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Comparative efficacy of sorafenib *vs.* best supportive care in recurrent hepatocellular carcinoma after liver transplantation: A case-control study

Carlo Sposito[1], Luigi Mariani[2], Alessandro Germini[1], Maria Flores Reyes[1], Marco Bongini[1], Glenda Grossi[1], Sherrie Bhoori[1], Vincenzo Mazzaferro[1,*]

[1]*The Hepato-Oncology Group, Gastro-Intestinal Surgery, Liver Transplantation and Hepatology, Fondazione IRCCS Istituto Nazionale Tumori (National Cancer Institute), Milan, Italy;* [2]*Biomedical Statistics, Fondazione IRCCS Istituto Nazionale Tumori (National Cancer Institute), Milan, Italy*

Background & Aims: The efficacy of sorafenib in the post-liver transplantation (LT) setting has been scarcely studied. The aim of this study was to evaluate the efficacy of sorafenib, compared to best supportive care (BSC), in two cohorts of patients which presented with hepatocellular carcinoma (HCC) recurrence after LT.

Methods: Data from patients who developed presentation or progression of HCC recurrence after LT not amenable to surgical/locoregional treatments (untreatable presentation/progression, UP) were retrieved. The cohort of patients receiving sorafenib starting from 2007 was compared to that of patients receiving BSC in the previous era. Disease outcome was investigated in terms of survival from recurrence or from UP by means of univariate and multivariate Cox regression models with event times left-truncated at the date of UP.

Results: Of a total of 39 patients, 24 received BSC and 15 sorafenib. The two groups were well matched at baseline, with time-related imbalances regarding mTOR-based immunosuppression and median time from LT to recurrence, significantly higher in the sorafenib group. Patients' outcome in the sorafenib group was significantly improved (median survival from recurrence 21.3 *vs.*11.8 months, HR = 5.2, $p = 0.0009$; median survival from UP 10.6 *vs.* 2.2 months, HR = 21.1, $p < 0.0001$). The only factor associated with survival after HCC recurrence in multivariate analysis was treatment with sorafenib (HR = 4.0; $p = 0.0325$). No severe adverse event was registered in this post-LT setting.

Conclusions: Although the use of historical controls weakens final interpretation, sorafenib seems to be associated with an acceptable safety profile and benefit in survival in HCC patients suffering recurrence after LT.

Keywords: Sorafenib; Liver transplantation; Hepatocellular carcinoma; HCC recurrence.

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* Corresponding author. Address: Department of Gastro-Intestinal Surgery and Liver Transplantation, Fondazione IRCCS Istituto Nazionale Tumori, via Venezian 1, Milan 20133, Italy. Tel.: +39 02 23902760; fax: +39 02 23903259.

E-mail address: vincenzo.mazzaferro@istitutotumori.mi.it (V. Mazzaferro).

Abbreviations: LT, liver transplantation; MC, Milan Criteria; HCC, hepatocellular carcinoma; CNI, calcineurine inhibitor; mTOR, mammalian target of rapamycin; UP, untreatable presentation/progression; BSC, best supportive care; AE, adverse event; CTCAE, common terminology criteria for adverse events; AFP, alpha-fetoprotein; SD, stable disease; PR, partial response; DCR, disease control rate.

Introduction

Ever since its introduction into clinical practice, liver transplantation (LT) appeared to be the ideal cure for both hepatocellular carcinoma (HCC) and cirrhosis, as it eradicates both the seeded tumor and the soiled carcinogenic liver disease. The observation that the probability of tumor recurrence after LT was strictly related to pre-LT tumor stage led to the development of restrictive criteria, such as the Milan Criteria (MC) [1]: the current benchmark and the basis for comparison with other suggested selection criteria [2,3].

Due to the application of stringent selection, the outcome of LT observed nowadays in patients with HCC is similar to that achieved for non-tumoral indications [4]. However, HCC recurrence after LT continues to occur in 8–20% of deceased- and living-donor transplantation, and leads to death in most cases even when aggressive and combined therapeutic approaches are applied [5–7]. In some patients, surgical resection of intra- or extrahepatic tumor deposits has proven to be effective in prolonging survival [5]. Nevertheless once tumor progression goes beyond treatments control, dismal prognosis invariably occurs and this acknowledges for the common experience that any prolonged survival after HCC recurrence in a transplanted patient is exceptional.

