

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Liver Transplant and Hepatocellular Carcinoma



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G&H How are donor livers currently allocated to patients in need of a transplant?

RW The current allocation system for patients with chronic liver disease is based upon patients' Model for End-Stage Liver Disease (MELD) score and allocates organs across 11 geographic regions in the United States. The overarching goal is to provide liver transplants first to the sickest patients, who are the ones in greatest need. This allocation system uses objective measures based upon laboratory tests (ie, MELD and MELD-Na scores) to determine the severity of liver disease. The MELD score is calculated from a patient's serum bilirubin level, international normalized ratio, and serum creatinine level, whereas the MELD-Na score is a recently adopted, modified MELD score that incorporates serum sodium. All revisions of the MELD score aim to improve the accuracy of determining prognosis and, thus, priority for liver transplantation.

The algorithm for organ distribution is complex, but the concept is that organs that become available are generally offered to patients within the same region as the donor, starting with the most urgent patients first. Recent changes to the allocation system have attempted to allow broader access to liver transplantation among those with the highest MELD scores. The Share 35 policy expands the geographic area of organ sharing for patients with MELD scores of 35 or greater before organs are offered to patients with lower MELD scores.

G&H Within the current allocation system, how does hepatocellular carcinoma factor into the MELD score?

RW Patients who meet certain criteria, such as having hepatocellular carcinoma (HCC), are given MELD exception points (ie, extra points) to increase their priority for receiving a liver transplant. The concept of the MELD exception point system is to better capture an individual's mortality risk. For conditions such as HCC, the biological MELD score may not accurately capture the patient's mortality risk given that the degree of hepatic dysfunction may not be very severe even though HCC increases near-term mortality. To improve prognostication, MELD exception points are given, which increases the chances of receiving a liver transplant.

However, many studies have suggested that patients with HCC are overprioritized with the MELD exception policy. Therefore, in 2015, the MELD exception policy for HCC was modified to include a 6-month waiting period prior to receiving MELD exception points. The impact of this revision on waitlist outcomes among patients with and without HCC remains to be seen.

G&H Do you think that patients with HCC are still overprioritized, or are they underprioritized now?

RW I think that the answer to this question cannot be determined yet. When MELD exception points were first granted to patients with HCC, several studies showed that these patients were overprioritized, meaning that they had much lower waitlist mortality compared with patients with decompensated liver disease. Current modifications to the MELD exception policy for HCC attempt to address this issue, and future studies will need to evaluate the impact of these changes on liver transplant waitlist

outcomes among patients with and without HCC in the United States.

The issue of prioritization is very tricky because a limited number of organs are available, the number of donor organs is not expected to increase significantly in the near term, and the number of patients being listed may be increasing. Thus, there is an imbalance between the number of patients who need a transplant and the number of organs available to be transplanted. Given this imbalance, allocation policies may be revisited to try to better equalize distribution of organs, but regardless of which policies are used, some groups will benefit more than others.

G&H Does a patient's α -fetoprotein level justify a change in MELD score?

RW The role of α -fetoprotein in patients with HCC is controversial because the prognostic value of this laboratory test is still not completely known. The current guidelines from the American Association for the Study of Liver Diseases do not recommend the use of α -fetoprotein for screening, but this test likely does have some prognostic value in patients who have confirmed HCC. Currently, there are no specific cutoffs for α -fetoprotein, and, in my opinion, a single value may not be very important. However, α -fetoprotein levels may have some prognostic value in the context of longitudinal changes (eg, doubling of levels among patients listed or being considered for liver transplant).

α -Fetoprotein is also useful in patients who are initially outside of criteria for transplant who receive locoregional therapy to bridge them to transplant. Monitoring α -fetoprotein levels after transarterial chemoembolization may add some prognostic value to determine whether or not these patients will have a high risk of posttransplant recurrence.

G&H What are the University of California, San Francisco downstaging criteria for patients with HCC?

RW Nationally and internationally, various sets of criteria have been used to evaluate eligibility for liver transplantation. The most common and internationally recognized criteria are the Milan criteria. The University of California, San Francisco (UCSF) criteria, which have been adopted by several centers, have also been shown in several studies by UCSF and other institutions to be able to expand eligibility while at the same time achieving very comparable outcomes.

According to UCSF downstaging criteria, patients with tumor burden that does not meet the current

thresholds for liver transplant in terms of size or number can be treated with locoregional therapy to fulfill the criteria for liver transplant. The goal of downstaging criteria is to bring transplant as a curative option into reach for patients who would not otherwise qualify using, for example, the Milan criteria. Some of the patients outside of the Milan criteria may still have the potential to achieve a curative response, in which case they may be good candidates for liver transplant.

G&H Are there any disadvantages to using downstaging criteria?

RW Downstaging criteria allow some patients to achieve long-term improved outcomes by qualifying them for curative treatment. However, although the criteria have been validated and have shown promise at attempting to predict recurrence, we still do not have good tools, markers, or models to accurately and consistently predict the risk of posttransplant recurrence.

Furthermore, although downstaging can help individual patients improve their outcomes by expanding access to liver transplant, we must be cautious when selecting the most appropriate patients who will benefit from liver transplant, especially given the continued imbalance between the number of patients awaiting liver transplant and the number of livers available for transplant.

G&H Should patients with small lesions who achieve complete ablation with liver-directed therapy receive MELD exception points in the absence of imaging evidence of HCC?

