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HEPATITIS C (J AHN, SECTION EDITOR)

Hepatitis C and Hepatocellular Carcinoma

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Abstract With the significant burden of hepatocellular carcinoma (HCC) attributable to hepatitis C (HCV), prevention of HCC should first and foremost include treatment of hepatitis C. At the very least, any patient who is at risk for liver disease progression to advanced fibrosis should have HCV treated. This is potentially one of the single most important interventions that can be employed long-term to decrease the incidence of HCV-related HCC. Furthermore, efforts should be made in proactively treating HCV in patients listed for liver transplant with HCC and those HCC patients with limited tumor burden treated with curative intent. Studies exploring more specifically which patients with HCC receiving liver-directed therapy should also have HCV treated need to be performed. The overall cost effectiveness of treating those with significant HCC tumor burden needs to be better understood. With new direct acting antivirals for the treatment of HCV, it is becoming increasingly difficult to find reasons to leave virtually any patient with hepatitis C untreated who is at risk for HCC or with HCC. Although there are limited data directly linking the treatment of HCV with the incidence of HCC, this is a tremendous opportunity to change the epidemiology of HCC by utilizing treatment for hepatitis C.

Keywords Hepatocellular carcinoma · Direct-acting antiviral agents · Hepatitis C · Sustained virologic response · Liver-directed therapies

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Introduction

Hepatocellular carcinoma (HCC) has increased in incidence over the past several decades, largely attributed to the hepatitis C virus (HCV) epidemic [1]. While there has been significant improvement in mortality for malignancies such as colon, breast, and lung cancer, the mortality associated with HCC continues to increase. The most recent Annual Report to the Nation on the Status of Cancer 1975–2012 in the USA highlighted the continued increase in liver cancer incidence and mortality. In fact, deaths from liver cancer have increased at the highest rate among all cancers and liver cancer had the second highest increase in incidence over time. Patients with HCV and HCC born in the baby boomer era (1945–1965) had the highest rate of death [2••]. Understandably, this has generated clinical concern and interest in HCC and our ability to optimally prevent incident cases and manage those with HCC.

In the vast majority of cases, HCC occurs in the setting of chronic liver disease, in particular those infected with chronic HCV and advanced fibrosis. All patients with cirrhosis, regardless of etiology, have an increased risk of HCC as compared to the general population. These patients with cirrhosis should be the group of greatest focus for surveillance of HCC. However, this risk is not equivalent in all etiologies of chronic liver disease leading to cirrhosis. For instance, the 5-year cumulative risk for HCC in the setting of HCV is greater than 15 % whereas the risk for HCC with biliary cirrhosis is less than 5 % [3]. In patients with chronic HCV, those with HCV-related cirrhosis are at greatest risk for developing HCC. The annual risk for HCC in patients with HCV cirrhosis is estimated at 1–4 % per year [4, 5]. It is also important to note that although the greatest risk of HCC occurs with HCV cirrhosis, HCV can occur the setting of non-cirrhotic liver such as in chronic hepatitis B, non-alcoholic steatohepatitis, and hemochromatosis.

Thus, to prevent HCC, in patients already infected with chronic HCV, the focus must be on the prevention of cirrhosis by way of treating HCV. The treatment of HCV has been revolutionized with the advent of direct acting antivirals. More than at any time before, treatment for HCV, if effectively implemented, can truly alter the epidemiology of HCC in the coming years.

How HCV Eradication Changes the Risk of HCC Development in Cirrhotics

In the era of direct acting antivirals for HCV, the potential impact of treatment and eradication of HCV on the incidence of HCC is considerable. Prior to the advent of interferon-free regimens for the treatment of HCV, only about one third of patients with chronic HCV were candidates for treatment of HCV given concerns around medication tolerability [6]. Therefore, very little could be done to modify the natural history of the progression from chronic HCV to cirrhosis and progression to HCC. These less-than-ideal circumstances have resulted in the current state of HCC—patients with HCV-related HCC have never been treated for HCV in the past or were not even aware that they had chronic liver disease.

Treatment regimens now being employed for HCV are exceptionally well tolerated in patients with and without cirrhosis. Increasing numbers of patients with decompensated cirrhosis are being considered for treatment in scenarios where this would have been a non-starter in the past. Furthermore and perhaps most impressively, HCV treatment response rates have more than tripled, with most regimens yielding greater than 90 % sustained viral response for all genotypes and degrees of fibrosis [7]. Virtually all patients are candidates for HCV treatment from a medical standpoint, and now the greatest limiting factor for access to treatment is underinsured or uninsured status [8, 9].

