Treatment of Hepatocellular Carcinoma with Sorafenib – Focus on Special Populations and Adverse Event Management

Therapie des hepatozellulären Karzinoms – Fokus auf besondere Indikationen und Management von Nebenwirkungen

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Zusammenfassung

Sorafenib, ein Tyrosinkinaseinhibitor mit antiproliferativer und antiangiogenetischer Wirkung, ist derzeit die einzige zugelassene Substanz in der Therapie von Patienten mit fortgeschrittenem hepatozellulären Karzinom. Es hemmt multiple Rezeptortyrosinkinasen, einschließlich dem VEGFR-2, dem PDGFR, dem c-Kit-Rezeptor und B-RAF. In den vergangenen 4 Jahren konnten umfangreiche Erfahrungen in dem Einsatz dieser Substanz in diesen Indikationen gewonnen werden. In dieser Übersicht diskutieren die Autoren die derzeitigen Erkenntnisse über den Einsatz von Sorafenib bei speziellen Indikationen, bspw. bei Patienten mit eingeschränkter Leberfunktion, Patienten nach Lebertransplantation etc. Zudem werden die häufigsten Nebenwirkungen und das Management im Detail erläutert. Schließlich soll diese Übersicht auch einen Überblick über weitere experimentelle Indikationen, wie bspw. Sorafenib im Zusammenhang mit der Chemoembolisation oder anderen zielgerichteten Substanzen, geben.

Abstract

Sorafenib, a receptor tyrosine kinase-inhibitor with anti-proliferative and anti-angiogenic activity, is currently the only approved systemic treatment for patients with hepatocellular carcinoma. It inhibits downstream signaling of VEGFR-2, PDGFR, c-Kit receptors and BRAF. Over the last four years comprehensive experience with sorafenib in this indication has been accumulated. In this review we discuss the current data on the use of sorafenib in patients with advanced HCC including special patient populations such as patients with impaired liver function, patients after transplantation, and others. The most frequent side-effects and practical tips on how to manage them are discussed in detail. In addition, we summarize the current experimental data on the use of sorafenib in combination treatment, e. g., together with transarterial chemoembolisation or other targeted agents.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide with an estimated annual incidence of more than 600 000 new patients. In advanced stage the treatment options are limited and the prognosis is poor [1]. Sorafenib is a receptor tyrosine kinase inhibitor (RTKI) with activity against the VEGFR-2, PDGFR and c-Kit receptors and additional activity against BRAF, all of which are involved in the pathogenesis of HCC [2]. Treatment with sorafenib has been shown to improve median survival as well as median time to progression in patients with advanced HCC [3, 4]. In this article we review the current knowledge on the use of sorafenib in patients with HCC with a focus on specific patient populations including patients with impaired liver function, renal insufficiency, and HIV infection. Furthermore, current experience with dosing strategies, side-effect management, determination of progression and combination of sorafenib with other treatment modalities are reviewed.

Indications for Sorafenib Treatment

Although no consented and generally accepted guidelines exist for the treatment of HCC, guidelines from the European (EASL [5]), American (AASLD [6]), and Asian-Pacific (APASL [7]) societies are available. An update of the EASL guideline and a German guideline are expected in 2012. Sorafenib usually is offered to patients who have

progressed beyond a stage in which curative treatment can be expected. However, it is unclear whether it should be reserved for those patients who have no option for local treatment due to extensive tumor burden or vascular invasion [Barcelona Clinic liver cancer (BCLC) stage C] or has a place in treating patients with advanced tumors still accessible for local therapies such as TACE (BCLC stage B). The published data are mainly based on the experience in patients with BCLC stage C. The SHARP trial included 82 % of patients with BCLC stage C and only 18 % with stage B, the phase III Asia-Pacific trial included more than 95 % of patients with BCLC stage C [3, 4]. In a subgroup analysis from the SHARP trial regarding the outcome of patients with BCLC stage B, the effect of sorafenib was more pronounced in patients with disease restricted to the liver, arguing for efficiency of sorafenib in patients with less extensive disease [8]. Likewise, the Asia-Pacific trial showed no survival benefit for patients with extrahepatic disease [3].

Nevertheless, insufficient data exist to recommend treatment of patients in BCLC stage B with sorafenib alone outside clinical studies, since locoregional treatment is the standard of care in BCLC stage B. Whether sorafenib treatment in combination with locoregional therapy is indicated in patients with BCLC stage B will be discussed in detail below.

