Advances in Understanding the Complexities of Recurrent HCC Following Liver Transplantation

Parissa Tabrizian, MD, MSc, FACS[1]

Despite stringent selection criteria, recurrence of hepatocellular carcinoma (HCC) after liver transplantation (LT) remains a significant challenge, affecting up to 20% of patients, primarily within the first 2–3 y posttransplant.[1] A large multicenter study found that the median time to recurrence was 17 mo, with recurrence rates of 5.1% at 1 y, 14.3% at 5 y, and 16.4% at 10 y.[1] Early recurrence, occurring within 1 y, is associated with a markedly worse prognosis. Recurrence is the result of tumor dissemination before or at the time of LT except in rare cases where de novo HCC arises many years after LT, usually in the setting of recurrent viral hepatitis. In a study from our institution, recurrence presented in the liver (16%), both in and outside the liver (32%), and extrahepatic (52%) with sites including lung, bone, lymph nodes, and adrenal glands.[1] Recurrence remains a problem despite advances in patient selection and neoadjuvant therapies. Its management is complex and requires a multidisciplinary approach to optimize outcomes.

The impact of immunosuppression on HCC recurrence after LT has been widely debated. Some studies suggest that immunosuppressive therapy might increase the risk of recurrence, and several retrospective studies and meta-analyses have linked mTORi (mammalian target of rapamycin inhibitor) usage to reduced recurrence rates and improved survival (13.8% versus 8.0%, $P < 0.001$).[2,3] A randomized controlled trial comparing mTORi-based immunosuppression to non-mTORi regimens showed a slight advantage in recurrence-free survival during the first 3–5 y, although this benefit diminished over time.[3]

Managing recurrent HCC post-LT shares similarities with the management of primary HCC, with curative-intent treatments offering clear benefits. Treatment options vary based on the location and extent of recurrence, which significantly impacts survival outcomes. It is crucial to consider curative options, especially for patients with isolated recurrences and favorable tumor biology, as they benefit most from resection or other locoregional treatments. A large retrospective study found that recipients who underwent surgical treatment for recurrence had a median survival of 31.6 mo.[1]

Systemic treatment options for recurrent HCC after LT are limited. Balancing anticancer efficacy with the immunosuppressive therapy required to prevent graft rejection can be challenging. Since the approval of sorafenib in 2008, tyrosine kinase inhibitors (TKIs) have played a key role in the management of advanced HCC, and these drugs can be safely used in patients after transplant.[4] Lenvatinib was proven noninferior to sorafenib in the REFLECT trial published in 2018, but it has subsequently proved to be the better drug with higher response rates and better overall survival, and it has largely supplanted sorafenib in clinical use in the United States; clinical trials in HCC that use a TKI currently recruiting according to clinicaltrials.gov favor lenvatinib (80 trials) over sorafenib (38 trials).[5,6] In the current issue of *Transplantation*, the authors present a retrospective study in which 15.9% of 352 patients transplanted for HCC experienced recurrence and were treated with either lenvatinib (n = 14) or sorafenib (n = 42).[7] The median overall survival was longer in the lenvatinib group (15.0 mo) compared with the sorafenib group (7.8 mo). Although a small study does not provide a high level of evidence, the results are concordant with the overall experience, showing lenvatinib to be superior to sorafenib in the treatment of HCC.

Immunotherapy with checkpoint inhibitors has revolutionized the management of advanced HCC, but their use for recurrent HCC in the post-LT presents unique challenges, potentially interfering with the immune tolerance of the transplanted liver.[8] Literature reviews report graft rejection rates ranging from 25% to 54%, often with rapid onset of irreversible rejection in affected patients.[9] Further research is essential to determine the optimal timing, dosing, and patient selection for immunotherapy in the post-transplant setting, carefully balancing the oncological benefits of immunotherapy and the immunological risks.[10] At this point, evidence is limited to a series of case reports of patients with progressive recurrent HCC after transplant to whom immunotherapy was given as a last resort after failure of all alternatives, and TKIs remain the drugs of choice to treat HCC recurrence in transplant recipients; among the TKIs, lenvatinib appears to be the most effective.

Received 6 September 2024. Revision received 14 September 2024.

Accepted 22 September 2024.

[1] *Mount Sinai Medical Center NY, Recanati/Miller Transplantation Institute, Transplantation, New York, NY.*

P.T. provided consultancy to Boston Scientific (Phoenix, AZ).

Correspondence: Parissa Tabrizian, MD, FACS, Liver Transplant and Hepatobiliary Surgery, Recanati/Miller Transplantation Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy, New York, NY 10029. (parissa.tabrizian@mountsinai.org).

ISSN: 0041-1337/20/0000-00

DOI: 10.1097/TP.0000000000005255

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