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ASO Author Reflections: Pre-transplant Treatments for Patients with Hepatocellular Carcinoma Before Liver Transplantation

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PAST

Liver transplantation (LT) is accepted as an ideal treatment for hepatocellular carcinoma (HCC).[1] Five-year overall survival rates after LT have been reported to be 70–90% in appropriately selected cases.[2] However, disease progression during waiting time for LT is one of the significant concerns. To reduce the risk of dropout from the waitlist, pre-LT HCC treatments are often provided for patients with HCC while they are on the waitlist. Pre-LT HCC treatment is also considered as downstaging or bridging therapies to LT for patients with advanced HCC.

According to a recent multicenter study, patients who achieved pathological complete response (pCR) showed significantly lower risk of post-LT recurrence and superior survival among patients who received pre-LT locoregional therapies.[3] However, it is unclear which modalities have possible superiority to achieve pCR, especially in patients with advanced HCC. In addition, while a multicenter study investigating the effects of bridging locoregional therapy within Milan criteria showed that receipt of three or more locoregional therapies was associated with HCC recurrence,[4] further investigations into the impact of pre-LT HCC therapies on post-LT outcomes are warranted.

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PRESENT

We reviewed 179 initial liver transplants for patients with HCC. Among them, 151 patients (84%) received pre-treatment for HCC before LT, and 42 (28% of treated patients) demonstrated pCR. Twenty-two (12%) patients experienced recurrence after LT. The proportions of patients who showed beyond transplant criteria at initial diagnosis were 35% (Milan criteria), 31% (University of California San Francisco [UCSF] criteria), 13% (Up to 7 criteria), and 17% (Japanese 5-5-500 criteria). Downstaging rates were 35% (Milan criteria), 53% (UCSF criteria), 39% (Up to 7 criteria), and 58% (Japanese 5-5-500 criteria), respectively. Compared with patients within transplant criteria at both initial diagnosis and LT, the cumulative incidence of post-LT HCC recurrence was significantly higher in patients who showed beyond transplant criteria at both initial diagnosis and LT ($p < 0.001$ in each criteria). There was no statistical difference between patients who showed within-transplant criteria at both initial diagnosis and LT and patients who showed downstaging ($p = 0.24$ in Milan criteria; $p = 0.10$ in UCSF criteria; $p = 0.74$ and $p = 0.22$ in Japanese 5-5-500 criteria). Cumulative incidence of post-LT recurrence was lower in the pCR group than the non-pCR groups (1-, 3-, and 5-year rates of 4.8%, 4.8% and 4.8% vs. 9.3%, 15.4% and 19.2%, respectively; $p = 0.03$). In bivariable analyses with other significant covariates, pCR significantly decreased the risk of recurrence. In multivariable analysis, the treatment modalities most strongly associated with pCR were Yttrium-90 (Y90; odds ratio [OR] 3.60, 95% confidence interval [CI] 1.23–10.50; $p = 0.01$) and ablation (OR 2.97, 95% CI 1.07–8.19; $p = 0.03$). Among the 137 patients without pCR (viable HCC in the explant), 28 (20%) had no pre-treatment (A), 70 (52%) had one treatment (B), and 39 (20%) had multiple treatments (C). The cumulative incidence of post-LT HCC recurrence was highest in Group C (1-, 3-,

and 5-year rates of 0%, 3.9% and 8.2% in Group A; 0%, 4.6% and 6.5% in Group B; and 21.1%, 30.5% and 39.6% in Group C, respectively; Group A vs. Group C, $p = 0.004$; Group B vs. Group C, $p < 0.001$). In bivariable analyses with other significant covariates, multiple treatments were significantly associated with recurrence.[5]

FUTURE

Our study indicates that pCR is associated with lower rates of post-LT recurrence in HCC patients who received pre-LT treatment, which concurred with the findings of the previous study.[3] The novel findings of this study include possible superiority of Y90 to achieve pCR, compared with other locoregional therapies. Because there are a variety of HCC treatment options, a choice of therapies for LT candidates should be carefully decided using a multidisciplinary approach. Of note, multiple pre-LT treatments may be associated with higher risk of HCC recurrence, which could be just secondary to advanced HCC status. However, after risk adjustment by tumor characteristics, the number of pre-LT treatments remained a significant factor associated with HCC recurrence. To improve post-LT outcomes in HCC patients, it is important to minimize the number of treatments by choosing appropriate therapeutic options.

DISCLOSURE Shingo Shimada, Marwan Abouljoud, and Shunji Nagai have no conflicts of interest to declare.

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