In the setting of chronic HCV infection, the risk of HCC increases as fibrosis staging increases, with almost a doubling in cumulative incidence of HCC over 3–5 years in patients with cirrhosis as compared to those with only bridging fibrosis. The cumulative risk of HCC in F0-F2 disease is approximately 2 % per year rather in contrast to a yearly incidence of up to 5 % in patients with cirrhosis [10]. In US veterans, the risk of HCC after SVR was 0.33 % per year [11••]. In other populations, the risk of HCC after sustained viral response has also been estimated at less than 1 % per year [12, 13]. Thus, for those patients with mild fibrosis related to HCV with a low annual incidence of HCC, treatment and subsequent cure of HCV would in effect eradicate the risk of HCC.

The National Health and Nutrition Examination Survey database estimates 2.7 million people infected with HCV in the USA [14]. This is likely an underestimation of the overall burden of HCV, however, as many patients with HCV do not know their HCV status and are not engaged in healthcare [15]. Without treatment of HCV, approximately 20 % would progress to have advanced fibrosis or cirrhosis. The tolerability and effectiveness of HCV treatment with direct acting antivirals (DAAs) provides a tremendous opportunity to not only decrease the number of patients progressing to cirrhosis but also to decrease the proportion of patients who then develop HCC.

Which Patients with HCC Should be Considered for HCV Treatment?

Prior to the wide availability of DAA treatments for HCV, attempts to eradicate the infection in patients with HCC seemed suspect at best, or outright folly at worst—the thought of treating a patient for a year with an interferon-based regimen and attendant side effects for a 50 % (or less) chance of viral clearance in a patient with deadly cancer might even strike one as irresponsible. Even the valiant effort to decrease rates of de novo HCC in patients with maintenance interferon seems brutal by today's standards (and was ineffective to boot [10]).

With the increased (and increasing) efficacy of DAAs in HCV eradication as well as markedly improved tolerability, providers have begun to question the wisdom of not treating HCV in patients with HCC. Current guidelines [16] suggest HCV treatment in patients with a predicted life expectancy of more than 12 months. While reasonable, this suggestion is based on very limited evidence and does not take into account (a) the possibility that HCV treatment itself might increase survival and (b) the possibility that even if there is limited life expectancy, the patient's quality of life might be improved with HCV eradication. In a small study from Europe, there was a high rate of early recurrence of HCC in patients with previously treated HCC followed by subsequent treatment of HCV after treatment with DAAs [17•]. Given the heterogeneity of the HCC population and complexity of management algorithms, one can only hope there will be clarifications to the questions surrounding management of HCV and HCC in the near future.

Is it likely that HCV eradication might increase survival in a patient with HCV-related cirrhosis and HCC? The answer to the question rests on the staging of cirrhosis and HCC. For patients with a reasonable chance of living several years with best HCC treatment, HCV cure is likely to improve overall survival from a cirrhosis-only point of view. In addition, patients with HCC are at risk for recurrence of the treated HCC lesions (unlikely to be affected with HCV cure) or de novo development of new HCC. This latter risk is likely to be decreased given studies showing HCV cure leads to markedly decreased incidence of HCC in at-risk patients [11••, 18]. For patients with decompensated cirrhosis and/or advanced HCC with expected <12-month life expectancy, HCV cure would not be expected to provide a benefit with respect to HCC recurrence or progression. However, data is mounting that

HCV cure results in significant and steady improvement in liver function as well as fibrosis regression [19]. Is this enough to argue for HCV treatment in patients with decompensated cirrhosis, advanced HCC, and no curative HCC treatment options? The data for such an argument is lacking at this time, and thus HCV treatment in these patients cannot be justified at this time for survival improvement.

