

Editorial



# Sorafenib for Recurrent Hepatocellular Carcinoma after Liver Transplantation

Bo Hyun Kim and Joong-Won Park

Center for Liver Cancer, National Cancer Center, Goyang, Korea

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**Address for Correspondence:**

**Joong-Won Park, MD, PhD**  
Center for Liver Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, Republic of Korea.  
E-mail: jwpark@ncc.re.kr

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**ORCID iDs**

Bo Hyun Kim   
<https://orcid.org/0000-0001-8355-3126>  
Joong-Won Park   
<https://orcid.org/0000-0001-9972-0494>

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The Milan criteria (1 lesion smaller than 5 cm or up to 3 lesions, each smaller than 3 cm) have long been used to identify patients with hepatocellular carcinoma (HCC) who are candidates for liver transplantation (LT).<sup>1</sup> However, these criteria may exclude some patients who would benefit from LT. Accordingly, there have been many attempts to expand the Milan criteria, such as the University of California San Francisco criteria or the up-to-Seven criteria.<sup>2</sup> In contrast to Western countries, living donor liver transplantation (LDLT) accounts for the majority of LT in Asian countries. As the social organ allocation system does not control grafts from living related donors, the wishes of the donor sometimes outweigh the recipient's overall prognosis or the risk of HCC recurrence after LT.

A higher pre-transplantation tumor burden confers a higher risk of HCC recurrence and thus an increased probability of receiving systemic chemotherapy after LT. In a retrospective review of 65 patients, Kang et al.<sup>3</sup> investigated the efficacy of sorafenib for recurrent HCC after LT. In a comparison of 45 patients receiving sorafenib and 20 receiving best supportive care (BSC), the median post-recurrence overall survival durations were 14.2 (95% confidence interval [CI], 9.6–18.8) and 6.8 months (95% CI, 1.7–16.7), respectively (hazard ratio [HR], 0.59; 95% CI, 0.28–0.89), whereas the median overall survival durations after untreatable progression (i.e., not amenable to resection or locoregional treatment) were 9.4 (95% CI, 6.6–12.2) and 3.2 months (95% CI, 2.8–3.6), respectively (HR, 0.17; 95% CI, 0.09–0.34). Kang and colleagues<sup>3</sup> therefore claimed that sorafenib appears to be beneficial for post-transplant HCC, and its use was an independent prognostic factor for survival after recurrence (HR, 0.25; 95% CI, 0.10–0.62). Although sorafenib has been the only systemic agent approved for HCC treatment for a decade, data regarding recurrent HCC after LT were scarce. Accordingly, the study by Kang et al.<sup>3</sup> provided valuable information about the feasibility and tolerability of sorafenib for unresectable HCC after transplantation from a relatively large cohort. However, a few limitations should be considered.

The prognosis of HCC depends on both the underlying liver function and tumor stage. Patients with untreatable progression are more likely to have a reduced hepatic reserve and poor performance, both of which could affect the likelihood of receiving sorafenib. Currently, sorafenib is usually administered to patients with advanced HCC in the pre-transplant setting who have a good performance status (Eastern Cooperative Oncology Group performance

status score 0–1) and liver function (Child–Pugh class A). A rational doubt that whether more patients with poor performance status and liver function would receive BSC only could have been cleared if information on underlying liver function or performance status was properly mentioned in this study.

Both overall survival and HCC recurrence after LT depend largely on the pre-transplantation tumor load.<sup>4,5</sup> Kang et al.<sup>3</sup> reported that 75.6% and 75.0% of patients in the sorafenib and BSC groups, respectively, were beyond the Milan criteria according to pre-transplantation tumor stage, and that microvascular invasion was present in 55.6% and 50.0% of these patients, respectively. However, some representative parameters, such as the serum alpha-fetoprotein level, maximal tumor diameter or presence of macrovascular invasion in the explanted liver, were not described in detail. Furthermore, the tumor status at the time of untreatable progression (i.e., sorafenib therapy initiation) was not described in detail, although the tumor stage also affects the overall survival of patients receiving sorafenib.<sup>6,7</sup>

The rate of progression might also affect the probability of receiving sorafenib, as a patient exhibiting rapid progression or deterioration would be less likely to select systemic chemotherapy. Furthermore, rapid progression suggests an aggressive tumor biology, which is a highly important prognostic factor. Considering higher alpha-fetoprotein levels at recurrence and a shorter time-to-untreatable progression, tumors in patients receiving BSC seems more aggressive.<sup>8</sup>

The above-mentioned study by Kang et al.<sup>3</sup> is the largest study of sorafenib for recurrent HCC after LT to date. Despite its limitations, as mentioned above, this study demonstrates that most patients with a recurrence of HCC after LT tolerated sorafenib well. Additionally, the adverse events experienced by these patients were comparable to those of patients receiving sorafenib in the pre-transplant setting. These findings are meaningful, given the infeasibility of conducting a randomized controlled study of sorafenib in this patient population.

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