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ORIGINAL ARTICLE

Sorafenib as an adjuvant therapy for resectable hepatocellular carcinoma: A single center experience

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Summary

Purpose: *Resectable hepatocellular carcinoma (HCC) is currently treated with surgical resection without any adjuvant therapy. We sought to assess the value of sorafenib as an adjuvant treatment in that clinical setting.*

Methods: *Of a total of 30 patients, 16 underwent curative-intent liver resection for HCC and subsequently received adjuvant sorafenib, while 14 underwent surgery alone. Clinicopathological characteristics were analyzed and the impact of adjuvant sorafenib on overall survival (OS) was assessed.*

Results: *The median follow up time was 38.2 months. The median patient age was 63.5 and 76.7% of them were male. The majority of patients had a solitary tumor (74.1%) with a median size of 7.75 cm. Five-year OS for the whole cohort was 60.2%. OS for patients who underwent only resection was 52.9 vs 68.1% for patients who underwent resection and received adjuvant sorafenib (p=0.19).*

Conclusion: *Sorafenib seems to be associated with an acceptable safety profile but does not confer any substantial clinical benefit in terms of survival in HCC patients who have undergone curative-intent liver resection.*

Key words: *hepatocellular carcinoma, liver resection, sorafenib*

Introduction

Primary liver cancer is the fifth most common cancer worldwide and the third more leathal malignancy in the world [1,2]. An increase in the rate of primary liver cancer cases has been noted and 782,000 new cases were recorded in 2012 [3]. HCC comprises almost 90% of primary liver cancer cases and represents the most common histologic type of primary liver cancer. Currently, the mainstay of HCC treatment is tumor resection and orthotopic liver transplantation [4]. In selected patients, as those belonging to early or very early stage as defined by the BCLC criteria, surgical resection offers a 5 year survival of 50-70% [5,6]. Recent advances in surgical care and substantial improvements in preoperative imaging as well as the refined surgical techniques have decreased significantly the morbidity associated with liver resections while tertiary high volume centers report mortality under 1% [7-9].

In 2007 sorafenib, a multikinase inhibitor agent that abrogates Raf signalling, VEGF, PDGF, and c-Kit, was the first systematic therapy that was shown to impact favorably on the survival of HCC patients in a phase 3, multicentre, randomized, double-blind, placebo-controlled trial of 602 patients. In their seminal study, Llovet et

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al. [10] utilized sorafenib as a monotreatment for patients with advanced disease who were deemed not amenable to surgical/locoregional treatments according to the BCLC staging system and demonstrated a significant benefit of extending survival by 3 months. The encouraging results and a better insight in biologic underpinnings of the disease have fuelled further studies and more promising agents have been tested in randomized clinical trials (RCTs) but, so far, none has been able to surpass sorafenib, up to date [11-14]. A recent meta-analysis showed that besides sorafenib only adjuvant IFN therapy can improve survival [15]. However, the benefits of utilizing this agent should be weighed carefully against its side effects. Recently Samuels et al. [16] published a review of 12 RCTs showing that none of them had efficacy in reducing the recurrence rate in either the adjuvant or the neoadjuvant clinical setting [10,17,18]. Despite the almost universal approval of sorafenib in the setting of unresectable HCC, reports on the impact of sorafenib, as an adjuvant treatment for resected HCC, on survival are relatively scarce.

Of note, most previous studies have been from a single institution and have included only a small number of patients while there is only a sole RCT investigating the utility of sorafenib in that particular clinical setting . The purpose of the present study was to further assess the clinical value of sorafenib as an adjuvant therapy using a retrospective cohort of patients undergoing curative-intent resection of HCC.

Methods

Study design

Patients who underwent curative-intent liver surgery for HCC, between January 2005 and January 2013, at the Second Department of Propaedeutic Surgery at the University of Athens were identified. Inclusion criteria were histologically proven HCC and the administration of sorafenib as adjuvant treatment for the patients who belonged to the second group of the study (treatment group). In group 1 liver resection was the sole therapy performed, while in group 2 sorafenib was added to the curative-intent resection. The University of Athens Institutional Review Board approved the study.

