HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Update on the Risk of Primary and Recurrent HCC With the Use of DAA Therapy for HCV Infection

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G&H What is the current understanding of the relationship between hepatocellular carcinoma and hepatitis C virus infection?

JF Hepatitis C virus (HCV) is a carcinogenic virus. There is a much higher rate of hepatocellular carcinoma (HCC) in patients infected with HCV than in patients with other types of cirrhosis. However, HCV infection almost never causes HCC in the absence of cirrhosis. Thus, the real risk factor for developing HCC among patients with HCV infection is the presence of cirrhosis.

G&H Could you discuss the report from several years ago that suggested a possible association between direct-acting antiviral therapy and increased recurrence of HCC?

JF Several years ago, a study conducted by Reig and colleagues raised the question of whether there might be a higher rate of HCC recurrence after patients achieve sustained virologic response (SVR) with direct-acting antiviral (DAA) therapy for HCV infection. The researchers of this European study found that these patients had a higher-than-expected rate of HCC recurrence (approximately 27% at 6 months). It is important to be aware of these data, but also to consider the limitations of this research and what has been reported since then. The biggest limitation with the initial study is that the researchers did not include patients with HCC and HCV infection who did not undergo treatment for their HCV, which would have comprised an important control group. When control groups have been looked at in a number of more recent studies, including a large French study and a large North American cohort of multiple sites, there does not seem to be an association between HCV cure with DAA agents and an increased risk of HCC recurrence.

G&H What, specifically, did the more recent studies find?

JF A number of studies have looked at this issue now. One of the largest was a study from France by the ANRS Collaborative Study Group on Hepatocellular Carcinoma, which looked at both primary and recurrent HCC in 3 different cohorts. The researchers found no increased risk of recurrence of HCC after HCV cure. Another study, led by Dr Amit Singal, examined a number of different centers, including the one where I work, and our findings were recently published in *Gastroenterology*. Similar to the French study, after controlling for a number of factors that could be associated with recurrence, there was no increased risk of recurrence in a group of patients who received HCV treatment compared with a group that was left untreated.

It has been suggested that perhaps there is not an increased risk of HCC recurrence, but earlier recurrence,

with DAA therapy. The study led by Dr Singal also looked at the time to recurrence. An earlier rate of HCC recurrence was not seen after HCV cure.

In addition to these 2 relatively large studies, a meta-analysis and systematic review were conducted by an Australian group led by Dr Gregory J. Dore. After controlling for follow-up time and the severity of underlying liver disease, the researchers found that DAA treatment was not associated with an increased risk of either primary or recurrent HCC compared with interferon-based HCV treatment.

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Therefore, collectively, the data suggest that there probably is not an increased risk of HCC recurrence. The reason I use the word "probably" is that the only way to know this for certain is to conduct a prospective study that randomizes patients to treatment or no treatment. Such a study would be very difficult to do and probably will never be done. Thus, we are left with using observational data and then trying to control for confounders.

G&H Has there been any recent research on the development of primary HCC after DAA treatment?

JF When providers started treating patients with DAA agents, they suddenly started to see more HCC than they were expecting. This raised the concern that DAA agents might be causing HCC. What I think is much clearer in primary or de novo HCC is that the risk is much lower in patients who are cured than in patients who are not cured. The reason that providers are seeing more HCC with DAA agents than they did with interferon is that they are treating older patients and patients with more advanced liver disease, as well as patients with more significant comorbidities or factors that might contribute to the risk of HCC, such as diabetes, fatty liver, and alcohol use. Some of these comorbidities and factors may have prevented providers from treating these patients with interferon-based therapy, but providers are still able to treat and cure these patients with DAA therapy. This is giving the impression of a higher rate of HCC in the DAA era.

There are many studies now that show that patients treated with DAA agents who achieve SVR have a much lower risk of HCC than patients who are either left untreated or who receive treatment and do not respond to DAA agents. After controlling for the severity of liver disease, the apparent increased risk with DAA agents compared with interferon disappears. The best confirmation of this likely comes from a large French study conducted by Carrat and colleagues. The results, which were recently published in *The Lancet*, showed that there was an apparent increase, but it completely disappeared after controlling for baseline factors.

G&H Has there been any recent research on whether the particular DAA regimen used affects the risk of HCC?

JF It is sometimes difficult to tease this answer out because most patients who have been treated with DAA agents have used combination regimens, often with a lot of overlap but not necessarily the same components. Most of the theories about the association between DAA agents and HCC relate more to viral clearance than to a specific carcinogenic effect of the drugs. In my opinion, the most convincing theory is that removing the virus from the liver reduces the inflammation of the liver and that some of the effect of the inflammatory cells in the liver is a nonspecific anticancerous effect from cytokines and other products. The possibility that the drugs themselves are cancer-causing has never been seriously considered, and HCC does not appear to be any more common with certain DAA regimens than others.

G&H Which patients appear to have the highest risk of primary and recurrent HCC after DAA treatment?

