Sorafenib: from literature to clinical practice

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Sorafenib is considered the standard systemic therapy for hepatocellular carcinoma (HCC), in patients with well-preserved liver function (Child-Pugh A class) and advanced-stage HCC (BCLC-C) or in patients with HCC progressing after locoregional therapies, with a high grade of recommendation. The approval of sorafenib for this indication was grounded on the efficacy and the safety results reported by two international randomized, controlled trials, the SHARP and the Asia-Pacific studies. In addition, the efficacy and the safety of sorafenib in clinical practice are addressed by several field-practice experiences, including the multinational GIDEON study and the SOFIA study. Finally, further research on sorafenib is ongoing to optimize the use of this molecule. This review aims to provide an overview of the most relevant clinical data on the efficacy and the safety of sorafenib in patients with HCC.

Key words: adverse events, clinical practice, observational studies, randomized clinical trials, sorafenib

introduction

Hepatocellular carcinoma (HCC) represents a global health problem and the incidence of this cancer in patients with cirrhosis is still increasing in several countries. The prognosis and the treatment options for HCC are generally related to the tumor stage at presentation. Surgical resection, transplantation and percutaneous ablation offer a high probability of complete response in patients with early HCC. In asymptomatic patients with multifocal HCC without vascular invasion or extrahepatic spread, chemoembolization can provide survival benefit.

Sorafenib, an oral multikinase inhibitor with activity against Raf-1, B-Raf, VEGFR2, PDGFR and c-Kit receptors, has a potent antiangiogenic and proapoptotic activity and therefore presents a marked antitumoral effect [1].

The improvement of survival in patients treated with sorafenib is supported by the highest level of evidence, and according to the recent guidelines by the European Association for the Study of Liver (EASL) and by the European Society for Molecular Oncology (ESMO)/European Society of Digestive Oncology (ESDO), sorafenib is considered the standard systemic therapy for HCC, in patients with well-preserved liver function (Child-Pugh A class) and advanced-stage HCC (BCLC-C) or in patients with HCC progressing after locoregional therapies, with a high grade of recommendation (Figure 1) [2,3].

Sorafenib was approved for the treatment of patients with advanced HCC on the basis of the efficacy and the safety results reported by two international randomized, controlled trials (RCTs), the SHARP (Sorafenib HCC Assessment Randomized Protocol) and the Asia-Pacific trials [4,5]. In addition, the efficacy and the safety of sorafenib in clinical practice are addressed by several field-practice experiences, including the multinational GIDEON study and the SOFIA study [6,7]. Finally, further research on sorafenib is ongoing to optimize the use of this molecule, and particularly, the efficacy of sorafenib in patients with Child-Pugh B cirrhosis, the possibility of modifying the dosing regimen and the potential existence of laboratory and/or genetic biomarkers of response are currently being explored.

This review aims to provide an overview of the most relevant clinical data on the efficacy and the safety of sorafenib in patients with HCC.

randomized, controlled trials

efficacy

The SHARP trial, conducted in Western countries, was a multicenter, phase III, double-blind, placebo-controlled study, in which 602 HCC patients (95% with Child-Pugh A cirrhosis and 82% with BCLC-C) who had not received any previous systemic treatment were assigned to receive sorafenib 400 mg bid in die (bid) or placebo [4]. The primary outcomes of the trial were overall survival (OS) of patients and the time to symptomatic progression, whereas the secondary outcomes included the time to radiologic progression (TTP) and safety. The study was stopped at the second planned interim analysis, due to a significantly shorter survival in the placebo arm. In detail, the median OS was 10.7 months in the sorafenib group versus 7.9 months in the placebo group [hazard ratio (HR): 0.69; 95% CI: 0.55–0.87; P < 0.001]. Although there was no difference in the median time to symptomatic progression, a
significant advantage for sorafenib over placebo was reported for TTP (5.5 versus 2.8 months; \( P < 0.001 \)).

