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Pre-transplant utilization of sorafenib is not associated with increased complications after liver transplantation

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Conflicts of interest
Dr. Frenette has served on the Speaker's Bureau for Onyx Pharmaceuticals.
Dr. Monsour has served on the Speaker's Bureau, advisory arrangements, and in a consulting role with Onyx Pharmaceuticals.
Dr. Ghobrial has served in a consulting role and in advisory arrangements with Onyx Pharmaceuticals.

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Summary

Hepatocellular carcinoma (HCC) is increasing in incidence, resulting in approximately 35% of orthotopic liver transplantation (OLT) performed each year. Sorafenib (SOR) is a multi-kinase inhibitor that is approved for the treatment of unresectable HCC. Concerns have been raised regarding the safety of SOR in patients undergoing major surgery. We retrospectively reviewed 79 consecutive patients with HCC receiving OLT. Patient data were compared for those who received SOR pre-OLT with those who did not. SOR was continued until time of transplant. During this time period, 15 patients received SOR pre-OLT and 64 did not. The two groups were similar with regards to demographic and clinical data. SOR patients were more likely to have larger tumors, more tumor nodules, and be outside of Milan criteria. The rate of recurrence of HCC was not different between the groups (13% in SOR group, 11% in no-SOR group). Surgical complications were not increased in patients receiving SOR prior to OLT. Survival rate was also similar between the two groups (median follow-up 19.7 months). In this small cohort of patients, use of SOR prior to liver transplantation does not confer an increased risk of surgical complications, even when continued until the day of surgery.

Introduction

Hepatocellular carcinoma (HCC) is a major health problem worldwide, ranking third in cancer-related deaths [1]. The treatment of HCC has rapidly progressed in the last decades. Improved survival after resection, increased options for locoregional therapy (LRT), and utilization of systemic therapy with sorafenib (SOR) have significantly increased survival outcomes [2]. Currently, orthotopic liver transplantation (OLT) remains the best treatment option for patients within the Milan criteria (one lesion up to 5 cm or up to 3 lesions, all <3 cm), with cure rates up to 95% in some series [3]. More recently, there has been increasing interest in expanding criteria for OLT in HCC patients. In some regions in the United States (US), patients with tumors beyond the Milan criteria have underwent OLT

with improved survival outcomes and lower recurrence rates [4].A major problem of OLT, as a primary treatment for HCC, remains the issue of waitlist dropout caused by tumor progression. In some centers, LRT utilized to decrease tumor progression and to ensure that patients remain within transplant criteria.

Sorafenib, a multi-kinase inhibitor with activity against HCC has been approved for treatment of HCC in patients with unresectable disease. SOR is not cytotoxic, but is rather cytostatic, and can result in stability of HCC tumor growth and disease control in up to 43% of patients [5]. The Sorafenib HCC Assessment Randomization Protocol trial was a large phase 3 multicenter study in which patients were randomized to SOR versus placebo for treatment of unresectable HCC. Patients on SOR had an improvement in overall survival of nearly 3 months, as well as an increased time to radiographic progression. In patients listed for liver transplant, this can be a complimentary treatment to LRT in order for them to remain within criteria and proceed to OLT [6–8].

As with any targeted therapy, there remains a concern about complications with use of SOR in patients undergoing major surgical procedures. We present a retrospective study of patients at our institution who were on SOR prior to liver transplantation to determine risk of complications related to SOR use.

Materials and methods

This retrospective study was performed at the J.C. Walter Jr., Department of Transplantation of the Methodist Hospital, Houston, Texas. A total of 194 patients underwent deceased donor OLT between April 2008 and March 2012 at our institution. Eighty-one consecutive patients older than 18 years with end stage liver disease (ESLD) and HCC were reviewed for analysis.

Pertinent demographic and clinical data were reviewed from the department of liver transplantation database and patient charts biological model for end-stage liver disease (MELD) and Child-Pugh scores were calculated at the time of or one day before OLT [9].

Further information pertaining to pre-OLT clinical tumor characteristics (number, size, and preoperative LRT, and estimated SOR dose and duration of use) were obtained in detail. Complications within 30 days post-OLT were collected, including incidences of biliary leak, wound infection or complications, bleeding, and bacteremia. Wound complications were considered significant if return to OR, prolonged antibiotics, or healing by secondary intention was required. Incisional hernia or biliary strictures within 1 year post-OLT were also collected. Pathologically confirmed mild/moderate/severe acute cellular rejection (ACR) within 1 year post-OLT, and occurrences of HCC tumor recurrence after transplantation were also identified.

