Sorafenib for the treatment of advanced hepatocellular cancer – a United Kingdom audit

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Abstract

Background: Sorafenib is the current standard treatment for advanced hepatocellular carcinoma (HCC). We performed a national audit of UK patients treated with sorafenib as standard-of-care and those treated with systemic therapy in first-line trials.

Method: Sorafenib-treated (ST) and trial-treated (TT) patients were identified via the Cancer Drugs Fund and local databases. Data were collected retrospectively from medical records according to a standard case report form. The primary outcome measure was overall survival (OS), estimated by the Kaplan-Meier method.

Results: Data were obtained for 448 ST patients from 15 hospitals. The median age was 68 years (range 17-89) and 75% had performance status of ≤1. At baseline, 77% were Child-Pugh (CP) A and 16.1% CP B, 38% were ALBI-1 and 48% ALBI-2, 23% were BCLC-B and 72% BCLC-C. Median time on sorafenib was 3.6 months with a mean daily dose of 590mg. Median OS for 448 evaluable ST patients was 8.5 months. There were significant differences in OS comparing; CP A vs CP B, (9.5 vs 4.6 months), ALBI-1 vs ALBI-2, (12.9 vs 5.9 months) and BCLC-B vs BCLC (13.0 vs 8.3 months). For TT patients (n=109), the median OS was 8.1 months and this was not significantly different from the ST treated patients.

Conclusion: For Child-Pugh A patients with good performance status, survival outcomes were similar to those reported in global randomised controlled trials. Patients with ALBI grade >1, Child Pugh B or poor performance status appear to derive limited benefit from sorafenib treatment.

Key words; Hepatocellular carcinoma, sorafenib, ALBI, prognosis, Child-Pugh

Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer death world-wide and accounted for 746,000 deaths in 2012 [1]. Overall, the prognosis is poor and the 5-year age-standardised net survival for adults with liver cancer in the UK is 9.3% [2]. To date, sorafenib remains the only drug licenced for the systemic treatment of HCC based on the results of two randomised clinical trials which demonstrated an improvement in median overall survival of between 2-3 months compared with placebo [3, 4]. On this basis, sorafenib was approved for HCC by the European Agency for the Evaluation of Medicinal Products (EMA) in 2007 and is recommended in international guidelines [5].

The National Institute for Health and Care Excellence (NICE) and Scottish Medicines Consortium (SMC) both published guidance in 2010 and recommended against the use of sorafenib for advanced HCC on the basis of cost-effectiveness. However, in England, the Cancer Drug Fund (CDF) which was established in April 2011, has provided funding for sorafenib as first-line therapy for patients with advanced HCC with CP A liver impairment or CP grade B7 liver impairment.

The clinicopathological characteristics and clinical outcome of patients with advanced HCC treated in the UK has not been previously reported and we therefore undertook a retrospective national audit to define the patient population treated with sorafenib in the UK and the outcome in terms of overall survival

Patients and Methods:

This was an investigator-initiated collaborative study without industry support. UK centres that treat HCC were identified via the UK database of cancer networks,

through which cancer care is geographically coordinated in the UK. The Patient Advice and Liaison office for each Hospital Trust provided contact details for all clinicians who managed patients with HCC, and they were invited to participate in the study. For each hospital, HCC patients who had received sorafenib as first-line systemic therapy were identified via local Cancer Drugs Fund records or locally held databases. Only patients treated within the NHS were included. In addition, we identified first-line drug trials for HCC that were recruiting in UK during the study period. Anonymised clinical and treatment data were collected from medical and pharmacy records according to a study-specific case report form. Although toxicity was not recorded according to CTC grade, we recorded the adverse events that resulted in dose reduction, interruption or termination of treatment and thereby captured toxicity of clinical relevance to patient management. The primary outcome measure was overall survival (OS). Ethics approval was granted for this research (REC reference 12/LO/1088).