Dosing of sorafenib

Based on the two pivotal trials, the target dose of sorafenib is 400 mg twice daily. Outside clinical trials the side-effect profile of sorafenib might cause both incompliance and early termination of treatment. Dose titration using a step-up approach, e. g., starting with 200 mg once or twice daily with a dose increase if the drug is tolerated well after 2 to 4 weeks to a total daily dose of 600 – 800 mg may be an option for selected patients [9]. Experience from the observational GIDEON study suggests that hepatologists in different regions of the world tend to start with 400 mg sorafenib twice daily, whereas oncologists more often use the step-up approach [10]. If side effects occur, dose reductions should be considered, and gradual re-escalation to the maximum tolerated dose is possible after cessation of the side effect.

Determination of progression

The evaluation of the treatment response in patients with HCC using the established response evaluation criteria in solid tumors (RECIST), which rely on the size measurement of the tumor, have yielded discouraging results for the past years [11]. With the advent of molecular targeted therapies it became clear that not only tumor shrinkage but also changes in vascularity indicate a response in solid tumors. The first tumor entity for which a reduction in the enhancement as a surrogate marker for a decrease in the vascularization was established as a response criterion under treatment was gastrointestinal stromal tumor [12].

The original RECIST criteria implemented in 2000 were widely adapted to determine tumor responses to treatment in solid tumors [13]. They were revised in 2009 to accommodate new knowledge from clinical trials and restricted the maximum number of measured lesions to five and to two per organ [14]. In addition, pathologically enlarged lymph nodes were incorporated in the group of lesions that can be included. However, the revised RECIST criteria still do not take into account changes to the morphology of lesions not accompanied by changes in the size. This fact was already acknowledged by an EASL conference in 2000, leading to the recommendation to use modified criteria for the definition of response to treatment in HCC by measuring only the viable tumor area as determined by contrast enhancement in the arterial phase of CT or MRI scans [5]. In a second attempt to implement the new criteria, an AASLD-JNCI consortium proposed the modified RECIST criteria for HCC (mRECIST) [11, 15]. The mRECIST for HCC criteria include changes in tumor viability as a marker of response. A partial response is defined as a 30 % decrease in the sum of diameters of viable target lesions, taking as reference the baseline sum of the diameters of target lesions. This approach relies on the accurate radiological interpretation and bears some risk for inconclusive interpretation, e. g., when the contrast enhancement of the lesion is not homogeneous. Although it is widely acknowledged that viability of the tumor as determined by its arterial perfusion is a crucial characteristic of a tumor lesion, the mRECIST for HCC criteria have to be validated in prospective trials. The EASL criteria proved valuable in a recent prospective trial of combination of doxorubicin-eluting bead (DEB)-TACE with sorafenib [16].

Since no single agent has proven efficacy in the second-line treatment of HCC, inclusion of patients in clinical studies should be encouraged whenever possible. However, in practice poor liver function or performance status often prohibit further treatment after progression.

Sorafenib in Special Patient Populations

Treatment of patients with non-hepatocellular primary liver tumors

Fibrolamellar carcinoma typically develops in non-cirrhotic livers in children or young adults. Aggressive surgical treatment offers the only chance of curative treatment. No studies have evaluated the effect of sorafenib in fibrolamellar carcinoma. Anecdotal reports suggest that fibrolamellar carcinoma may not respond to sorafenib [17].

The susceptibility of cholangiocarcinoma cells to sorafenib was demonstrated in vitro [18, 19]. The first published phase II study evaluating sorafenib in 46 patients with advanced cholangiocarcinoma demonstrated an objective response rate of 2 % and a disease control rate of 32.6 % after 12 weeks of treatment [20].

No data regarding the efficacy of sorafenib in undifferentiated carcinoma of the liver exist. This type of liver tumor is characterized by histology that comprises both aspects of hepatocellular carcinoma and cholangiocarcinoma without clear differentiation towards either type. At present, treatment of tumor entities other than HCC cannot be recommended outside of clinical studies.

