HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Update on HCC Management and Review of the New EASL Guidelines

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G&H How and when were the new European guidelines for hepatocellular carcinoma management developed?

AA As part of its educational activities, the European Association for the Study of the Liver (EASL) provides clinical practice guidelines for the management of a range of liver diseases, including hepatocellular carcinoma (HCC). The last HCC guidelines were published in 2012. The goal is to regularly update guidelines to provide new guidance and reflect new data and changes in clinical practice. In 5 years, these guidelines will be reevaluated because the field is changing quickly. Development of the new HCC guidelines was a multidisciplinary effort consisting not only of clinical hepatologists, but also experts in pathology, radiology, and surgery. The development process started more than a year ago, and the full set of new guidelines was released during the most recent annual International Liver Congress, which was held this past April in Paris, France. The guidelines take into account all matters related to HCC, ranging from prevention and surveillance to diagnosis and treatment.

G&H What is the current status of surveillance of HCC? Do the new guidelines reflect any important recent changes in this area?

AA The EASL surveillance recommendations mainly reflect the patients seen in Europe, as the etiology of the underlying liver disease differs in Europe, the United States, and Asia. Thus, the recommendations mainly consider patients with chronic hepatitis C virus infection and cirrhosis due to nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), or alcohol. In contrast, most HCC patients in Asia have cirrhosis due to chronic hepatitis B virus infection. Thus, the etiology of HCC affects which groups should be surveyed and how. It is important to understand which group(s) of people are at risk for developing HCC, identify those patients, enact a surveillance strategy that allows for the diagnosis of HCC, and then implement a course of management. Thus, the first question is who should undergo surveillance. According to the new guidelines, the answer is all people with cirrhosis as well as people with advanced fibrosis (ie, F3 fibrosis or bridging fibrosis) of any etiology.

However, there is no consensus on whether surveillance protocols should be used in patients with moderate fibrosis, as these patients have a very low risk of developing HCC, even in the presence of other factors associated with the development of this disease, such as family history, age, or chronic hepatitis B virus infection. Thus, the people who have to be surveyed are the cirrhotics or precirrhotics of any etiology.

In terms of surveillance modalities, the new EASL guidelines recommend abdominal ultrasound, which is widely and easily available across Europe and considered to be common clinical practice here. It is not the most sensitive or specific measure; data have shown that computed tomography (CT) or magnetic resonance imaging (MRI) can provide higher sensitivity. However, in terms of cost-effectiveness, abdominal ultrasound has been proven to be the best method.

As for serologic markers, clinicians routinely use ultrasound plus α-fetoprotein; however, α-fetoprotein is not endorsed by EASL as part of its surveillance protocol due to the high rate of false-negative test results (ie, people with HCC may have normal α-fetoprotein values) as well as some cases of false-positive test results (ie, people with elevated α-fetoprotein values may not have HCC) and the lack of a validated recall policy. False-negative and -positive test results are common in diseases where there is a high grade of inflammation of the liver and, thus, high values of transaminases. Also routinely used in clinical practice, particularly in Japan, are des-γ-carboxy prothrombin and prothrombin induced by vitamin K absence-II, but these tools are not endorsed by the new EASL guidelines due to a lack of high sensitivity, specificity, or increase in diagnostic rate compared to ultrasound.

G&H What are the most significant changes or recommendations involving the diagnosis of HCC?

AA The main change is that the new guidelines reintroduce the use of contrast-enhanced ultrasonography, which was part of the guidelines before 2012 but was then removed due to several papers showing that this modality misclassified cholangiocarcinoma as HCC in some patients. Contrast-enhanced ultrasonography returned to the guidelines because recent studies have shown that using this modality to evaluate the top end of elimination of contrast in nodules in the liver at a later time point, compared to the previous standard, demonstrated good sensitivity and specificity for HCC. However, contrast-enhanced ultrasonography is not widely available in all centers.

Overall, in patients who are under surveillance (ie, cirrhotics or F3 fibrosis patients), the diagnosis of HCC is based upon detection of a new nodule larger than 1 cm via ultrasound. The new guidelines recommend contrast-enhanced CT or MRI as the diagnostic test of choice for HCC. As for the question of whether CT or MRI should be used, all data show that in nodules under 2 cm, MRI is more accurate and has a better sensitivity and specificity compared to CT. However, MRI machines are not widely available across Europe and, when available, they are usually not dedicated to liver diseases, making it difficult for MRI to be a first-line option. That is one of the reasons why the guidelines state that CT and MRI can be used independently

G&H How do the new guidelines address liver organ allocation for HCC patients?

AA Who should receive a liver transplant for HCC is a complicated issue. The general recommendation that EASL supports is that patients within the Milan criteria, which means patients with 1 lesion less than 5 cm or 3 pre-HCC lesions of less than 3 cm, should be evaluated for liver transplantation. However, liver transplantation is not used as the first-line treatment for these patients because there has been debate as to whether liver resection or thermoablation should be used first and then, eventually, liver transplantation for HCC recurrence. The issue is whether transplantation should be based on urgency, which means transplanting the patients who are the sickest and most in need of receiving a new liver, or whether it should be based on utility, which means transplanting the patients who would have the longest survival after receiving a new liver. In this scenario, some patients would be dying of liver disease but would not receive a transplant because they have a worse long-term prognosis than other patients. On the other hand, patients with a single nodule that is perfect for local therapy might receive a liver (because they have a better survival) even though their survival might have been similar with just local treatment instead of liver transplant.