Statistics

Analyses were performed using Stata version 12.1. OS survival curves were generated using Kaplan-Meier methods from commencement of sorafenib to date of death or to date of last follow-up. The log-rank test used for comparisons between survival curves. Cox proportional hazards regression analysis was used to obtain univariate hazard ratios. All variables in Table 1 were considered for inclusion in the multivariable model, except where there was co-linearity with existing variables or where there was greater than 10% missing data. Continuous variables were analysed as categorical variables, with the cut-offs decided as: lower limit of normal range for albumin and bilirubin, and AFP; 400 ng/ml. ECOG performance status (PS) was included as a categorical variable with three levels (0; 1; 2 or 3). Baseline variables

which were associated with overall survival in a univariable Cox model ($p<0.1$) were included in the multivariable model. Kaplan-Meier estimated survival curves were used to compare sorafenib and trial-treated patients, and the effect of CP grade, albumin-bilirubin (ALBI) grade [6] and BCLC stage [7] amongst sorafenib-treated patients. The mean daily dose of sorafenib was established by calculating the mean daily dose per patient during the course of their treatment and reporting the median mean dose for the whole population.

Results:

Sorafenib treated (ST) patients

Overall, 17 hospitals were invited to participate and 15 provided data by the agreed deadline. In total 448 ST patients were commenced on sorafenib from 1st July 2007 to 24th July 2013. Baseline characteristics are shown in Table 1. The majority of patients were ECOG PS ≤ 1 (75%), 77% were CP A and 72% BCLC-C. Extra-hepatic disease was reported in 38% of which the most common site was lymph node followed by lung and then bone. There was a high rate of missing data for vascular invasion but among the 252 patients in whom it was recorded, 39% had vascular invasion. the rate of vascular involvement was 39% among those in whom it was reported. Of patienThe most common single aetiology of background liver disease was alcohol in 25%, and 42% had previously received prior local therapy for HCC, of whom 74% had undergone trans-arterial (chemo) embolisation and 12% had received radiofrequency ablation (RFA).

Treatment dose and toxicity

Full treatment data were available for 436 patients. The median time on sorafenib treatment was 3.6 months with a mean daily sorafenib dose of 590 mg. Overall, 271 (62%) started at 800mg daily, 143 (33%) started at 400mg daily and the remainder started at 200mg (4%) or 600mg (1%) daily. A dose reduction was required in 140 (52%) patients, and 84 (31%) had their treatment temporarily interrupted due to toxicity. The main toxicities leading to a dose reduction or treatment interruption are shown in Table 2. Fatigue, deterioration in PS and diarrhoea were the most common listed. The frequency of adverse events was similar for CP A and CP B patients with the exception of liver dysfunction which was more common in those with CP B disease: 18% vs 40% for CP A vs B, respectively. The reason sorafenib was discontinued was known for 336 patients, of whom 98 (29%) had progressed radiologically, 84 (25%) stopped due to toxicity, 63 (19%) had progressed clinically and 65 (19%) died.

Efficacy

The median OS for 448 evaluable ST patients (342 events) was 8.5 months. In the univariate analysis, a significantly decreased risk of death was seen in patients with ECOG PS 0, those who had undergone previous local therapy, those with a baseline albumin of ≥ 36g/L, bilirubin <17μmol/L, , AFP <400ng/ml and those without vascular invasion (Table 3). In the multivariate analysis, the independent predictors of mortality were: performance status, previous local therapy, bilirubin, albumin and AFP. Vascular invasion was omitted due to high proportion of missing data. The albumin-bilirubin (ALBI) grade has recently been described as an alternative to CP as an objective measure of liver function that can independently influence survival in patients with HCC (6). CP grade, ALBI grade and BCLC stage were included in univariate analysis, but omitted from the multivariate analysis due to their co-linearity with albumin, bilirubin

or PS. There were significant differences in survival between patients with CP A (n=343) vs CP B (n=72); 9.5 vs 4.6 months (Figure 1A). For patients with ALBI-1 (n=168) vs ALBI-2 (n=214), the median survival was 12.9 vs 5.9 months (Figure 1B). For BCLC B (n=104) vs C (n=322), the median survival was 13.0 vs 8.3 months (Figure 1C).

Trial treated (TT) patients

Data were collected on 109 TT patients who were recruited to five first line trials for advanced HCC in five of the contributing hospitals. Details of the study and recruitment are given in Table 4. The baseline characteristics are listed in Table 1 and, compared to the ST cohort; the TT cohort tended to have a higher proportion of ECOG PS 0 and CP A patients, but also had a greater proportion with vascular involvement and extra-hepatic disease. The median time on trial drug was 3.7 months. Median OS was 8.1 months for 109 TT patients (91 events). There was no difference in survival between ST vs TT patients: unadjusted HR = 0.95 (95%CI 0.71-1.20), p=0.69 (Figure 1D).