Data collection

Standard demographic and clinicopathologic data were collected, including sex, age, and HCC characteristics. The specific HCC features, including exact tumor location and size, were recorded. Tumor size was defined as the maximal diameter of the tumor in the resected specimen, and the largest lesion was used as the index lesion in the case of patients with more than one tumor lesions. Information on HCC histology was collected based on the Edmodson classification and data on microscopic/macroscopic vascular invasion as well as surgical margin status were recorded. Furthermore, treatment-related variables, such as type of hepatic resection and preoperative AFP, bilirubin, AST, ALT and ALP were acquired. Major hepatectomy was defined as the resection of three or more liver segments according to Couinaud's classification. Hepatic resection was mainly performed using Cavitron Ultrasonic Surgical Aspirator (Misonix) and Lotus Dissecting Shears (S.R.A. Developments Ltd, Bremridge House, Ashburton, Devon, UK). The postoperative treatment modalities were recorded if applicable and patients were classified according to their postoperative treatment in two groups (control vs sorafenib).

Sorafenib was administered at an initial dosage of 200 mg once daily, in order to define any serious side effects from the drug. The dose increased to 400 mg daily in 3 weeks and progressively to 400 mg and 200 mg or 400 mg twice daily continuously, except in cases in which the drug was discontinued owing to death or serious adverse effects in all patients belonging to the sorafenib group. Neither sorafenib nor systemic anticancer therapy were given in the control group. Short-term clinical outcomes were assessed until 30 days after the operation and postoperative complications were graded for severity using the established Clavien–Dindo classification (a major complication is defined as one of grade III or higher) [19]. Long-term clinical outcomes were also assessed and perioperative 90-day mortality was calculated from the date of liver resection to the date of last follow-up. Date of last follow-up and vital status were collected in all patients.

Statistics

Continuous variables were described as median values with interquartile range (IQR) unless otherwise indicated. Categorical variables were described as totals and percentages. Differences were evaluated by x^2 test for categorical variables and by Student's t-test or Mann–Whitney U test for continuous variables, as appropriate. OS was estimated using the Kaplan–Meier method and differences among the two separate groups were evaluated using the log-rank test. Statistical analyses were carried out with the STATA 11.2 (Stata Corp., College Station, TX) statistical software package and the statistical significance was set at $p<0.05$.

Results

Demographic, clinicopathologic and perioperative features

Patient features and treatment characteristics

are summarized in Tables 1 and 2. Among the 30 patients that were recruited for the purposes of testing sorafenib in the adjuvant setting, the median age at diagnosis was 63.5 years ((IQR: 54-69) and the majority were male (N=23, 76.7%). All patients were of Caucasian origin. Only 8 of the patients (27.6%) did not have any chronic viral hepatitis, whereas 16 (55.2%) and 4 (13.8%) were infected with hepatitis B and C virus, respectively; 1 patient (3.4%) had both hepatitis B and C. Concerning the functional liver enzymes, the median value of AST was 45.5 (IQR:26-73), the median value of ALT was 47.5 (23-71) and the median value of ALP was 151 (91-202).

Most patients had a single tumor (N=20, 74.1%), and the median size of the largest hepatic lesion was 7.75 cm (IQR: 5.9-10.6). Overall, the majority of patients (N=27, 89.7%) had unilateral dis-