The second trial with a similar design was conducted in the Asia-Pacific region, where chronic infection by hepatitis B virus (HBV) represents the more common etiological factor of chronic liver disease [5]. In total, 226 patients with HCC were randomized to receive sorafenib 400 mg bid or placebo with a 2:1 ratio (150 and 76 patients, respectively). The wide majority of patients were classified as Child-Pugh A (97%) and BCLC-C (95%). The efficacy of sorafenib was overall similar to that reported in the SHARP trial. The median OS was 6.5 months in the sorafenib group, compared with 4.2 months in the placebo group, with an HR similar to that observed in the SHARP trial (HR: 0.68; 95% CI: 0.50–0.93; \( P = 0.014 \)), whereas the median TTP was 2.8 months in the sorafenib group compared with 1.4 months in the placebo group (\( P = 0.0005 \)).

It must be observed that the two trials have enrolled different populations: patients included in the SHARP trial were mostly of Caucasian ethnicity and had a high prevalence of hepatitis C virus infection; conversely, patients observed in the Asia-Pacific trial were more largely infected by HBV and presented a more advanced stage of HCC and a worse liver function. These differences can explain the difference in OS observed between the two trials; however, the HR for survival, which can be regarded to as a measure of sorafenib efficacy, was similar (0.69 and 0.68, respectively).

safety

In both the SHARP and the Asia-Pacific trials, sorafenib was generally well tolerated, but, like other drugs of the same class, it caused a range of adverse events (AEs). In the SHARP trial, the incidence of serious AEs was 52 and 54% in treated and placebo groups, respectively [4]. However, grade 3 drug-related AEs were more common in the sorafenib group and included diarrhea (8%), hand–foot skin reaction (HFSR) (8%), hypertension (2%) and abdominal pain (2%). The rate of patients who discontinued treatment was similar in the two groups (38 and 37%, respectively), but treatment was permanently discontinued due to toxicity in 11% of sorafenib-treated patients versus 5% of placebo patients. In the Asia-Pacific trial, the most frequent grade 3/4 drug-related AEs in the sorafenib group were HFSR (10.7%), diarrhea (6.0%) and fatigue (3.4%) [5]. The most common AEs resulting in dose reductions were HFSR (11.4%) and diarrhea (7.4%), but these AEs were overall manageable and rarely led to discontinuation of treatment.

clinical practice studies

RCTs provide the highest level of evidence for the rigorous design, the application of strict selection criteria for the inclusion of patients, and the precise evaluation of the efficacy and the safety in a well-defined population. However, patients enrolled in RCTs often do not closely represent the clinical practice, due to the necessary absence of potential confounding factors like concomitant diseases or other treatments [7,8]. Observational studies can complement findings from RCTs, as they assess treatment effectiveness in patients encountered in day-to-day clinical practice [8]. Therefore, results from well-designed observational studies can expand upon the outcomes of RCTs, thanks to the observation of the large cohort of patients who present co-morbidities and receive concomitant medications. Furthermore, observational studies can identify clinically important differences among therapeutic options and provide data on drug efficacy and safety over a longer-term follow-up than RCTs.

At present, the results of two real clinical experiences conducted on sorafenib are available: the GIDEON study (Global Investigation of therapeutic DECisions in hepatocellular carcinoma and Of its treatment with sorafeNib), conducted on a very large population of HCC patients in more than 40 countries [6], and the SOFIA (SOraFenib Italian Assessment) study, conducted in Italy [7]. These two studies reported the clinical outcomes of patients on treatments and, particularly, addressed the management of sorafenib-related AEs in daily clinical practice.

the GIDEON study

The GIDEON study, still ongoing, is a global phase IV, international, prospective, open-label, multicentre, non-interventional post-marketing study of patients with advanced-stage HCC receiving sorafenib under real-life conditions [6]. A very large cohort of 3275 patients have been recruited from Europe, Latin America, the USA and the Asia-Pacific regions. The main goal of the study was to evaluate the safety and efficacy of sorafenib in different patient subgroups, especially in subjects with Child-Pugh B cirrhosis, where data were limited. Additional aims of this study were to compile a large database and to analyze potential local, regional and global differences in baseline characteristics, disease etiology, treatment, practice patterns and treatment outcomes. The study completion is expected by 2013.