Discussion:

Further to the data obtained from randomised clinical trials, observational studies provide important additional information on the efficacy and toxicity of therapy when applied to a larger and more diverse population which is distinct from the highly selected trial population [8]. Moreover, for the treatment of hepatocellular carcinoma, where geographical and aetiological differences result in profound differences in outcome [9], it is important to understand the relevance of a global trial such as the SHARP trial to the local population. The UK data presented here show that median OS survival of ST patients in the UK was equivalent to that reported in clinical trials

when the key selection criteria are considered. An exploratory multivariate analysis within the SHARP trial identified, among other factors, ECOG PS and CP status as having a significant impact on survival [3]. In SHARP, 54% were PS 0 and 95% CP A compared with 26% and 77% respectively in our study. In a sub-analysis of SHARP, those with a PS of 0 had an OS of 13.3 months compared to 8.9 months for those with PS 1-2 illustrating the relevance of PS to OS [10]. In subsequent global, randomised trials in which sorafenib has been used as the control arm, the reported OS for sorafenib treated patients has ranged from 8.5 to 10.2 months [11-14]. Recruitment to many of these trials was ongoing in the UK and approximately 20% of UK patients receiving systemic therapy went into first-line trials. We therefore included these patients in a parallel analysis to explore the possibility that the exclusion of these patients from routine care biased the study. Surprisingly, we found no difference in median OS between the trial and non-trial treated cohorts. However, the imbalance between the treatments received and some baseline characteristics prevents further interpretation of this observation.

There are few large, multicentre observational studies with which to compare our data. An Italian collaborative study group (SOFIA) has published a field-practice study including prospective data from 296 patients from six centres and reported a median OS of 10.5 months; 8.5 months in BCLC-C and 20.6 months in BCLC-B [15]. In this study 56% had PS0 and 88% were CP A so were more comparable with the SHARP population. Additionally, 51% had hepatitis C only as a cause of chronic liver disease compared with 16% in our population and hepatitis C has been proposed as a positive predictive factor for survival with sorafenib [10]. In common with both SHARP and the SOFIA study, we show that bilirubin and albumin are significant independent

predictors of survival for patients treated with sorafenib. Another multicentre retrospective study from Austria has also been reported including 148 patients from 11 institutions [16]. Median OS was 7.4 months but only 52% were CP A, and CP score was a significant prognostic factor in multivariate analysis. This raises the question to what extent those with impaired liver function benefit from sorafenib. Since all large randomised trials including sorafenib for HCC have excluded CP B patients, information regarding toxicity and efficacy is predominantly available from other sources. The GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib) study is an industry sponsored global non-interventional study designed primarily to assess safety of sorafenib in the real life population [17]. The first interim analysis included 479 patients of which 143 were European and demonstrated that overall, 28% of those treated had CP B disease. While they reported similar toxicity comparing patients with CP A and B, they did not provide a breakdown by specific toxicity and it was noted that sorafenib was discontinued due to toxicity in 40% CP B patients compared with 25% CP A patients. Here, we show that deterioration in PS and liver function was more frequent in CP B patients, in keeping with data reported from a small German study [18]. Moreover, compared with CP A, the survival in patients with CP B disease was significantly worse at 4.6 months. The inferior survival of CP B patients treated with sorafenib has been shown in other studies and ranges from 2.0-7.7months and the appropriate stratification of patients according to liver function is therefore of key importance [15, 18-22]. Recently, the ALBI grade has been developed and proposed as an alternative to CP method to assess liver function in patients with HCC [6]. The ALBI grade is based only on albumin and bilirubin measured as continuous variables, and avoids the inherent subjectivity of some elements of CP score. As part of its validation, the ALBI

grade was evaluated in 1,132 patients receiving sorafenib on clinical trials of which 96% were CP A. Our analysis presented an opportunity to evaluate the ALBI grade in sorafenib-treated patients outside clinical trials and compare with broader range of CP grade. Interestingly we found that survival of patients with ALBI grade 1 was very similar when comparing our cohort (12.9 months) with the ALBI 1 trial cohort (12.7 months). For the ALBI 2 grade, the survival for our cohort was worse at 5.9 months compared with 7.2 months in the trial cohort which presumably reflects the inclusion of more CP B patients in our ALBI 2 cohort. The ALBI score may therefore provide a useful method of stratification in trials which are predominantly CP A and help with prognostication in the clinic. However CP seems to provide information to help select those with a particularly poor outlook that may not benefit from sorafenib.

