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ORIGINAL ARTICLE

High toxicity of sorafenib for recurrent hepatocellular carcinoma after liver transplantation

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Summary

Treatment options of recurrent hepatocellular carcinoma (HCC) after liver transplantation are limited and data on systemic compounds for advanced tumor stages in transplant recipients are sparse. We retrospectively analyzed the toxicity, tolerability, and efficacy of sorafenib in combination with mTOR inhibitors (mTORi), or calcineurin inhibitors (CNI) in transplant recipients with recurrent HCC. In total, 20 of 92 patients transplanted for HCC within a 10-year time period, experienced tumor recurrence. In case of ineligibility for other treatment options, patients received sorafenib (n = 13). In addition, CNI were stopped and switched to mTORi in nine patients, whereas CNI were continued in four patients. Grade 3–4 adverse events were observed in 92% of all patients necessitating sorafenib discontinuation in 77%. The most common severe adverse events were acute hepatitis, diarrhea, hand-foot – skin reaction and bone marrow suppression. In patients receiving sorafenib/mTORi one patient achieved partial response, and four achieved stable disease. In this cohort of liver transplant recipients side effects prevented full dosing of sorafenib and necessitated discontinuation of sorafenib in the majority of patients, yet antitumor efficacy seemed promising in combination with mTORi.

Introduction

Orthotopic liver transplantation (OLT) is an established treatment option for patients with hepatocellular carcinoma (HCC) within the Milan criteria achieving 5-year survival rates of about 70% comparable to other indications [1]. Despite declining recurrence rates of HCC after OLT over the past decades, recurrence of HCC still emerges in about 10–30% [2]. Therapy in these patients constitutes a challenge, since in the majority of cases multiple organs are involved. In addition, in transplant recipients, tumor growth may be promoted by calcineurin inhibitors (CNI) [3,4], whereas mTOR inhibitors (mTORi) have been demonstrated to display antitumoral efficacy in several solid tumors [5,6]. Only retrospective data exist comparing the impact of both immunosuppressive regimens with respect to prevention of HCC recurrence or impact on progression of recurrent disease after OLT [7]. However, a survival benefit for patients receiving mTORi-based regimens or mTORi in combination with CNI compared with CNI-based immunosuppressive regimens after OLT was repeatedly reported [8–10]. Further prospective studies are being conducted to assess the impact of mTORi on HCC recurrence after OLT [11].

At present, the only licensed substance with proven efficacy in advanced HCC is the multi – kinase inhibitor, sorafenib. It has been shown to achieve a survival benefit of 2.8 months in non-transplant patients with advanced HCC and compensated cirrhosis [12]. Data on systemic antitumoral therapies within the post-transplant setting

are yet only anecdotal [13–18]. Enhanced anticancer properties *in vitro* and *in vivo* were suggested when sorafenib was combined with mTORi [16,19,20]. In this retrospective analysis, we present data on toxicity, tolerability, and efficacy of sorafenib after liver transplantation.

Patients and methods

All patients undergoing OLT for HCC between January 2000 and December 2009 at the University Medical Centre Hamburg – Eppendorf were identified (100 patients, 8/100 lost to follow-up [FU]). Twenty of 92 patients experienced tumor recurrence. Diagnosis of HCC recurrence was verified by biopsy and/or two different radiological imaging techniques, i.e. computed tomography (CT) or magnetic resonance imaging (MRI).

Patients receiving sorafenib (13/20) were included in the data analysis and followed until November 2010. Chemotherapy with sorafenib was only administered, if patients were not eligible for surgical or locoregional therapy, or progression was evident afterwards. Five of 20 patients did not receive sorafenib, either because of contraindications, patients' refusal, or HCC recurrence prior to the sorafenib era. In the remaining two patients with HCC recurrence surgical resection in curative intention was performed. These patients were excluded from further analysis.

