The prognostic value of inflammation-based scores in advanced hepatocellular carcinoma patients prior to treatment with sorafenib

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ABSTRACT

Background and Aims: The multikinase inhibitor sorafenib is the only currently approved drug for the indication of advanced hepatocellular carcinoma (HCC). It provides a limited gain in survival time but is frequently associated with adverse events. We currently lack simple prognostic factors in sorafenib-treated HCC patients. Various inflammation-based scores (IBSs) have been evaluated as predictors of tumor recurrence and survival in various malignancies (including HCC). The objective of the present study was to determine the prognostic value of IBSs for overall survival (OS) in advanced HCC patients prior to the initiation of sorafenib therapy.

Methods: Patients with Barcelona Clinic Liver Cancer stage C HCC were enrolled retrospectively between October 2007 and September 2015. To identify prognostic factors for OS, bivariate and multivariate analysis were performed using a Cox proportional hazards regression model.

Results: 161 patients (87.0% males; median age: 67; median OS: 9.1 months) were enrolled. A multivariate analysis identified a body mass index <25kg/m² (hazard ratio (HR)=1.55, p<0.017), macroscopic vascular invasion (HR=1.63, p< 0.001), an AST level >38 U/L (HR=2.65, p<0.001), Child Pugh B stage (HR=2.59, p<0.001) and a systemic immune-inflammation index (SII) ≥600 x 10⁹ (HR 1.72, p=0.002) as independent risk factors for OS in advanced HCC.

Conclusion: IBSs (such as the SII) are novel, simple, low-cost prognostic indices in patients with advanced HCC. They may be of value in determining whether these patients may benefit from sorafenib therapy.
INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related death in the world [1]. Early-stage HCC is poorly symptomatic, and so most cases are diagnosed at an advanced stage [2]. The oral multi-tyrosine kinase inhibitor sorafenib is the only currently authorized drug for Barcelona Clinic Liver Cancer (BCLC) stage C-HCC. Sorafenib treatment is associated with a limited gain in survival (around three months, giving a median overall survival (OS) time of 10.7 months in the SHARP trial [3, 4]). Advanced HCC is a heterogeneous disease; it includes symptomatic tumors and those with an invasive tumor pattern (i.e. macroscopic vascular invasion/extrahepatic spread) [5-7]; hence, reliable predictive factors for clinical outcomes in sorafenib-treated patients have yet to be identified [8]. Recent attention has been focused on cancer-associated inflammation - a key determinant of disease progression and survival in several solid tumors. It has been shown that scoring systems based on the systemic inflammatory response (referred to below as inflammation-based scores (IBSs)) are of prognostic value in patients with solid tumors [9-17]. In particular, various combinations of hematological parameters (including the neutrophil-lymphocyte ratio (NLR), the derived-NLR (dNLR), the lymphocyte-to-monocyte ratio (LMR), the platelet-lymphocyte ratio (PLR), the systemic-immune inflammation index (SII) and the prognostic nutritional index (PNI)) have been evaluated as predictors of recurrence and/or survival in HCC [18-27]. The objective of the present study was to investigate the prognostic value of pre-treatment IBSs for the OS of advanced HCC patients subsequently treated with sorafenib.