If a patient's survival cannot be increased in patients with the most advanced cirrhosis and/or HCC, could their quality of life be improved with HCV treatment? Certainly, this question could have been answered with a resounding "No!" in the case of interferon-containing regimens. But now with a treatment that may have no side effects at all, even small improvements in quality of life for these patients might make treatment worthwhile. Indeed, many positive effects of HCV eradication have been noted which are not related to survival, but to an improved quality of life [20–22]. Any improvements in ascites or hepatic encephalopathy management, though less likely, would only further improve upon quality of life. There are data showing that treatment of decompensated patients is not only feasible, but results in excellent SVR rates with extremely tolerable side effect profiles [23, 24]. Once again, it seems one is looking for reasons WHY NOT to treat patients with HCV.

Given the above arguments, the management strategy should be to treat HCV in many if not most patients with HCC. Once again, though, the affordability barrier is limiting. While the cost of HCV treatment is declining, it is still very expensive, and even at significantly lower cost, there will likely be some patients in whom it does not make sense to treat [25, 26]. In an attempt to clarify the current state of HCV treatment in the setting of HCC, Table 1 notes patients with differing stages of HCC and the predicted survival rates of patients in these stages given best available treatments. If cost was not an issue, HCV treatment for cure could easily be recommended for all patients with the exception of those with decompensated cirrhosis. Since cost is an issue (and always will be to some extent), one may consider prioritization of patients according to the expected benefit as listed in the table. With current HCV treatment pricing, it probably does not make sense to treat decompensated cirrhotics with HCC, even if there is the a possibility of an increased quality of life with HCV cure.

Lastly, if one is going to treat HCV in patients with HCC, there is the question of timing. Given concerns of HCV treatment precipitating liver decompensation, many providers elect to treat the HCC first with locoregional therapy or resection and then wait to observe good tumor response prior to embarking on HCV therapy. This disarticulation of HCV and HCC treatment is a holdover from the days of interferon/ribavirin (and first-generation protease inhibitor) regimens, where hepatic decompensation with treatment was an ever-present reality. With the available DAA regimens, however, liver decompensation rarely develops, and there is less of an impetus to treat HCC and HCV serially rather than in parallel. Good data to support concomitant treatments are lacking, but the mounting evidence of DAA safety suggests that HCV can be treated while in the midst of the HCC treatment plan. While toxicities related to interactions of HCC treatments and DAAs have not been reported, they are possible and more data needs to be collected to guide management in this field.

Conclusions

Rarely in modern times has such a marked and sudden improvement in a mortal disease occurred as in the field of hepatology with HCV infection. Most medical advancements are incremental, but the advent of new DAAs for HCV treatment can hardly be described as gradual, especially when remembering the many patients suffering through interferon-anchored regimens for the last 20 years. With these new medications, it is becoming increasingly difficult to find reasons to leave virtually any patient untreated. However, while it is generally accepted that patients with advanced fibrosis, co-infection with HIV, post-liver transplant, and extra-hepatic manifestations of HCV should be prioritized for treatment, it has been more difficult for the healthiest (little or no fibrosis)

Table 1 Benefits and prioritization of HCV treatment in patients with HCC

Characteristics of patients with HCC	BCLC stage	Predicted survival	HCV treatment benefit
Listed for liver transplant	A, B, D	75–80%[a] 5 year [28]	Nearly certain
Resection or ablation one tumor ≤ 3 cm	0, A	82–87 % 5 year [29]	Highly likely
Resection or ablation > 3 cm/multifocal	A, B	40–76 % 5 year [30–32]	Probable
Non-curative locoregional therapy	A, B, C[b]	25–40 % 5 year [33]	Probable
Systemic chemotherapy	C	44 % 1 year [34]	Questionable
Decompensated cirrhosis	D	<6 months [35]	Unlikely

[a] Patients within Milan criteria who are transplanted and who are not too ill to tolerate treatment prior to liver transplant

[b] BCLC C patients without metastatic disease, good liver function who are amenable to locoregional therapies such as radioembolization (Y90), DEB-TACE, or SBRT

or sickest (cirrhosis with HCC) patients. HCC had been a classic contraindication to HCV treatment in the interferon days because "the math" did not work out: why subject a patient with a serious cancer to a long, expensive, toxic, and inefficacious therapy for unknown benefit? In just a handful of years, though, these realities have been turned on their heads with now-available DAA regimens. So dramatic has been the change that many in the field see HCV as a disease of the past and look forward to the next challenge regarding HCC—fatty liver, which already eclipses HCV in the USA as the greatest population-attributable cause of HCC [27•]. That may be so, but first, there must be a way to pay for this newfound silver bullet.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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