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Sorafenib as Adjuvant Therapy Post–Liver Transplant: A Single-center Experience

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Background. Hepatocellular carcinoma (HCC) has a rising incidence and mortality in North America. Liver transplantation (LT) with adjunctive therapies offers excellent outcomes. However, HCC recurrences are associated with high mortality. We investigate whether adjuvant systemic therapy can reduce recurrence, as shown with other malignancies. **Methods.** Medical records of patients undergoing LT for HCC at a single center between January 2016 and December 2022 were retrospectively reviewed. Patients were stratified into 3 groups: (1) recipients of adjuvant sorafenib, (2) nonrecipients at high recurrence risk, and (3) nonrecipients at low risk by explant pathology features. The outcomes were overall survival (OS) and recurrence-free survival (RFS). Adjuvant sorafenib recipients were also propensity score matched 1:2 to nonadjuvant recipients based on recurrence risk features. **Results.** During the study period, 273 patients with HCC underwent LT and 16 (5.9%) received adjuvant sorafenib therapy. Adjuvant sorafenib recipients were demographically similar to nonrecipients and, on explant pathology, had greater tumor burden, lymphovascular invasion, and poorer differentiation (all $P < 0.001$). Adverse events were observed in 12 adjuvant sorafenib recipients (75%). OS was similar among the 3 groups ($P = 0.2$), and adjuvant sorafenib was not associated with OS in multivariable analysis (hazard ratio, 1.31; 95% confidence interval, 0.45-3.78; $P = 0.62$). RFS was significantly lower in sorafenib patients (hazard ratio, 6.99; 95% confidence interval, 2.12-23.05; $P = 0.001$). Following propensity matching, adjuvant sorafenib use was not associated with either OS ($P = 0.24$) or RFS rates ($P = 0.65$). **Conclusions.** In this single-center analysis, adjuvant sorafenib was not associated with OS. Recipients were observed to have shorter RFS, likely due to the increased prevalence of high-risk features, and sorafenib use was associated with high frequencies of adverse events.

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Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide. In the United States, HCC has the fastest-growing prevalence of any cancer.[1,2] Liver transplantation (LT) offers a potential cure to patients with unresectable HCC.[3,4] Unfortunately, >10% of these LT recipients will experience HCC recurrence, which is associated with high mortality.[3,4] Many of the strongest predictors of recurrence, such as lymphovascular invasion (LVI) and tumor differentiation, are not usually known until after LT is performed.[5-7] Therefore, effective treatments are needed to reduce the risk of recurrence in patients whose HCC is revealed to have high-risk features on explant.

Tyrosine kinase inhibitors (TKIs) suppress key pathways involved in tumor angiogenesis and cellular proliferation. TKIs have been successfully used in the advanced setting to treat many types of cancer, including HCC.[8] The multicenter phase 3 sorafenib as adjuvant treatment in the prevention of recurrence of hepatocellular carcinoma trial found the TKI sorafenib, when used in the adjuvant setting, did not affect recurrence-free survival (RFS) after hepatic resection or ablation,[9] although a meta-analysis of 13 studies did report improved postresection outcomes.[10] Similarly, TKI utility in the posttransplant adjuvant setting is unclear. Sorafenib has been studied in several retrospective, single-center studies of LT recipients. When directly compared with patients who did not receive adjuvant sorafenib, 2 studies (n = 7 and n = 25 adjuvant) found that adjuvant sorafenib did not affect RFS or overall survival (OS).[11,12] Another study (n = 5) found sorafenib significantly improved RFS and OS in patients with high tumor burden.[13] Several series without control arms suggested possible benefits of adjuvant sorafenib but with high adverse events.[14-17] More recent single-center studies of LT recipients in China showed that adjuvant lenvatinib, another TKI, may also extend RFS but not OS.[18,19] Thus, it is unclear whether adjuvant TKI use may reduce the risk of recurrence in contemporary North American cohorts.

The purpose of this study was to investigate whether adjuvant sorafenib use was associated with RFS or OS in a diverse contemporary cohort. Outcomes of adjuvant sorafenib recipients are compared with matched nonrecipients to control for the heightened recurrence risk because adjuvant sorafenib may be given to at-risk patients in our center at the discretion of treating oncologists.