Two large randomized control trials (RCTs) in non-transplanted patients have demonstrated that systemic treatment with the multikinase inhibitor agent sorafenib prolongs survival in patients presenting with advanced HCC not amenable to surgical/locoregional treatments [8,9]. Post-transplant status is in most cases an exclusion criteria for RCTs testing molecular target agents in HCC and, therefore, only a few retrospective cohort studies lacking control arms and isolated case reports have been

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published so far, investigating both safety and efficacy of sorafenib in the post-LT setting [10–15]. In such a condition, concerns do arise for potential drug interactions and for the course of HCC, with or without specific anticancer treatment, which could be negatively influenced by immunosuppression [16]. The aim of this study was to evaluate the efficacy of sorafenib, compared to best supportive care, in two consecutive cohorts of transplanted patients presenting with HCC recurrence deemed untreatable either at presentation or after tumor progression beyond eligibility to conventional treatments. Such a case-control study was favored by the unicentricity of the experience comparing two different attitudes in management of HCC recurrence after LT. As described below, the sole difference among groups was determined by the availability of sorafenib, being the rest of conventional care equally applied throughout the study periods.

Patients and methods

Patient grouping

Data on consecutive patients with HCC recurrence after LT followed at the Istituto Nazionale Tumori (National Cancer Institute) of Milan between January 1994 and January 2011, were extracted from a prospectively collected database. The following factors were considered: demographics and medical history, etiology of the underlying liver disease, pre-transplant treatments, laboratory results, pre- and post-operative histological and radiological tumor staging, immunosuppressive regimens, type and number of treatments performed for HCC recurrence. Patients were divided into two groups according to differences in treatment introduced when HCC recurrence was deemed untreatable, at first presentation or after disease progression beyond eligibility to conventional surgical or ablative or locoregional treatments (untreatable presentation/progression: UP).

In Group 1 (control arm) best supportive care (BSC) was the sole strategy available, while in Group 2 (treatment arm) sorafenib was added, before or after an immunosuppression switch from calcineurine inhibitor (CNI: cyclosporine or tacrolimus) to an mTOR inhibitor-based regimen (sirolimus or everolimus) was considered. The study aimed at assessing, in patients with HCC recurrence after LT, whether or not sorafenib added to BSC at the time of UP achieves competitive survivals with respect to historic controls that received only BSC. The possible contribution of contemporary mTOR immunosuppression to patient care was also investigated.

Among the comprehensive data collection within each groups, the analysis pointed out at factors related to tumor, immunosuppressive, and anticancer regimens, which are summarized below.

Conventional treatment strategy of post-transplant HCC recurrence

After LT, patients were monitored with thoraco-abdominal CT scan every 6 months for the first 3 years, and then annually, alternating with abdominal US and chest X-ray. Monitoring of AFP was performed every 6 months together with radiological controls. In all patients, the hepatocellular cancer nature of recurrence was confirmed at histology, whilst in case of intrahepatic recurrence, non-invasive radiologic criteria were added [17].

Treatment strategy was thoroughly discussed within the multidisciplinary hepato-oncology board and aimed, whenever possible, at surgical removal of recurrence with no limits in size and number of lesions. Should the patients' condition be marginal or the HCC bulk judged not amenable for removal, radiofrequency ablation (RFA) was performed. For patients with liver-only although non-resectable graft tumor deposits and in those presenting with repeated recurrences after resection or ablation, transarterial chemoembolization (TACE) or ^{90}Yttrium radioembolization was performed according to tumor extension. Tumor response was evaluated after each treatment and every three months with chest-abdominal CT, MRI, and alpha-fetoprotein (AFP) serum level determination; response assessment was performed according to RECIST 1.1 [18] and retrospectively with modified RECIST (mRECIST) criteria [19].

Untreatable progression, best supportive care, and sorafenib treatment

Patients with a first diagnosis of HCC recurrence or with a progression of recurrence deemed not anymore eligible to surgical, ablative or locoregional treatment were defined as having UP. Until 2007 patients presenting with a UP received BSC only, including local radiotherapy for bone or brain metastasis with a palliative intent. This subset (Group 1) accounted for the historical control group for the subsequent cohort of patients receiving sorafenib as a molecular target agent (Group 2).

Considering the lack of data on safety of sorafenib in the post-transplant setting, patients in Group 2 were additionally monitored according to an institutional protocol. Sorafenib was started at the target dose of 400 mg twice daily, to be adjusted in case of grade 1–3 toxicity according to common terminology criteria for adverse events (CTCAE) 3.0 [20] and withdrawn in case of prolonged or serious adverse events. A further reason for sorafenib withdrawal was tumor radiological progression according to RECIST 1.1 criteria. Treatment was re-challenged at full dosage after complete recovery of AEs, or maintained at the same dosage in case of unmanageable toxicity. Clinical visits were performed every four weeks on an outpatient basis, and included physical examination, laboratory analysis, and AE monitoring.