The second preplanned interim analysis available has been presented at the Annual Congress of the American Association for the Study of Liver Diseases (AASLD) in November 2011 [9]. The interim analysis reported the efficacy and safety data of sorafenib in clinical practice in two subgroups of patients: a group who started the treatment with the standard dose of
800 mg/day and a group who started the treatment with 400 mg/day or other doses.

In total, 1571 patients had valid data for the safety evaluation and 1612 patients for the efficacy evaluation. At baseline, 61% of patients had a Child-Pugh A and 23% a Child-Pugh B cirrhosis, 54% of patients had a BCLC-C and 19% a BCLC-B, 40% of patients had a performance status (PS) 0 and 43% a PS 1 and 55% of patients received a previous locoregional treatment. In most cases (75%), patients initiated sorafenib at the recommended dose of 800 mg/day. The remaining patients received 400 mg/day (22%) or other dosages (3%). The two groups were comparable for the Child-Pugh score, BCLC stage, PS and rate of patients who received a previous surgery or locoregional treatment.

The interim analysis showed a trend toward more evident benefits for sorafenib at the recommended dose, when compared with the lower dose of 400 mg/day. In particular, patients who initiated sorafenib at the dose of 800 mg/day tended to stop treatment later than patients who started sorafenib with a dose of 400 mg/day (12.3 versus 9.7 weeks) and present a longer OS (9.3 versus 7.1 months) and TTP (4.5 versus 3.6 months) [9].

The most commonly reported AEs in both dose groups were diarrhea, HFSR and fatigue, and these AEs were in most cases mild (grade 1/2). No significant differences in the type and the incidence of AEs between the recommended dose group and the 400 mg/day dose group were reported [9]. This analysis suggests that initiating sorafenib treatment at the full recommended dose of 800 mg/day may be associated with some advantages in terms of duration of therapy, OS and TTP versus a 400 mg/day starting dose, without any relevant worsening of the safety profile of the molecule [9].

the SOFIA study
The SOFIA study was a smaller multicenter, investigator-driven, observational, non-interventional study conducted in six referral Italian centers with the aim to assess sorafenib safety in clinical practice and to evaluate treatment efficacy in terms of OS, early radiologic response and TTP [7]. In total, 296 consecutive patients (88% Child-Pugh A) with advanced-stage HCC (75%) or intermediate-stage HCC and/or not eligible to or who failed ablative therapies (25%) were enrolled. At the initiation of therapy, sorafenib was administered at dose of 800 mg/day in all patients and treatment was down-dosed or interrupted according to the drug label. Grade 3/4 AEs, deterioration of liver function and radiologic or symptomatic progression of HCC were criteria for dose modification or interruption.

The median duration of treatment was 3.8 months, 90 patients (30%) were treated for more than 6 months and 41 patients (14%) were treated for more than 12 months.

The overall incidence of AEs was 91%, and 45% of them were of grade 3/4. Fatigue (25%), HFSR (9%), arterial hypertension (7%), weight loss (6%) and diarrhea (6%) were the most frequent severe AEs.

Treatment was down-dosed in 161 (54%) patients (in 133 because of AEs and in 28 because of liver function worsening) and was permanently discontinued in 233 (79%) patients (40% for AEs and 60% for severe liver function deterioration or HCC progression).

Regarding the effectiveness of sorafenib, the SOFIA study reported a median OS of 10.5 months, a finding consistent with the survival observed in patients treated with sorafenib [3, 6]. The OS reported in the 74 BCLC-B patients was longer than that observed in the 222 BCLC-C patients (20.6 versus 8.4 months; P < 0.0001). OS was 21.6 months in the 77 patients treated for more than 70% of the time with a half dose versus 9.6 months in the 219 patients treated for more than 70% of the time with a full dose (P = 0.0006).