JF For primary HCC, the risk is clearly associated with the severity of the liver disease. The best supporting data come from comparing patients with decompensated vs compensated cirrhosis. Several long-term follow-up studies of the registration trials conducted by Gilead have shown that patients who had decompensated cirrhosis at the time of DAA therapy had a very high risk of HCC, approximately 2.6% per year, compared with less than 1% per year in patients who had compensated cirrhosis and an even lower rate in patients who did not have cirrhosis. (Data on other DAA regimens are likely similar.) All of these data show that patients with advanced liver disease who could not be treated in the interferon era are now able to be successfully cured with DAA agents, but because their cirrhosis is so advanced, they have the highest risk of HCC and, clearly, still need surveillance.

However, it can be challenging to determine whether a patient has cirrhosis or not. This may seem like an easy distinction to make, but it may not be clear for many patients. Some useful data on this issue come from large Veterans Affairs (VA) studies that categorize patients based on their baseline Fibrosis-4 score, showing that patients who have a score less than 3.25 at the time of starting DAA therapy have a very low risk of HCC. Follow-up studies have shown that this tool is useful for determining who should undergo surveillance from a cost-effectiveness perspective. It is cost-effective to continue surveillance in patients who have a Fibrosis-4 score above 3.25 at baseline, but not in patients below that threshold.

G&H When HCC does develop, approximately how long after DAA treatment does it usually occur?

JF It is difficult to answer this question. The highest HCC risk seems to be soon after DAA treatment, but it is important to keep in mind that there are 2 competing factors. One is that as time passes from viral clearance, the risk of HCC likely decreases from a virologic effect. However, as the patient accrues time free of virus, the patient's age increases, which raises the risk of HCC. When looking at large VA studies, the risk of HCC looks fairly linear, suggesting that these 2 factors likely counterbalance or cancel each other out. Therefore, for patients who have a persistent risk, it seems to be fairly stable over time at least out to 5 years, which means that patients who need surveillance should continue it long term.

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G&H Based on the research conducted to date, what are the key points involving HCV treatment and the risk of HCC? Should providers make any adjustments to traditional management of these patients?

JF The key point is that in patients with cirrhosis, providers still need to be vigilant about looking for HCC after SVR. It is critical that a fibrosis assessment be performed before treatment. As treatment is becoming easier, sometimes there has been a sense that a fibrosis assessment before treatment is not needed. However, many of the tools used to evaluate fibrosis (such as transient elastography) are not reliable after SVR. Therefore, the risk for fibrosis should be evaluated before treatment. For patients who have cirrhosis, surveillance is clearly needed, but for patients without cirrhosis, the risk appears to be low enough that providers do not need to conduct post-SVR surveillance. A tool such as the Fibrosis-4 score can be used to figure out who has cirrhosis. However, additional data are needed for confirmation.

Once patients have undergone treatment for HCC, it is very important to confirm complete response and absence of the tumor prior to starting DAA therapy, and then to be vigilant about following these patients for recurrence.

G&H Should providers wait a certain amount of time after HCC therapy before starting HCV treatment?

JF I recommend waiting not so much because I think there is a higher recurrence risk, but simply because it gives the provider some time to observe the biology of the tumor. If a patient is going to have an aggressive, early recurrence, waiting 3 to 6 months after HCC cure will help the provider define the tumor. In addition, several studies, although not all, have shown a reduced likelihood of SVR if DAA therapy is given in the presence of active HCC, suggesting that there is value in treating the HCC first. A fairly compelling VA study showed that patients with active or recently treated HCC had an approximately 20% lower likelihood of SVR than patients who never had HCC or who were treated after liver transplantation for HCC. The reduced likelihood of SVR in the presence of HCC may be because of changes in drug delivery due to the presence of the tumor (ie, the drug may be going to the tumor), or the virus may be in the tumor and may not be receiving the drug.

G&H Are there any other preventive measures that should be undertaken?

JF It is important to minimize the other risk factors for HCC, most importantly alcohol, and reduce ongoing injury to the liver. In terms of active interventions, no therapies or approaches are currently available to reduce the risk of HCC. However, it has been fairly consistently found that caffeinated coffee seems to reduce the risk of HCC in patients with advanced liver disease, so it may be reasonable to advocate that patients with advanced fibrosis or cirrhosis drink coffee at the time of HCV cure.

G&H What are the next steps of research in this area?

JF Most patients, even with cirrhosis, will never develop HCC after SVR, but surveillance is still required long term and perhaps even lifelong. Better biomarkers are needed to improve the risk stratification of patients so that providers can identify which patients do not need surveillance. A number of ongoing studies are looking at this issue and hopefully will identify either pretreatment or posttreatment factors that can determine which patients can stop undergoing surveillance.

In addition, a better understanding is needed of how and why HCC forms. We know that cirrhosis is the main risk factor, but we still do not have a clear understanding of how HCC occurs in the setting of a cirrhotic liver. This lack of understanding makes it difficult to develop good systemic therapies for HCC.

Further research is also needed to develop better biomarkers for early cancer detection. When HCC is found early, it is usually curable, but when patients present with symptomatic cancer, the outcomes are often much worse.

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Suggested Reading

ANRS Collaborative Study Group on Hepatocellular Carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: data from three ANRS cohorts. *J Hepatol*. 2016;65(4):734-740.

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