Immunosuppression regimens and mTOR therapy

Single-drug immunosuppression regimen with calcineurine inhibitor (CNI) was followed in all cases, since steroids were tapered within the first post-LT month. Coincidentally with the introduction of sorafenib (Nexavar, Bayer), three patients undergoing LT for HCC received a mammalian target of rapamycin (mTOR) inhibitor (sirolimus: Rapamune, Pfizer; target through level of 4–10 ng/ml) continued at the same dosage in case of HCC recurrence. During the same time interval (2007–2011), four other patients with HCC recurrence during the post-LT follow-up were shifted from CNI inhibitors to the mTOR inhibitor everolimus (Certican, Novartis; target through level of 4–10 ng/ml).

Statistical analysis

We used standard statistics (median and range for continuous variables, percentage for categorical variables) to describe baseline series characteristics and safety data, and non-parametric tests (Kruskal-Wallis for continuous variables, Pearson's Chi-Square test for categorical variables) to compare characteristics distribution in the two identified study groups.

The outcome event of interest was death for any cause. Survival time was computed in two ways: (i) as the interval between tumor recurrence after LT and death (survival after recurrence); (ii) as the interval between assessment of UP and death (survival after UP). Survival time was censored at the date of last contact in living patients. Survival curves were estimated in each treatment arm with the non-parametric Kaplan-Meier method, and statistically compared by means of univariable Cox regression models. Furthermore, considering that the compared study groups were not achieved through randomization, careful search of possible confounders was carried out. The limited number of outcome events recorded hampered confounder investigation within a single joint multivariable model. Therefore, we assessed singly taken confounders with Cox models stratified by received treatment, and finally entered all factors with p <0.10 and treatment into a multivariable Cox model. The 10% p-value threshold chosen in the confounder selection phase yielded a reasonable event per variable ratio of 6.6 (33 deaths/5 variables, considering that time to recurrence (TTR) accounted for 2 variables), in order to limit the risk of model overfit.

Furthermore, in Cox models for the analysis of survival after recurrence, event times were left-truncated at the date of UP. Such an approach was necessary considering that investigated patients were selected as having had UP, and were thus at risk of dying only some known time after the natural time origin of the phenomenon under study (recurrence after LT). In other words, death risk was zero between recurrence and UP, and non-zero thereafter; disregarding such a data structure would imply a less powerful analysis.

Calculations were done using SAS™ version 9.2 (SAS Institute Inc., Cary, NC, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria). Two-sided p values below the 5% conventional threshold are reported as statistically significant.

Results

Study groups and balancing

The main characteristics of the entire study series, as well as differences between the study groups, are described in Table 1, while study design and patients grouping are reported in Fig. 1.

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Table 1. Characteristics of 39 consecutive patients with HCC recurrence after LT, grouped according to main treatment after untreatable presentation/progression (UP).

	Entire series (39 pts)	GROUP 1 sorafenib (15 pts)	GROUP 2 BSC (24 pts)	*p* value
Age at recurrence (yr)				
Median (min, max)	57 (17-71)	57 (17-71)	56 (44-66)	0.2653
Sex (male)	35 (89.7)	15 (100)	20 (83.3)	0.0951
Aetiology of liver disease				
HCV	24 (61.5)	8 (53.3)	16 (66.7)	0.3714
HBV	14 (35.9)	6 (40.0)	8 (33.3)	
Other	1 (2.6)	1 (6.7)	-	
Tumor stage (pre-LT radiology)				
MC in	34 (87.2)	14 (93.3)	20 (83.3)	0.3635
MC out	5 (12.8)	1 (6.7)	4 (16.7)	
Number of treatments (pre-LT)				
<2	17 (43.6)	6 (40.0)	11 (45.8)	0.3050
2-3	13 (33.3)	7 (46.7)	6 (25.0)	
>3	9 (23.1)	2 (13.3)	7 (39.2)	
Tumor stage (post-LT histology)				
MC in	21 (53.8)	10 (66.7)	11 (45.8)	0.2042
MC out	18 (46.2)	5 (33.3)	13 (54.2)	
Micro-vascular invasion (histology)				
Present	14 (36.8)	4 (26.7)	10 (43.5)	0.2937
Absent	24 (63.2)	11 (73.3)	13 (56.5)	
n.a.	1	-	1	
Main immunosuppression				
Cyclosporine	26 (66.7)	7 (46.7)	19 (79.2)	**0.0362**
Tacrolimus	13 (33.3)	8 (53.3)	5 (20.8)	
Episodes of acute rejection				
No	33 (84.6)	13 (86.7)	20 (83.3)	0.7789
Yes	6 (15.4)	2 (13.3)	4 (16.7)	
Time-to-recurrence				
Median (min, max)	20.6 (0.9-218.0)	38.1 (4.5-218.0)	15.7 (0.9-58.5)	**0.0025**
<13 months	11 (28.2)	1 (6.7)	10 (41.7)	0.0613
13-24 months	12 (30.8)	6 (40.0)	6 (25.0)	
>24 months	16 (41.0)	8 (53.3)	8 (33.3)	
Pattern of recurrence				
Single	24 (61.5)	11 (73.3)	13 (54.2)	0.2313
Multiple	15 (38.5)	4 (26.7)	11 (45.8)	
AFP at recurrence				
Median (min, max)	16.2 (0.6-33,480)	3.9 (0.6-26,850)	72.7 (0.9-33,480)	0.0625
<400	34 (87.2)	13 (86.7)	21 (87.5)	0.9396
≥400	5 (12.8)	2 (13.3)	3 (12.5)	
Child at recurrence				
A	37 (94.9)	15 (100.0)	22 (91.7)	0.3622
B	2 (5.1)	-	2 (8.3)	
mTOR inhibitor* immunosuppression				
Yes	8 (20.5)	7 (46.7)	1 (4.2)	**0.0014**
No	31 (79.5)	8 (53.3)	23 (95.8)	
First treatment at recurrence				
Resection	20 (51.3)	9 (60.0)	11 (45.8)	0.6826
Loco-regional treatment	10 (25.6)	3 (20.0)	7 (29.2)	
Untreatable (sorafenib/BSC)	9 (23.1)	3 (20.0)	6 (25.0)	
N° treatments after recurrence				
<2	20 (51.3)	10 (66.7)	10 (41.7)	0.1286
≥2	19 (48.7)	5 (33.3)	14 (58.3)	
Time-to-UP				
Median (min, max)	9.1 (0.5-77.6)	8.8 (0.5-77.6)	10.2 (0.5-63.3)	0.7538