Treatment of patients with impaired liver function

Liver function is a major predictor of survival of patients with HCC. No systematic evaluation of patients with advanced cirrhosis treated with sorafenib was undertaken so far. Both pivotal studies excluded patients with CP-B cirrhosis, and very few of these patients were included in these studies despite this exclusion criteria. If patients with CP-B cirrhosis were allowed on study, ascites, encephalopathy, and coagulation disorders were usually exclusion criteria, limiting access of CP-B patients to those with a score of 7. The phase II study by Abou-Alfa [21] included 38 CP-B patients. Sorafenib was slightly slower metabolized in CP-B than in CP-A patients, with higher AUC and C_{max} values. Differences in outcome and side effects between these two groups were not reported in this study. A phase I study from Japan reported plasma levels from 14 CP-B and 13 CP-A patients treated with different doses (200 mg or 400 mg twice

daily) of sorafenib. In this study, AUC and C_{max} values were slightly lower in CP-B than in CP-A patients, although this difference was not considered clinically relevant [22]. Adverse events were generally more frequent in the higher dose group but were not related to CP stage. A phase II study from Asia included 36 CP-A, 13 CP-B, and 2 CP-C patients [23]. The CP stage was not predictive of the outcome in this study. Grade 3 or 4 hematological toxicity was more frequent in patients with CP-B or CP-C than in patients with CP-A (33 vs. 17 %). Likewise, deterioration of liver function occurred numerically more frequently in CP-B and CP-C patients than in CP-A patients (73 vs. 56 %). In contrast, non-hematological toxicities occurred at similar levels (47 %) in both groups. In a cohort-study Wörns et al. reported 15 patients with no apparent cirrhosis or CP-A, 15 patients with CP-B, and 4 patients with CP-C [24]. Deterioration of liver function was significantly more likely in patients with CP-C (75 %) or CP-B (73 %) cirrhosis than in patients with CP-A cirrhosis (33 %). Other toxicities were not more frequent in patients with impaired liver function, although the small number of patients with CP-C cirrhosis precluded a meaningful statistical analysis. However, the discontinuation rate in CP-C patients was 100 % compared to 53 % and 60 % in CP-A and CP-B patients, strongly argueing against the treatment of CP-C cirrhosis patients with sorafenib.

Ozenne et al. evaluated 17 patients with CP-B cirrhosis and 33 patients with CP-A cirrhosis [25]. Although the overall frequency of adverse events was similar between both groups, CP-B patients discontinued treatment more frequently due to adverse events, leading to a shorter duration of treatment (1.8 vs. 5 months). CP-B patients also had a lower median survival than CP-A patients (2 vs. 8.9 months). Pinter et al. reported a cohort study including 26 CP-A patients, 23 CP-B patients, and 10 CP-C patients who were treated with sorafenib [26]. Median survival was 8.3 months for CP-A patients, 4.3 months for CP-B patients, and 1.5 months for CP-C patients. Besides the level of liver function, BCLC stage significantly correlated with survival. Adverse events were not more frequent in patients with more advanced cirrhosis, however, gastrointestinal bleeding, nausea, and vomiting occurred only in CP-B and CP-C patients.

Recent data from the GIDEON trial confirmed that dosing and frequency of side-effects are similar in patients with CP-A or CP-B cirrhosis. However, the main duration of treatment was 14 weeks in CP-A patients and 9 weeks in CP-B patients. In CP-C patients, the duration of treatment was only 4 weeks, underlining that such patients should not be treated with sorafenib [27].

Given the paucity of data and the very limited life expectancy of patients with BCLC stage D disease or CP-C cirrhosis, treatment of these patients with sorafenib is not recommended. In patients with CP-B cirrhosis, an individual decision is warranted, taking into account liver function, BCLC stage, performance status, and patient motivation. Most data from CP-B patients are restricted to patients with a score of 7. Possibly, such patients can be treated in the same way as patients with CP-A cirrhosis. Clinical signs of decompensation such as ascites or encephalopathy should be regarded as strong indicators against treatment. Also, bilirubin levels seem to be a reliable predictor of tolerability. Miller et al. demonstrated that dose-limiting toxicity occurred in 2/2 patients on 200 mg sorafenib every other day and 3/6 patients on 200 mg every 3 days when bilirubin excessed 3 × ULN [28]. Therefore hyperbilirubinemia excessing 3 × ULN should be considered as a contraindication for sorafenib.