Sorafenib was started with a dosage of 200 mg b.i.d, and increased subsequently to 400 mg b.i.d, if possible. In addition, patients were switched from CNI-based immunosuppression to mTORi (9/13) whenever cost coverage was given by their insurance. Either sirolimus or everolimus was administered depending on the investigator's discretion. Target trough levels for sirolimus and everolimus were 5–7 ng/ml, and 4–6 ng/ml, respectively. In the remaining patients who continued to receive CNI, dosage of cyclosporine A (CSA) and tacrolimus (TAC) were adjusted to reach target trough levels of 75–125 ng/dl, and 4–6 ng/dl, respectively.

Radiological imaging (CT or MRI) was done every 12 weeks to assess response to therapy. Adverse events were evaluated according to the National Cancer Institute – Common Terminology criteria 3.0 (NCI – CTC 3.0) [21].

Statistical analysis was performed using SPSS 15.0 (SPPS Inc, Chicago, IL, USA). Calculation of survival data was done using Kaplan–Meier analysis and log-rank test.

Results

Patient characteristics and HCC recurrence

Demographic patient data, underlying diagnosis, and HCC characteristics before OLT are given in Table 1.

Table 1. Patient characteristics at time of OLT. Tumor staging was done according to explant histologies. AFP values <2 months prior to OLT are given.

	Sorafenib	Sorafenib/mTORi	Sorafenib/CNI
	(*n* = 13)	(*n* = 9)	(*n* = 4)
Gender (m:f)	12:1	8:1	4:0
Age (years)			
Median	60	60	61
Range	44–68	44–68	44–66
Diagnosis (%)			
HCV	54	56	50
HBV	31	33	25
ALD	15	11	25
Within Milan (%)	39	33	50
Within UCSF (%)	62	44	100
Vascular invasion (%)	62	67	50
AFP (kU/L)			
Median	9.3	130.8	4.9
Range	1.5–1284	1.5–1284	2–637
TTR (months)			
Median	13.6	13.6	14.4
Range	1.7–66.3	1.7–66.3	3–54.2

AFP, alpha – fetoprotein; ALD, alcoholic liver disease; CNI, calcineurin inhibitor; HCV, hepatitis C; HBV, hepatitis B; TTR, time to recurrence; UCSF criteria, University of California San Francisco.

Based on explant histology results, tumor size at the time of OLT was outside Milan criteria in 61% and outside University of California San Francisco (UCSF) criteria in 38% of patients. Details concerning tumor localization, immunosuppression and ECOG Performance Status at the time of HCC recurrence are given in Table 2. The majority of patients had either combined hepatic and extrahepatic tumor recurrence, or extrahepatic manifestations only. At the time of sorafenib initiation, none of the patients showed clinical signs of liver cirrhosis or elevation of aminotransferases ≥2.5-fold the upper limit of normal (ULN).

Sorafenib treatment, toxicity and tolerability

The median time between tumor recurrence and initiation of sorafenib was 2.3 months (range: 0.3–53.3 months). Median duration of sorafenib treatment was 16.9 weeks (range: 4.2–88 weeks). Patients receiving sorafenib in combination with mTORi were treated substantially longer (37.1 weeks, range: 9.6–88 weeks), as compared to patients receiving sorafenib/CNI (7.4 weeks, range: 2.6–16.9 weeks). Mean dosage of sorafenib was similar in both groups (average mean sorafenib dosage ± SD: 418 mg ± 173.3 versus 414 mg ± 28.5). Median trough level of everolimus (2/9 patients) and sirolimus (7/9) was 5.1 ng/ml (range: 2.1–11.5), and 6.1 ng/ml (range: 2.6–22.2), respectively.

Table 2. Patient characteristics at time of tumor recurrence. Patients treated with a CNI based immunosuppressive regimen at the time of recurrence were switched to either sirolimus or everolimus, if cost coverage was granted by their insurance.