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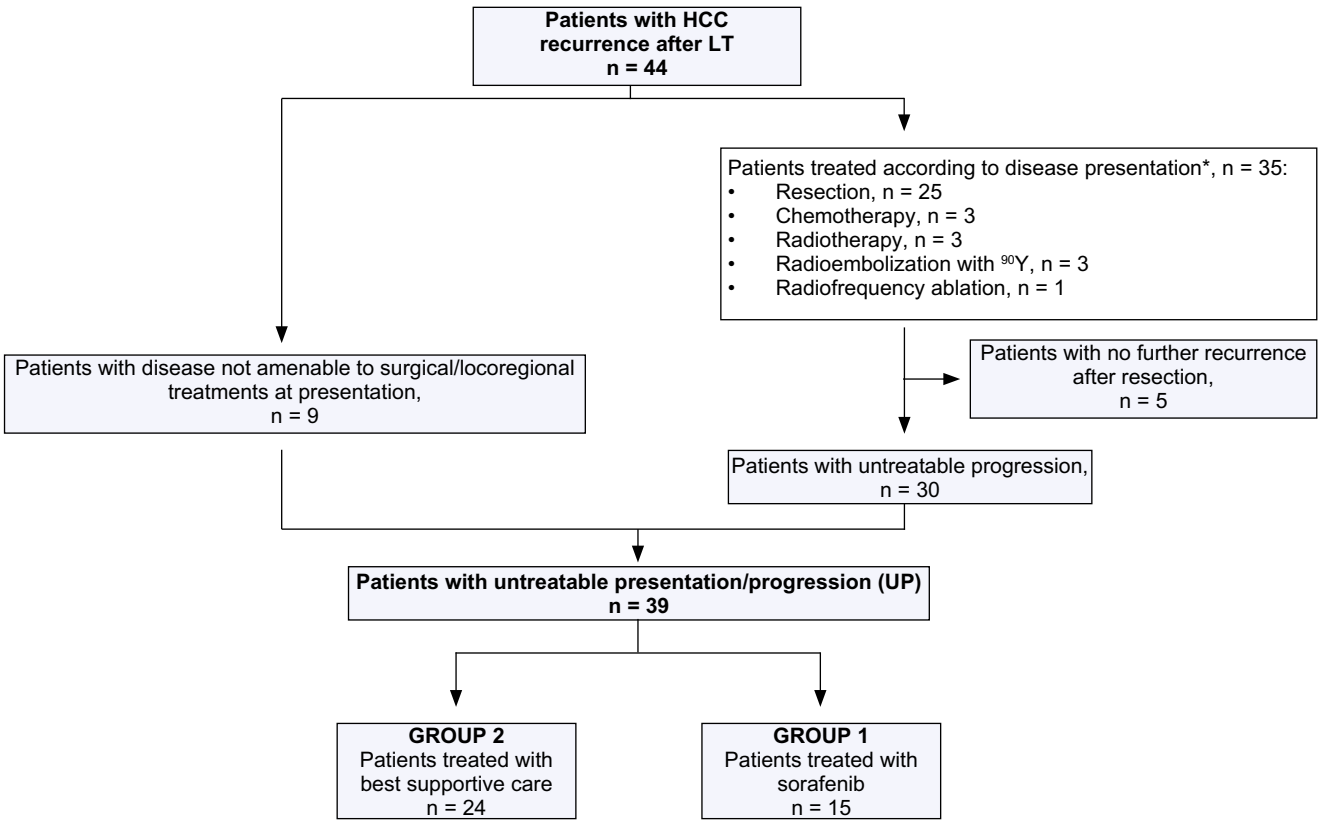