The results reported by the SOFIA study, although retrieved in a smaller population respect the global GIDEON study, confirm the safety and effectiveness of sorafenib in a real-life scenario, even with a reduced dose. The effectiveness of half-dose sorafenib might have some implications for clinical practice, especially for a tailored therapy in patients who do not tolerate full-dose treatment. However, the authors of the SOFIA study pointed out the existence of two main caveats for this study, namely the post hoc nature of the analysis of the effectiveness of full- versus half-dose sorafenib and the lack of stratification before treatment of survival predictors.

management of AEs in clinical practice
Sorafenib appeared well-tolerated in both the GIDEON and the SOFIA studies [6, 7]; however, in both real-life studies, a number of AEs were reported. The underlying liver disease and, in particular, its complications can negatively affect the tolerability and the efficacy of sorafenib in HCC patients.

The most frequent sorafenib-associated AEs are dermatological lesions, cancer-related fatigue and diarrhea. Conversely, treatment-related liver AEs are overall less frequently reported. Grade 3/4 liver dysfunction has been reported in the same percentage (3%) of patients assuming sorafenib or placebo in the supplementary appendices of the SHARP trial [4] and in 1% of patients taking sorafenib in the GIDEON study [10].

dermatological lesions
Dermatological lesions, mainly represented by HFSR, are one of the most frequent AEs associated with multi-kinase inhibitors and represent a major cause of dose reductions and/or treatment interruptions. In addition, they determine relevant physical and psychological distress to patients. The early detection of symptoms is crucial and, when possible, preventive measures should be taken in patients with high risk of developing HFSR. Although not tested in clinical trials, some preventive measures are believed to reduce pain, risk of infection and patient discomfort and to avoid the dose reduction or discontinuation of sorafenib (Table 1) [11]. Once established, HFSR can be relieved by symptomatic treatment (Table 1) [11]. As shown in the SHARP study and according to clinical experience, treatment of HFSR may require sorafenib dose reduction or interruption according to the severity of the skin lesions (Table 2) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021923s012lbl.pdf).
Cancer-related fatigue is a multifactorial condition that affects cancer patients before the beginning of therapy, increases during therapy and can persist thereafter. In patients with HCC, the fatigue can be related to liver cirrhosis and cancer. Moreover, treatment-related fatigue may require dose modifications or treatment interruptions. However, the management strategies for preventing or reducing the severity of targeted therapy-related fatigue described in literature were experience-based rather than evidence-based.

### Table 1. Techniques identified from the literature for preventing and managing HFSR (reproduced from Edmonds et al. [11], with permission)

<table>
<thead>
<tr>
<th>Prophylactic management</th>
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<tbody>
<tr>
<td>Advise patients to have a manicure and pedicure before and during treatment</td>
</tr>
<tr>
<td>Stress the importance of identifying and reporting skin reactions</td>
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<tr>
<td>Advise patients on the frequent prophylactic use of over-the-counter skin emollients</td>
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<tr>
<td>Avoid constrictive footwear and excessive friction</td>
</tr>
<tr>
<td>Wear thick cotton gloves/socks and shoes with padded insoles</td>
</tr>
<tr>
<td>Symptomatic management</td>
</tr>
<tr>
<td>Treatment with topical urea singly or plus tazarotene/fluorouracil results in ≥2 grade improvement in the majority of patients</td>
</tr>
<tr>
<td>Avoid hot water</td>
</tr>
<tr>
<td>Use thick, intense moisturizing products and anti-itch products (containing 1% dimethicone, 0.1% camphor). Apply creams at least five times a day and any time after hands or feet get wet</td>
</tr>
<tr>
<td>Dose interruptions at grade 3/4 may be necessary</td>
</tr>
<tr>
<td>During treatment advise patients to wear comfortable shoes, use shock absorbers for pressure points and relieve pressure on the affected parts</td>
</tr>
<tr>
<td>Advise patients to avoid excessive sport (e.g. avoid pressure and friction to the affected areas)</td>
</tr>
<tr>
<td>Advise patients to take cooling hand or foot baths</td>
</tr>
<tr>
<td>Advise patients to wear two pairs of cotton socks, a thick padded pair as the inner layer and a thinner pair as the outer layer and wear soft shoes and padded insoles</td>
</tr>
<tr>
<td>Advise patients to wear gloves at night after applying urea- and/or salicylate-containing creams</td>
</tr>
<tr>
<td>Use non-fragranced products and shower gels instead of soaps</td>
</tr>
<tr>
<td>Light/topical analgesics may be prescribed for pain relief</td>
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### Table 2. Dose modifications for skin toxicity (available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021923s012lbl.pdf).

