Growing need of adjuvant therapy and expanded access for liver transplant in hepatocellular carcinoma

V. V. Pavan Kedar Mukthinuthalapati[1]^, Shweta Gupta[2]

[1]Division of Gastroenterology, University of Massachusetts Chan Medical School-Baystate, Springfield, MA, USA; [2]Department of Medicine Quality Council, John H Stroger Jr. Hospital of Cook County, Chicago, IL, USA

Correspondence to: V. V. Pavan Kedar Mukthinuthalapati, MD. Division of Gastroenterology, University of Massachusetts Chan Medical School-Baystate, 759 Chestnut St., Springfield, MA 01109, USA. Email: mvvpavankedar@gmail.com.

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Hepatocellular carcinoma (HCC) accounts for about 75% of all liver cancers (1). Viral hepatitis, alcoholic liver disease, and non-alcoholic fatty liver disease are the most common risk factors of cirrhosis, and HCC worldwide (2). Close to 80% of the HCC cases arise in the background of cirrhosis (3). Localized or resectable HCC can be treated with ablation or surgical resection (4). Surgical resection as a curative treatment account for the planned treatment of only 5–10% of HCC patients in Western countries and is associated with survival rates of nearly 70% at 5 years (4). However, such an approach is not feasible in patients with limited hepatic reserve, as seen in patients with cirrhosis with portal hypertension or impaired liver synthetic function. Liver transplantation (LT) offers an optimal treatment for both underlying liver disease and HCC (4). Currently, HCC is the largest indication for LT in the United States and comprises 15-50% of LT recipient indications in various countries. However, the organs available for transplant are in short supply throughout the world and need to be judiciously allocated to this population (5).

Efforts to widen selection criteria for liver transplantation

There have been numerous ongoing efforts to select patients who will benefit the most from LT. In the landmark trial by Mazzaferro *et al.* in 1996, Milan criteria were used for selecting patients for LT, which included solitary HCC <5 cm or 3 lesions ≤3 cm in size (6). The 4-year overall survival and recurrence free survival rates for patients meeting the Milan criteria in this trial were 85% and 92%, respectively (6). Numerous other criteria have been proposed for LT selection such as University of California San Francisco (UCSF) criteria, Up-to-seven criteria, Total tumor volume and alpha-fetoprotein (AFP) criteria, Kyoto criteria and Extended Toronto criteria, that have led to the respective overall survival (OS)/at years of follow-up of 81%/5 years, 71%/5years, 75%/4 years, 65%/5years, and 68%/5years (5,7). Currently, Milan criteria remain the benchmark for allocation, with most widespread acceptance. However, there has been a gradual paradigm shift towards selecting patients based on tumor biology rather than radiological criteria (7).

Efforts to downstage HCC

Downstaging the HCC tumor to within the acceptable Milan criteria through neo-adjuvant treatment of HCC has been reported with some success (8). Varying loco-regional treatments (LRTs) such as trans arterial chemoembolization

^ ORCID: 0000-0003-3687-1927.

(TACE), selective radioembolization with yttrium-90 labeled microspheres, and/or radiofrequency ablation (RFA) have been tried. The type of LRT is contingent upon location of tumor, underlying liver function, as well as local expertise for each treatment modality (8). In 2016, United Network for Organ Sharing (UNOS) adopted the UCSF criteria for selecting patients towards downstaging. A recent systematic review and meta-analysis validated this approach and showed that the patients with HCC selected using UNOS-Downstaging Criteria (UNOS-DS) were more likely to have a successful downstaging response. Close to half of the patients who were down staged using UNOS-DS criteria underwent transplantation, with post-LT 1-year and 5-year survival rates of 94% and 74%, respectively (9). The results also reveal that there is an upper limit of the tumor, beyond which the downstaging approach may not be commensurate with good survival outcomes. These survival rates are very close to those selected for LT using Milan Criteria. European association of liver disease currently recommends against downstaging approach (10). However, this approach is recommended by American Association for the Study of Liver Diseases (AASLD) (4). Some authors have postulated that the successful downstaging response to LRT can be viewed as a function of favorable tumor biology (11). American Association for the Study of Liver Diseases (AASLD) recommends this approach while the European Association of Liver Disease currently recommends against downstaging (4,10).

