HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Hepatocellular Carcinoma Surveillance Following Hepatitis C Virus Cure

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G&H What is the current understanding of the effect of hepatitis C virus cure on the risk of hepatocellular carcinoma?

PK There have been tremendous advances in the treatment of patients with hepatitis C virus (HCV) infection. More than 95% of patients infected with HCV can now achieve sustained virologic response (SVR), or cure, with short courses (8 or 12 weeks) of direct-acting antiviral (DAA) treatment. Remarkably, those high cure rates extend to patients who have advanced disease as well as what used to be referred to as special or difficult-to-treat populations. When individuals infected with HCV first see a doctor now, they are essentially told that cure can be expected. However, anyone with advanced liver disease, particularly cirrhosis owing to HCV infection, is at increased risk for developing hepatocellular carcinoma (HCC) subsequently. HCV cure reduces that risk substantially by approximately 70%, but does not completely eliminate the risk. Thus, when clinicians see a patient with HCV infection, they should assess for the presence of cirrhosis or advanced fibrosis, as these conditions increase the risk of HCC. Patients who are at higher risk for HCC need to understand that even when their viral infection is successfully treated, they are still at risk for developing HCC after they have been cured. It is not uncommon to see in clinic individuals who were treated successfully for HCV infection who did not follow up appropriately after their cure and so return years later with advanced liver cancers that may not be amenable to locoregional therapies with or without liver transplant and are thus challenging to treat.

G&H Why does HCV treatment with DAA agents reduce the risk of HCC?

PK There are multiple postulated mechanisms. One is that HCV sets up an inflammatory cascade within the liver, which lays down a fibrotic matrix. Over time through the process of cellular injury with repair, the patient develops preneoplastic foci within the liver that, with ongoing inflammation, can subsequently lead to the development of neoplasia (HCC). Because DAA therapies effectively and abruptly stop HCV replication, they essentially reduce and subsequently arrest the inflammatory process created by the virus within the liver. It is well known that the liver is one of the organs with substantial reparative processes. For a variety of diseases, including hepatitis B and C, we know that arresting the inflammatory injurious process to the liver not only causes the inflammation to subside, but also leads to fibrosis regression over time. Thus, if patients with, say, mild to moderate fibrosis achieve SVR with DAA therapy, they can demonstrate substantial or complete regression of fibrosis if followed over time, which is highly beneficial. However, if patients develop concomitant liver diseases, the benefits of SVR may not be as significant. For example, if an individual infected with HCV is successfully treated but then has problematic alcohol consumption, the patient could still be at risk for progressive liver injury, fibrosis, and other complications.

G&H What are the main risk factors for the development of HCC in patients who have achieved SVR?

PK The driving risk factor is the degree of fibrosis. Patients with cirrhosis are at the highest risk for developing HCC. There are other risk factors as well. The type of HCV can make a difference; genotype 3 HCV infection is associated with a higher risk. Other risk factors reported to be associated with HCC risk include older age, male sex, and biochemical values reflecting more advanced liver disease. For example, a low platelet count likely reflects fibrosis and is also a risk factor for subsequent development of HCC after successful DAA treatment. Liver stiffness, as measured by elastography, is another risk factor; the higher the stiffness of the liver, the greater the risk of HCC.

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G&H What guidance has been offered regarding HCC surveillance pre- and post-SVR?

PK Treatment is generally offered to all individuals infected with HCV unless they have limited life expectancy. According to guidance from the American Association for the Study of Liver Diseases (AASLD), patients with cirrhosis (defined via liver biopsy, elastography score >12 kPa, or a noninvasive test such as the Fibrosis-4 index) should undergo HCC screening via ultrasound and alpha-fetoprotein every 6 months indefinitely. In many patients with cirrhosis, the fibrosis level can improve and cirrhosis can even be reversed. However, even with reversal, HCC screening should not be discontinued. The European guidance is quite similar; it consists of ultrasound every 6 months, but without including alpha-fetoprotein. In the presence of cirrhosis, surveillance is not controversial.

Where the societies differ is with individuals who have advanced fibrosis, or stage 3 fibrosis. The AASLD guidance is that, after achieving SVR, patients with advanced fibrosis do not need to continue HCC surveillance, whereas the European guidance states that HCC surveillance with ultrasound every 6 months should be continued in patients who had compensated advanced chronic liver disease before achieving SVR.

One of the most challenging aspects is that fibrosis is a continuum. It can be difficult to determine if what appears to be stage 3 fibrosis is actually stage 4 fibrosis transitioning to stage 3. These individuals have a greater risk of developing HCC than those who have stage 2 to 3 fibrosis. Classifying a patient's fibrosis stage can be another challenge because the fibrosis assessment may be incorrect. There are no perfect staging systems, so it is important to contextualize the level clinically, and using multiple noninvasive biomarkers can be helpful.

