Sorafenib As Adjuvant Therapy For High-Risk Hepatocellular Carcinoma in Liver Transplant Recipients: Feasibility and Efficacy

Sammy Saab,[1,2] Michael McTigue,[1] Richard S. Finn,[3] Ronald W. Busuttil[2]

Abstract

Objectives: **Liver transplant can be a definitive treatment for hepatocellular carcinoma. However, recurrence limits long-term survival. Sorafenib is the first agent to improve survival for patients with advanced hepatocellular carcinoma.**

Materials and Methods: **A retrospective, case-control match analysis was performed, along with assessment of safety and tolerability. The endpoints of the study were recurrence incidence, episodes of rejection, and disease-free overall survival. Eight patients who underwent liver transplant for hepatocellular carcinoma between May 2007 and April 2009, and tolerated adjuvant therapy with sorafenib were matched with patients who did not receive sorafenib according to age, sex, year of transplant, tumor burden, and presence of vascular invasion.**

Results: **During follow-up, there were no episodes of rejection in either group. Eight patients were able to tolerate a predetermined duration of therapy. During a mean (± standard deviation [SD]) follow-up of 17.75 ± 6.26 months, 1 of 8 patients (12.5%) treated with sorafenib developed hepatocellular carcinoma recurrence. During a mean (± SD) follow-up of 31.63 months (± 22.30 months), 4 of 8 matched controls (50.0%) developed hepatocellular carcinoma recurrence. Disease-free 1-year survival for sorafenib and control group was 85.7% and 57.1%. Overall, 1-year survival for sorafenib and control group was 87.5% and 62.5%.**

Conclusions: **Our study demonstrates the safety and potential benefit of sorafenib in reducing the incidence of hepatocellular carcinoma recurrence and in extending disease-free and overall survival for high-risk liver transplant recipients. A prospective trial is needed to fully assess the role sorafenib as prophylaxis against hepatocellular carcinoma recurrence.**

Key words: *Hepatocellular carcinoma; Liver transplantation*

Hepatocellular carcinoma is one of the most-common malignancies in the world, and the third most-frequent cause of cancer-related death (1). Hepatocellular carcinoma usually develops in the background of cirrhosis, and is thus, potentially cured by liver transplant (2, 3). Liver transplant not only removes the tumor, but it deals with the setting from which it arose. Thus, liver transplant has been increasingly used for the treatment of cirrhosis complicated by hepatocellular carcinoma.

Initial experience of liver transplant in patients with hepatocellular carcinoma was disappointing, with patient survival compromised by recurrent tumors (4-8). Patient survival improved as criteria for listing was better defined (9). With this predetermined criteria in selecting liver transplant candidates, Mazzaferro and colleagues showed an overall, 4-year, actuarial survival rate and nonrecurrence rate of 75% and 83%. Other classification systems have been developed, but undoubtedly, as the acceptable tumor burden increases, the risk of recurrent hepatocellular carcinoma increases and patient survival decreases (10, 11). One exception is the University of California,

From the [1]Departments of Medicine, [2]Surgery, and [3]Hematology/Oncology at the University of California at Los Angeles, Los Angeles, CA, USA

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Address reprint requests to: *Sammy Saab, MD, MPH, AGAF, Pfleger Liver Institute, UCLA Medical Center, 200 Medical Plaza, Suite 214, Los Angeles, CA 90095*

Phone: *+1 310 206 6705* ***Fax:*** *+1 310 206 4197* ***E-mail:*** *SSaab@mednet.ucla.edu*

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San Francisco criteria that allows for greater tumor burden without significantly compromising long-term survival if patients could be down-staged to meet the Milan criteria, or if UCSF criteria was strictly adhered to on explant pathology (12).