MATERIALS AND METHODS

Medical records of patients undergoing LT for HCC at a single center between January 1, 2016 and December 31, 2022 were retrospectively reviewed. Our transplant center adheres to the United Network for Organ Sharing requirements for HCC MELD score exceptions and Organ Procurement and Transplantation Network clinical practice guidelines for pre-LT management. All patients who received exception points had dynamic contrast-enhanced CT or MRI of the liver and had neither evidence of macrovascular invasion of the main portal vein or hepatic vein, nor tumor rupture, nor extrahepatic metastases, and nor T1 stage HCC. Center practice includes transplantation of patients beyond the University of California, San Francisco, criteria whose disease is considered biologically amenable to transplantation.[20] Out-of-criteria patients with radiologic tumor stability for at least 9 mo after neoadjuvant therapy (usually locoregional therapy [LRT]) are considered for LT. Adjuvant sorafenib was initiated in patients with advanced HCC on explant at the discretion of the patient's medical oncologist. Immunosuppression was not influenced by adjuvant systemic therapy use. Universal immunosuppression for these patients included steroid bolus intraoperatively at transplant (methylprednisolone 500 mg), then gradual taper, tacrolimus (goal 6–8), and mycophenolate for 1 mo, switched to tacrolimus (goal 3–5) and everolimus (goal 3–5) after 1 mo.

Patients were stratified into 3 groups based on high-risk features for recurrence and adjuvant sorafenib use: (1) adjuvant sorafenib recipients, (2) no adjuvant sorafenib and high-risk features, and (3) no adjuvant sorafenib and low-risk features. High-risk features were defined as LVI, positive surgical margins, lymph node spread, >3 tumor nodules, and maximum tumor size >5 cm.

This work was conducted under Houston Methodist Institutional Review Board protocol Pro00000587, which included a waiver of informed consent provided by the board.

General Statistical Analysis

Demographic and clinical characteristics were reported as frequencies and proportions for categorical variables and as medians and interquartile ranges (IQRs) for continuous variables. Differences in characteristics between the 3 patient groups were identified using the chi-square or Fisher exact tests for categorical variables and Kruskal-Wallis for continuous variables. Time-to-event analyses for OS and RFS were conducted using Cox proportional hazards models or log-rank tests. Variables were selected for multivariable models using stepwise regression with backward elimination. Time-to-event outcomes were measured from the day of the transplant. All analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Propensity Score Matching Analysis

Patients receiving adjuvant sorafenib were propensity score matched 1:2 with patients who did not receive adjuvant sorafenib. Patients were matched on the basis of alpha-fetoprotein (AFP) at referral, age at transplant, sex, race, use of neoadjuvant LRT, whether background cirrhosis was present pre-LT, tumor focality, tumor maximum size, LVI, and American Joint Committee on Cancer TNM stage.

RESULTS

Of the 273 patients undergoing LT for HCC during the study period, 16 (5.9%) received adjuvant sorafenib. A majority of patients who did not receive adjuvant sorafenib had low-risk features (low-risk patients: n = 150; high-risk patients: n = 107) on explant. Recipient age ($P = 0.67$), sex ($P = 0.19$), and prevalence of cirrhosis ($P = 0.56$) were similar between the 3 groups (Table 1). High-risk patients with HCC had significantly higher AFP levels at referral (30.3 ng/mL; IQR, 6.2–109.1) than adjuvant sorafenib recipients (12.2 ng/mL; IQR, 6.8–119.8) or low-risk patients with HCC (4.5 ng/mL; IQR, 2.8–8.6; $P < 0.001$). The high-risk patients were also more likely to receive neoadjuvant LRT ($P = 0.04$).

On explant, adjuvant sorafenib recipients had higher American Joint Committee on Cancer TNM stages ($P < 0.001$), a greater number of HCC lesions ($P < 0.001$), and larger lesions ($P < 0.001$; Table 1). A greater proportion of patients were beyond the Milan and University of California, San Francisco,

TABLE 1.