RESULTS

Characteristics of the patients and the tumors

Out of 200 consecutive sorafenib-treated patients with advanced BCLC-C HCC meeting the inclusion criteria, 161 were included in the study (males: 87.0%; median (range) age: 67.1 (44.6-80.1); Eastern Cooperative Oncology Group performance status of 0-1: 87.0%) (Figure 1). The study population’s baseline characteristics are summarized in Table 1. The median (range) follow-up period was 11.74 months (0.2–73.0) and the median duration of sorafenib therapy was 130 days. The median OS time was 9.1 months (7.9-10.1), and 148 patients (91.9%) died. The OS rates [95% CI] at 6, 12 and 24 months were 77.4% (72.4–82.3%), 60.8% (55.6–66.0%) and 47.2% (41.7–52.7%), respectively.
months were 67.5% [59.7-74.2], 35.0% [27.6-42.4%] and 13.0% [8.1-19.0%], respectively. Chronic liver diseases (due to excessive alcohol consumption in 49.0% of the patients) were classified as CP-A and CP-B in 75.8% and 24.2% of cases, respectively. The cause of cirrhosis was multifactorial in 11.8% of the patients. Seven cases of HCC were diagnosed by liver biopsy; all the other were diagnosed using imaging. Extrahepatic spread was found in 62.7% of cases and vascular invasion was found in 44.7%. Prior to initiation of sorafenib, 95 patients (59.0%) had received one or more specific drugs. Sorafenib was withdrawn in 95.0% of the patients, following the onset of unacceptable toxicity (in 35.1% of withdrawals), tumor progression (21.4%), a worsening of liver function (28.6%) and death (14.9%). The patients’ baseline laboratory data are summarized in Table 2.

Prognostic factors for HCC

The cut-off levels chosen for their clinical significance were the upper limits for WBC, PLT, ALT, AST, and ALP, and the lower limit for PT. The cut-offs for age, albumin and AFP were taken from literature reports of thresholds with proven prognostic value. The cut-offs for GGT, NLR, dNLR, PLR, LMR, PNI, and SII corresponded to the values that maximized the probability in the bivariate Cox model.

The results of the bivariate analysis are presented in Table 3. The variables significantly associated with OS were: BMI >25 kg/m² (HR [95% CI]=0.63 [0.44-0.91]), macroscopic vascular invasion (HR [95% CI]=1.74 [1.26-2.42]), CP-B (HR [95% CI]=2.40 [1.75-3.47]), AST >38 IU/L (HR [95% CI]=2.57 [1.63-4.03]), AFP ≥ 400 ng/mL (HR [95% CI]= 1.43 [1.03-2.00]), and ALP >120 IU/L (HR [95% CI]= 2.54 [1.64-3.95]). The WBC and the platelet count alone were not predictive of OS, and there was no significant difference between treatment-naïve and pre-treated patients (HR [95% CI]=0.749 [0.54-1.04]; p=0.08), including those having undergone liver surgery. Each IBS was found to be a risk factor for OS, as follows: NLR ≥ 4 (HR [95% CI]= 1.74 [1.25-2.40]); dNLR ≥ 3 (HR [95% CI]= 2.28 [1.59-3.28]); PLR ≥ 200 (HR [95% CI]= 1.54 [1.09-2.18]); LMR <3 (HR [95% CI]= 1.45 [1.02-2.06]); PNI < 45 (HR [95% CI]= 2.01 [1.40-2.88]); and SII ≥600 x 10³ (HR [95% CI]= 1.54 [1.11-2.13]).

The results of the multivariate analysis of the whole study population are summarized in Table 4. The final model identified five significant independent predictors of OS: AST >38 IU/L (HR 2.65 [1.67-4.19]); BMI < 25 kg/m² (HR 1.55 [1.08-2.24]); SII >600 x 10³ (HR 1.72 [1.22-2.43]); CP-B (HR 2.59 [1.75-3.28]); and macroscopic vascular invasion (HR 1.63 [1.16-2.30]). The independent variables’ discriminant power for OS was represented with Kaplan-Meier survival curves (Figure 2A). The median survival time for patients (n=6) with all five independent risk factors was 2.6 months (versus 35.6 months for patients with none of the risk factors).

The multivariate model was also applied to a CP-A patient subgroup. SII ≥600 x 10³ was found to have negative prognostic value for OS (HR = 1.49 [1.01-2.20]), along with AST >38 IU/L (HR = 2.28 [1.37-3.79]), BMI < 25 kg/m² (HR = 1.89 [1.25-2.86]) and macroscopic vascular invasion (HR = 1.57 [1.06-2.34]) (Table 5). The independent variables’ discriminant power for OS is shown in Figure 2B. Similarly, the median OS for CP-A patients (n=13) with all four independent risk factors was 5.8 months.