Patients were not randomized to treatment arms. Use of SOR was initiated at the decision of the treating physician and transplant team for patients who were considered high risk for progression of disease or drop-out from the transplant list. Per center protocol, this included patients with tumors outside of Milan criteria, poorly differentiated on biopsy (if biopsy was available) and elevated alpha-fetoprotein (AFP), or progression of disease after or inadequate response to LRT. As SOR was not initiated as part of a prospective clinical trial, informed consent was done with the treated physician in a standard of care fashion. SOR was started at 400 mg twice daily per package insert recommendations. Dose reductions or discontinuation for side effects were managed by the treating physician. SOR was continued until the day of transplant once a suitable donor organ had been accepted by the transplant team.

One patient who discontinued SOR prior to OLT because of unacceptable side effects (diarrhea) and was not included in the analysis. This patient had received 6 weeks of SOR and stopped 6 months before OLT, and it was felt that this could confound the results in an unclear way. One patient who was not receiving SOR died during the transplant surgery because of heart failure related to concomitant pulmonary hypertension and was excluded from the analysis. After transplantation, all patients received standard immunosuppression per center protocol of tacrolimus, mycophenolate mofetil (MMF), and steroids. Tacrolimus levels were held between 8 and 10 ng/ml for the first 6 months after transplantation. Steroids and MMF were tapered per center protocol. Explant pathology was reviewed for each patient, and patients who had high-risk criteria were started on an mammalian Target of Rapamycin inhibitor as part of their immunosuppression in combination with low-dose tacrolimus. High-risk criteria were defined as tumor beyond Milan criteria, poorly differentiated tumor, vascular or biliary invasion, or extrahepatic disease or capsular breach.

A total of 79 recipients were included in this analysis. Fifteen of the 79 OLT patients received SOR while waiting for OLT. In all SOR patients, treatment was continued until the date of the transplantation. The remaining 64 who did not receive SOR were used as a control group to compare post-OLT complications between both groups. This research study has been reviewed by the Methodist Hospital, Houston Committee for the Protection of Human Subjects, and appropriate Institutional Review Board (IRB) approvals were obtained.

Statistical methods

Chi-square or Fisher's Exact tests were used to compare categorical variables. Continuous variables were compared

by *t*-tests. Six-month and 1-year survival estimate were calculated by means of Kaplan–Meier estimates, and Log-Rank test was used for comparing survival curves between the two groups. Two-tailed tests with *P*-value of ≤0.05 were considered to be statistically significant. All analyses were performed using STATA software package, version 11 (Stata Corp LP, College Station, TX). Multivariate analyses were not performed because of the small number of patients.

Results

During the period of April 2008 and March 2012, a total of 194 patient charts were screened for inclusion into the study. Patients were included if they underwent OLT for a diagnosis of hepatocellular carcinoma. Patients who had incidental HCC on explant pathology review were excluded. A total of 79 patients were included in the analysis. The first group included 15 patients who received SOR prior to OLT (SOR group). The 64 patients who did not receive SOR prior to OLT were included in the no-SOR (control) group. Median follow-up was 19.7 months (range 1.6–48.9 months). The median follow-up was 12.3 months in the SOR group and 19.7 months in the no-SOR group.

Patient characteristics are described in Table 1. All patients were cirrhotic and met transplant listing criteria at our transplant center. Our center accepts patients for transplantation who are outside of Milan criteria but within region 4 transplant criteria: single tumor up to 6 cm, or up to three tumors, all <5 cm with total tumor diameter <9 cm. As shown in Table 1, 93% of patients in the SOR group were outside of Milan criteria, compared with 33% of patients in the no-SOR group. All patients underwent LRT, either with transarterial chemoembolization (TACE), radiofrequency ablation (RFA), or surgical resection. There was no difference in the type of LRT or the number of patients receiving LRT between the groups. The type of LRT appropriate for each patient was decided based on clinical characteristics by a multidisciplinary tumor board.

Patient characteristics were well-matched between the groups. Median age, gender, race, presence of viral hepatitis, biological MELD, cold and warm ischemia times were similar between the groups. BMI was higher in the SOR group and there were more patients with DM. However, such differences were not statistically significant. The median wait time was similar in the SOR group and the no-SOR group (210 days vs. 214 days, *P* = NS).

