepatic venous pressure gradient predict hepatic decompensation in patients who achieved sustained virologic response to interferon-free therapy. Hepatology 2020;71:1023–1036. https://doi.org/10.1002/hep.30885.
[13] Kozbial K, Moser S, Al-Zoairy R, Schwarzer R, Datz C, Stauber R, et al. Follow-up of sustained virological responders with hepatitis C and advanced liver disease after interferon/ribavirin-free treatment. Liver Int 2018;38:1028–1035. https://doi.org/10.1111/liv.13629.
[14] Belli LS, Berenguer M, Cortesi PA, Strazzabosco M, Rockenschaub S-R, Martini S, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: a European study. J Hepatol 2016;65:524–531. https://doi.org/10.1016/j.jhep.2016.05.010.
[15] Foster GR, Irving WL, Cheung MCM, Walker AJ, Hudson BE, Verma S, et al. Cohort study of the impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016. https://doi.org/10.1016/j.jhep.2016.01.029.
[16] Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015;373:2618–2628. https://doi.org/10.1056/NEJMoa1512614.
[17] Knop V, Mauss S, Goeser T, Geier A, Zimmermann T, Herzer K, et al. Dynamics of liver stiffness by transient elastography in patients with chronic hepatitis C virus infection receiving direct-acting antiviral therapy—results from the German Hepatitis C-Registry. J Viral Hepat 2020;27:690–698. https://doi.org/10.1111/jvh.13280.
[18] Mauro E, Crespo G, Montironi C, Londoño MC, Hernández-Gea V, Ruiz P, et al. Portal pressure and liver stiffness measurements in the prediction of fibrosis regression after sustained virological response in recurrent hepatitis C. Hepatology 2018;67:1683–1694. https://doi.org/10.1002/hep.29557.
[19] Bachofner JA, Valli PV, Kröger A, Bergamin I, Künzler P, Baserga A, et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2017;37:369–376. https://doi.org/10.1111/liv.13256.
[20] Lens S, Alvarado-Tapias E, Mariño Z, Londoño MC, LLop E, Martinez J, et al. Effects of all-oral anti-viral therapy on HVPG and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis. Gastroenterology 2017;153:1273–1283. https://doi.org/10.1053/j.gastro.2017.07.016. e1.
[21] Mandorfer M, Kozbial K, Schwabl P, Freissmuth C, Schwarzer R, Stern R, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J Hepatol 2016;65:692–699. https://doi.org/10.1016/j.jhep.2016.05.027.
[22] Mendizabal M, Piñero F, Ridruejo E, Wolff FH, Anders M, Reggiardo V, et al. Disease progression in patients with hepatitis C virus infection treated with direct-acting antiviral agents. Clin Gastroenterol Hepatol 2020. https://doi.org/10.1016/j.cgh.2020.02.044.
[23] Verna EC, Morelli G, Terrault NA, Lok AS, Lim JK, Di Bisceglie AM, et al. DAA therapy and long-term hepatic function in advanced/decompensated cirrhosis: real-world experience from HCV-TARGET cohort. J Hepatol 2020. https://doi.org/10.1016/j.jhep.2020.03.031.
[24] Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode C, et al. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. Lancet 2019;393:1453–1464. https://doi.org/10.1016/S0140-6736(18)32111-1.
[25] Gentile I, Scotto R, Coppola C, Staiano L, Amoruso DC, De Simone T, et al. Treatment with direct-acting antivirals improves the clinical outcome in patients with HCV-related decompensated cirrhosis: results from an Italian real-life cohort (Liver Network Activity—LINA cohort). Hepatol Int 2019;13:66–74. https://doi.org/10.1007/s12072-018-9914-6.
[26] Nahon P, Bourcier V, Layese R, Audureau E, Cagnot C, Marcellin P, et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. Gastroenterology 2017;152:142–156. https://doi.org/10.1053/j.gastro.2016.09.009. e2.
[27] Pascasio JM, Vinaixa C, Ferrer MT, Colmenero J, Rubin A, Castells L, et al. Clinical outcomes of patients undergoing antiviral therapy while awaiting liver transplantation. J Hepatol 2017;67:1168–1176. https://doi.org/10.1016/j.jhep.2017.08.008.
[28] Belli LS, Perricone G, Adam R, Cortesi PA, Strazzabosco M, Facchetti R, et al. Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol 2018;69:810–817. https://doi.org/10.1016/j.jhep.2018.06.010.
[29] Cabibbo G, Celsa C, Calvaruso V, Petta S, Cacciola I, Cannavò MR, et al. Direct-acting antivirals after successful treatment of early hepatocellular carcinoma improve survival in HCV-cirrhotic patients. J Hepatol 2019;71:265–273. https://doi.org/10.1016/j.jhep.2019.03.027.
[30] Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719–726. https://doi.org/10.1016/j.jhep.2016.04.008.
[31] Cammà C, Cabibbo G, Craxì A. Direct antiviral agents and risk for HCC early recurrence: much ado about nothing. J Hepatol 2016;65:861–862. https://doi.org/10.1016/j.jhep.2016.04.033.
[32] Reig M, Torres F, Mariño Z, Forns X, Bruix J. Reply to "Direct antiviral agents and risk for hepatocellular carcinoma (HCC) early recurrence: much ado about nothing. J Hepatol 2016;65. https://doi.org/10.1016/j.jhep.2016.05.036.
[33] **Reig M**, **Boix L**, Mariño Z, Torres F, Forns X, Bruix J. Liver cancer emergence associated with antiviral treatment: an immune surveillance failure? Semin Liver Dis 2017;37:109–118. https://doi.org/10.1055/s-0037-1601349.
[34] **Conti F**, **Buonfiglioli F**, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727–733. https://doi.org/10.1016/j.jhep.2016.06.015.
[35] Chi CT, Chen CY, Su CW, Chen PY, Chu CJ, Lan KH, et al. Direct-acting antivirals for patients with chronic hepatitis C and hepatocellular carcinoma in Taiwan. J Microbiol Immunol Infect 2019. https://doi.org/10.1016/j.jmii.2019.09.006.
[36] Lin WC, Lin YS, Chang CW, Chang CW, Wang TE, Wang HY, et al. Impact of direct-acting antiviral therapy for hepatitis C–related hepatocellular carcinoma. PLoS One 2020;15. https://doi.org/10.1371/journal.pone.0233212.
[37] Dang H, Yeo YH, Yasuda S, Huang CF, Iio E, Landis C, et al. Cure with interferon-free direct-acting antiviral is associated with increased survival in patients with hepatitis C virus-related hepatocellular carcinoma from both east and west. Hepatology 2020;71:1910–1922. https://doi.org/10.1002/hep.30988.
[38] Beste LA, Green PK, Berry K, Kogut MJ, Allison SK, Ioannou GN. Effectiveness of hepatitis C antiviral treatment in a USA cohort of veteran patients with hepatocellular carcinoma. J Hepatol 2017;67:32–39. https://doi.org/10.1016/j.jhep.2017.02.027.
[39] Sanduzzi-Zamparelli M, Boix L, Leal C, Reig M. Hepatocellular carcinoma recurrence in HCV patients treated with direct antiviral agents. Viruses 2019;11. https://doi.org/10.3390/v11050406.
[40] Sapena V, Enea M, Torres F, Celsa C, Rios J, Rizzo GEM, et al. Hepatocellular carcinoma recurrence after direct-acting antiviral therapy: an individual patient data meta-analysis. Gut 2021. https://doi.org/10.1136/gutjnl-2020-323663. Published Online First: 19 March 2021.
[41] Cabibbo G, Petta S, Barbàra M, Missale G, Virdone R, Caturelli E, et al. A meta-analysis of single HCV-untreated arm of studies evaluating outcomes after curative treatments of HCV-related hepatocellular carcinoma. Liver Int 2017. https://doi.org/10.1111/liv.13357.
[42] Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: a systematic review, meta-analyses, and meta-regression. J Hepatol 2017;13:5188–5195. https://doi.org/10.1016/j.jhep.2017.07.025.
[43] Singal AG, Rich NE, Mehta N, Branch AD, Pillai A, Hoteit M, et al. Direct-acting antiviral therapy for hepatitis C virus infection is associated with increased survival in patients with a history of hepatocellular carcinoma. Gastroenterology 2019. https://doi.org/10.1053/j.gastro.2019.07.040.