Sorafenib in patients with renal insufficiency

Little is known about the treatment of HCC patients with renal insufficiency, but an extensive body of literature exists regarding patients with renal cell carcinoma (RCC) treated with sorafenib who have renal insufficiency or undergo hemodialysis. Since sorafenib is extensively metabolized by the liver and excreted in bile, renal insufficiency is not expected to lead to accumulation of the drug. Indeed, two studies confirmed that plasma levels of sorafenib or its metabolites do not increase in patients with renal insufficiency [28, 29].

Parsa et al. retrospectively analyzed 32 patients with (n = 14) or without (n = 18) renal insufficiency defined by a creatinine clearance below 60 mL/min. They reported higher incidences of diarrhea and hand-foot skin reaction in patients with renal insufficiency although the frequency of overall toxicity was not statistically different between the two groups. However, dose reductions and interruptions were more frequently required in patients with impaired renal function [30]. Khan et al. retrospectively analyzed 39 patients treated with sorafenib (n = 15) or sunitinib (n = 24) who either had renal insufficiency at start of treatment (n = 21) or developed renal insufficiency during the course of treatment (n = 18). Dose reduction was more likely due to side effects than to an increase in creatinine levels and the authors concluded that both drugs could be safely administered in patients with renal insufficiency provided that kidney function is closely monitored [31].

Several case reports on sorafenib treatment of RCC patients undergoing hemodialysis were published. In most cases, treatment was initiated with a reduced dose of 400 mg daily and the dose was increased to 400 mg twice daily if the drug was well tolerated. Indeed some of the patients on hemodialysis tolerated the full dose although dose reductions due to side effects occurred frequently [32 – 36].

The comprehensive approach by Miller et al. suggests that RCC patients with mild renal insufficiency (creatinine clearance above 40 mL/min) tolerate treatment with sorafenib 400 mg twice daily whereas dose reduction is required for patients with more severely compromised kidney function. Patients on hemodialysis in this study (n = 15) received 200 mg every other day, 200 mg daily, or 200 mg twice daily. Dose limiting toxicity occurred in 3 of 5 patients on 200 mg twice daily but in none of the patients in the other groups [28], leading to the authors' recommendation of 200 mg daily as the preferred starting dose in hemodialysis patients. A case report also suggests that sorafenib can be safely applied after kidney transplantation [37].

In clinical practice, HCC patients with mildly impaired renal function might therefore be started on full dose sorafenib with close monitoring for side effects and adequate dose reduction once toxicity occurs. HCC patients with more severely compromised renal function (creatinine clearance below 40 mL/min) should probably be started on a reduced dose (400 mg daily) and escalated after approximately two weeks if treatment is tolerated.

Sorafenib in patients with chronic viral hepatitis

Subgroup analyses from the SHARP trial, the phase III Asia-pacific trial of sorafenib, and other smaller trials from Asia and Europe have demonstrated that patients infected with HBV or HCV [3, 4, 23, 38, 39] benefit from treatment with sorafenib. In patients with HBV infection, suppression of HBV replication with nucleoside/nucleotide analogues is usually warranted, and no interactions of the commonly prescribed antivirals, which are eliminated renally, are of relevance. In general, treatment with a drug

with a high resistance barrier is recommended in patients with cirrhosis and active HBV infection. Therefore tenofovir and entecavir are most likely to be combined with sorafenib in this setting. Since immunosuppression observed with chemotherapy may lead to reactivation of inactive HBV infection especially in inactive HBsAg carriers, prophylactic treatment of such patients is also recommended before initiation of sorafenib treatment.

In the case of HCV infection, treatment of the underlying viral infection is usually no longer warranted if the HCC treatment is not potentially curative. Therefore, pegylated interferon/ribavirin will generally not be co-administered with sorafenib. Although pilot studies have evaluated the value of interferon-alpha as a treatment for advanced HCC alone [40] or in combination with 5-fluorouracil [41], convincing data are lacking. In principle, combinations of interferon-alpha/ribavirin and sorafenib could occur in a setting of adjuvant sorafenib treatment in a patient after curative resection of HCC also suffering from HCV infection. Although this approach would clearly be experimental, no significant drug interactions would be expected since both interferon-alpha and ribavirin do not interfere with cytochrome P450 enzyme metabolism.