Prior to transplantation, in the SOR group there was 27% Child's A patients, 33% Child's B patients, and 40% Child's C patients. Despite progression to Child's C cirrhosis in SOR group, SOR was well tolerated and did not require more dose reductions than in patients with earlier stage of cirrhosis. The stage of cirrhosis was not significantly different in patients treated with SOR versus patients not receiving treatment with SOR, and the change in biologic MELD was similar between the groups (i.e. use of sorafenib did not appear to worsen progression of liver disease). The median biological MELD score at time of transplantation was also similar between both groups, at 15 in

Table 1. Baseline demographic and clinical characteristics in patients receiving sorafenib compared with the patients not receiving sorafenib prior to liver transplantation.

Study variable	Sorafenib *n* = 15 (%)	No sorafenib *n* = 64 (%)	*P*-value*
Age†	61 ± 7	60 ± 7	0.62
Gender			
Male	13 (87)	45 (70)	0.12
Race			
Caucasian	8 (53)	45 (70)	0.21
BMI	30 ± 7	27 ± 6	0.10
Bio-MELD†	17 ± 6	14 ± 8	0.18
Bio-MELD‡	15 (7–30)	12 (6–40)	
Ex-MELD†	26 ± 5	27 ± 3	0.32
Ex-MELD‡	28 (13–33)	28 (22–40)	
HCV	9 (60)	51 (80)	0.11
History of DM	7 (47)	22 (34)	0.37
Child-Pugh			
A	4 (27)	21 (33)	0.39
B	5 (33)	29 (45)	
C	6 (40)	14 (22)	
Albumin level at OLT	3.23 ± 0.90	3.42 ± 0.76	0.40
Ascites at OLT	7 (47)	41 (64)	0.21
Encephalopathy at OLT	6 (40)	29 (45)	0.71
CIT†	6.7 ± 1.6	6.3 ± 2.1	0.49
WIT†	0.33 ± 0.07	0.35 ± 0.12	0.54
HCC imaging outside milan	14 (93)	21 (33)	0.0001
Imaging tumor characteristics			
Tumor number‡	3 (1–10)	2 (1–5)	–
Max tumor size†	5.0 ± 2.7	3.3 ± 1.8	0.004
Total tumor size†	7.8 ± 2.0	4.5 ± 2.2	0.0001
Explant tumor characteristics			
Tumor number‡	3 (1–7)	2 (1–11)	–
Max tumor size†	4.6 ± 4.2	3.2 ± 1.9	0.05
Total tumor size†	7.7 ± 4.3	5.1 ± 3.9	0.03
Microvascular invasion	3 (20)	7 (11%)	0.39
Locoregional therapy			
TACE	12 (80)	54 (84)	0.70
RFA	3 (20)	18 (28)	0.75
Tumor resection	2 (13)	3 (5)	0.24
Waiting list time‡, days	210 (2–403)	214 (2–1618)	–
Donor age†	40 ± 15	36 ± 16	0.39

*Significance set at $\alpha < 0.05$;
†Mean ± SD;
‡Median, range.
BMI, body mass index; MELD, model for end stage liver disease; Bio-MELD, biologic MELD; Ex-MELD, exception MELD; HCV, hepatitis C; DM, diabetes mellitus; OLT, orthotopic liver transplantation; CIT, cold ischemia time; WIT, warm ischemia time; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

the SOR group and 12 in the no-SOR group. The patients in the SOR group also had more advanced HCC compared with the control group, with more tumor nodules (3 compared with 2, $P = 0.004$) and larger tumors (5.5 cm compared to 3.3 cm, $P = 0.0001$).

The SOR median daily dose was 400 mg daily, with a range of 200–800 mg daily. Dose adjustment was based on patient tolerance to side effects. Eleven of the 15 patients required dose reduction in SOR: four patients for gastrointestinal side effects, three patients for worsening liver function and hyperbilirubinemia, two patients for thrombocytopenia, one patient for rash, and one for fatigue. The estimated duration of SOR prior to OLT was a median of 87 days, with a range of 12–360 days. There were no major bleeding complications (such as variceal bleeds) prior to OLT in the SOR group. The mean AFP prior to starting SOR was 132 ± 169 ng/ml, and at time of transplant the mean AFP had decreased to 41.4 ± 74 ng/ml.

In patients listed for transplantation for HCC during this time period, 15 of 94 dropped off the list for tumor progression: three of these were on SOR and 12 were not. The incidence of dropout was 20% in SOR group versus 18.8% in control group ($P = 1.00$).