Patients	IS at HCC recurrence	IS after HCC recurrence	Localization of recurrence	ECOG performance status
Sorafenib/mTORi				
1	Tacrolimus Steroids	Sirolimus Steroids	Liver, bones, lung	2
2	Cyclosporine A MMF Steroids	Sirolimus	Liver	1
3	Tacrolimus Everolimus Steroids	Everolimus Steroids	Lung	0
4	Tacrolimus Steroids	Sirolimus	Lung	0
5	Tacrolimus MMF	Sirolimus	Liver, bones, adrenal gland, peritoneum	2
6	Tacrolimus	Sirolimus	Liver retroperitoneum	1
7	Cyclosporine A Everolimus Steroids	Everolimus Steroids	Lung, retroperitoneum	1
8	Cyclosporine A MMF	Sirolimus	Liver, lung	1
9	Cyclosporine A Sirolimus	Sirolimus	Liver	0
Sorafenib/CNI				
10	Cyclosporine A MMF	Cyclosporine A MMF	Lymph nodes	1
11	Tacrolimus	Tacrolimus	Liver, bones, pancreas	2
12	Cyclosporine A Steroids	Cyclosporine A Steroids	Lung	1
13	Tacrolimus	Tacrolimus	Liver, Bones	1

ECOG, Eastern Cooperative Oncology Group; IS, immunosuppression; MMF, mycophenolate mofetil.

Median trough level of TAC (2/2 patients) and CSA (2/2 patients) was 5.1 ng/ml (range: 3.9–9.2), and 89.5 ng/ml (range: 85–150).

Overall, sorafenib was poorly tolerated, and achieving full dosage was not possible in the majority of patients (10/13). In 92% (12/13) of patients grade 3–4 adverse events occurred and were responsible for discontinuation of sorafenib in as many as 77% (10/13) of patients (Table 3). On the other hand, sorafenib was discontinued attributable to tumor progression in only 15.4% (2/13). Only one patient (patient no. 7) was able to continue sorafenib treatment until the end of FU.

Grade 3–4 adverse events necessitating sorafenib discontinuation were diarrhea (3/13), hand-foot – skin reaction (2/13), anemia (1/13), and leukopenia (1/13). In one case with therapy resistant diarrhea acute reversible renal failure developed (sorafenib/mTORi). Notably, sorafenib had to be discontinued because of liver toxicity in three patients.

In two patients (patient no. 11 and 12), treated with sorafenib/CNI, acute cholestatic hepatitis developed. Aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), and gamma-glutamyl transferase (GGT) increased up to 10- to 20-fold the ULN within 2 weeks of sorafenib treatment, accompanied by a rise of serum bilirubin to 20.1 mg/dl, and 11.3 mg/dl, respectively. Liver histology in both cases was consistent with toxic liver damage showing disseminated centrilobular necroses, and lymphoplasmacellular infiltration of the portal tracts. In addition, in patient no. 11, significant eosinophilic infiltration of the portal tracts, consistent with a hyperallergic drug reaction was evident. In patient no. 12, histological characteristics of mild acute rejection (Banff grade 2/9) were present, thus in addition to sorafenib discontinuation, steroid bolus treatment was started. Within 6 weeks after cessation of sorafenib, liver function tests (LFTs) normalized in both patients.

In the third case (patient no. 2), a patient with HCV infection receiving sorafenib/mTORi, AST and ALT

Table 3. Incidence of drug-related adverse events. AE grading was done according to National Cancer Institute – Common Terminology Criteria, version 3.0.