Hepatocellular carcinoma recurrence in liver transplant recipients ranges from 6.4% to 56.5% (13-22). Tumor size and presence of microvascular invasion have been shown repeatedly to be the 2 prominent risk factors associated with increased hepatocellular carcinoma recurrence and lower overall survival (18, 23-40). A recent study found that 3-year survival for patients exceeding UCSF criteria and with presence of microvascular invasion was 15%, while 3-year survival for patients without those 2 independent risk factors was 96% (40). Additionally, it has been shown that increasing tumor size and poor differentiation predicts vascular invasion (41, 42). For patients considered to be high-risk for recurrence, the use of adjuvant chemotherapy has not been shown to improve patient outcome.

Although an earlier study demonstrated improved survival in high-risk liver-transplant recipients treated with 6 months of intravenous fluorouracil, doxorubicin, the comparison group was a historical cohort and has not been prospectively assessed (43). Other studies have not shown this benefit in the adjuvant setting (44-47). Most recently, the use of neoadjuvant chemotherapy also has not shown to be beneficial in a prospective, randomized trial (48). Pretransplant transarterial chemo-embolization also has not been shown to reduce recurrence (49-52).

Treatment strategies in liver-transplant recipients with recurrent hepatocellular carcinoma are limited, usually because of systemic metastases (53). Aggressive surgical intervention is limited to the small percentage of patients with resectable hepatic or extrahepatic tumor burden (54-56). One recent observation suggests that sorafenib may have a role in the treatment of recurrent hepatocellular carcinoma after liver transplant (57). Sorafenib is an oral, multitargeted, tyrosine kinase inhibitor of the vascular endothelial growth factor receptor, raf kinase, and platelet-derived growth factor receptor has been shown in 2 randomized Phase III studies to improve survival in advanced hepatocellular carcinoma (58, 59). Given the survival benefit in patients treated with sorafenib for advanced hepatocellular carcinoma and the lack of established treatments for recurrent hepatocellular carcinoma, we assessed our experience using sorafenib in patients at high risk for recurrence after liver transplant.

Although not proven, we hypothesized that patients undergoing a liver transplant and with high-risk features on explant pathology may have prolonged disease-free survival with the use of sorafenib in the adjuvant setting. Currently there are randomized studies evaluating the safety and efficacy of sorafenib after curative resection (60). Here, we describe our experience in regards to safety, tolerability, and preliminary efficacy analysis in a liver transplant population.

Materials and Methods

Patients

We retrospectively analyzed clinical data from 8 patients who received adjuvant sorafenib after liver transplant for hepatocellular carcinoma performed between May 2007 and April 2009. Preoperative diagnosis of hepatocellular carcinoma was performed through imaging modalities including computed tomography and magnetic resonance imaging scans, according to the American Association for the Study of Liver Diseases guidelines (61). Biopsies are rarely performed before liver transplant. Patients who were found to have macrovascular invasion or positive lymph nodes or metastases on explant pathology were excluded. Patients were excluded if they received other forms of systemic chemotherapy adjuvantly or neoadjuvantly. Patients who died within the first 4 months after transplant for other reasons (besides recurrence) were excluded. All protocols, experimental studies, and clinical trials involving human subjects were approved by the Ethics Committee of the Institution before the study began, and the protocols conformed to the ethical guidelines of the 1975 Helsinki Declaration.

The 8 patients considered for treatment with adjuvant sorafenib based on presence of poor tumor differentiation, tumor staging beyond the Milan criteria, and presence of lymphovascular invasion, along with requirement of oncology follow-up with imaging studies. Clinical data obtained includes cirrhotic liver status, hepatitis B virus status, hepatitis C virus status, other causes of cirrhosis, presence of pretransplant treatments, and dosing and course of

sorafenib administered. Explant tumors were staged using the Modified Tumor-Node-Metastases classification (62, 63). Explant tumor differentiation was classified using Edmondson-Steiner classification system (64).