Postoperative complications were similar in each group, and are summarized in Table 2. There were no biliary issues in the SOR group and two in the control group. There was no difference in immediate wound complications or delayed wound complication of incisional hernia between the groups. The need for return to OR was similar in each group (20% in SOR group and 14% in control, $P = 0.69$). The three returns to OR in the SOR group were for the following reasons: bleeding (one pt), wound infection (one pt), and a planned delayed biliary anastomosis (one pt). In the control group, return to OR was done for the following reasons: bleeding (6 pts), wound infection (2 pts), and exploration for possible bile leak (one pt, no bile leak was found at surgery). There were no episodes of ACR in the SOR group, compared with six episodes of ACR in the control group. All episodes were treated with increase in immunosuppression and responded well. No grafts were lost as a result of rejection.

Table 2. Post operative complications in patients receiving sorafenib compared with the patients not receiving sorafenib prior to liver transplantation.

Complication	Sorafenib $n = 15$ (%)	No sorafenib $n = 64$ (%)	*P*-value*
Bile leak†	0 (0.0)	0 (0.0)	1.00
Biliary stricture‡	0 (0.0)	2 (3)	1.00
Bleeding†	1 (7)	6 (9)	1.00
Wound infection†	1 (7)	2 (3)	0.48
Back to OR†	3 (20)	9 (14)	0.69
Incisional hernia‡	0 (0.0)	1 (2)	1.00
Cellular rejection, mild-moderate‡	0 (0.0)	6 (9)	0.59
Bacteremia†	0 (0.0)	5 (8)	0.58
HCC recurrence	2 (13)	7 (11)	0.68

*Significance set at $\alpha < 0.05$;
†30-days of follow-up;
‡1-year of follow-up.

Overall survival and recurrence of HCC were similar in each group. The Kaplan–Meier survival curve is shown in Fig. 1. In the SOR patients, the overall survival at years 1, 2, and 3 was 93%. In the no-SOR patients, overall survival at years 1, 2, and 3 was 97%, 89%, and 83%, respectively. Graft survival was the same as patient survival (i.e. no patients required re-transplantation). There

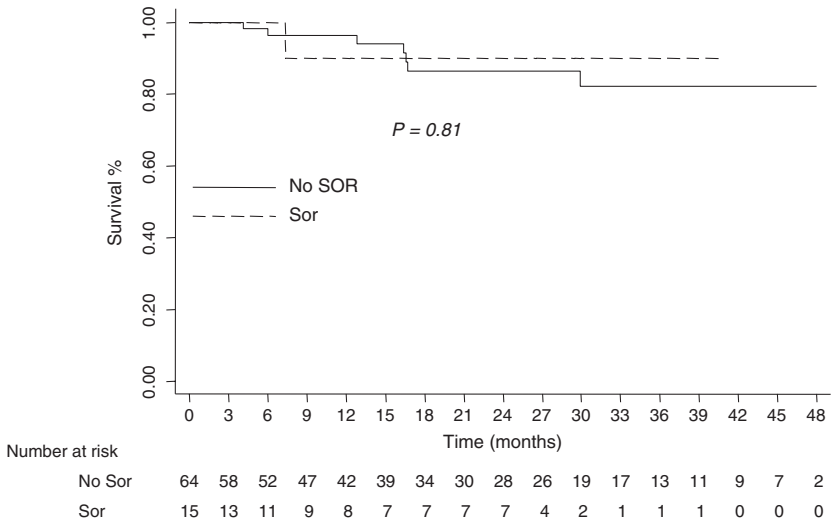

Figure 1 Overall post-transplant survival in patients receiving sorafenib before liver transplant compared with the patients who did not.

was no statistical difference in HCC recurrence between the groups. The SOR group had 13% HCC recurrence and the no-SOR group had 11% recurrence.

Discussion

The number of patients undergoing OLT for HCC has continued to increase in the last several years. There is a continuous search for ways to maintain control of HCC as the wait time for transplantation becomes longer. As a targeted systemic therapy, SOR may serve as an adjuvant treatment for patients awaiting OLT. However, SOR has not been widely adopted in transplantation regimens.

Few data are available regarding safety and efficacy of SOR in OLT. One case series by Saidi *et al.* demonstrated its safety, although this was a mixed patient population where some patients received sorafenib before and others received it after OLT [6]. A subsequent cost-benefit analysis showed that SOR neoadjuvant therapy appeared to be cost effective in patients awaiting OLT with stage T2 HCC, particularly with wait times <6 months [7]. The largest study published thus far by Truesdale *et al.* is a pilot cohort study of 10 patients treated with SOR compared with 23 untreated patients who served as controls [10]. In this study, patients received SOR until time of transplantation, with a mean duration of treatment 19.2 weeks. These patients treated with SOR had a very high rate of biliary complications (67% compared with 17% of controls) and ACR (67% compared with 22% of controls). In our study, we did not see an increased rate of biliary complications or ACR in SOR -treated patients. Thus, our study suggests that SOR use prior to transplantation with discontinuation only on the day of transplantation appeared to be safe without increased risk of surgical or transplant-related complications.