Fig. 1. CONSORT diagram of study design and patients' distribution according to treatment allocation. *Only 1st treatment options are reported.

All patients underwent deceased-donor LT. The median age at HCC recurrence was 57 years (range 17–71), 89.7% of the patients were males and HCV was the predominant etiology of the underlying liver disease (61.5%). Twenty-two patients (56.4%) underwent 2 or more treatments for HCC before LT, and most of them (87.2%) were within MC at pre-transplant staging. Conversely, in this particular subset of HCC patients recurring after LT, the MC were met only in 53.8% at explant pathology, with presence of micro-vascular invasion in 36.8% of the cases. Six patients (15.4%) showed at least one episode of acute rejection after LT requiring steroid treatment.

Out of 44 consecutive patients showing HCC recurrence after LT, 5 were cured by means of the sole surgical removal of HCC tumor deposit – 3 in the liver graft and two for lung and peritoneal single lesions, respectively – and did not need any further treatment. Four of these patients are still alive and free of disease at a median time of 35.6 months from surgery. One patient died 9 months after liver resection because of liver failure due to HCV recurrence, and autopsy did not reveal any tumor recurrence.

Of the remaining 39 patients, 9 presented upfront with a disease not amenable to surgical, ablative or locoregional treatments, while 30 developed an untreatable progression after multiple treatments either for repeated recurrence in different sites or for tumor progression in the same known locations.

After UP was assessed, 24 patients received BSC (historic controls, Group 1) while after 2007, sorafenib was added to BSC in 15 patients (treated patients, Group 2).

At recurrence, most patients (94.9%) were Child-Pugh A; the site of recurrence was single in 24 cases (61.5%), and for 20 patients (51.3%) surgical resection was the primary treatment. Patients underwent a median of one single treatment (range: 0–6) before untreatable progression, and the median time from recurrence to UP was 9.1 months (range 0.5-77.6).

The two study groups were well matched at baseline with two expected imbalances: the adopted immunosuppressive strategy and the observed TTR from LT. In particular, CNIs were maintained in 96% of historic controls (23 out of 24) whilst 46.7% of patients of Group 2 receiving sorafenib (7 out of 15) were judged eligible to mTOR inhibitors ($p = 0.0014$), with 3 patients remaining on sirolimus from the time of transplant and 4 switched to everolimus after the diagnosis of HCC recurrence. No patients discontinued immunosuppression in either group; however, the given dosages of each compound were targeted at the minimum tolerable trough level in all patients of either group.

With respect to median TTR – equal to 20.6 (0.9–218.0) months in the entire population – patients treated with sorafenib recurred at 38.1 months *vs.* 15.7 months in the historic controls

Values are expressed as number (percentage) or median (ranges) where specified.
BSC, best supportive care; LT, liver transplantation; MC, Milan Criteria; UP, untreatable presentation/progression; n.a., not available.
*mTOR inhibitors were rapamycin or everolimus (see text).

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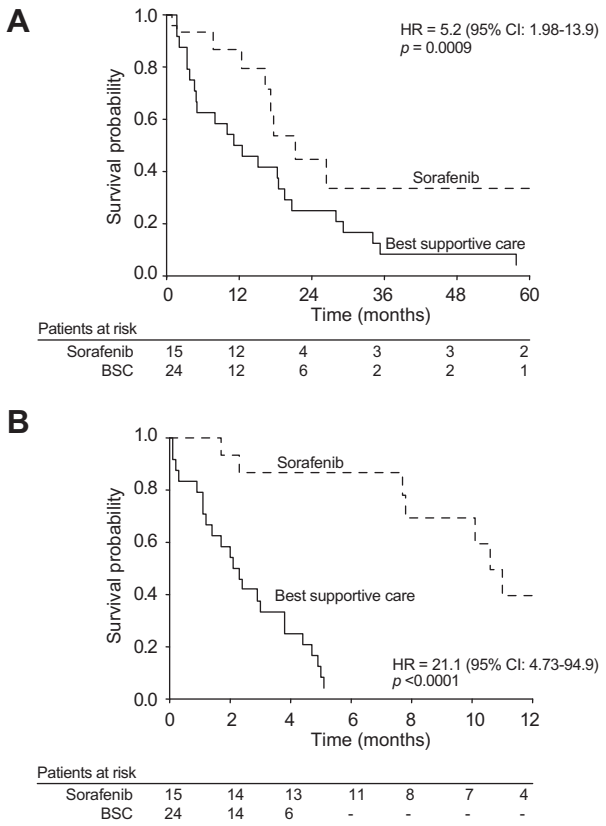

Fig. 2. Patients survival after diagnosis of recurrence (upper panel) or from the time of untreatable progression (lower panel).