Patients treated with sorafenib were followed closely for adverse effects, along with monitoring of complete blood count and metabolic panel, with reductions in dosing and discontinuation when poorly tolerated. These 8 patients all tolerated at least 7 of the first 8 weeks of therapy. Patients who did not tolerate this duration of therapy were not included in this study. The goal minimum duration of therapy was 6 months. These patient cases were matched for case controls for age (± 10 years), sex, year of transplant (± 5 years), exceeding Milan criteria, and presence of microvascular invasion. The case controls were derived from both historical controls between January 2003 to April 2007 predating use of sorafenib in patients receiving no adjuvant chemotherapy, along with patients receiving liver transplant between May 2007 and April 2009 who elected to not receive sorafenib. Matching was performed with blinding of patient outcomes.

Immunosuppression and prophylaxis

Immunosuppression regimens after liver transplant consisted of combinations of cyclosporine, prednisone, tacrolimus, sirolimus, and mycophenolate mofetil. According to our protocol, patients initially received 1 g of intravenous methylprednisolone the day of transplant; this was then tapered to 20 mg/d over 1 week. Oral prednisone was subsequently started at 20 mg/d and tapered as tolerated. All patients were treated with trimethoprim-sulfamethoxazole for 1 year. Our protocol for posttransplant target immunosuppression levels has been previously described (65). Patients were followed closely for signs and symptoms of allograft rejection.

Surveillance for hepatocellular carcinoma recurrence

After transplant, patients with known hepatocellular carcinoma were followed regularly in the outpatient hepatology and liver-cancer clinics. Per our program guidelines, surveillance with computed tomography images was obtained at 3 months, 6 months, 12 months, and annually thereafter. Alpha-fetoprotein levels were followed as well. If there was concern for hepatocellular carcinoma recurrence, whole body computed tomography/magnetic resonance imaging, and positron emission tomography scan, was ordered at the discretion of the physician. All recurrent hepatocellular carcinomas were confirmed with tissue diagnosis when appropriate.

Statistical analyses

Mean and standard deviations were used for descriptive statistics. Formal statistical analyses were not performed because of the small number of patients.

Results

Demographics

A retrospective review of our liver transplant database was performed for 222 patients who underwent liver transplant for hepatocellular carcinoma between January 2006 and April 2009 at the Pfleger Liver Institute. A total of 8 patients were found to have received sorafenib treatment as adjuvant prophylaxis owing to high-risk features found on explant pathology and tolerated it for at least 7 of the first 8 weeks of therapy. Table 1 outlines the patient demographics at the time of transplant for the 8 patients meeting the duration criteria and 8 control matches. Table 2 details the explant pathology characteristics for the 2 groups. The mean follow-up is 17.75 months (± 6.26 months) for the sorafenib group and 31.63 months (± 22.30 months) for the control group. Mean follow-up for living

Table 1. Baseline demographic characteristics.

Variables	Sorafenib group (n=8)	Control group (n=8)
Mean age (y) (SD)	51.5 (7.6)	52.3 (7.9)
Sex		
Male	5	5
Female	3	3
Cirrhosis	8	8
Cause of liver disease		
Hepatitis B	2	3
Hepatitis C	5	4
Alcohol	1	0
Cryptogenic	0	1
Pretransplant intervention	4	7
Transarterial chemoembolization	2	3
Radiofrequency ablation	1	4
Percutaneous ethanol	0	1
Pretransplant alfa-fetoprotein (ng/mL)		
< 10	1	1
> 10, < 300	4	5
> 300	3	2

patients in the sorafenib group is 21.80 months (± 4.23 months).

Table 2. Explant pathology characteristics.