The main limitations of our study were that it was retrospective. To minimise the impact of this, we chose a robust OS primary endpoint and sufficient follow-up such that the endpoint had been met in 76% cases at the time of analysis. Moreover, for most of the key prognostic variables data were available in around 90% cases. The exception was vascular invasion for which there was a high rate of missing data. However the reported rate of 39% is consistent with the SHARP trial in which vascular involvement was reported in 36% and 41% in the sorafenib and placebo arms respectively. Although toxicity was not recorded according to CTC criteria, we were able capture clinically relevant toxicity that resulted in dose reductions, interruption or termination of therapy. We did not collect data on post-sorafenib therapy but this would have been supportive care or second-line trials. Since all second-line trials conducted during this period were negative, we do not believe that post-sorafenib therapy influenced outcome. Finally, in the absence of an untreated control group, it is difficult to evaluate

the absolute benefit of sorafenib in the UK population. However previously published data from UK patients deemed suitable for sorafenib but for whom funding was denied suggests a median OS of 4.1 months [23].

In summary our large collaborative study provides the first comprehensive survey of sorafenib use for HCC in the UK. We have defined the patient population in which it has been used, the outcome in terms of survival and associated prognostic variables. We have shown that the survival of the CP A population is in keeping with results reported in recent global randomized clinical trials and equivalent to that of patients treated in first-line UK trials. However, patients with Child-Pugh B liver function and poor performance status appear to derive limited benefit from sorafenib treatment and may be better managed with supportive care.

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Table 1: baseline demographic and clinical characteristics of HCC patients who received sorafenib as first line systemic therapy or were treated first line on clinical trials

	Observational (N=448)	**Trial (N=109)**
Age at entry; median (range)	68 (17.0 - 89.0)	68 (26.0 - 85.0)
Sex		
Male	325 (72.5%)	87 (79.8%)
Female	66 (14.7%)	13 (11.9%)
No data	57 (12.7%)	9 (8.3%)
Extra-hepatic disease		
No	269 (60.0%)	42 (38.5%)
Yes	172 (38.4%)	61 (56.0%)
Lymph node	66 (14.7%)	32 (29.4%)
Lung	59 (13.2%)	19 (17.4%)
Bone	29 (6.5%)	12 (11.0%)
No data	7 (1.6%)	6 (5.5%)
ECOG PS		
0	117 (26.1%)	48 (44.0%)
1	218 (48.7%)	58 (53.2%)
2	94 (21.0%)	3 (2.8%)
3	6 (1.3%)	-
No data	13 (2.9%)	-
Previous local therapy		
No	258 (57.6%)	52 (47.7%)
Yes	190 (42.4%)	57 (52.3%)
Vascular invasion		
No	161 (35.9%)	58 (53.2%)
Yes	91 (20.3%)	36 (33.0%)
No data	196 (43.8%)	15 (13.8%)
Bilirubin (µmol/L)		
< 17	238 (53.1%)	68 (62.4%)
≥ 17	158 (35.3%)	36 (33.0%)
No data	52 (11.6%)	5 (4.6%)

Albumin (g/L)		
< 36	121 (27.0%)	29 (26.6%)
≥ 36	276 (61.6%)	75 (68.8%)
No data	51 (11.4%)	5 (4.6%)
Hepatitis B		
No	393 (87.7%)	96 (88.1%)
Yes	55 (12.3%)	13 (11.9%)
Hepatitis C		
No	378 (84.4%)	97 (89.0%)
Yes	70 (15.6%)	12 (11.0%)
Alcohol		
No	338 (75.4%)	92 (84.4%)
Yes	110 (24.6%)	17 (15.6%)
Child Pugh		
A	343 (76.6%)	100 (91.7%)
B	72 (16.1%)	7 (6.4%)
C	2 (0.4%)	-
No data	31 (6.9%)	2 (1.8%)
ALBI grade		
1	168 (37.5%)	47 (43.1%)
2	214 (47.8%)	57 (52.3%)
3	14 (3.1%)	1 (0.9%)
No data	52 (11.6%)	4 (3.7%)
AFP (ng/ml)		
<400	227 (50.7%)	51 (46.8%)
≥400	141 (31.5%)	51 (46.8%)
No data	80 (17.9%)	7 (6.4%)
BCLC		
A	3 (0.7%)	1 (0.9%)
B	104 (23.2%)	11 (10.1%)
C	322 (71.9%)	95 (87.2%)
No data	19 (4.2%)	2 (1.8%)