Table 1. Clinicopathological characteristics of patients with resectable HCC

Characteristics	*All patients (N = 30)* N (%)	*Surgery alone (N = 14)* N (%)	*Surgery + Sorafenib (N = 16)* N (%)	*p value*
Age at diagnosis, yr; median (range)	63.5 (54-69)	65.5 (53-71)	62 (55-67.5)	0.69
Male gender	23 (76.7)	10 (71.4)	13 (81.3)	0.53
Caucasian race	30 (100)	14 (100)	16 (100)	1.00
Comorbidity				
Hypertension	14 (46.7)	5 (35.7)	9 (56.3)	0.26
Hyperlipidemia	1 (3.3)	1 (7.1)	0	0.28
Coronary heart disease	5 (16.7)	3 (21.4)	2 (12.5)	0.51
Noninsulin-dependent diabetes mellitus	9 (30.0)	2 (14.3)	7 (43.8)	0.08
Insulin-dependent diabetes mellitus	1 (3.3)	1 (7.1)	0	0.28
Hemochromatosis	1 (3.3)	1 (7.1)	0	0.28
Other	5 (16.7)	3 (21.4)	2 (12.5)	0.51
Hepatitis status (N=29)				
No chronic viral hepatitis	8 (27.6)	4 (30.8)	4 (25.0)	0.64
Hepatitis B	16 (55.2)	8 (61.5)	8 (50.0)	
Hepatitis C	4 (13.8)	1 (7.7)	3 (18.8)	
Both hepatitis B and C	1 (3.4)	0	1 (6.2)	
Preoperative liver enzymes				
AST	45.5 (26-73)	48.5 (41-82)	33.5 (22.5-70.5)	0.15
ALT	47.5 (23-71)	61.5 (27-102)	28 (16-63.5)	0.03
ALP	151 (91-202)	177.5 (141-243)	132 (70.5-166.5)	0.06
Bilirubin	1.05 (0.69-1.50)	1.11 (0.69-2.49)	0.97 (0.68-1.21)	0.38
AFP	13.9 (4.2-50.2)	45.2 (8.8-4512)	6.9 (4.2-30)	0.10
Solitary tumor (N=27)	20 (74.1)	8 (72.7)	12 (75.0)	0.90
Tumor size, cm; median (range)	7.75 (5.9-10.6)	8.1 (5.4-14.3)	7.8 (6.0-9.8)	0.93
Bilobar tumor distribution (N=29)	3 (10.3)	3 (23.1)	0	0.04
Macrovascular invasion (N=21)	1 (4.8)	1 (10.0)	0	0.28
Microvascular invasion (N=23)	12 (52.2)	4 (40.0)	8 (61.5)	0.31
Presence of satellite lesions (N=28)	5 (17.9)	2 (16.7)	3 (18.8)	0.89
Presence of intrahepatic metastases (N=28)	6 (21.4)	3 (25.0)	3 (18.8)	0.69
Edmonson grade (N=26)				
Well differentiated	3 (11.5)	1 (9.1)	2 (13.3)	0.76
Moderately differentiated	11 (42.3)	4 (36.4)	7 (46.7)	
Poorly differentiated	12 (46.2)	6 (54.5)	6 (40.0)	

Table 2. Treatment characteristics of patients with resectable HCC

Characteristics	*All patients N = 30 N (%)*	*Surgery N = 14 N (%)*	*Surgery + Sorafenib N = 16 N (%)*	*p value*
Treatment type				
Resection	25 (83.4)	13 (92.9)	12 (75.0)	0.19
Resection + ablation	5 (16.7)	1 (7.1)	4 (25.0)	
Extent of liver resection (N=28)				
Minor hepatectomy	18 (64.3)	9 (75.0)	9 (56.3)	0.31
Major hepatectomy	10 (35.7)	3 (25.0)	7 (43.7)	
Surgical margin (N=28)				
R0	21 (75.0)	9 (75.0)	3 (25.0)	1.00
R1	7 (25.0)	12 (75.0)	4 (25.0)	
Lymphadenectomy (N=21)	5 (23.8)	3 (27.3)	2 (20.0)	0.70
Postoperative complications				
Grade I-II	1 (3.3)	1 (7.2)	0	0.01
Grade III-IV	5 (16.7)	5 (35.7)	0	

ease. Median preoperative AFP level was 13.9 ng/ml (IQR: 4.2-50.2). Regarding the treatment modality, 25 patients (83.4%) underwent surgery and 5 (16.6%) patients underwent combined surgery and tumor radiofrequency ablation. At the time of surgery, hepatic resection involved either a minor (N=18, 64.3%) or major (N=10, 35.7%) hepatectomy and 5 patients (23.8%) required lymphadenectomy during liver resection. At histology, the surgical margin was deemed microscopically negative (R0) in the majority of patients (N=21, 75%). On histopathological analysis, 3 (11.5%) patients had well-differentiated tumors, 11 (42.3%) moderately differentiated tumors, while 12 (46.2%) had poorly differentiated lesions. Macrovascular invasion was noted in only 1 (4.8%) patient, microvascular invasion in 12 (52.2%), intrahepatic satellite lesions in 5 patients (17.9%) and intrahepatic metastatic lesions in 6 patients (21.4%).

Regarding the short-term outcomes, postoperative mortality was zero. The severity of postoperative morbidity was assessed based on the Clavien-Dindo classification. Almost one fifth of the patients (N=6, 20%) experienced a complication within 30 days postoperatively with 5 of them suffering from severe complications (16.7%). Concerning the administration of sorafenib, no grade 3 or 4 events were recorded in our study.

Overall survival

1-, 3- and 5-year OS for the entire cohort was 79.9, 76.2 and 60.2%, respectively. The 5-year OS among patients treated with adjuvant sorafenib was 68.1% compared with 52.9% for those treated only with surgery (p=0.19).