<table>
<thead>
<tr>
<th>Skin toxicity grade</th>
<th>Occurrence</th>
<th>Suggested dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient’s normal activities</td>
<td>Any occurrence</td>
<td>Continue treatment with NEXAVAR and consider topical therapy for symptomatic relief</td>
</tr>
<tr>
<td>Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient’s normal activities</td>
<td>First occurrence</td>
<td>Continue treatment with NEXAVAR and consider topical therapy for symptomatic relief. If no improvement within 7 days, see below</td>
</tr>
<tr>
<td></td>
<td>No improvement within 7 days or second or third occurrence</td>
<td>Interrupt NEXAVAR treatment until toxicity resolves to grade 0–1 When resuming treatment, decrease NEXAVAR dose by one dose level (400 mg daily or 400 mg every other day)</td>
</tr>
<tr>
<td></td>
<td>Fourth occurrence</td>
<td>Discontinue NEXAVAR treatment</td>
</tr>
<tr>
<td>Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet or severe discomfort that causes the patient to be unable to work or perform activities of daily living</td>
<td>First or second occurrence</td>
<td>Interrupt NEXAVAR treatment until toxicity resolves to grade 0–1 When resuming treatment, decrease NEXAVAR dose by one dose level (400 mg daily or 400 mg every other day)</td>
</tr>
<tr>
<td></td>
<td>Third occurrence</td>
<td>Discontinue NEXAVAR treatment</td>
</tr>
</tbody>
</table>

### Cancer-related fatigue

Cancer-related fatigue is a multifactorial condition that affects cancer patients before the beginning of therapy, increases during therapy and can persist thereafter. In patients with HCC, the fatigue can be related to liver cirrhosis and cancer. Moreover, treatment-related fatigue may require dose modifications or treatment interruptions. However, the management strategies for preventing or reducing the severity of targeted therapy-related fatigue described in literature were experience-based rather than evidence-based.

Some of the recommendations for managing fatigue are based on ruling out or treating hypothyroidism, anemia, depression and malnutrition. In addition to a possible benefit for treatment-related fatigue, prevention of malnutrition is particularly important in cirrhotic patients with HCC during sorafenib treatment, since reducing the risk of hypoalbuminaemia and muscle catabolism prevents the appearance of ascites and encephalopathy. Treatment-free intervals and dose reductions may be considered in case of grade 3/4 fatigue.
diarrhea
It is important to educate patients on the occurrence and presentation of diarrhea during sorafenib therapy, since an early recognition of this AE may prevent severe diarrhea and its complications.

Sorafenib-induced diarrhea is usually treated with loperamide, based on experience and analogy with chemotherapy-induced diarrhea rather than on clinical studies. In addition to general measures to improve diarrhea such as a low-fiber diet and increased liquid assumption, in cirrhotic patients, lactulose should be stopped, if taken. Dehydration and electrolyte disturbances must be rapidly corrected to avoid the appearance of ascites, renal insufficiency and encephalopathy in cirrhotic patients. For grade 2–4 diarrhea, treatment-free intervals and/or dose reductions may be necessary [4].

Hollebecque et al. [13] reported the results of a prospective experience on sorafenib efficacy in 120 patients with advanced HCC and 20 of them had Child-Pugh B cirrhosis. The OS in the cohort was 11.1 months with a significantly longer median survival in Child-Pugh A patients than Child-Pugh B patients (13 versus 4.5 months, \( P = 0.0008 \)). However, statistical analysis did not disclose any correlation among Child-Pugh class and TTP, frequency of AEs and discontinuation of sorafenib. The authors suggested that the shorter OS in Child-Pugh B patients could be attributed, at least in part, to poorer liver function.