($p = 0.0025$). This was expected considering the time bias between the two study cohorts.

Survival analysis

The median follow-up of the entire study population from diagnosis of HCC recurrence was 87.0 months (95% CI: 55.1–87.0); during this period 33 deaths were registered.

Curves describing survival after recurrence and after UP are shown in Fig. 2. In the sorafenib group, median survival (95% CI) was 21.3 months (12.4-61.6) after recurrence and 10.6 months (7.7-19.5) after UP, whilst 11.8 (4.6–19.5) and 2.2 (1.1–3.8) months, respectively, were observed in control patients. Patients within the sorafenib group were significantly favored with respect to historic controls both for survival after recurrence (HR = 5.2; 95% CI: 1.98–13.9; $p = 0.0009$) and survival after UP (HR = 21.1, 95% CI: 4.73–94.9; $p < 0.0001$).

At the multivariate analysis presented in Table 2, the survival benefit achieved with sorafenib added to conventional supportive care was confirmed. In fact, the adjusted hazard ratio related to sorafenib treatment with respect to controls (HR = 4.0, 95% CI: 1.12–14.3; $p = 0.0325$) was only slightly lower than the unadjusted estimate reported at univariable analysis for survival after recurrence (HR = 5.2). The effect of TTR as a continuous variable, and the potential of an interaction between TTR and sorafenib were also investigated in a multivariable model. For that purpose, Cox models were performed incorporating the same covariates of the multivariable model shown in Table 2, but TTR was modeled as a continuous (linear and non-linear) covariate and its interaction with sorafenib was included. Whatever approach in modeling was chosen, the sorafenib effect tended to decrease at low values of TTR, even though between 1 and 3 years – the interval during which the highest number of events occurred – the effect of the treatment was self-evident. Detailed results are shown in Supplementary Material.

Subgroup analysis of patients receiving sorafenib

When HCC recurrence not amenable to surgical/locoregional treatments was assessed, the administration of sorafenib to all patients of Group 2 started at the full dosage of 800 mg/day. Out of 15 patients treated with sorafenib, HCC recurrence was deemed untreatable at first presentation in 3 patients and after disease progression in the remaining 12; their median time on sorafenib was 4.3 months and 8.3 months, respectively, and 6.9 months overall. In patients receiving sorafenib and BSC, the best radiological tumor response according to RECIST 1.1 was stable disease (SD), that was assessed in 11 patients (73.3%); the best radiological response according to modified RECIST was partial response (PR) in 4 patients (26.7%), accounting for a disease control rate (SD + PR) of 73.3%. The median time-to-progression was 8.5 (4.4–13.6) months (Fig. 3).

The combination of sorafenib with mTOR-based immunosuppression was not associated with a significant difference in disease control rate (DCR) that was 71.4% in mTOR-based *vs.* 75% in CNI-based therapies ($p = 1$). Noteworthy, the association of sorafenib with mTOR-based immunosuppression was close to statistical significance when PR was assessed according to modified RECIST [PR was 57.1% *vs.* 0% in 7 mTOR *vs.* 8 CNI-treated patients respectively; ($p = 0.0699$)].

The predominant adverse events (AEs) during sorafenib treatment were: hand-foot skin reaction (9 patients, 60%), diarrhea (6 patients, 40%) and fatigue (4 patients, 16.7%); the majority of the observed AEs were grade 1–3 in severity, and no drug-related grade 4 or 5 (death) event occurred [20]. Dose reduction to 400 mg/day occurred in 8 patients (53.3%); of those patients, 4 recovered and continued treatment at full dosage, while the other 4 patients continued treatment at the 400 mg/day dosage without any further dose adjustment. Sorafenib was withdrawn for progression of disease in 10 patients (66.7%) and in one patient for development of renal and hepatic insufficiency, while it is still ongoing in 4 patients (26.7%) at the time of the present analysis.

Discussion

The therapeutic armamentarium for patients diagnosed with HCC not amenable to surgical, ablative, and locoregional treatments is limited. In 2007, sorafenib was the first agent to demonstrate a significant improvement in the overall survival of patients with advanced HCC [8,9], and since then has become the standard of care for these patients [21].