G&H What methods have been studied or are currently undergoing study for HCC surveillance after SVR is achieved?

PK Right now, the standard of care is ultrasound with alpha-fetoprotein every 6 months for the detection of HCC. The sensitivity and specificity of this combination are fairly reasonable, so clinicians should enroll all individuals with cirrhosis in surveillance programs. A recent meta-analysis was performed on the use of ultrasound for detecting early-stage HCC. The sensitivity was 47%, but adding alpha-fetoprotein increased the sensitivity to above 60%.

Although ultrasound with alpha-fetoprotein every 6 months is the most widely accepted method of HCC surveillance, other methods are also being studied. For instance, the GALAD score (based on gender, age, Lens culinaris agglutinin-reactive alpha-fetoprotein, total alpha-fetoprotein, and des-gamma-carboxy-prothrombin) is a prognostic risk score for the prediction of subsequent HCC. It is currently being tested against ultrasound to see if it can perform in an equivalent manner, which would be important because it would eliminate ultrasound. One of the biggest challenges associated with ultrasound use is access for routine procedures. There is also ongoing research on blood-based biomarkers looking at cell-free DNA to detect early cancer, which may have a role in the future. Multiple tests are currently in development, such as Oncoguard Liver.

G&H How cost-effective is HCC surveillance in patients who have achieved SVR and have cirrhosis or advanced fibrosis?

PK To be cost-effective, HCC surveillance should only include people with a high risk of developing HCC. Historically, HCC surveillance was recommended in those with an annual HCC risk above 1.5% because surveillance was considered cost-effective above that threshold. However, the thresholds are falling. In a cost-effectiveness

analysis of individuals infected with HCV, an annual HCC incidence greater than 1.3% met what was referred to as a meaningful willingness-to-pay threshold with an incremental cost-effectiveness ratio of less than $50,000 per quality-adjusted life year. No studies to date have looked at this issue prospectively with HCC and mortality yet.

However, most people are now adopting a more conservative threshold by considering HCC surveillance to be cost-effective when the annual HCC risk is greater than 1%. This makes surveillance of individuals with cirrhosis cost-effective. The risk of HCC in patients with advanced fibrosis (stage 3) is lower, so surveillance of these patients is not considered to be cost-effective when just considering the stage of fibrosis. That is why some people have advocated for using risk models rather than just the stage of fibrosis to decide who should be enrolled in surveillance programs and who can be successfully dismissed from clinic.

G&H How well are the recommendations for HCC surveillance being adhered to in clinical practice?

PK This is a major challenge right now. Even with our knowledge base, patients do not come back for surveillance as regularly as they should. Our group at Stanford University presented data on this issue at last year's Digestive Disease Week. We looked at patients in our center with HCV infection and documented cirrhosis who had achieved SVR and then identified those who had what we considered perfect initial follow-up. Of the 40 individuals who achieved HCV cure and subsequently developed HCC, only approximately 38% had undergone continued optimal surveillance. This was despite the fact that all patients had documentation of their first surveillance visit (ordering of their first ultrasound and alpha-fetoprotein) as well as documentation of a follow-up appointment. This experience is not different from that of many other groups. There have been multiple ongoing efforts to devise various interventions (eg, nurse phone calls) to try to improve the adherence rate for surveillance programs.

A large study from a Veterans Affairs hospital showed that patients undergoing routine surveillance were diagnosed with earlier-stage HCC than those not in surveillance programs. It is inevitable that some people are going to develop HCC despite achieving HCV cure. The key to a good outcome after developing HCC is early detection, when there are more treatment options, including resection, ablation, and liver transplant. Although we are now able to cure people of their HCV infection effectively, a number of them are having less-than-optimal outcomes when developing HCC because they are not adhering to recommended surveillance.

G&H What are the priorities of research?

PK One of the priorities is to devise optimal care models to make sure that the individuals who require surveillance for HCC remain in surveillance programs. Another priority is to make sure that these patients are educated about good liver health overall. This means reducing risk factors that can lead to liver fibrosis and inflammation progression. The 2 major risk factors being faced nowadays are alcohol use disorder and metabolic dysfunction-associated steatotic liver disease.

Additionally, it would be ideal to have an effective blood-based biomarker that could be used for HCC surveillance. This would not completely eliminate ultrasound use, but it would certainly help reduce some of the logistical barriers patients face trying to obtain an ultrasound every 6 months.

Disclosures

Dr Kwo has served as a consultant for AbbVie, Aligos, Amgen, Arbutus, Drug Farm, Durect, Genentech, Gilead, HepQuant, Inventiva, Mallinckrodt, Mirum, and Surrozen; has received grant and/or research support from Altimmune, Arrowhead, Fractyl, Gilead, Novo Nordisk, Target Registries, and Ultragenyx; and has been a stockholder of Durect.

Suggested Reading

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