DISCUSSION

The present study assessed the prognostic value of six IBSs in advanced HCC patients subsequently treated with sorafenib. Our results demonstrate that IBSs are significantly correlated with OS, and that the SII is the strongest independent predictor of OS in sorafenib-treated patients with advanced HCC. The SII is a routine, reliable, simple, low-cost laboratory measurement. It is a more objective, comprehensive marker than indexes like the NLR and PLR or its components alone (i.e. neutrophil, lymphocyte and platelet counts). An elevated SII is suggestive of severe inflammatory status and/or a weak immune response. Given that sorafenib is not necessarily of benefit in CP-B patients [28], the SII is a valuable, independent predictive factor of OS when only CP-A patients are analyzed.

Our results are consistent with previous clinical studies in which a high SII was a risk factor for poor survival. The SII was initially described as an independent prognostic factor after curative resection for HCC BCLC 0+A in two independent Chinese cohorts, for both time to progression (HR [95% CI]=1.92 [1.04-3.54]; p=0.037) and OS (HR [95% CI]=2.10 [1.14-3.85]; p=0.017) [29]. The SII was also significantly associated with a poor OS following TACE in BCLC stage A, B and C HCC patients [27]. Advanced HCC patients receiving sorafenib with SII ≥360 showed also lower median PFS (2.6 vs. 3.9 months, p=0.026) and OS (5.6 vs. 13.9 months, p=0.027) compared to those with SII <360 [30]. As in the present study, the SII was a better prognostic factor than the other indices (PLR, NLR, tumor number, AFP, etc.). Hu and al. concluded that the high recurrence rate in resected patients with high SII scores might be due to high circulating tumor cell counts. Hu and al.’s optimal SII cut-off (330 x 10³) was lower than the value determined in the present study (600 x 10³), but most of the Chinese patients were hepatitis-B-virus–positive and staged as BCLC 0 or A. Our findings agree with those of another study in which patients with BCLC stage C HCC also had significantly higher SII scores than those with BCLC stages A to B HCC (p< 0.0001) [27] and with those showing SII as an independent prognostic factor for OS in BCLC-C HCC.
Table 1: Baseline demographic and clinical characteristics of patients with advanced HCC

| Characteristic                                      | Patients (n=161) |
|-----------------------------------------------------|-----------------|
| Mean age ±SD (years)                                |                 |
| Upon diagnosis of HCC                               | 66.0 ±8.3       |
| At initiation of sorafenib                          | 67.2 ±8.6       |
| Gender (n, %)                                       |                 |
| Male                                                | 140 (86.96%)    |
| Female                                              | 21 (13.04%)     |
| BMI (kg/m²) (mean ± SD)                             | 27.3 ±6.37*     |
| PS (n, %)                                           |                 |
| 0                                                   | 59 (36%)        |
| 1                                                   | 81 (50.31%)     |
| 2                                                   | 21 (13.04%)     |
| Etiology of cirrhosis (n, %)                         |                 |
| Alcohol abuse                                       | 82 (50.93%)     |
| Chronic hepatitis B                                 | 16 (9.94%)      |
| Chronic hepatitis C                                 | 31 (19.25%)     |
| Metabolic syndrome                                 | 31 (19.25%)     |
| Hemochromatosis                                     | 7 (4.35%)       |
| Others                                              | 8 (4.97%)       |
| Cirrhosis (n, %)                                    | 140 (86.96%)    |
| Child-Pugh stage (n, %)                              |                 |
| A5                                                  | 79 (49.07%)     |
| A6                                                  | 43 (26.71%)     |
| B7                                                  | 21 (13.04%)     |
| B8                                                  | 13 (8.07%)      |
| B9                                                  | 5 (3.11%)       |
| Ascites (n, %)                                      | 27 (16.77%)     |
| Nodules (n, %)                                      |                 |
| 1-2                                                 | 48 (29.81%)     |
| ≥3                                                  | 113 (70.19%)    |
| Macrovascular invasion (n, %)                        | 72 (44.72%)     |
| Lymph node involvement (n, %)                        | 53 (32.92%)     |
| Distant metastasis (n, %)                            | 48 (29.81%)     |
| Lung                                                | 24 (14.90%)     |
| Bone                                                | 14 (8.70%)      |
| Carcinomatosis                                      | 12 (7.45%)      |
| Adrenal                                             | 6 (3.73%)       |
| Others                                              | 2 (1.24%)       |