Variables	Sorafenib group (n=8)	Control group (n=8)
Largest tumor size ≥ 5 cm	4	4
Modified transmission tumor stage		
T1	0	0
T2	0	0
T3	1	0
T4a	0	1
T4b	7	7
Milan criteria exceeded		
Yes	8	8
No	0	0
University of California, San Francisco criteria exceeded		
Yes	6	7
No	2	1
Nodularity		
Solitary	2	1
Multinodularity	6	7
Differentiation (highest nuclear grade)		
Grade 1	0	2
Grade 2	4	5
Grade 3	5	2
Grade 4	1	1
Presence of vascular invasion	7	7
Milan criteria exceeded and vascular invasion	7	7
University of California, San Francisco criteria exceeded and vascular invasion	5	6

Tolerability and safety

All patients were initiated on sorafenib between 6 and 12 weeks after liver transplant. All patients initiated on 400 mg twice daily were unable to tolerate this dosing and eventually required a dosage reduction. Owing to this early experience, the last 6 patients were initiated on 200 mg twice daily. Overall, 6 of 8 patients (75%) included in the study required a dosage reduction. One patient tolerated a dosage increase to 400 mg twice daily 4 weeks after initiation of therapy. Six patients (75%) completed a 6-month course of sorafenib and 1 of these patients (12.5%) completed a 10-month course. Five of these 6 patients (83.3%) did not have hepatocellular carcinoma recurrence. One patient receiving sorafenib died secondary to *Cytomegalovirus* viremia and subsequent multiorgan system failure. This patient did have grade 3 neutropenia on 400 mg twice daily dosing, which resolved completely with reduction to 200 mg twice daily. This patient last had neutropenia 2 months before presentation with *Cytomegalovirus* viremia and did not have any cytopenias at the time of presentation. Sorafenib was discontinued at the time of admission, and the patient died 2 months after admission.

Six of 8 patients could tolerate a 6-month course of sorafenib. One patient in the sorafenib group had sorafenib discontinued after 8 weeks owing to mildly elevated liver tests, which resolved incompletely with discontinuation, with persistent elevation consistent with recurrent hepatitis C. The patient in the sorafenib group who died of *Cytomegalovirus* viremia had 14 weeks of therapy before discontinuation at time of hospitalization. A third patient in the sorafenib group died at 14 months after liver transplant secondary to recurrent hepatitis C and development of acute renal failure. This patient was found to have recurrent hepatitis C on initial posttransplant liver biopsy. There was no evidence of disease recurrence at time of death.

Recurrence

One patient in sorafenib group (12.5%) and 4 patients in control group (50%) had hepatocellular carcinoma recurrence during follow-up. Overall, 4 of 5 patients (80%) with recurrence had hepatocellular carcinoma recurrence within the first year. Of patients with recurrence, 1 patient in the sorafenib group (100%) and 3 of 4 of the control group (75%) had a recurrence in the first year. The final patient in the control group had recurrence at 26 months. The mean time to recurrence for hepatocellular carcinoma for sorafenib and control group was 5.0 and 11.3 months (± 9.2 months), respectively. Disease-free, 1-year survival for sorafenib and control group was 85.7% and 57.1%. All patients within the sorafenib group without recurrence had at least 16 months of follow-up after liver transplant. One patient in the control group who developed recurrence in the lung at 12 months underwent a surgical resection, and is now living without evidence of recurrence at 33 months' follow-up.

Survival

Three patients in the sorafenib group (37.5%) and 4 patients in the control group (50.0%) died during follow-up. Overall survival for the sorafenib and control groups during follow-up was 62.5% and 50%. Overall, 1-year survival for sorafenib and control group was 87.5% and 62.5%. Each group had 1 patient die of nonhepatocellular carcinoma recurrence causes in the first year, both at 6 months after liver transplant. The patient in the sorafenib

group died of *Cytomegalovirus* viremia and eventual multisystem organ failure. He was not neutropenic or lymphopenic at the time of diagnosis. The patient in the control group died of bacterial sepsis and resulting multisystem organ failure. A second patient in the sorafenib group died of recurrent hepatitis C and acute renal failure 14 months after liver transplant.