Up to now, no prospective studies on the efficacy of sorafenib have been conducted in the particular setting of HCC recurrence after LT, although recent reports have confirmed an acceptable safety profile in this setting, with no apparent drug-to-drug interaction with immunosuppressive medications [11,14,15].

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Table 2. Univariate and multivariate analysis for survival after HCC recurrence, corrected by entry time (time from recurrence to UP).

		Univariate analysis		Multivariate analysis	
Predictor	Category	Hazard ratio (95% CI)	*p* value	Hazard ratio (95% CI)	*p* value
Aetiology of liver disease	HBV + other HCV	1.878 (0.721-4.893) 1.00	0.1970		
Tumor stage (pre-LT radiology)	MC in MC out	0.112 (0.011-1.164) 1.00	0.0668	0.530 (0.128-2.194) 1.00	0.3803
Number of treatments (pre-LT)		1.259 (0.909-1.740)	0.1664		
Tumor stage (histology)	MC in MC out	0.855 (0.344-2.122) 1.00	0.7354		
Vascular invasion (histology)	Present Absent	0.777 (0.310-1.947) 1.00	0.5897		
Main immunosuppression	Cyclosporine Tacrolimus	0.502 (0.178-1.415) 1.00	0.1924		
Episodes of acute rejection	No Yes	1.032 (0.190-5.606) 1.00	0.9709		
Time-to-recurrence	>24 months 13-24 months <13 months	0.288 (0.092-0.901) 0.424 (0.156-1.155) 1.00	0.0762	0.994 (0.309-3.191) 0.997 (0.254-3.914) 1.00	0.9866
MELD at recurrence		1.079 (0.928-1.255)	0.3246		
Sites of recurrence	Multiple Single	0.724 (0.263-1.988) 1.00	0.5303		
AFP at recurrence	≥400 <400	1.235 (0.371-4.103) 1.00	0.7309		
mTOR inhibitor*	No Yes	2.476 (0.715-8.580) 1.00	0.1528	1.696 (0.503-5.714)	0.3943
Primary treatment for recurrence	Locoregional treatment Untreatable Resection	1.185 (0.325-4.317) 0.956 (0.148-6.162) 1.00	0.9590		
N° treatments after recurrence		1.149 (0.564-2.339)	0.7021		
Treatment after UP	BSC Sorafenib	5.240 (1.978-13.880) 1.00	**0.0009**	4.010 (1.123-14.322)	**0.0325**

*mTOR inhibitors were rapamycin or everolimus (see text).

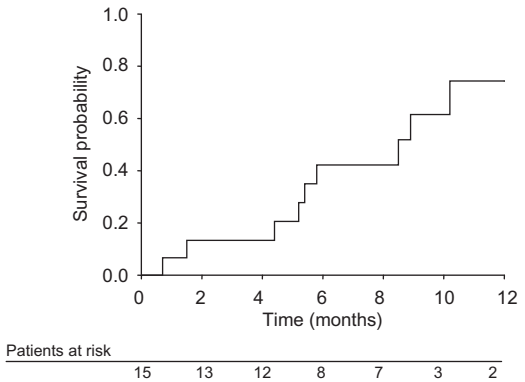

Fig. 3. Time-to-progression according to RECIST 1.1 in patients treated with sorafenib.

The aim of our comparative study was to evaluate the effectiveness of sorafenib in prolonging survival of patients diagnosed with an HCC recurrence after LT: a condition almost always associated with dismal prognosis. For this purpose, we sought to compare the survival of our series of HCC-recurrent patients in the pre-sorafenib era (1994–2007) with that observed in more recent years when sorafenib entered clinical practice. The most relevant results emerging from the comparison of our two liver-transplant study groups is that a highly significant difference in median survival after HCC recurrence was found in sorafenib-treated patients with respect to historic controls (21.3 *vs.*11.8 months: $p = 0.0009$). Such difference was even more remarkable when survival was calculated from the time of untreatable presentation/progression (UP), demonstrating an increase to a median of 10.6 months in patients treated with sorafenib from a baseline of 2.2 months in control patients ($p < 0.0001$).

It could be argued that the detected survival differences between the two study groups might be influenced by many factors, including those regarding the different eras in which the two groups were treated. Actually, the presented case-control study was favored by the single-center nature of this investigation, with both cohorts receiving equally intensive surgical/ablative/locoregional therapies and best supportive care over time, and being the sole difference among groups determined by the availability of sorafenib and mTOR immunosuppression. This is demonstrated by the homogeneities in transplant- and tumor-related determinants of prognosis between groups, as reported in Table 1, particularly by: (a) tumor presentation both before LT and at recurrence; (b) first therapeutic approach to recurrence; (c) number of treatments before untreatable progression; (d) time from

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recurrence to untreatable progression, that did not differ in sorafenib-treated patients with respect to historic controls.