(Continued)
| Characteristic | Patients (n=161) |
|---------------|-----------------|
| Previous treatments (n, %) | 95 (59.01%) |
| Liver resection | 17 (10.56%) |
| Liver transplantation | 3 (1.86%) |
| TACE | 67 (41.62%) |
| Radiofrequency ablation | 15 (9.31%) |
| Stereotactic body radiation | 6 (3.73%) |
| Intra-arterial iodine-131-iodized oil hepatic injection | 16 (9.94%) |

* missing data: n=3

Abbreviations: SD = standard deviation; BMI = body mass index; PS = performance status; MS= metabolic syndrome; TACE = transarterial chemoembolization;

Figure 2: Kaplan-Meier estimates of survival curves with advanced BCLC-C HCC. (A) Kaplan-Meier estimates of survival curves with advanced BCLC-C HCC, depending on the presence of the identified independent prognostic factors. (A) No independent risk factor. (B) BMI < 25 kg/m². (C) Macroscopic vascular invasion. (D) SII > 600.10⁹. (E) Child-Pugh B. (F) AST > 38 UI/L. (G) Presence of all risk factors. (B) Kaplan-Meier estimates of survival curves with advanced BCLC-C HCC in the subgroup of CP-A patients, depending on the presence of the identified independent prognostic factors. (A) no independent risk factor. (B) BMI < 25 kg/m². (C) macroscopic vascular invasion. (D) SII > 600.10⁹. (E) AST > 38 UI/L. (F) of all risk factors.
patients [30]. Moreover, our cut-off is similar to the value selected in patients with metastatic renal carcinoma or metastatic colorectal cancer [31, 32].

A systemic inflammatory response is known to promote tumor angiogenesis, invasion and metastasis through a variety of mechanisms, and is associated with poor survival in various types of cancer [33]. Firstly, lymphocytes enhance the antitumor immune response and control tumor defense by inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration. Secondly, neutrophils promote cancer cell invasion, proliferation and metastasis, and modify the tumor micro-environment [34, 35]. Thirdly, platelets interact with tumor cells and facilitate tumor cell survival and metastasis through a variety of mechanisms, including the protection of circulating tumor cells against shear stresses [18,36–40].

The other independent prognostic factors for poor OS identified in our study have often been described in the literature; they include an elevated AST, CP-B status, macroscopic vascular invasion [8, 28, 41, 42], and BMI < 25 kg/m² [43-45] (although BMI has not been analyzed very frequently in the literature). Low BMI (< 25 kg/m²) is associated with dose-limiting toxicity of sorafenib in patients with advanced HCC, and especially in patients with sarcopenia [43-45].

We found that the median OS for patients with all of the risk factors was 2.6 months (versus 5.8 months for a CP-A patient). Thus, a physician may decide not to initiate sorafenib treatment in patients meeting most of the criteria.

The present study had several limitations. Its retrospective design meant that CRP was not assayed systematically; hence, we could not assess the Glasgow