Abbreviations - ST: sorafenib treated; TT: trial treated; ECOG PS: Eastern Cooperative Group Performance Status; ALBI: albumin-bilirubin score; AFP: alphafetoprotein; BCLC: Barcelona Clinic Liver Cancer stage classification

Table 2: Adverse events leading to a dose reduction or treatment interruption for ST patients

	Overall % n=224	CP A % n=181	CP B % n=43
Fatigue	45	45	47
PS deterioration	33	32	47
Diarrhoea	32	33	30
Skin toxicity	24	23	33
Liver Function	22	18	40
Nausea	12	12	16
Weight Loss	9	10	5
Gastrointestinal bleed	7	7	5
Myelosuppression	5	6	2
Other	17	17	21

CP: Child Pugh; PS: drop in performance status; Liver Function (bilirubin or transaminases)

Table 3: Risk factors for overall mortality in HCC patients treated with sorafenib

Variable		Univariable HR (95% CI)	p-value	Multivariable* HR (95% CI)	p-value
ECOG PS	0	-		-	
	1	1.45 (1.11 - 1.88)	0.008	1.41 (1.05 - 1.89)	0.055
	2 or 3	1.54 (1.13 - 2.11)		1.39 (0.98 - 1.97)	
Previous local therapy	No	-	0.004	-	0.023
	Yes	0.73 (0.58 - 0.90)		0.74 (0.58 - 0.96)	
Bilirubin µmol/L	< 17	-	< 0.001	-	<0.001
	≥ 17	1.56 (1.24 - 1.97)		1.68 (1.30 - 2.16)	
Albumin g/L	< 36	-	< 0.001	-	0.025
	≥ 36	0.60 (0.47 - 0.76)		0.74 (0.56 - 0.96)	
AFP ng/ml	<400	-	0.001	-	0.008
	≥400	1.51 (1.19 - 1.93)		1.41 (1.09 - 1.82)	
Sex	Male	-	0.726		
	Female	1.06 (0.78 - 1.44)			
Extra-hepatic disease	No	-	0.521		
	Yes	1.07 (0.86 - 1.34)			
Vascular invasion	No	-	0.013		
	Yes	1.44 (1.08 - 1.91)			
Hepatitis B	No	-	0.792		
	Yes	0.96 (0.69 - 1.33)			
Hepatitis C	No	-	0.070		
	Yes	1.30 (0.98 - 1.73)			
Alcohol	No	-	0.477		
	Yes	1.10 (0.85 - 1.41)			
Child Pugh	A	-	0.003		
	B	1.53 (1.16 – 2.03)			
ALBI grade	1	-	<0.001		
	2	1.92 (1.51 – 2.44)			
BCLC	2	-	0.006		
	3	1.45 (1.11 – 1.89)			

Abbreviations: ECOG PS – Eastern Cooperative Group Performance Status; AFP: alpha fetoprotein; ALBI: albumin-bilirubin score; BCLC: Barcelona Clinic Liver Classification

*Vascular invasion omitted from multivariable model due to missing data. Child Pugh, ALBI and BCLC omitted from multivariable model due to co-linearity with albumin, bilirubin or performance status.

Table 4: First-line systemic therapy trials for HCC in which the TT patients were enrolled.