	Sorafenib (n = 13)		Sorafenib/mTORi (n = 9)					Sorafenib/CNI (n = 4)				
	Any Grade		Any Grade	Grade 1–2		Grade 3–4		Any Grade	Grade 1–2		Grade 3–4	
Toxicity	n	%	%	n	%	n	%	%	n	%	n	%
Hematologic	11	84.6										
Anemia	6	46.2	55.6	4/9	44.4	1/9	11.1	25	0/4	0	1/4	25
Leucopenia	7	53.8	33.3	3/9	33.3	0/9	0	100	3/4	75	1/4	25
Thrombocytopenia	8	61.5	55.6	5/9	55.6	0/9	0	75	3/4	75	0/4	0
Dermatologic	6	46.1										
Hand-foot skin reaction	3	23.1	22.2	0/9	0	2/9	22.2	25	0/4	0	1/4	25
Skin rash/desquamation	5	38.5	44.4	3/9	33.3	1/9	11.1	25	1/4	25	0/4	0
Stomatitis	3	23.1	22.2	1/9	11.1	1/9	11.1	25	1/4	25	0/4	0
Alopecia	1	7.7	11.1	1/9	11.1	0/9	0	0	0/4	0	0/4	0
Gastrointestinal	9	69.2										
Nausea/vomiting	2	15.4	22.2	1/9	11.1	1/9	11.1	0	0/4	0	0/4	0
Diarrhea	8	61.5	88.9	4/9	44.4	4/9	44.4	0	0/4	0	0/4	0
Abdominal pain	1	7.7	11.1	1/9	11.1	0/9	0	0	0/4	0	0/4	0
Weight loss	5	38.5	33.3	3/9	33.3	0/9	0	50	2/4	50	0/4	0
Liver	11	84.6										
Elevation of liver function tests	11	84.6	77.8	6/9	66.7	1/9	11.1	100	2/4	50	2/4	50
Others	9	69.2										
Sweat	1	7.7	11.1	1/9	11.1	0/9	0	0	0/4	0	0/4	0
Hypertension	4	30.8	33.3	1/9	11.1	2/9	22.2	25	1/4	25	0/4	0
Myalgia/arthralgia	3	23.1	22.2	1/9	11.1	1/9	11.1	25	1/4	25	0/4	0
Fatigue	2	15.4	11.1	1/9	11.1	0/9	0	25	1/4	25	0/4	0
Pneumonia/cough	2	15.4	22.2	2/9	22.2	0/9	0	0	0/4	0	0/4	0
Acute renal failure	1	7.7	11.1	0/9	0	1/9	11.1	0	0/4	0	0/4	0
Overall toxicity	13	100	100	9/9	100	8/9	88.9	100	4/4	100	4/4	100

started to rise 3 weeks after sorafenib initiation, reaching their maximum of 15-fold the ULN after 9 weeks. GGT and bilirubin were only mildly elevated. The patient's liver histology was compatible with toxic liver damage including disseminated centrilobular necroses, intralobular cholestasis, and lymphoplasmacellular infiltration of the portal tracts, but showed no histological evidence of HCV recurrence. However, normalization of LFTs did occur after sorafenib discontinuation, and subsequent initiation of antiviral combination therapy.

Efficacy and outcome

Median time of FU from OLT to end of FU or death was 29 months (range: 1.7–121.8 months). Mean time to TTP during sorafenib treatment was 7 months (95%CI: 4.5, 9.4) (Fig. 1a), 8.8 m (95%CI: 5.9, 11.6) in patients receiving sorafenib/mTORi, but only 2.9 (95%CI: 2.4, 3.4) in patients on sorafenib/CNI (P = 0.012). Mean overall survival (OS) was 19.4 months (95%CI: 13.4, 25.5) (Fig. 1b), (sorafenib/mTORi: OS = 25.6 months; 95% CI: 20.5, 30.7; sorafenib/CNI: OS = 7.3 months; 95% CI: 2.3, 12.4; P = 0.001).

The 1-year survival rate was 69% (9/13), 89% (8/9) in patients receiving sorafenib/mTORi, and 25% (1/4) in patients with sorafenib/CNI treatment. At the end of FU, total survival rate was 54% (7/13; all patients with sorafenib/mTORi). Main reason for death was tumor progression. Applying RECIST criteria for best response to antitumoral treatment showed four of nine patients with stable disease (SD), and one patient with partial response (PR) under sorafenib treatment (Table 4).