Thus, there has been a good deal of debate on this issue. Many physicians think that the right approach is to evaluate the so-called transplant benefit, which looks at potential survival following transplantation vs after local regional therapy, with the organ going to the patient with a longer delta in survival after transplantation. However, this approach is not endorsed by the new EASL guidelines. The guidelines have a long section debating the pros and cons of this approach, but, in the end, could not reach a consensus. Thus, liver allocation policies for HCC patients are still in development, and most liver transplant centers in Europe have different policies, particularly in different countries, but even within the same country.

G&H How are downstaging and bridging therapy addressed in the new guidelines?

AA It is universally accepted in Europe, and, thus, reflected in the new EASL guidelines, that HCC patients can be downstaged, which means that once they are diagnosed with HCC and are beyond liver transplant criteria, they can undergo treatment for the nodule(s) to be downstaged in order to re-enter the liver transplant criteria and then undergo liver transplantation. The use of bridging therapy is also accepted by the guidelines, which recommend that a patient with HCC within the transplant criteria undergo bridging treatment for HCC while on the transplant waiting list so that the burden of the cancer does not progress to reach values beyond the transplant criteria.

G&H According to the new EASL guidelines, what are the current recommendations for systemic therapy in HCC patients?

AA Systemic therapy applies to Barcelona Clinic Liver Cancer (BCLC) stage C patients, who have an advanced stage of HCC (ie, either portal invasion or extrahepatic spread) but have preserved liver function. Until last year, these patients had only 1 treatment option (sorafenib; Nexavar, Bayer). Sorafenib is a tyrosine kinase inhibitor that has been shown to be effective and to improve survival compared to placebo by at least a mean of 3 or 4 months. However, some patients have to stop treatment either due to side effects or lack of response. Data are now available on another first-line drug, lenvatinib (Lenvima, Eisai). Compared to sorafenib, lenvatinib is not inferior in terms of efficacy and has a very similar safety profile.

In the past, there was a lack of data on second-line therapies, which meant that the patients who failed or had to discontinue sorafenib were left without other systemic treatment options and were just undergoing general management (eg, nutritional support, pain control). Data are now available for regorafenib (Stivarga, Bayer), which has been shown to improve survival compared to placebo as a second-line therapy, and has been approved by the European Medicines Agency. There are also some data available on the promising checkpoint inhibitor nivolumab (Opdivo, Bristol-Myers Squibb), which has not yet been approved in Europe, but is approved in the United States.

G&H What is the current status of other therapeutic options for HCC?

AA According to the guidelines, the BCLC system is still the standard of care to guide treatment for HCC. In this system, physicians need to evaluate the tumor burden (number of lesions), presence of extrahepatic disease, grade of liver function, presence of portal hypertension, and performance status. Based on these variables, patients can be classified as having BCLC 0, A, B, C, and D. Survival in these patients ranges from 5 years in the least advanced BCLC stage to 3 months in the most advanced BCLC stage; thus, the endpoint of HCC treatment differs among these classes. BCLC 0 and A qualify for curative treatment options (liver transplantation, radiofrequency thermal ablation, percutaneous ethanol injection, and surgical resection), whereas patients with BCLC B qualify for transarterial chemoembolization/transarterial embolization as first-line treatment. BCLC stage C and D patients, on the other hand, qualify for systemic treatment or best supportive care, as mentioned above.

G&H Do the new guidelines note any other important changes in HCC management?

AA The guidelines offer a slight refinement involving HCC diagnosis, in which liver biopsy in the presence of undefined nodules exceeding 1 cm has a more prominent role. Thus, if there is a new nodule on the liver that cannot be diagnosed as HCC using CT or MRI, liver biopsy should be used immediately to assess the potential of this nodule being an anaplastic lesion. Previous guidelines had recommended using repeated radiologic assessments rather than liver biopsy in such a situation.

G&H What are the most important areas for future research in HCC management?

AA HCC is lagging behind other types of oncology in terms of predictors of failure, progression, and rapid progression survival, as we are still using techniques from 10 or 20 years ago, such as liver function, α-fetoprotein values, the number of nodules, and the presence of vascular invasion. In addition, there has been a lack of research on molecular classification of HCC subtypes and the prognostic role of this classification on survival and on response to treatment. There are several issues with this. The first is that a liver biopsy is not being performed on all nodules, which means that there is a lack of information on the histologic features of most HCCs because the diagnosis is being based on CT or MRI. The second is that there is extreme heterogeneity in the cancer cells and in the underlying liver disease, and different causes of liver disease lead to different types of inflammation and activation of pathways leading to HCC. Liver biopsy is not a good tool to assess the expression of genes or pathways. New markers are needed to definitively improve diagnostic yield.

In addition, there is a need for better biomarkers in terms of surveillance and diagnosis. α-fetoprotein is far from perfect. As mentioned previously, it is not endorsed by the EASL guidelines, has been used for decades, and has a low sensitivity and specificity.

Dr Aghemo has no relevant conflicts of interest to disclose.

Suggested Reading

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