Trial name	**Description**
SEARCH [14] N=41	Phase III sorafenib+ erlotinib vs sorafeninb +placebo
Nintedanib N=35	Phase I Nintedanib Phase II Nintedanib vs Sorafenib
BRISK FL [13] N=26	Phase III sorafenib vs brivanib
SHARP[3] N=6	Phase III RCT Sorafenib vs placebo
E7050 N=3	Randomised Phase Ib/II sorafenib +E7050 vs sorafenib

Figure Legend

Figure 1. Kaplan Meier survival curves of OS comparing A) Child-Pugh A vs Child-Pugh B, B) ALBI 1 vs ALBI 2, C) BCLC B vs BCLC C, D) Sorafenib treated (observational) vs Trial treated (trial)

Reference List

[1] Ferlay J., Soerjomataram I., Dikshit R., Eser S., Mathers C., Rebelo M. et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012 Int J Cancer 2015;136:E359-E386

[2] Allemani C., Weir H.K., Carreira H., Harewood R., Spika D., Wang X.S. et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2) Lancet 2015 ;385:977-1010

[3] Llovet J.M., Ricci S., Mazzaferro V., Hilgard P., Gane E., Blanc J.F. et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008 ;359:378-90

[4] Cheng A.L., Kang Y.K., Chen Z., Tsao C.J., Qin S., Kim J.S. et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34

[5] European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012 ;56:908-43

[6] Johnson P.J., Berhane S., Kagebayashi C., Satomura S., Teng M., Reeves H.L. et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade J Clin Oncol 2015;33:550-8

[7] Llovet J.M., Bru C., Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999 ;19:329-38

[8] Silverman S.L. From randomized controlled trials to observational studies. Am J Med 2009 ;122:114-20

[9] Park J.W., Chen M., Colombo M., Roberts L.R., Schwartz M., Chen P.J. et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int 2015;35(9):2155-66

[10] Bruix J., Raoul J.L., Sherman M., Mazzaferro V., Bolondi L., Craxi A. et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57:821-9

[11] Cheng A.L., Kang Y.K., Lin D.Y., Park J.W., Kudo M., Qin S. et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013;31:4067-75

[12] Cainap C., Qin S., Huang W.T., Chung I.J., Pan H., Cheng Y. et al. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2015;33:172-9

[13] Johnson P.J., Qin S., Park J.W., Poon R.T., Raoul J.L., Philip P.A. et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013;31:3517-24;

[14] Zhu A.X., Rosmorduc O., Evans T.R., Ross P.J., Santoro A., Carrilho F.J. et al. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2015;33:559-66

[15] Iavarone M., Cabibbo G., Piscaglia F., Zavaglia C., Grieco A., Villa E. et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in ItalyHepatology 2011;54:2055-63

[16] Pinter M., Sieghart W., Hucke F., Graziadei I., Vogel W., Maieron A. et al. Prognostic factors in patients with advanced hepatocellular carcinoma treated with sorafenib. Aliment Pharmacol Ther 2011;34:949-59

[17] Lencioni R., Kudo M., Ye S.L., Bronowicki J.P., Chen X.P., Dagher L. et al. First interim analysis of the GIDEON (Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafeNib) non-interventional study. Int J Clin Pract 2012;66:675-83;2012

[18] Worns M.A., Weinmann A., Pfingst K., Schulte-Sasse C., Messow C.M., Schulze-Bergkamen H. et al. Safety and efficacy of sorafenib in patients with advanced hepatocellular carcinoma in consideration of concomitant stage of liver cirrhosis. J Clin Gastroenterol 2009;43:489-95

[19] Pressiani T., Boni C., Rimassa L., Labianca R., Fagiuoli S., Salvagni S. et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol 2013 ;24:406-11

[20] Ozenne V., Paradis V., Pernot S., Castelnau C., Vullierme M.P., Bouattour M. et al. Tolerance and outcome of patients with unresectable hepatocellular carcinoma treated with sorafenib Eur J Gastroenterol Hepatol 2010;22:1106-10

[21] Hollebecque A., Cattan S., Romano O., Sergent G., Mourad A., Louvet A. et al. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. Aliment Pharmacol Ther 2011;34:1193-201

[22] Pinter M., Sieghart W., Graziadei I., Vogel W., Maieron A., Konigsberg R. et al. Sorafenib in unresectable hepatocellular carcinoma from mild to advanced stage liver cirrhosis. Oncologist 2009;14:70-6

[23] Palmer D.H., Hussain S.A., Smith A.J., Hargreaves S., Ma Y.T., Hull D. et al. Sorafenib for advanced hepatocellular carcinoma (HCC): impact of rationing in the United Kingdom. Br J Cancer 2013;109:888-90;2013