Discussion

Sorafenib is the only chemotherapeutic agent that has been approved for use in patients suffering from HCC and is established as the standard of care for advanced HCC [20]. However, currently the agent is indicated only for those who are deemed unresectable according to the BCLC criteria [10.21]. While the mainstay treatments offer a possibility of cure for HCC, the long-term outcomes after surgery or ablation therapy are discouraging since HCC recurs in 70% of all cases, either as a result of intrahepatic dissemination of primary cancer cells or due to the development of a *de novo* tumor [22]. This study was undertaken to evaluate the efficacy of sorafenib and the potential expansion of indications by administering the compound also to patients with resectable HCC. Our results point towards a lack of survival benefit by administering adjuvant sorafenib to HCC patients with resectable tumor. However, it seems that there is a trend for increasing OS since OS among patients treated with adjuvant sorafenib was higher although without reaching statistical significance (5-year OS in patients treated with adjuvant sorafenib 68.1% vs 52.9% for those treated with surgery alone; p=0.19).

It is quite important that no serious (grade 3/4) adverse events were reported in the current study while in the literature the incidence of major adverse events is reported to range between 8.7-52% [10,21]. Our results are in accordance with a recent large multicenter RCT that demonstrated a lack of efficacy for sorafenib in that particular setting [23]. Up to now, STORM trial is the sole RCT investigating the efficacy of sorafenib admin-

istration that has been conducted in that particular setting. STORM trial assessed the impact of sorafenib administration on the relapse free survival (RFS) and concluded that the compound did not change significantly RFS [23]. Our study is the first retrospective study from a European, tertiary academic center that sought to evaluate the efficacy of sorafenib in that setting. Besides the STORM trial, the only two studies that have been undertaken in order to evaluate the efficacy of sorafenib come both from Asia [17,18].

Our results contradict those deriving from a recent pilot study conducted by Wang et al [18]. The authors concluded that patients who received sorafenib as adjuvant treatment after the resection of HCC had improved survival compared to those who underwent only surgery. Of note, the participants of that pilot study were selected to represent a high risk for recurrence cohort and consequently had many adverse characteristics of the disease. Specifically, all eligible patients had tumors that histologically were poorly differentiated (histological grade 3), and also had microvascular invasion and/or microscopic satellite lesions. In contrast, we did not investigate a strictly selected cohort in an effort to avoid any selection bias. The present study was comparable in terms of cohort size with those studies. The other study, that comes from China, concluded that while adjuvant sorafenib did not decrease tumor recurrence, it significantly reduced the mortality and prolonged OS of HCC patients after curative resection, probably by inhibiting tumor growth after tumor recurrence [17]. The controversial results between the current study and STORM trial on the one side and the two other studies on the other side could be perhaps attributed to the different origin of the cohorts. For example, our study and STORM involved Western patients while the other two studies came from Asia raising the question of a possible variable impact of sorafenib on diffent cohorts [23].

Furthermore, another reason that could explain the contradiction in terms of results is based on recent insights from a mouse model that correlated the efficacy of sorafenib with the levels of expression of HIV-1 Tat interactive protein 2 (HTATIP2) in tumors [24]. Thus, sorafenib may have a significant efficacy only in selected patients with certain activated signalling pathways. Molecular biomarkers that permit a more specific subgrouping of patients are warranted in order to assess more precisely the clinical efficacy of sorafenib. Interestingly and adding to the reported conflicting results, Wang et al. [25] recently showed that sorafenib inhibits tumor growth and prevents metastatic recurrence after resection of HCC in nude mice. Those results were further confirmed by the experiments conducted by Feng et al [26]. who elegantly showed, utilizing an established orthotopic xenograft model of HCC, that sorafenib plays a pivotal role in preventing the recurrence of HCC and improving the OS of animals.

The current study has several inherent limitations since its nature was retrospective. Of note, we did not choose to conduct a case-control study that could eliminate possible baseline differences among the two populations. However, it should be taken into account that statistical comparison of the baseline characteristics revealed no significant differences among the two populations. The relatively small size of the examined cohort and the fact that all patients came from a single institute belong to the weaknesses of the undertaken study and limit the strength of the presented results.

Collectively, our analysis has shown that sorafenib, when used in the adjuvant setting, does not appear to improve the OS of patients with HCC. No substantial role for sorafenib can be established based only on our study but the controversial results of the few studies that have been already undertaken warrant further in depth investigation, ideally in the prospective randomized setting of a high-quality, multicenter trial.

Conflict of interests

The authors declare no confict of interests.

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