Discussion

With application of Milan and UCSF criteria to liver transplant for hepatocellular carcinoma eligibility, long-term survival has significantly improved (9, 10). Despite these advancements, there continues to be minimal improvement in reducing hepatocellular carcinoma recurrence for those patients found on explant to have microvascular invasion and pathology exceeding Milan (and UCSF) criteria. This is the first report to describe the potential role of sorafenib as adjuvant therapy in reducing hepatocellular carcinoma recurrence after liver transplant for patients at high risk for recurrence. With careful management, it is feasible to deliver sorafenib at dosages used in the registration studies in advanced hepatocellular carcinoma. Though a small group of patients, the case matches analysis demonstrates a 75% relative risk reduction of hepatocellular carcinoma recurrence for patients treated with sorafenib.

Lai and associates recently reported a 5-year recurrence rate of 63% for patients with microvascular invasion, 68% for patients exceeding UCSF criteria, and 79% for those patients with both features (40). Our study showed results of 57%, 43%, and 50% for the control group and 0%, 17%, and 0% for the sorafenib group. Yao and colleagues showed 50% 1-year recurrence for patients exceeding UCSF criteria on pathology (12). In validation of UCSF criteria with preoperative imaging, Yao and colleagues showed a 40% 5-year recurrence rate for patients exceeding UCSF criteria (64). Our control group recurrence rates compare well with these historical controls, giving confidence that this group represents the natural history of hepatocellular carcinoma transplanted beyond accepted criteria.

Safety and tolerability analysis cannot be fully assessed in a retrospective study. This study showed that no patient could tolerate full dosing of sorafenib at 400 mg twice daily as initial dosing. Cytopenias, hand-foot skin reaction, diarrhea, and fatigue were most common at this dosing and generally improved with dosage reduction. One patient could be dose-escalated to 400 mg twice daily after initial 4 weeks on 200 mg twice daily. It is hypothesized that significant immunosuppression and increased potential for drug-drug interactions in the posttransplant setting contributes to this intolerance of 400 mg twice daily dosing. Better patient compliance and duration of therapy was noted in patients initiated on lower dosage of 200 mg twice daily. It is also unclear how dosage reduction affects clinical efficacy in the liver transplant population. Future investigations of sorafenib in this patient population should consider this lower starting treatment dosage, with a dosage escalation as tolerated. It is reassuring that no cases of allograft rejection occurred in sorafenib group and that no increase in clinically significant infections occurred in the sorafenib group compared with the control group in this already immunocompromised population.

Limitations of this study include its retrospective analysis and small number of patients treated with sorafenib. Additionally, this study is the experience of a single liver transplant center only. Owing to sorafenib only being FDA-approved for metastatic or unresectable hepatocellular carcinoma in November 2007, the application in the adjuvant setting is limited to the past 2 years only. This fundamental limitation results in a shorter sorafenib follow-up compared with the control group. Additionally, the overwhelming majority of patients with high-risk features opted to pursue adjuvant sorafenib, limiting potential case controls during same time. Secondary to this short follow-up, the study may not be capturing future recurrences. However, 3 of 4 patients in our control group had recurrence within the first 12 months after liver transplant, and all patients in the sorafenib group had at least 16 months' follow-up. It is also possible that sorafenib is delaying onset of recurrence and therefore extended follow-up may find additional recurrences. A multicenter study would be required to obtain a larger population of patients, as few patients are transplanted for hepatocellular carcinoma each year at each center, which are then found to have vascular invasion and tumor pathology exceeding Milan criteria.

Our findings suggest a possible therapeutic role for sorafenib in extending survival after recurrence and overall survival. This adjuvant chemotherapy was not tolerated well at full dosing. Initial dosage reduction of sorafenib should be strongly considered

in the posttransplant population, given concomitant immunosuppression. A prospective, multicenter trial is needed to further evaluate this retrospective study's results, as well as to better assess safety and tolerability in an immunosuppressed population of patients.

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