[44] Singal AG, Rich NE, Mehta N, Branch A, Pillai A, Hoteit M, et al. Direct-acting antiviral therapy not associated with recurrence of hepatocellular carcinoma in a multicenter north American cohort study. Gastroenterology 2019. https://doi.org/10.1053/j.gastro.2019.01.027.

[45] Sieghart W, Hucke F, Pinter M, Graziadei I, Vogel W, Muller C, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013;57:2261–2273. https://doi.org/10.1002/hep.26256.

[46] Reverter E, Ott P. Compensated cirrhosis and 20 mm Hg: a point of No return? Am Coll Gastroenterol 2020. https://doi.org/10.14309/ajg.0000000000000770.

[47] **Cabibbo G**, **Celsa C**, Enea M, Battaglia S, Rizzo GEM, Grimaudo S, et al. Optimizing sequential systemic therapies for advanced hepatocellular carcinoma: a decision analysis. Cancers (Basel) 2020;12:1–16. https://doi.org/10.3390/cancers12082132.

[48] **Reig M**, **Rimola J**, Torres F, Darnell A, Rodriguez-Lope C, Forner A, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology 2013;58:2023–2031. https://doi.org/10.1002/hep.26586.

[49] **Iavarone M**, **Cabibbo G**, Biolato M, Della Corte C, Maida M, Barbàra M, et al. Predictors of survival of patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib. Hepatology 2015. https://doi.org/10.1002/hep.27729.