Discussion

Treatment of recurrent HCC after OLT is a clinical challenge. Sorafenib has been validated in patients with advanced HCC and compensated liver function [12]. However, data on efficacy and tolerability of sorafenib in liver transplant recipients are sparse. In this retrospective, single center study of 13 OLT recipients toxicity of sorafenib was high. Grade 3 or 4 adverse events occurred in about three quarter of patients independent of the underlying immunosuppressive therapy with CNI or mTORi, and ultimately resulted in discontinuation of the drug. In contrast, in the

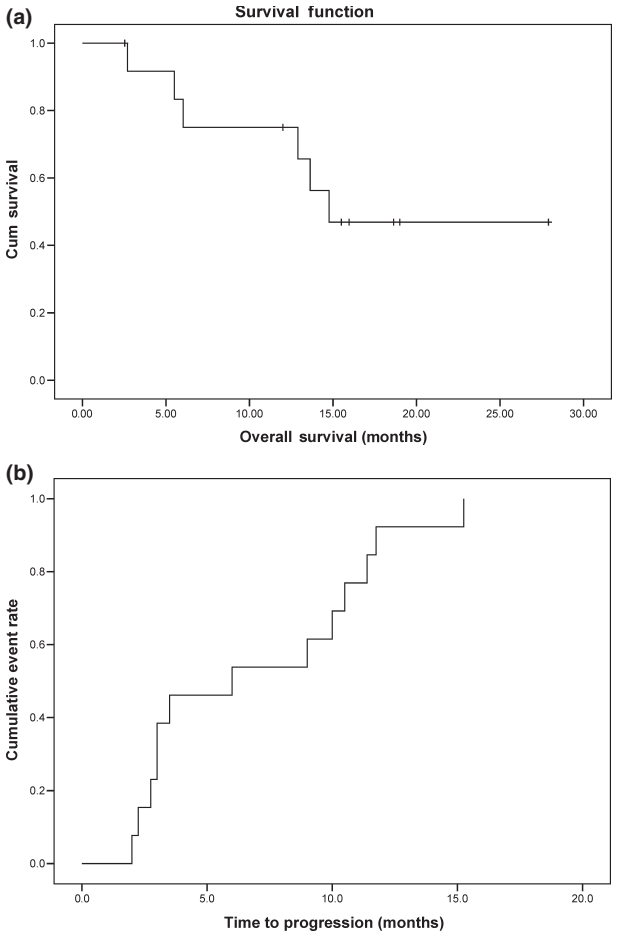

Figure 1 Kaplan–Meier analysis of overall survival and time to progression. (a) TTP (mean; 95% CI), from time of sorafenib initiation till progression was calculated. TTP was 7 months (4.5, 9.4). (b) OS (mean; 95% CI), from time of sorafenib initiation till the end of FU or death was 19.4 months (13.4, 25.5). OS, overall survival, TTP, Time to progression.

few previous case series of OLT recipients treated with sorafenib side effects, although common, appeared to be less pronounced. Higher grade toxicities were reported in 25–30% (Yoon *et al.*: 4/13 patients, Pfiffer *et al.*: 2/8 patients) under sorafenib/CNI combination therapy [22,23] and in 55% (Kim *et al.*: 5/9 patients) in another series using sorafenib in combination with mTORi [24]. In a recently published retrospective Spanish multicenter analysis including the largest number of OLT recipients reported so far dose reduction owing to side effects was necessary in just 8 of 26 (31%) patients treated with sorafenib/mTORi [25]. In agreement with our data, diarrhea and hand-foot – skin reaction belonged to the most common serious side effects seen in previous reports. Bone marrow suppression seemed to be of particular importance affecting more than half of OLT recipients whereas hematologic toxicity in non-transplant patients receiving sorafenib was reported in less than 4% [12].

However, in our study we observed significant hepatic toxicity in a number of patients. Mild to moderate, spontaneously reversible elevation of LFTs despite of continued sorafenib treatment occurred in 61.5% (8/13) of patients. Cessation of sorafenib treatment was necessary in three cases owing to a steep increase of bilirubin and transaminases. Thereafter, LFTs normalized within few weeks in all three cases. In addition to an OLT recipient included in this study who has been separately reported before [26], two more cases of sorafenib induced acute hepatitis were previously described in patients with cirrhosis [26–28], underlining the importance of this possibly fatal complication. A closer look at the patients reported here suggests that sorafenib hepatotoxicity may well be aggravated by additional factors such as acute rejection (patient no. 12, sorafenib/CNI) or hepatitis C reactivation (patient no. 2, sorafenib/mTORi).