RW There is no clear consensus on this issue. Many patients who have very small or solitary lesions that are limited to a single lobe undergo nontransplant curative treatments. Surgical resection (if the lesion meets size guidelines) or radiofrequency ablation can be curative in these patients.

If patients do not qualify for surgical resection or radiofrequency ablation, the big question—after determining whether the tumors have undergone an adequate amount of locoregional therapy—is whether the patients still require transplant. The answer is probably yes, because locoregional treatment (with the exception of radiofrequency ablation) is not curative. However, it is unclear whether these patients still require the same amount of priority that they would be assigned with the current MELD exception policies. This is an area that deserves further research to determine how to prioritize HCC patients who seem to have been adequately treated with locoregional therapy and how to monitor them as they wait for liver transplant.

G&H What is the role of sorafenib in patients with HCC who are waiting for liver transplant?

RW The role of sorafenib (Nexavar, Bayer) became well known based upon the results of the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial, which evaluated sorafenib use in patients with HCC who were not candidates for surgery. This study showed improvement in mortality with sorafenib compared with standard treatment. Although sorafenib has not been shown to cure HCC or shrink tumors, multiple studies have demonstrated that it is able to delay disease progression and growth. For that reason, there may be a role for sorafenib in controlling tumor spread or growth in patients with HCC who are awaiting liver transplant.

A cost-benefit analysis was conducted by Vitale and colleagues on the use of sorafenib in HCC patients prior to liver transplantation. Using a Markov model approach, the researchers compared 2 strategies: sorafenib as neoadjuvant therapy prior to liver transplantation vs no therapy while waiting for liver transplantation. Patients in the sorafenib arm were 5% more likely to receive liver transplant than those who did not receive sorafenib and also had a net health benefit of 37 quality-adjusted life days. However, in a study of 33 patients with HCC who were listed for liver transplantation, Truesdale and colleagues observed higher complications following transplantation among patients who had been treated with sorafenib (n=10) than among those who had not (n=23).

Overall, the current evidence suggests that sorafenib is effective in select cohorts to prevent disease progression, which makes sense based upon the mechanism of the drug, but it is currently reserved for patients whose condition is not amenable to surgical or locoregional therapy. I think the drug also has potential as an earlier line of therapy to treat HCC recurrence or even in the management of initial HCC in combination with other locoregional therapies, but more data are needed to understand the clinical outcomes achieved and whether use of the drug is cost-effective.

G&H What are the next steps in research in terms of HCC and liver transplant?

RW I think one area of exciting research as it relates to HCC and liver transplantation involves developing better prediction models for waitlist mortality as well as for post-liver transplant outcomes, including recurrence. Utilizing molecular markers may help us develop assays or models to predict recurrence and to better understand the character of HCC, such as its natural history and risk of disease progression. We currently treat patients with HCC similarly in many ways, but many providers who care for these patients have seen variations in disease progression. Different HCCs may have different natural histories, aggressiveness, disease progression, and risk of recurrence. Better understanding this information would help providers develop individualized patient-centered treatment options. It is also important from a public health perspective to understand the risk of recurrence and to prognosticate outcomes in order to guide therapies for all HCC patients. Having better prediction models might trigger changes in the therapeutic approach to HCC.

Dr Wong has no relevant conflicts of interest to disclose.

Suggested Reading

- Bhat M, Ghali P, Dupont B, et al. Proposal of a novel MELD exception point system for hepatocellular carcinoma based on tumor characteristics and dynamics [published online October 14, 2016]. *J Hepatol*. doi:10.1016/j.jhep.2016.10.008.
- Heimbach JK, Hirose R, Stock PG, et al. Delayed hepatocellular carcinoma Model for End-Stage Liver Disease exception score improves disparity in access to liver transplant in the United States. *Hepatology*. 2015;61(5):1643-1650.
- Truesdale AE, Caldwell SH, Shah NL, et al. Sorafenib therapy for hepatocellular carcinoma prior to liver transplant is associated with increased complications after transplant. *Transpl Int*. 2011;24(10):991-998.
- Vitale A, Volk ML, Pastorelli D, et al. Use of sorafenib in patients with hepatocellular carcinoma before liver transplantation: a cost-benefit analysis while awaiting data on sorafenib safety. *Hepatology*. 2010;51(1):165-173.
- Washburn K, Edwards E, Harper A, Freeman R. Hepatocellular carcinoma patients are advantaged in the current liver transplant allocation system. *Am J Transplant*. 2010;10(7):1643-1648.
- Wedd JB, Nordstrom E, Nydam T, et al. Hepatocellular carcinoma in patients listed for liver transplantation: current and future allocation policy and management strategies for the individual patient. *Liver Transpl*. 2015;21(12):1543-1552.
- Wong RJ, Devaki P, Nguyen L, Cheung R, Cho-Phan C, Nguyen MH. Increased long-term survival among patients with hepatocellular carcinoma after implementation of Model for End-Stage Liver Disease score. *Clin Gastroenterol Hepatol*. 2014;12(9):1534-1540.e1.
- Young K, Aguilar M, Gish R, et al. Lower rates of receiving Model for End-Stage Liver Disease exception and longer time to transplant among nonalcoholic steatohepatitis hepatocellular carcinoma. *Liver Transpl*. 2016;22(10):1356-1366.

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