Similar results were reported by Kim et al. [16] in an Asian cohort of 225 patients with HCC evaluated according to Child-Pugh score (68 with Child-Pugh B). The disease control rate was higher in patients with Child-Pugh A than Child-Pugh B cirrhosis, but did not differ among patients with Child-Pugh score B7 and those with Child-Pugh score B8 or B9. No differences in the rate of grade 3/4 AEs were reported among patients with different Child-Pugh classes. The authors concluded that patients with Child-Pugh score B7 can be included in future clinical trials, in order to collect further and robust evidence on the treatment with sorafenib in this group of patients. Similar figures on the tolerability were observed by Ozene et al. [17] in a small cohort of 50 patients with HCC that included 17 patients with a Child-Pugh B cirrhosis.

In the second interim analysis of the GIDEON study, 368 (23%) of 1571 analyzed patients were classified in Child-Pugh B class and 35 patients (2%) in Child-Pugh C class [18]. Overall, sorafenib demonstrated a comparable safety profile in Child-Pugh A and Child-Pugh B patients (Table 3), with the exception of a greater percentage of Child-Pugh B patients who discontinued sorafenib for AEs (38 versus 24%) or who experienced severe AEs (15 versus 8%). In addition, on-treatment deaths were more frequent in Child-Pugh B patients (34 versus 16%), but this finding is likely to be related to severity of liver disease in Child-Pugh B patients.

Pressiani et al. [19] have reported the clinical outcomes obtained in a population of 300 consecutive patients with sorafenib in patients with Child-Pugh B cirrhosis

It is widely accepted that the natural history of HCC is markedly related to liver function, with a median survival of untreated HCC \( \sim 2.5 \) times lower in patients with Child-Pugh B cirrhosis versus those with Child-Pugh A cirrhosis [12]. Moreover, liver function may alter the safety of systemic treatments, thereby diminishing the clinical benefit of treated cirrhotic patients [13].

In the SHARP and the Asia-Pacific trials, more than 95% of patients were classified as having Child-Pugh A cirrhosis [4, 5] and the potential benefits of sorafenib in Child-Pugh B patients could not be investigated in those trials. On these bases, a deeper evaluation of the clinical outcomes of Child-Pugh B patients with advanced HCC treated with sorafenib has been advocated [14, 15].

Four main studies reported data on patients with Child-Pugh B cirrhosis [12, 16–19].

### Table 3. Overview of treatment-emergent safety data by Child-Pugh status in the second interim analysis of the GIDEON study [16]

<table>
<thead>
<tr>
<th>% of Total (n = 1571)</th>
<th>Child-Pugh A (&lt;7) (n = 957)</th>
<th>Child-Pugh B (7–9) (n = 367)</th>
<th>Child-Pugh C (&gt;9) (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs (all grades)</td>
<td>83</td>
<td>82</td>
<td>89</td>
</tr>
<tr>
<td>Drug-related AEs (all grades)</td>
<td>64</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>AEs (grade 3/4)</td>
<td>30</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Drug-related AEs (grade 3/4)</td>
<td>23</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>SAEsb</td>
<td>37</td>
<td>29</td>
<td>56</td>
</tr>
<tr>
<td>Drug-related SAEsc</td>
<td>9</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>AEs resulting in permanent discontinuation of sorafenibd</td>
<td>28</td>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>Deathsb</td>
<td>22</td>
<td>16</td>
<td>34</td>
</tr>
</tbody>
</table>

|a| Data at study entry.  
|b| Child-Pugh status missing or not evaluable for 56 patients.  
|c| A SAE is defined as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening, hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect and medically important event.  
|d| Any AE.  
|e| Treatment-emergent deaths occurring up to 30 days after last sorafenib dose. AEs, adverse events; SAEs, serious adverse events.
either Child-Pugh A or Child-Pugh B treated with sorafenib. For patients with Child-Pugh A versus B status, progression free survival was 4.3 versus 2.1 months, TTP was 4.2 versus 3.8 months and OS was 10.0 versus 3.8 months, and the AE profile was similar in the two groups: these findings suggest that patients with Child-Pugh B liver function can tolerate treatment and may still benefit from sorafenib [19]. As a whole, data collected on the safety of sorafenib in Child-Pugh B patients seem to suggest the potential feasibility of this treatment in this population, taken into account that poorer clinical outcomes are to be expected due to worse liver function. However, more robust studies are necessary before confirm or discard the use of sorafenib in this subset of patients.