Demographics and clinical characteristics of patients undergoing liver transplantation for hepatocellular carcinoma, stratified by adjuvant sorafenib use and recurrence risk

Characteristics	Adjuvant sorafenib (N = 16)	No adjuvant sorafenib		*P*
		Low risk (N = 150)	High risk (N = 107)	
Age at transplant, y, median (IQR)	63.5 (61.0–68.0)	64.0 (58.0–68.0)	64.0 (58.0–67.0)	0.67
Sex, n (%)				0.19
Female	3 (18.8)	50 (33.3)	26 (24.3)	
Male	13 (81.2)	100 (66.7)	81 (75.7)	
AFP at referral, ng/mL, median (IQR)	12.2 (6.8–119.8)	4.5 (2.8–8.6)	30.3 (6.2–109.1)	<0.001
Background liver cirrhosis, n (%)				0.56
No	0 (0)	8 (5.3)	7 (6.5)	
Yes	16 (100)	142 (94.7)	100 (93.5)	
Any neoadjuvant LRT, n (%)				0.04
No	3 (18.8)	32 (21.3)	10 (9.3)	
Yes	13 (81.2)	118 (78.7)	97 (90.7)	
AJCC TNM stage, n (%)				<0.001
0	0 (0)	46 (30.7)	14 (13.1)	
1	5 (31.2)	74 (49.3)	33 (30.8)	
2	8 (50)	30 (20)	47 (43.9)	
3	3 (18.8)	0 (0)	13 (12.1)	
No. of tumor nodules, median (IQR)	2.0 (1.0–4.0)	1.0 (1.0–2.0)	2.0 (1.0–4.0)	<0.001
Max. tumor diameter, cm, median (IQR)	3.5 (1.7–5.1)	1.9 (1.0–3.1)	2.8 (1.7–4.5)	<0.001
Tumor differentiation, n (%)				<0.001
Well	2 (12.5)	40 (26.7)	23 (21.5)	
Moderate	11 (68.8)	55 (36.7)	55 (51.4)	
Poor	3 (18.8)	0 (0)	15 (14.0)	
Not available	0 (0)	55 (36.7)	14 (13.1)	
Focality, n (%)				<0.001
Solitary	6 (37.5)	106 (70.7)	47 (43.9)	
Multifocal	10 (62.5)	44 (29.3)	60 (56.1)	
Milan and UCSF criteria, n (%)				<0.001
Within Milan	4 (25)	102 (68)	37 (34.6)	
Within UCSF	5 (31.2)	47 (31.3)	22 (20.6)	
Beyond UCSF	7 (43.8)	1 (0.7)	48 (44.9)	
Lymphovascular invasion, n (%)				<0.001
Absent	7 (43.8)	150 (100)	85 (79.4)	
Present	9 (56.2)	0 (0)	22 (20.6)	
Margins, n (%)				<0.001
R0	15 (93.8)	150 (100)	107 (100)	
R1/R2	1 (6.2)	0 (0)	0 (0)	
Time from transplant to adjuvant therapy start, d, median (IQR)	54 (29.5–79.5)	–	–	
Duration of adjuvant therapy, d, median (IQR)	120 (28.5–610.3)	–	–	
Recurrence post-LT, n (%)				
No	11 (68.8)	144 (96)	91 (85)	
Yes	5 (31.2)	6 (4)	16 (15)	
RFS, d, median (IQR)	1156.0 (603.0–2061.0)	1281.0 (632.0–1829.0)	976.0 (544.0–1649.0)	
Postrecurrence systemic therapy, n (%)				1.0
No	2 (40)	3 (50)	8 (50)	
Yes	3 (60)	3 (50)	8 (50)	
Patient status, n (%)				
Alive	10 (62.5)	127 (84.7%)	87 (81.3%)	
Deceased	6 (37.5)	23 (15.3%)	20 (18.7%)	
Overall survival, d, median (IQR)	1404.5 (830.5–2356.0)	1267.5 (487.0–1902.0)	996.0 (392.5–1816.5)	

AFP, alpha-fetoprotein; AJCC, American Joint Committee on Cancer; IQR, interquartile range; LRT, locoregional therapy; LT, liver transplantation; max, maximum; RFS, recurrence-free survival; UCSF, University of California, San Francisco.

criteria in the adjuvant sorafenib and high-risk groups compared with the low-risk group ($P < 0.001$). These patients were also more likely to have LVI (n = 9; 56.2%) than high-risk (n = 22; 20.6%) and low-risk (n = 0; 0%) patients ($P < 0.001$). The only patient who had positive margins received adjuvant sorafenib.