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**Table 2: Baseline laboratory parameters in the study population (n=161)**

| Variable               | Median; Mean (±SD)                  |
|------------------------|------------------------------------|
| Hemoglobin (g/L)       | 13.00; 12.98 ±1.99                 |
| WBC (×10⁹/L)           | 6.11; 6.60 ±2.94                   |
| Platelet count         | 163.00; 204.52 ±136.77             |
| Neutrophil count (×10⁹/L) | 4.27; 4.75 ±2.54           |
| Lymphocyte count (×10⁹/L) | 1.10; 1.21 ±0.59           |
| Monocyte count (×10⁹/L) | 0.49; 0.52 ±0.26                   |
| PT (%)                 | 83.00; 81.63 ±12.86                |
| Creatinine (µmol/L)    | 9.10; 11.35 ±11.78                 |
| MDRD (ml/min/1.73 m²)  | 88.00; 88.41 ±31.29                 |
| Total bilirubin (µmol/L) | 17.00; 23.10 ±19.92          |
| Albumin (g/dL)         | 35.90; 35.96 ±5.33                   |
| ALT (U/L)              | 48.00; 62.78 ±59.28                 |
| AST (U/L)              | 76.00; 105.02 ±110.66               |
| AFP (ng/mL)            | 126.00; 13222.18 ±80027.31         |
| GGT (U/L)              | 251.50; 334.94 ±285.26             |
| ALP (U/L)              | 178.00; 236.38 ±236.28             |
| NLR                    | 3.97; 4.80 ±4.101                   |
| dNLR                   | 2.28; 2.52 ±1.48                    |
| PLR                    | 161.47; 200.90 ±181.269            |
| LMR                    | 2.28; 2.97 ±2.95                    |
| PNI                    | 41.83; 42.03 ±26.550                |
| SII (× 10⁹)            | 614.94; 1051.64 ±1317.67           |

Abbreviations: WBC= white blood cell count; PT= prothrombin time; ALT= alanine aminotransferase; AST = aspartate aminotransferase; AFP= alpha-fetoprotein; ALP= alkaline phosphatase; GGT= gamma-glutamyltranspeptidase; NLR= neutrophil-to-lymphocyte ratio; dNLR= derived neutrophil-to-lymphocyte ratio; PLR= platelet-to-lymphocyte ratio; LMR= lymphocyte-to-monocyte ratio; PNI= prognostic nutritional index; SII= systemic-immune inflammation index.
In conclusion, an abnormally high AST level, SII >600 x 10^9, BMI <25 kg/m^2, macrovascular invasion, and CP-B cirrhosis are predictive of poor OS in patients with advanced HCC. The SII is a non-invasive, routine, low cost index with prognostic value in patients with advanced HCC. It can potentially be used to guide the treatment strategy. Confirmation of the present results in prospective studies is now required.

Table 3: Prognostic factors for overall survival in the study population: bivariate analyses

| Variable                              | Description       | HR [95% CI]     | p value |
|---------------------------------------|-------------------|-----------------|---------|
| Age ≥ 65                              | 103 (64.0%)       | 0.76 [0.55;1.07]| 0.114   |
| BMI ≥25 kg/m^2                        | 107 (68.1%)       | 0.63 [0.44;0.91]| 0.014   |
| Ascites                               | 27 (16.77%)       | 0.83 [0.54;1.26]| 0.380   |
| Cirrhosis                             | 140 (87.0%)       | 1.22 [0.75;1.99]| 0.412   |
| Number of lesions≥3                   | 113 (70.2%)       | 1.30 [0.90;1.86]| 0.151   |
| Macroscopic vascular invasion         | 72 (44.7%)        | 1.74 [1.26;2.42]| 0.001   |
| Lymph node involvement                | 53 (32.9%)        | 1.36 [0.96;1.91]| 0.080   |
| Distant metastasis                    | 48 (24.2%)        | 0.90 [0.62;1.29]| 0.550   |
| Child Pugh score B (vs A)             | 39 (24.2%)        | 2.40 [1.75;3.47]| <.001   |
| Previous locoregional treatment       | 95 (59.0%)        | 0.75 [0.54;1.04]| 0.084   |
| WBC >10 x10^9/L                       | 14 (8.7%)         | 1.56 [0.88;2.76]| 0.130   |
| Platelet count ≥150 G/L               | 88 (55%)          | 0.98 [0.70;1.36]| 0.882   |
| PT < 70%                              | 27 (18%)          | 1.85 [1.20;2.84]| 0.005   |
| Total bilirubin >17 μmol/L            | 79 (49.1%)        | 1.61 [1.16;2.22]| 0.004   |
| Albumin <3.5 g/dL                     | 68 (43.0%)        | 1.62 [1.16;2.26]| 0.004   |
| ALT >40 U/L                           | 101 (63.1%)       | 1.63 [1.16;2.30]| 0.006   |
| AST >38 U/L                           | 133 (82.6%)       | 2.57 [1.63;4.03]| <.001   |
| AFP ≥400 ng/mL                        | 60 (37.3%)        | 1.43 [1.03;2.00]| 0.033   |
| ALP >120 U/L                          | 129 (81.1%)       | 2.54 [1.64;3.95]| <.001   |
| GGT >250 U/L                          | 81 (51.9%)        | 1.67 [1.19;2.34]| .0027   |
| NLR≥4                                 | 78 (48.5%)        | 1.74 [1.25;2.40]| 0.001   |
| dNLR≥3                                | 45 (28.1%)        | 2.28 [1.59;3.28]| <.001   |
| PLR≥200                               | 54 (33.8%)        | 1.54 [1.09;2.18]| 0.014   |
| LMR<3                                 | 112 (69.6%)       | 1.45 [1.02;2.06]| 0.037   |
| PNI<45                                | 106 (67.1%)       | 2.01 [1.40;2.88]| <.001   |
| SII≥600 (×10^9)                       | 84 (66.9%)        | 1.54 [1.11;2.13]| 0.010   |

