Editorial

The risk of *de novo* hepatocellular carcinoma still exists in the in the direct acting antiviral era

Stephen H. Gray[1], Mohamed G. Shoreibah[2], Jayme E. Locke[1], Jared A. White[1]

[1]Department of Surgery, Division of Transplantation, University of Alabama at Birmingham, Birmingham, AL, USA; [2]Department of Medicine, Division of Gastroenterology, University of Alabama at Birmingham, Birmingham, AL, USA

Correspondence to: Stephen Henry Gray. Department of Surgery, Division of Transplantation, University of Alabama at Birmingham, Birmingham, AL, USA. Email: sgray@uabmc.edu.

Comment on: Kwong AJ, Kim WR, Flemming JA. De Novo Hepatocellular Carcinoma Among Liver Transplant Registrants in the Direct Acting Antiviral Era. Hepatology 2018. [Epub ahead of print].

Received: 15 September 2018; Accepted: 25 September 2018; Published: 12 October 2018.

doi: 10.21037/amj.2018.09.09

View this article at: http://dx.doi.org/10.21037/amj.2018.09.09

Hepatitis C (HCV) has contributed substantially to the near doubling of hepatocellular carcinoma (HCC) incidence over the last 20 years. HCC represents the most common primary hepatic malignancy the 5th most common malignancy worldwide and the 2nd leading cause of cancer related death (1). HCC is the leading cause of death among patients with cirrhosis. HCC has the fastest growing death rate of any cancer in the United States (1). Currently, HCV is the leading indication for liver transplantation (LT) in the United States (2), without treatment HCV recurrence in the transplant allograft is nearly universal.

Successfully treating patients with HCV can lead to a sustained virologic response (SVR) and lower incidence of HCC. Research has shown that patients with SVR have lower recurrence rates compared to patients who do not achieve SVR (3). Interferon (IFN)-based therapy has demonstrated to reduce the risk of HCC in patients with cirrhosis (4,5). The estimated level of risk reduction in patients achieving SVR was 77% according to a recent meta-analysis among patients treated with IFN (5). Unfortunately, IFN based therapy is not suitable for patients with advanced disease, and often precludes use in patients with advanced liver disease listed for liver transplant. Prior to the release of DAAs many hepatologists would forego treatment in patients with advanced liver disease or require them to be listed for transplant prior to IFN based therapy.

Recently, direct-acting antivirals (DAA) have revolutionized HCV treatment and transplant outcomes. The rate of SVR in HCV patients treated with DAAs is in the vicinity of 95–98% (6). Furthermore, DAAs are better tolerated by patients with liver dysfunction, which may allow for treatment of patients at higher risk of developing HCC; such as patients with advanced liver disease. Therapy with DAAs is expected to lead to a progressive decrease in HCV-related HCC. Initially a cumulative increase of HCC may be observed because a longer at-risk period among older patients with treated HCV. The period at-risk for HCC development may be longer due to the lower risk of liver decompensation and the higher survival expectancy of cirrhotic patients with SVR following DAA therapy (7). With DAA treatment, achieving SVR may reduce the risk of HCC recurrence and occurrence (8,9). In addition, HCV treatment may result in improved liver health as evidenced by fibrosis regression, improvements in portal hypertension, and liver function (10). Importantly, HCC patients with prior SVR and compensated cirrhosis at the time of tumor diagnosis have prolonged overall survival than viremic patients (11). Therefore, DAA therapy may not only clear virus but also lead to better quality of life and overall survival. It is known that, even after SVR, the risk of HCC, although lower, persists mainly in patients already with cirrhosis (11). If patients treated with DAAs live longer there is more potential for HCC development, even if the virus is eradicated. Further research is needed to determine the appropriate HCC surveillance and characteristics that suggest increased risk.

Recent retrospective studies have questioned the safety of treatment with DAAs suggesting that DAA therapy is

associated with higher HCC incidence and recurrence rates (12,13). A study by Reig *et al.* suggested that DAA therapy may increase the risk of HCC recurrence by reduced immune surveillance dysregulating the anti-tumor response allowing for the growth of microscopic HCC tumor clones (13). Conti *et al.* found that patients previously treated for HCC have still a high risk of tumor recurrence suggesting that DAA-induced SVR does not seem to reduce occurrence of HCC (12). Both studies created significant controversy with respect to the efficacy and safety of DAA therapy. The increase in the risk of HCC may have been confounded by a shift in demographics as well as the clinical presentation where older patients with more advanced liver disease are being treated. This could be related to the better tolerability of DAAs compared to IFN.

Recently, a meta-analysis found no difference in HCC incidence or recurrence following SVR from DAA and IFN-based therapy (14). Following statistical adjustment for study follow-up time and age, there was no trend toward higher risk for HCC in DAA treated patients (14). A study performed within the Veterans' Affairs Health System found a 71% reduction in HCC risk, and no additional risk of HCC when DAA-induced SVR is compared to IFN based therapy (7).