Adjuvant Sorafenib Use and Adverse Events

Of the 16 patients who received adjuvant sorafenib, the median time to start therapy posttransplant was 54 d (IQR, 29.5–79.5), and the median duration of therapy was 120 d (IQR, 28.5–610.3). There were 12 patients (75.0%) who

TABLE 2.

Adverse events experienced by patients receiving adjuvant sorafenib after liver transplantation for hepatocellular carcinoma

Adverse event	N	Proportion (%)
Feeling clumsy	1	6.25
Diarrhea	1	6.25
Dysesthesia	4	25.0
Hair loss	1	6.25
Heart problems	1	6.25
Hypertensive urgency	1	6.25
Loss of balance	1	6.25
Muscle pain	1	6.25
Nausea and vomiting	2	12.5
Pain, not otherwise specified	1	6.25
Peripheral neuralgia	2	12.5
Skin peeling	2	12.5
None	4	25.0

experienced adverse events (Table 2). These patients experienced a median of 1 adverse event (IQR, 0–2) each, ranging from 0 to 3. The most frequent adverse event was dysesthesia (n = 4; 25.0%). Three patients ceased therapy due to toxicity. There were no liver-related adverse events.

Survival Analysis

At the last follow-up, a higher proportion of adjuvant sorafenib recipients experienced recurrence post-LT (n = 5; 31.2%) than high-risk (n = 16; 15%) or low-risk (n = 6; 4%) patients (Table 1). RFS probability at 1 and 3 y for the entire cohort was 96.5% (95% CI, 94.2%–98.8%) and 90.3% (95% CI, 86.4%–94.3%), and by patient grouping, it was 87% and 73%, 93% and 84%, and 100% and 97%, for the adjuvant sorafenib group, high-risk group, and low-risk group, respectively. By univariable and multivariable Cox proportional hazard models, RFS was significantly shorter in the adjuvant sorafenib (hazard ratio [HR], 6.99; 95% confidence interval [CI], 2.12-23.05; $P = 0.001$) and high-risk groups (HR, 3.19; 95% CI, 1.20-8.45; $P = 0.02$; Table 3; Figure 1). RFS was also associated with maximum tumor diameter (HR, 1.19; 95% CI, 1.07-1.33; $P = 0.002$).

Also, at the last follow-up, there were 49 deaths, including 6 (37.5%) in the adjuvant sorafenib group, 20 (18.7%) in the high-risk group, and 23 (15.3%) in the low-risk group (Table 1). OS probability at 1 and 3 y for the entire cohort was 93.5% (95% CI, 90.7%–96.6%) and 83.6% (95%

TABLE 3.

Variables associated with survival (overall or recurrence-free) after liver transplantation for hepatocellular carcinoma