Abbreviations: WBC= white blood cell count; PT= prothrombin time; ALT= alanine aminotransferase; AST = aspartate aminotransferase; AFp= alpha-fetoprotein; ALp= alkaline phosphatase; GGT= gamma-glutamyltranspeptidase; NLR= neutrophil-to-lymphocyte ratio; dNLR= derived neutrophil-to-lymphocyte ratio; PLR= platelet-to-lymphocyte ratio; LMR= lymphocyte-to-monocyte ratio; PNI= prognostic nutritional index; SII = systemic-immune inflammation index

The WBC, PT, PLT, ALT, AST, ALP cut-offs were defined according to the clinical significance of their normal upper limit. The age, albumin and AFP cut-offs were chosen according to previous published thresholds with proven prognostic value. The GGT, NLR, dNLR, PLR, LMR, PNI, and SII cut-off levels corresponded to the value that maximized the probability in the bivariate Cox model.
MATERIALS AND METHODS

Patients

Eligible patients were treated with sorafenib for an indication of advanced HCC (stage C, according to the updated BCLC staging system [5]) in the Department of Hepatology and Gastroenterology at Nancy University Medical Center (Nancy, France) from October 2007 to September 2015. The radiologic and/or histologic diagnostic criteria for HCC were based on the American Association for the Study of the Liver guidelines [6]. Some patients had undergone liver transplantation, surgical resection and/or locoregional therapies (radiofrequency ablation, transarterial chemoembolization (TACE), radioembolization with microspheres containing yttrium-90, or stereotaxic body radiation therapy) prior to the initiation of sorafenib treatment. All patients had undergone contrast-enhanced computed tomography or magnetic resonance imaging prior to the initiation of sorafenib treatment. The study was approved by the local institutional review board (Comité de réflexion éthique hospitalo-universitaire CREHNU).

Data collection

The Department of Hepatology and Gastroenterology’s case database for the period between October 2007 and September 2015 was systematically searched with the term “sorafenib”. All patients involved in clinical trials were included, after study blinding had been lifted. The patients’ demographic, clinical and biological data were collected retrospectively from their medical charts. Variables recorded at inclusion were as follows: gender, age, body mass index (BMI), Child Pugh (CP) score (albumin, prothrombin time (PT), total bilirubin, ascites, and encephalopathy), the etiology of cirrhosis (hepatitis C or B virus, alcoholic or non-alcoholic steatohepatitis, or hemochromatosis), the number of tumors and the tumor characteristics. The results of routine blood tests, liver function tests and alpha-fetoprotein (AFP) assays performed in the month preceding the initiation of sorafenib treatment were also recorded, if available.