dose escalation/reduction with sorafenib

The potential efficacy of sorafenib dose escalation has been reported by the research group of Santoro [20]. In this phase II, randomized trial, 101 patients (selected from the previously described population of 300 patients [19]) with progression of HCC after sorafenib treatment at standard dose (400 mg bid) were assigned to increased-dose sorafenib (600 mg bid) plus best supportive care or to best supportive care alone. Overall, increased-dose sorafenib showed a trend toward an improved progression-free survival (HR: 0.67, 95% CI: 0.43–1.06, P = 0.089), TTP (HR: 0.59, 95% CI: 0.33–1.05, P = 0.070) and OS (HR: 0.71; 95% CI: 0.47–1.08, P = 0.107) versus best supportive care alone, although the results did not reach statistical significance. No differences in the safety profile and in the incidence of AEs were reported between the two arms. According to these results, the authors suggested that increased or standard dose of sorafenib beyond progression should be tested in larger phase II–III trials.

In another preliminary experience on 42 HCC patients, conducted in a clinical-practice setting, Sacco et al. [21] have applied a ‘rump-up’ dosing strategy, which consisted in the administration of sorafenib at a starting dose of 400 mg/day; in the absence of toxicity, this dosage was gradually increased to 800 mg/day after 3 weeks. Despite the number of patients treated with this strategy was limited (n = 13), the clinical outcomes observed following the rump-up administration of sorafenib were comparable with those reported in the overall population, and no grade 3/4 AEs were observed in the rump-up group.

search for biomarkers of response

Biomarkers able to predict patient prognosis or response to therapy may represent a major advance toward a more personalized, tailored treatment in cancer patients [22]. However, HCC is a highly heterogeneous disease and the identification of biomarkers is complex and has been poorly explored so far [22]. The recent EASL-EORTC Clinical Practice Guidelines pointed out that further research in this field is necessary [2]. Llovet et al. [23] have recently reported the results of the analysis on 10 plasma biomarkers potentially implicated in the pathogenesis of HCC and in the response to sorafenib treatment conducted in 491 patients at baseline and in 305 after 12 weeks of treatment in the SHARP trial. The results documented a significant correlation between two angiogenesis biomarkers, Ang2 and VEGF, and survival. In fact, the median survival of patients assigned to sorafenib with low- and high-baseline Ang2 concentrations was 14.1 and 6.3 months, respectively, and the median survival of patients with low- and high-baseline VEGF concentrations was 10.6 and 6.2 months, respectively. None of the plasma biomarkers tested reached statistical significance in predicting response to sorafenib, although a trend toward an enhanced survival benefit from sorafenib was observed in patients with high s-c-KIT or low hepatocyte growth factor concentrations at baseline.

The lack of significant predictors of response to sorafenib was confirmed in another subanalysis of the SHARP trial published by Raoul et al. [24]. In this post hoc analysis, 602 patients were grouped by baseline concentrations of alanine aminotransferase/aspartate aminotransferase, α-fetoprotein (AFP) and bilirubin. Overall, all these markers were associated with a shorter OS in both the sorafenib and the placebo arm, and no differences in the safety profiles were observed among patients with normal versus elevated concentrations of any of these biomarkers. These findings suggest that sorafenib is safe and effective regardless of baseline alanine aminotransferase/aspartate aminotransferase, AFP or bilirubin concentrations. A similar subset analysis of the Asia-Pacific trial reached the same result [25].