	Univariable		Multivariable		Final	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Overall survival						
HCC group						
Low-risk, no adjuvant sorafenib	Reference		Reference			
High-risk, no adjuvant sorafenib	1.35 (0.74-2.46)	0.32	0.99 (0.50-1.98)	0.98		
Adjuvant sorafenib	2.18 (0.89-5.37)	0.09	1.31 (0.45-3.78)	0.62		
Age at transplant, y	1.03 (0.99-1.08)	0.15	1.03 (0.98-1.07)	0.26		
AFP at referral, ng/mL	1.00 (1.00-1.00)	0.56	1.00 (1.00-1.00)	0.62		
Neoadjuvant LRT						
No	Reference		Reference			
Yes	1.75 (0.69-4.41)	0.24	1.81 (0.71-4.65)	0.22		
No. of tumor modules	1.01 (0.98-1.05)	0.43	0.98 (0.94-1.03)	0.55		
Maximum tumor diameter, cm	1.12 (1.03-1.23)	**0.01**	1.12 (0.98-1.28)	0.11	1.09 (0.99-1.19)	0.07
Lymphovascular invasion						
Absent	Reference		Reference		Reference	
Present	2.75 (1.40-5.40)	**0.003**	2.23 (0.97-5.13)	0.06	2.35 (1.15-4.80)	**0.02**
Recurrence-free survival						
HCC group						
Low-risk, no adjuvant sorafenib	Reference		Reference		Reference	
High-risk, no adjuvant sorafenib	4.21 (1.65-10.76)	**0.003**	2.90 (1.05-7.95)	**0.04**	3.19 (1.20-8.45)	**0.02**
Adjuvant sorafenib	8.05 (2.45-26.38)	**<0.001**	5.66 (1.51-21.16)	**0.01**	6.99 (2.12-23.05)	**0.001**
Age at transplant, y	1.00 (0.95-1.05)	0.93	0.99 (0.94-1.05)	0.72		
AFP at referral, ng/mL	1.00 (1.00-1.00)	0.73	1.00 (1.00-1.00)	0.67		
Neoadjuvant LRT						
No	Reference		Reference			
Yes	1.67 (0.50-5.56)	0.40	1.66 (0.47-5.85)	0.43		
No. of tumor modules	1.03 (1.00-1.07)	**0.04**	0.99 (0.94-1.04)	0.64		
Maximum tumor diameter, cm	1.24 (1.13-1.37)	**<0.001**	1.20 (1.02-1.41)	**0.03**	1.19 (1.07-1.33)	**0.002**
Lymphovascular invasion						
Absent	Reference		Reference			
Present	4.19 (1.83-9.60)	**<0.001**	1.77 (0.67-4.64)	0.247		

Bold values denote $P < 0.05$.

AFP, alpha-fetoprotein; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; LRT, locoregional therapy.

CI, 78.9%–88.6%), and by patient grouping, it was 100% and 80%, 91% and 81%, and 94.5% and 86%, for the adjuvant sorafenib group, high-risk group, and low-risk group, respectively. In univariable and multivariable Cox proportional hazard analyses, OS was only associated with LVI (HR, 2.35; 95% CI, 1.15-4.80; $P = 0.02$; Table 3) and not with adjuvant sorafenib or recurrence risk category.

Analysis of Propensity-matched Patients

Propensity score matching adequately balanced demographics and explant pathology characteristics between patients who received adjuvant sorafenib (n = 16) and patients who did not (n = 32, all $P > 0.05$; **Table S1, SDC,** http://links.lww.com/TXD/A728). In this matched cohort, there were no significant differences neither in OS ($P = 0.24$; Figure 2A) nor in RFS ($P = 0.65$; Figure 2B).

DISCUSSION

This study provides evidence that adjuvant sorafenib does not affect posttransplant OS or RFS for patients undergoing LT for HCC. Per explant pathology, adjuvant sorafenib recipients had HCC with more aggressive features than the high-risk patients, including higher TNM staging, greater tumor burden, and more LVI. These differences may explain why adjuvant sorafenib recipients had significantly lower RFS before matching. OS and RFS were statistically similar when matched to patients who did not receive adjuvant sorafenib based on correlates of HCC-related outcomes. Thus, adjuvant sorafenib did not affect outcomes in patients with similar tumor biology.

Empiric adjuvant systemic therapy improves outcomes after resection for some cancer types, such as pancreatic cancer,[21] but this observation may not extend to LT for HCC. The results presented here align with other single-center reports that also found adjuvant sorafenib did not alter posttransplant survival (**Table S2, SDC,** http://links.lww.com/TXD/A728).[11,12] Although 2 recent papers from China reported improved RFS with adjuvant lenvatinib,[18,19] this may be confounded by differences in underlying tumor biology.[22] It is important to note that many studies on adjuvant TKI in

