

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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The Use of Albumin-Bilirubin Grade in Patients With Hepatocellular Carcinoma



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G&H How and why did albumin-bilirubin grade come to be used in patients with hepatocellular carcinoma?

PG Over a decade ago, the SHARP trial demonstrated the effectiveness of systemic therapy for patients with hepatocellular carcinoma (HCC). This was the first systemic therapy trial to consider liver function and use Child-Pugh A status as an inclusion criterion. There had been many earlier trials of systemic therapy for patients with HCC, but all had failed. These trials were unable to demonstrate antitumor impact from systemic therapy because the patient populations were heterogeneous. The confounding impacts of liver disease and liver function were underestimated, which did not allow for differentiation of death caused by liver disease from death caused by tumor. However, Child-Pugh scoring also has disadvantages in that it includes objective and subjective components. In particular, the quantification of symptoms such as ascites and encephalopathy is difficult. Doctors have tried to use easier and more objective measures to assess liver function. Albumin-bilirubin grade enables doctors to evaluate the function of the liver by using only 2 parameters (albumin, an indicator of synthetic liver function, and bilirubin, an indicator of excretory liver function), rather than the 5 parameters of the Child-Pugh score. Albumin and bilirubin have been shown to be reliable and to have prognostic value in all settings of patients with HCC, from early-stage disease to advanced-stage disease.

G&H Why is assessment of liver function so important in patients with HCC?

PG If assessment of liver function is neglected, it may be difficult to see the impact of antitumor therapy. Good liver function is needed for a patient to live long enough to demonstrate whether a therapy has antitumor efficacy.

A large number of mostly retrospective analyses have shown that albumin-bilirubin grades 1, 2, and 3 are predictive of overall survival, progression-free survival, and objective response in patients with HCC.

In addition, there is still a tendency to underestimate the role that liver function plays in patients with HCC. In this setting, doctors need to consider more than just the tumor. There is underlying liver cirrhosis and there

may also be ongoing inflammation contributing strongly to the patient's outcome.

G&H How is albumin-bilirubin grade calculated and categorized?

PG Albumin-bilirubin grade is a score determined by a mathematic equation that takes both albumin and bilirubin into account. Thresholds are used to categorize albumin-bilirubin grades 1, 2, and 3, with grade 1 signifying good liver function and grade 3 signifying poor liver function. A modification has also been developed to separate grade 2 into 2a and 2b to fine-tune prognostic value.

G&H What research has demonstrated the prognostic value of using albumin-bilirubin grade in patients with HCC?

PG A large number of mostly retrospective analyses have shown that albumin-bilirubin grades 1, 2, and 3 are predictive of overall survival, progression-free survival, and objective response in patients with HCC. These analyses have included patients with HCC being treated with resection, ablation, liver transplantation, transarterial chemoembolization, and various systemic therapies (mainly tyrosine kinase inhibitors). For example, the phase 3 REFLECT trial, which compared lenvatinib (Lenvima, Eisai) with sorafenib (Nexavar, Bayer), clearly demonstrated that patients with lower (ie, better) albumin-bilirubin grades had higher objective response rates. This trial also showed that both lenvatinib-treated patients and sorafenib-treated patients had a longer median overall survival if their albumin-bilirubin grade was 1 compared with 2. In contrast, a higher albumin-bilirubin grade has been shown to correlate with the development of treatment-emergent adverse events.

G&H Could you discuss the use of albumin-bilirubin grade in HCC patients receiving immunotherapy, such as atezolizumab and bevacizumab combination therapy?

PG A retrospective, post-hoc subgroup analysis of the IMbrave150 trial separated patients with albumin-bilirubin grade 1 from those with albumin-bilirubin grade 2. The hazard ratio for patients treated with atezolizumab (Tecentriq, Genentech) and bevacizumab (Avastin, Genentech) vs sorafenib was the lowest (best) in albumin-bilirubin grade 1 patients. It was very clear that patients with albumin-bilirubin grade 1 did much better than patients with albumin-bilirubin grade 2. Both progression-free survival and overall survival were better in

patients with albumin-bilirubin grade 1 vs albumin-bilirubin grade 2.

These correlations go beyond the new standard of care, atezolizumab and bevacizumab. Patients with low albumin-bilirubin grades who are treated with nivolumab (Opdivo, Bristol Myers Squibb) and pembrolizumab (Keytruda, Merck) have also shown improved overall survival. Thus, the prognostic value of albumin-bilirubin grade is consistent across therapies as well as stages of HCC.

G&H Overall, what other advantages are there to using albumin-bilirubin grade, particularly in comparison with the Child-Pugh score?

PG Albumin-bilirubin grade is a simple tool to use and is objective. Albumin and bilirubin are typically part of routine laboratory workup in patients with HCC, so these 2 parameters are usually already on file and doctors are

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familiar with them. Albumin and bilirubin are 2 of the 5 components of the Child-Pugh score, so it is attractive to reduce the number of components needed for assessment as well as eliminate subjective parameters.

In addition, albumin-bilirubin grade is a more fine-tuned assessment of liver function and can stratify patients who have the same Child-Pugh score. For example, the IMbrave150 trial included only Child-Pugh A patients, but albumin-bilirubin grade provided further assessment and allowed researchers to separate approximately 60% of patients into albumin-bilirubin grade 1 vs approximately 40% into albumin-bilirubin grade 2.

G&H Are there any disadvantages to using albumin-bilirubin grade?

PG The main disadvantage is that most of the analysis performed on albumin-bilirubin grade has been retrospective and this grading system has not been used as a stratification factor in clinical trials until recently. Therefore, the available evidence is limited. Having said that, a large

number of recent trials in all stages of HCC with all therapies, beginning with curative-intent therapies and ending with palliative treatment with immunotherapy, have shown the prognostic value of albumin-bilirubin grade.

G&H Should this grading system be avoided in any patients with HCC?

PG Albumin-bilirubin grade appears to be a global assessment tool. Although it is less relevant in patients receiving a liver transplant, for example, because the transplant dramatically affects liver function, it has been shown to predict outcome in transplanted patients.

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

PG At my institution, my colleagues and I routinely assess albumin-bilirubin grade. However, prospective assessment in clinical trials is needed in which albumin-bilirubin grade is used as a stratification factor in order to prove that what has been postulated in retrospective trials holds true in a prospective setting. I have no doubt that albumin-bilirubin grade would also perform well in prospective clinical trials, which would provide higher-grade evidence. As mentioned, the evidence thus far mainly consists of retrospective, post-hoc analyses. There are several trials currently underway, in various stages of HCC (including intermediate-stage HCC), in which albumin-bilirubin grade is being used for stratification. These studies will have more clearly separated patient subgroups, albumin-bilirubin grade 1 vs grade 2, upfront.

What is most urgently needed in HCC, however, is not just a prognostic tool but a predictive tool that can

help doctors make treatment decisions. That does not exist yet. Although a high albumin-bilirubin grade indicates poor liver function and we know that treatment will not work as well in such a setting, albumin-bilirubin grade is not helpful for therapeutic decision-making. Prediction of therapeutic outcome is more complex. Liver function can be a part of clinical predictive markers, but is not sufficient to be a predictive biomarker by itself.

Disclosures

Dr Galle has received honoraria from Bayer, Boston Scientific, AstraZeneca, Adaptimmune, BMS, Eisai, MSD, Sirtex, Lilly, Roche, Guerbet, and Ipsen.

Suggested Reading

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