OLT for HCC has resulted in excellent survival and low recurrence outcomes. Unfortunately, wait list dropout risk remains a major issue. Overall dropout risk in the first 6 months of listing is estimated at 20% [11]. Dropout risk is dependent on multiple factors, including wait list time, tumor characteristics, and Child-Pugh status of the patient [12–15]. In this study OLT was performed at median MELD of 28, which is equivalent to a wait time of 12 months. SOR has been shown to increase time to progression (TTP) by a median of 2.7 months. Theoretically, this may allow some patients to be maintained within transplant criteria long enough to reach OLT [5]. The dropout rate in our study was the same in both groups, around 20%, which is what is described in the literature. Our patients treated with SOR had very advanced HCC, with 93% being outside of Milan criteria, so a higher dropout rate would have been expected. This study is too small to fully assess whether SOR may have had an impact on dropout, and larger studies are warranted to address this issue. There is concern that provides SOR to patients who are at risk of dropout may mask some patients who will have a higher risk of post-transplant recurrence of HCC. Long wait times, also known as "ablate and wait" allow patients with aggressive tumor biology to declare themselves, and drop off the list rather than progress to transplant and have cancer recurrence post-transplant [16]. We did not see an increased risk of recurrence in our SOR-treated patients compared with controls, despite the higher tumor burden seen in these patients.

Of the 15 patients treated with SOR in our study, 13 received concomitant LRT, 12 with TACE and 3 with RFA. During these treatments SOR was continued without interruption. There are concerns with using SOR prior to OLT because of the interaction with locoregional treatment, which is often needed to maintain tumor control. In our patients, there was no increased rate of complications with the combination of therapies, despite the fact that SOR was not stopped for any LRT. Lencioni *et al.* presented early results of the Sorafenib or placebo in combination with transarterial chemoembolization for intermediate-stage HCC trial, a randomized, placebo-controlled trial of TACE with doxorubicin-eluting beads in combination with SOR [17]. There was no difference between the groups in adverse events, serious adverse events, or treatment emergent events. This study did show a prolongation in time to progression and time to metastatic disease or extrahepatic spread, but no difference in overall survival. The prolonged TTP may decrease the risk of dropout in patients waiting for transplant treated with SOR in combination with LRT, and this will need to be address in larger trials.

Lastly, in our study SOR was continued to the day of transplant in all patients who tolerated it. Only one patient stopped for adverse events, and this patient was not included in our analysis. With targeted therapies, there has been concern for increased surgical complications, and with some, there is well-known wound healing issues. A mouse model of adjuvant SOR after liver resection showed less intense scar formation in mice treated with SOR after surgery [18]. In data from patients with renal cell carcinoma, there was no increased risk of surgical complications when SOR was used as neoadjuvant therapy [19]. Because of these concerns, some centers that use SOR prior to OLT discontinue the medication when patients increase their MELD exception scores to levels where they can reasonably expect an organ offer. In our patients, SOR-treated patients also did not have increased wound infections, delayed healing, or incisional hernias. In our study, we did not interrupt SOR use prior to transplantation because of concerns of tumor rebound with discontinuation, which has been

reported in use of tyrosine kinase inhibitors in other cancers.

This study has significant limitations, including its retrospective nature and the small sample size. It was also not randomized, and use of SOR was based on physician preference rather than specific criteria. The survival data must be interpreted cautiously given the small numbers of patients. Despite these limitations, this is the first case series to suggest no increased risk of complications with SOR use prior to OLT. Our analysis suggests that SOR is safe in these patients when continued until the day of transplant, and is not associated with an increased rate of complications in OLT recipients. While these data are too small to address the change in the risk of dropout while waiting for transplant with the use of SOR, the lack of increased complications seen suggest that proceeding with larger randomized controlled trials in this patient population may be warranted.

Authorship

CTF: performed research/study, wrote the article, analyzed data, collected data. MB: collected and analyzed data, contributed to writing the article. SGB, AK, TAA, JG, AOG, HM: performed research/study. RMG: performed research/study, edited article, analyzed data.

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