Improving post-transplant outcomes

Tumor recurrence after LT occurs at a median of 12 to 16 months post transplantation (12). This is thought to be likely secondary to failure of accurate pre-transplantation staging (12). Late recurrence occurs when seeding of such cells remain latent and less in number for a long time. This is rare in the case of HCC (12). Attempts at adjuvant treatment modalities is based on an intent to eliminate these occult metastases.

Sirolimus has anti-proliferative and anti-vascular endothelial growth factor (anti-VEGF) properties. Post-transplant immunosuppression modifications in the form of replacement of other agents with sirolimus, which has anti-proliferative and anti-VEGF properties, has been shown in various retrospective studies to have a modest effect in decreasing the recurrence rate of HCC post-LT (13-18). However, randomized controlled trial (RCT) data did not show any significant benefit in reducing HCC recurrence with such modifications (19). The benefit was also more commonly noted in those within Milan's criteria for selection, keeping the importance of the original selection criteria for transplant (19).

Adjuvant systemic treatments have been tried in several studies. Single agent sorafenib was the first approved first line systemic treatment for advanced HCC (20). Some retrospective studies have shown that sorafenib decreased the recurrence rates of HCC after LT (21,22). However, strength of the evidence is weak, retrospective in nature or without a prospectively enrolled control group, and with inconsistent results (21-24). Currently, the most effective frontline systemic treatment for advanced HCC is the combination of atezolizumab and bevacizumab. This has a very durable and highest recorded improvement in survival till date (25,26). Atezolizumab being an immunotherapeutic agent (check-point inhibitor) would increase the risk of rejection and hence cannot be used in the post-transplant setting (27). Single agent Lenvatinib which has a wide range of tyrosine kinase activity was proven to be non-inferior to sorafenib in treatment of advanced HCC (28). A case-control retrospective study found potential of Lenvatinib for prolonging survival in the adjuvant setting after LT, but the study was very small with a sample size of only 23 patients (29).

In the current issue of the journal, Guo *et al.* discuss their findings in the article: "*Efficacy and safety of Lenvatinib for preventing tumor recurrence after liver transplantation in hepatocellular carcinoma beyond the Milan criteria*" (30). This is the largest study to date on this subject with 242 patients and adds evidence to this field. The authors report a retrospective study, in which Lenvatinib was recommended in those with high risk of recurrence. High risk features for Lenvatinib administration included multiple lesions, microvascular invasion on pathology, poor differentiation of tumor and positive post-operative AFP, or positive prothrombin induced by vitamin K absence-II. The adjuvant treatment was given for a period of 2 years. There was no difference in time to recurrence or overall survival between the Lenvatinib and control group in the overall population. However, a positive treatment effect in the form of significantly decreased incidence of early recurrence and 2-year post-transplant recurrence was noted in patients beyond the Milan criteria who underwent LT.

Based on prior experiences, selection criteria beyond Milan's criteria likely selected a group that was already at a higher risk of early recurrence. Hence, it is understandable that the authors noted the highest treatment effect in

patients who were beyond Milan's criteria. Also, despite a better recurrence free survival, there was no difference in OS between the groups in the study. The sample size and follow-up duration may not have been enough to show an OS benefit in the current study. Another caveat that prohibits the external validity of these conclusions is that despite being the largest study on this topic, it is retrospective in nature. The authors have commendably used propensity matching to decrease the selection bias in the study to decrease the risk of this. Bigger RCTs would be needed to study this further and to recommend this treatment.

Lenvatinib was better tolerated in this study than in the original RCT, with 31% grade 3 treatment related adverse events, compared to 75% in the original RCT of Lenvatinib (31). This is noted in spite of a longer median duration of treatment in this currently study. The better tolerance may be secondary to absence of impaired liver function after the LT in this study. Overall, this study serves as a great steppingstone towards further research on this topic. Several questions would need to be answered before widespread use of adjuvant Lenvatinib for HCC post-LT. For example, would adjuvant Lenvatinib be useful in all HCC patients who undergo transplant? Would addition of adjuvant Lenvatinib help widen the selection criteria beyond Milan's criteria for transplant? Would down-staged HCC patients undergoing transplant have better outcomes with adjuvant Lenvatinib? As the authors pointed out, large RCTs with multi-center design would be the next step before Lenvatinib's role for these indications can be studied.

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