Considering the time bias in patient grouping, differences at baseline were observed with respect to TTR from LT and immunosuppression schedules.

Differences in median TTR are frequently reported when comparing different eras of LT [22,23]. This may be mainly explained by a longer time-exposure in Group 1, responsible for a greater chance to show disease recurrence in the more recent era. Moreover, as shown in Table 1, recurrences within the first post-LT year in Group 2 were more frequent (41.7% *vs.* 6.7%). A cause for this could be sought in a more accurate staging of patients and in a longer waiting time on list in recent years. Both impeded transplantation in patients at risk of an occult extrahepatic disease, and determined a more thorough pre-LT selection. Longer TTR might be considered a surrogate of a less aggressive tumor biology, and this impression is sustained also by some detectable although non-significant imbalancements towards tumors with lower AFP and more frequent single-site recurrences in the sorafenib group (Table 1). However, it should be noted that sorafenib in the treated patients was introduced only at the time of untreatable progression, namely when disease aggressiveness was at its maximum. Furthermore, in order to remove possible biases in such respect, a large number of possible confounders were investigated and selectively adjusted for such factors in a multivariate analysis of survival after recurrence. This analysis substantially confirmed the results of univariable analysis, retaining the treatment with sorafenib as the only factor influencing survival (HR = 4.010, $p = 0.0325$).

Although the immunosuppression strategy in patients with post-LT HCC recurrence varied in recent years with respect to historic controls, the introduction of mTOR inhibitors in about half of our patients receiving sorafenib did not apparently influence their survival (HR = 1.7, $p = 0.3943$), even though tumor response assessed with mRECIST criteria correlated with the combination of sorafenib with mTOR inhibitor, with a $p = 0.0699$, therefore in proximity of statistical significance, confirming previous reports [14,24].

In order to capture the proper indicators of efficacy and considering that the investigated patients were selected as having UP, event times were left-truncated at the date of UP in Cox models for the analysis of survival after recurrence. This statistical approach was necessary considering that death risk was zero between recurrence and UP and non-zero thereafter.

With these assumptions, the overwhelming effect of sorafenib in prolonging survival of patients diagnosed with HCC recurrence after LT was confirmed. In particular, the difference in median survival was even more noticeable when calculated from the time when sorafenib was given, namely when tumor burden was not amenable to surgical/ablative/locoregional treatments. From the time of UP, the patients treated with sole BSC showed a poor median survival of 2.2 months that increased to 10.6 with the addition of the effect of sorafenib. This figure of survival, along with a TTP of 8.8 months and a DCR of 73.3%, is in line with previous studies in the non-transplant population [8], and the high hazard ratio observed in our setting probably reflected the aggressive features of HCC in immunosuppressed patients when no other approach, different from supportive care, is allowed.

There are some obvious limitations to our study. First, even if, to the best of our knowledge, this is the largest consecutive series of patients treated with sorafenib in the post-transplant setting, the small sample size and the absence of randomization limit the strength of the results. Secondly, the evaluation of the impact of mTOR inhibitors as immunosuppressive agents during sorafenib therapy was beyond the study objectives, since the heterogeneity of treatment and schedules in the treated patients – receiving sirolimus or everolimus at the time of transplantation or at the time of HCC recurrence – may have hampered our data dissection. This bias cannot be obviated by statistical analysis and thus, whether there is a subgroup of patients that benefit most from mTOR inhibitors, is an issue that still needs to be ascertained. Finally, the intrinsic variations in tumor burden, localizations, and pattern of progression observed for HCC recurrence after LT could not be completely captured by categorical variables, despite the prospective data collection; this means that there could be other hidden differences between groups that may have influenced the observed patient outcome.

On top of the consistent number of restrictions influencing interpretation of clinical trials in the post-transplant setting, this study owns limitations related to the inclusion of historic controls as well as potentials for having missed significant variables. With such boundaries, however, this study provided a convincing statistical demonstration that sorafenib added to the best supportive care at the time of untreatable post-transplant HCC recurrence, does prolong survival with respect to controls. A time-to-progression that is in line with previous reports and an acceptable safety profile further strengthen the indication of treatment with sorafenib in the setting of patients with HCC recurrence not amenable to surgical/ablative or locoregional treatments. Further studies on larger series are needed in order to confirm our data and to investigate more in depth the possibly positive effect of an mTOR inhibitor-based immunosuppression regimen in these patients.

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Conflict of interest

The authors have received lecture fees from Bayer Healthcare for training courses with educational purposes on hepatocellular carcinoma.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2013.02.026.

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