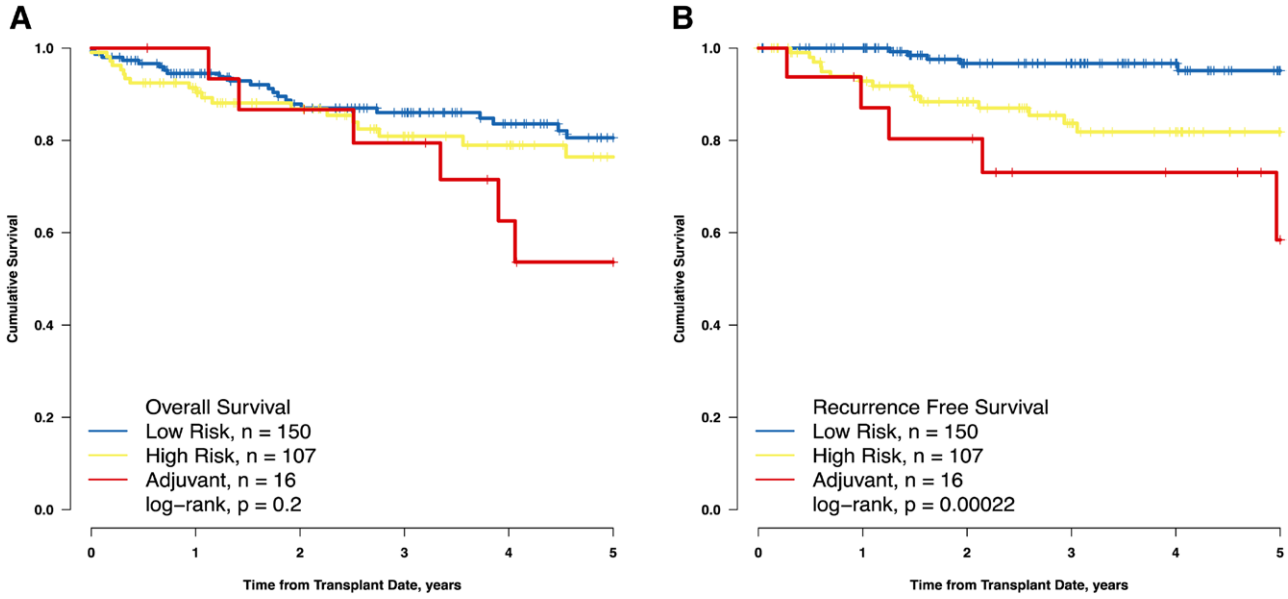

FIGURE 1. Survival after liver transplantation for hepatocellular carcinoma, stratified by patients who received adjuvant sorafenib and those who did not. Patients not receiving adjuvant sorafenib are further divided into high- and low-risk groups based on explant pathologic findings: overall survival (A) and recurrence-free survival (B).

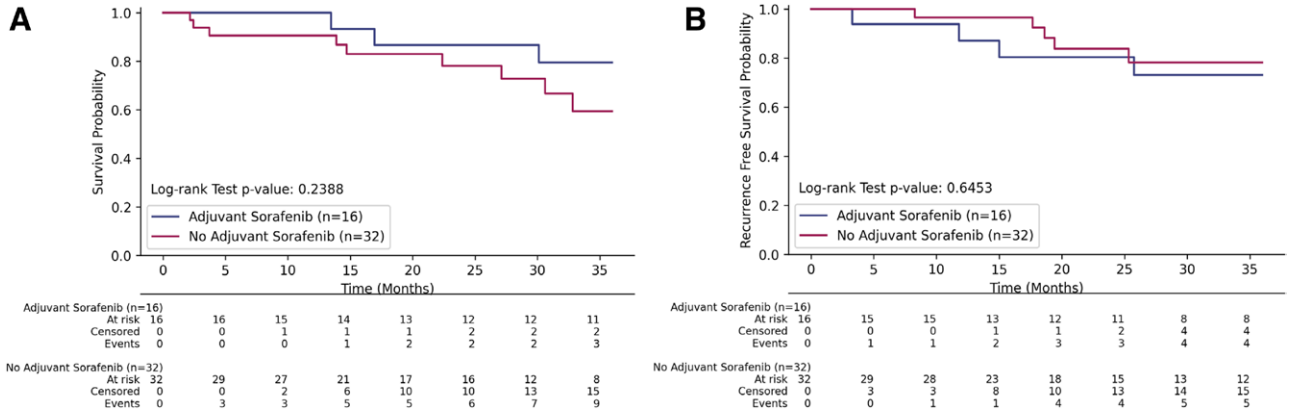

FIGURE 2. Survival after liver transplantation for hepatocellular carcinoma in patients receiving adjuvant sorafenib and propensity-matched patients who did not receive adjuvant sorafenib: overall survival (A) and recurrence-free survival (B).