To identify baseline risk factors associated with OS in HCC, we evaluated 10 clinical/radiologic parameters (age, BMI, ascites, cirrhosis, number of lesion >3, macroscopic vascular invasion, lymph node or distant metastasis, the CP score, and previous locoregional treatment), 11 biological factors (the white blood count (WBC), the platelet count, the PT, and total bilirubin, albumin, ALT, AST, AFP, and alkaline phosphatase (ALP) levels), and six IBSs (the neutrophil-to-lymphocyte ratio (NLR), the derived NLR, the platelet-to-lymphocyte ratio (PLR), the monocyte-to-lymphocyte ratio (MLR), the prognostic nutritional index (PNI) and the systemic-immune inflammation index (SII) [29]. The six IBSs at baseline were calculated from serum complete blood counts using the following equations, where M, L, N, P, W are the absolute monocyte, lymphocyte, neutrophil, platelet and white blood-cell counts, respectively: NLR = N/L; dNLR = N/(W-N); MLR = M/L; PLR = P/L; PNI = serum albumin + 0.005 x L; SII = P x N/L.
Treatments and patient follow-up

The prescribed dose of sorafenib was 400 mg per os bid. The patients' clinical and toxicity profiles were assessed at least every 4 weeks. If adverse drug reactions occurred (and depending on the latter's grade), the dose of sorafenib was reduced. Treatment was continued until the onset of unacceptable toxicity, radiologic or clinical progression, death or patient refusal.

Statistical analysis

Statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC). The threshold for statistical significance was set to p<0.05. OS was defined as the time interval between the first day of sorafenib treatment and the day of death. Surviving patients were censored at the date of last follow-up or 4 years after the start of sorafenib treatment. The association between OS and each prognostic factor was first investigated using bivariate and multivariate Cox proportional hazards models. The results were expressed as a hazard ratio (HR) [95% confidence interval (CI)]. Quantitative variables were transformed into binary variables. We used two approaches to choose thresholds: (i) assessment of known clinical significance; (2) value that best separates patient outcomes according the minimum P-value method in the bivariate Cox model.

The validity of the proportional hazard (PH) assumption was checked by determining the scaled Schoenfeld residuals (SSR). The PH assumption was tested for each covariate by correlating the corresponding SSR with the rank of time [49]. All variables with a p-value <0.1 in the bivariate Cox model were introduced in a multivariate Cox model with backward selection at p=0.10. The model’s stability was investigated using a bootstrap resampling method [50]. A multivariate Cox model with backward selection (p<0.1) was run on each of these replicates. The variable was retained in the final model if it was selected in at least 70% of the 500 analyses [50]. To address the problem of correlated variables, the selection frequencies of all possible pairs of variables were also considered. If a pair of variables was selected in more than 90% of replicates, the covariate with the higher inclusion frequency was selected [50]. The results of the final multivariate model were presented as the adjusted HR [95% CI]. The same model was applied to a CP-A subgroup. For each independent prognostic factor, the discriminant power for OS in a multivariate analysis was represented as a Kaplan-Meier survival curve. The predicted survival function (S(t)) for particular sets of risk factors were computed using the “phreg” procedure and the “baseline” statement in SAS. The median survival time was determined as the smallest value of the time t so that S(t)≤0.50.

Author contributions

Guillaume Conroy: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript; Julia Salleron: statistical analysis, study design, drafting of the manuscript; Arthur Belle, Mouni Bensenane, Abdelbasset Nani, Ahmet Ayav, Didier Peiffert, Anthony Lopez, Cédric Baumann, Hélène Barraud: critical revision of the manuscript for important intellectual content.

JPB: study supervision, study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

CONFLICTS OF INTEREST

G.C., J.S., A.B., M.B., A.N., A.A., D.P., A.L., C.B., H.B. declare no conflicts.
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