The reason behind the inconsistent frequency and type of side effects reported in the literature is not clear. This variability might reflect the small number of OLT recipients having undergone sorafenib treatment up to now, particularly in combination with mTORi. On the molecular level, inhibition of multiple target pathways by combination of sorafenib with an mTORi may be responsible for aggravation of side effects [5,20], but may also have the potential of significantly improved tumor response [14,29]. The potential clinical efficacy of the combination of sorafenib with mTORi for OLT recipients with HCC recurrence was first illustrated by two case reports showing significant treatment responses under this combination therapy [16,29].

In our case series of transplant recipients receiving sorafenib a high OS of 19.4 months (95%CI: 13.4, 25.5) was observed, whereas patients on mTORi had a notably good OS of 25.6 months (95%CI: 20.5, 30.7). Likewise, TTP was 7 months (95%CI: 4.5–9.4) in the whole patient cohort, and 8.8 months (95%CI: 5.9, 11.6) in patients with sorafenib/mTORi combination. At the end of FU seven of nine patients (78%) who had received sorafenib/mTORi were still alive.

These promising data certainly have to be interpreted with caution because of the small number of patients, however, support our findings. Mean OS of OLT recipients under sorafenib plus mTORi therapy was 19.3 months in a Spanish case series (24 evaluable pts) [25] and 18.8 months in the series reported by Valdivieso *et al.* (5 pts). Sorafenib treatment of OLT patients without mTORi on the other hand was associated with mean OS in a range between 2.9 and 6.7 months in other series [14,22,23].

Table 4. Antitumoral therapy and outcome. Treatment prior and after sorafenib is summarized. Of note, sorafenib was only initiated if patients were no longer eligible for surgical or locoregional therapy, or tumor progression was nevertheless evident. BR is indicated according to RECIST criteria. Patient no. 12 received sorafenib <4 weeks, so that RECIST criteria could not be applied. Survival rate was 54% at the end of FU. Clinical benefit rate was 39% in all patients.

Patients	Treatment prior to sorafenib	Treatment after sorafenib	BR	Outcome (Reason for death)
Sorafenib/mTORi				
1	–	Radiation	SD	Alive
2	TACE	–	PD	Alive
3	Resection	Doxorubicin* Epirubicin* Sunitinib*	PD	Deceased (Tumor progression)
4	Resection	–	SD	Alive
5	Resection Radiation	–	SD	Alive
6	Resection TACE	Doxorubicin	PR	Alive
7	–	–	PD	Alive
8	–	–	PD	Deceased (Tumor progression)
9	Resection TACE RFA	–	SD	Alive
Sorafenib/CNI				
10	–	Doxorubicin*	PD	Deceased (Sepsis)
11	Radiation	–	PD	Deceased (Tumor progression)
12	–	–	–	Deceased (Tumor progression)
13	Radiation	–	PD	Deceased (Tumor progression)

*Discontinuation owing to tumor progression.
BR, best response; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria of solid tumors; RFA, radiofrequency ablation; SD, stable disease; TACE, transarterial chemoembolization.

In conclusion, side effects seem to be much more common and more severe in liver transplant recipients than in non-transplant patients with compensated cirrhosis preventing full dosing of sorafenib. Patients have to be carefully monitored for adverse events, especially with regard to liver toxicity and hematologic side effects. Sorafenib in combination with mTORi could be a promising antitumor treatment for OLT recipients with recurrent advanced HCC. To further analyze the efficacy and tolerability of sorafenib, in particular in combination with mTORi prospective trials are needed in this patient population.

Authorship

KS: design of study, collection and analysis of data, writing of manuscript. LF: writing of manuscript. BS: collection of data. EV: analysis of data. BN: writing of manuscript. MS: collection of data, and writing of manuscript.

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