In the current study Kwong *et al.* reported the association between HCC and listing era, specifically the incidence of *de novo* HCC in the DAA era (15). Those researchers conducted a retrospective analysis of registrants listed for LT in the Scientific Registry for Transplant Recipients database from January 2003 to December 2015. The authors divided patients into 3 eras based on listing date: Eras 1 [2003–2010], 2 [2011–2013] and 3 [2014–2015]. Era 3 is the era in which DAA based therapy became available. In order to ascertain incidence and not prevalent HCC, patients with HCC at listing or HCC exception within 180 days were excluded. The authors found the incidence of HCC was 49% higher in the DAA era. Additionally, multivariate analysis demonstrated a higher hazard of HCC in the DAA era compared to the earliest era (HR 1.22; 95% CI, 1.01–1.48). Importantly, after analysis adjusting for the competing risks of death and LT for HCC incidence, era was no longer associated with HCC (sHR 0.83; 95% CI, 0.69–1.00).

We believe this is an important study for the following reasons; firstly, this is one of the largest population-based observational cohort studies to describe HCC incidence among patients listed for LT in the United States. Importantly, the authors' methods excluded prevalent HCC cases from the analysis within the limits of the SRTR data. Secondly, the data corroborate a rising incidence of HCC in patients with HCV. The higher HCC risk among patients treated with DAA can be explained by the fact that the patients are older and have more advanced disease when compared to patients treated with IFN (14). Thirdly, the competing risk analysis appropriately considers that waitlist candidates have three potential outcomes HCC development, LT and death. Conventional survival analysis would likely censor LT and death. Importantly, one of the reasons for the increase in HCC seen in the DAA era it that HCV patients have longer waitlist time, which highlights the importance of accounting for the competing risks. The longer at-risk period is evidenced by less frequent waitlist removal for death or being too sick to undergo transplant.

In summary, this study provides very important information. It recognizes the shift in patients' demographics as well as the presentation and course of liver disease as potential risk factors for the increased risk of HCC in the DAAs era. Hence, the incidence of HCC amongst HCV patients with advanced cirrhosis, remains high. The controversy regarding HCC incidence and recurrence in patients treated with DAAs, remains a subject of debate. Meanwhile, we should all recognize the additional emphasis on close HCC surveillance in patients with advanced liver disease, especially as the age of transplant candidates increases.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *AME Medical Journal*. The article did not undergo external peer review.

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.09.09). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? Hepatology 2014;60:1767-75.
2. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2016 Annual Data Report: Liver. Am J Transplant 2018;18 Suppl 1:172-253.
3. Nagata H, Nakagawa M, Asahina Y, et al. Effect of interferon-based and -free therapy on early occurrence and recurrence of hepatocellular carcinoma in chronic hepatitis C. J Hepatol 2017;67:933-9.
4. Morgan TR, Ghany MG, Kim HY, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833-44.
5. Morgan RL, Baack B, Smith BD, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med 2013;158:329-37.
6. Jakobsen JC, Nielsen EE, Feinberg J, et al. Direct-acting antivirals for chronic hepatitis C. Cochrane Database Syst Rev 2017;9:CD012143.
7. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2017. [Epub ahead of print].
8. Knop V, Hoppe D, Welzel T, et al. Regression of fibrosis and portal hypertension in HCV-associated cirrhosis and sustained virologic response after interferon-free antiviral therapy. J Viral Hepat 2016;23:994-1002.
9. Foster GR, Irving WL, Cheung MC, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64:1224-31.
10. Cabibbo G, Petta S, Barbara M, et al. Hepatic decompensation is the major driver of death in HCV-infected cirrhotic patients with successfully treated early hepatocellular carcinoma. J Hepatol 2017;67:65-71.
11. Bruno S, Di Marco V, Iavarone M, et al. Improved survival of patients with hepatocellular carcinoma and compensated hepatitis C virus-related cirrhosis who attained sustained virological response. Liver Int 2017;37:1526-34.
12. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727-33.
13. Reig M, Marino Z, Perello C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719-26.
14. Waziry R, Hajarizadeh B, Grebely J, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. J Hepatol 2017;67:1204-12.
15. Kwong AJ, Kim WR, Flemming JA. De Novo Hepatocellular Carcinoma Among Liver Transplant Registrants in the Direct Acting Antiviral Era. Hepatology 2018. [Epub ahead of print].

doi: 10.21037/amj.2018.09.09
Cite this article as: Gray SH, Shoreibah MG, Locke JE, White JA. The risk of *de novo* hepatocellular carcinoma still exists in the in the direct acting antiviral era. AME Med J 2018;3:100.