Personeni et al. [26] have investigated the prognostic usefulness of a serum AFP response, defined as a >20% decrease in AFP during 8 weeks of treatment with sorafenib and compared it with the RECIST criteria. In total, 32 of 85 patients (37.6%) were classified as AFP responders, whereas 58 of 82 patients (70.7%) achieved disease control according to the RECIST criteria. Statistical analysis showed that only AFP response (HR = 0.52; P = 0.009) and Cancer of the Liver Italian Program dichotomized stage (HR = 0.42; P = 0.002) are prognostic factors of survival. According to these findings, authors concluded that the assessment of AFP response may be considered as an alternative to RECIST to monitor sorafenib activity in HCC [26].

conclusions

Sorafenib was the first agent that demonstrated a benefit on survival of patients with advanced HCC and is currently the standard treatment of this disease. Despite the robustness of the results collected in randomized clinical trials, which represent the basis for the evaluation of efficacy and safety for each new drug, the importance of observational studies and clinical practice experience is increasing in the current scientific debate. In fact, observational studies offer a chance to unravel the safety and toxicity of a given drug in clinical practice and are able to expand upon the findings of phase III trials.

The main clinical practice studies conducted so far, namely the GIDEON and SOFIA studies, confirm the benefit of
sorafenib on OS, which was previously observed in RCTs. The safety profile of sorafenib was similar, although a slightly higher rate of AEs and need for dose reduction was reported when compared with the landmark phase III trials. However, this finding may be attributed, at least in part, to the presence of multiple concomitant conditions in patients included in the observational experiences.

In addition, a proper management of sorafenib-associated AEs reduces the risk of dose reductions and/or treatment interruptions, thus optimizing the clinical benefits associated with this molecule.

The results of the global GIDEON study, albeit still preliminary, suggest that whenever possible, full dose of sorafenib should be maintained. However, if severe AEs occur, dose could be reduced without decreasing effectiveness, as documented in the SOFIA study. It will be of great interest to identify the clinical, laboratory and genetic characteristics of these patients.

New indications and treatment modalities of sorafenib are being explored by current research. In particular, the effectiveness and safety of this molecule in Child-Pugh B patients deserves, in our opinion, further investigations. The results collected show poorer outcomes in patients with Child-Pugh B cirrhosis treated with sorafenib, when compared with patients with Child-Pugh A cirrhosis. However, this finding can be likely attributed to a more severe liver dysfunction and more compromised conditions of these patients and not to an effect of the drug itself. Noteworthy, available evidence is consistent in showing that the safety profile of sorafenib is comparable in Child-Pugh A and Child-Pugh B patients. An alternative treatment approach could be the administration of increased-dose sorafenib in patients with HCC progression, but this therapeutic scheme has been investigated only in one trial, and therefore, we believe that additional research on its efficacy and safety is advisable.

Lastly, the results of subset analyses of the registrative trials consistently show that the efficacy and safety of sorafenib are maintained irrespective of several biochemical parameters observed at baseline. This result supports the use of sorafenib in different classes of liver disease severity. However, we think that, in the future, the identification of biomarkers predicting prognosis of HCC and/or response to sorafenib or other treatments for this condition may facilitate a more personalized treatment of oncological patients. Further investigation on the potential use of sorafenib in the adjuvant setting is ongoing (the STORM study; NCT00692770), and it will provide new information on the use of sorafenib after surgical resection or local ablation.

**funding**

Editorial assistance was provided by Luca Giacomelli, PhD, on behalf of inScience Communication, Springer Healthcare; this assistance was funded by Bayer Italy.

**disclosure**

CV has received research funding from Bayer. Other authors declare no conflict of interest directly relevant to this paper.

**references**

cancer (HCC) with disease progression on prior sorafenib treatment [abstract].
J Clin Oncol 2011; 29(suppl): abstr 4115.

advanced-stage hepatocellular carcinoma: what can we learn from routine

548–552.

Plasma biomarkers as predictors of outcome in patients with advanced

24. Raoul JL, Bruix J, Greten TF et al. Relationship between baseline hepatic status
and outcome, and effect of sorafenib on liver function: SHARP trial subanalyses.

25. Cheng AL, Guan Z, Chen Z et al. Efficacy and safety of sorafenib in patients with
advanced hepatocellular carcinoma according to baseline status: Subset analyses
of the phase III Sorafenib Asia-Pacific trial. Eur J Cancer 2012; 48(10):
1452–1465.

response in patients treated with sorafenib for advanced hepatocellular