transplant recipients report on patients who developed HCC in the background of hepatitis B or C.[13,17,23] Their applicability may be limited to regions where hepatitis B rates are highest and not in the direct-acting antiviral era.

Given this uncertainty in the literature, TKI administration as part of adjuvant therapy after LT is primarily guided by clinical judgment. Medical oncologists assess risk factors for recurrence, including stage and LVI. In several small retrospective studies of LT recipients, recurrence rates have been reported as lower compared with control groups with either no adjuvant or cytotoxic adjuvant therapies in North America.[13-17] However, sorafenib use was also associated with a high incidence of adverse events. Medical oncologists' decision to use sorafenib after LT had to balance potential therapeutic benefits against the risk and management of such complications. In this study, we observed adverse events in 75% of patients, with 3 requiring therapy discontinuation. Thus, this adds to the evidence against adjuvant sorafenib use. Further research may refine selection criteria and optimize treatment protocols to maximize efficacy and minimize the toxicity of sorafenib in high-risk patients.

Unfortunately, many of the features associated with poor outcomes post-LT are only determined via explant pathology. As more patients with HCC who initially present outside of criteria are successfully downstaged and undergo LT,[20] an increasing number of patients with these biologically unfavorable tumors will likely undergo transplant and experience recurrence.[24] More research is needed to identify these high-risk patients pre-LT, potentially through modalities such as liquid biopsy[25] or artificial intelligence algorithms.[26] Nonetheless, there will probably be a growing need for effective adjuvant therapy. This study adds to the growing evidence that adjuvant TKI use does not prevent recurrence. Although immunotherapies alone and in combinations have been reasonably effective at treating HCC in the advanced/palliative setting,[27,28] their safety in the neoadjuvant pretransplant[29] and in the recurrence posttransplant[30] settings is in question, particularly for fear of greater graft loss.[31] Other emerging therapies may be effective in the adjuvant setting, such as personalized cancer vaccines, which have recently been successfully trialed in HCC and should not theoretically increase the risk of allograft rejection.[32]

This study has several limitations. This is a single-center, retrospective study, which limits the external validity of the conclusions that can be drawn from its results. There are a small number of patients in the adjuvant sorafenib treatment arm (n = 16). However, this treatment arm is contrasted with a relatively large number of patients with HCC undergoing LT at a single center (total n = 273), including 150 at low risk and 107 at high risk of recurrence according to traditional risk factors. The retrospective, "real world" study design prevents us from identifying reasons why many patients with high-risk features were not given adjuvant sorafenib, as this was at the discretion of the individual multidisciplinary teams. Additionally, the small number of recurrence events (n = 27) limits the power of the multivariable analysis. However, using propensity score matching to analyze outcomes in HCC patients with similar recurrence risk helps support the significance of our findings. Also, given that all patients in this study underwent LT in the direct-acting antiviral era, these results are more applicable to anticipated future HCC cases[33] than previous studies.

In conclusion, we found that adjuvant sorafenib did not affect posttransplant survival outcomes in patients whose HCC lesions had similar pathologic features. Patients in the adjuvant sorafenib and high-risk no sorafenib groups had an equally higher risk of post-LT recurrence, likely due to their advanced stage and high incidence of LVI. When deciding whether to use adjuvant sorafenib, multidisciplinary teams should consider the high number of adverse events associated with its use, weighed against its lack of observed effectiveness in this population. Additional studies are needed to determine whether other modalities in the adjuvant setting may effectively reduce post-LT recurrence risk.

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