Sorafenib in patients with HIV infection

Given the increased life expectancy of HIV-infected patients and the frequent co-infection with HBV or HCV in this group, the incidence of HCC in this population is likely to increase over the next years. In principle, treatment of these patients should not differ from treatment of HIV-negative patients with HCC. However, comorbidities, especially viral hepatitis, impaired immune function, and medication with anti-retroviral drugs make the treatment of HCC in this group of patients challenging. HBV infection in HIV-infected patients is treated as part of the anti-retroviral regimen, i. e., by including at least one drug with activity against HBV, most frequently tenofovir and/or emtricitabine. HCV infection is more difficult to treat in this patient population. In analogy to HIV-negative patients with HCC there is no indication for HCV treatment if tumor treatment is not curative. When considering therapy with sorafenib, care must be taken to avoid drug interactions as much as possible and to carefully monitor plasma levels of drugs that show significant interactions with sorafenib. For further reference a comprehensive overview of known or expected drug interactions between anti-retroviral drugs and targeted cancer therapies is recommend [42]. To date, only single case reports on the combination of sorafenib with HAART have been published [43, 44].

Sorafenib is metabolized mainly by CYP3A4 and UGT1A9, and therefore, care must be taken in patients treated with drugs that may interfere with these pathways. However, alternative pathways exist that may explain why no changes in plasma levels of sorafenib occur in healthy volunteers concomitantly taking the CYP3A4 inhibitor ketoconazol [45]. Therefore, dose adjustment of sorafenib is generally not necessary in patients taking CYP3A4 inhibitors. In contrast, sorafenib plasma levels declined when the CYP3A4 inducer rifampicin was co-administered, suggesting that the dose of sorafenib should be increased under such circumstances (Bayer, data on file). On the other hand, sorafenib does not seem to induce CYP3A4.

In clinical practice, surveillance of plasma levels of protease inhibitors is recommended in patients treated with sorafenib because all HIV protease inhibitors are metabolized by CYP3A4. Since it is unknown whether sorafenib plasma levels are altered by co-administration of an HIV protease inhibitor, a reduced starting dose of sorafenib (e. g., 400 mg daily) and subsequent escalation to full dose is recommended.

When combined with non-nucleotide reverse transcriptase inhibitors, caution must be taken since efavirenz and nevirapine induce CYP3A4 and may lower plasma levels of sorafenib. Since plasma levels of sorafenib cannot be routinely monitored, these drug combinations should be avoided, if possible. Nucleoside reverse transcriptase inhibitors are not metabolized by CYP3A4 and therefore cause no interactions when combined with sorafenib. Sorafenib inhibits UGT1A1, which metabolizes the integrase inhibitor raltegravir.

In summary, significant drug interactions are relatively unlikely when sorafenib is combined with HAART. The combination of a protease inhibitor and two nucleoside reverse transcriptase inhibitors seems to be of least potential for drug interactions. Plasma levels of the protease inhibitors should be monitored.

Sorafenib as bridging therapy in liver transplant candidates

In most Western countries repeated TACE is the standard bridging therapy in patients awaiting liver transplantation. Based on a Markov model analysis, sorafenib was suggested to be beneficial compared with a no-treatment strategy [46]. However, in allocation systems that priorize patients with HCC, this might not turn out to be cost-efficient. To date, a single retrospective case series of 7 patients has been published, which did not reveal any unexpected safety issues [47].

A prospective, controlled phase II study (HeiLivCa) with TACE and sorafenib as bridging therapy is currently recruting patients and will answer whether sorafenib has a role as bridging therapy. At current, sorafenib should not be used in this setting outside of clinical studies.

Treatment of recurrent HCC after liver transplantation

The prognosis of recurrent HCC after orthotopic liver transplantation is fatal, especially in patients with early recurrence. The critical role of mTOR signaling for hepatocarcinogenesis is documented preclinically [48], and inhibition of the mTOR pathway after liver transplantation for HCC may lead to higher survival rates in some groups of patients [49]. Targeting the Ras pathway with the multikinase inhibitor sorafenib in addition to mTOR inhibition has synergistic effects on reducing tumor growth in xenograft mice [50]. These data back the current rationale to switch patients with recurrent HCC after liver transplantation from calcineurin inhibitors to mTOR inhibitors such as sirolimus or everolimus, and to start sorafenib in addition [51]. Side-effects of sorafenib and mTOR inhibitors overlap (e. g., fatigue, diarrhea, skin toxicity) and therefore can lead to unacceptable toxicity. Dose finding studies for this combination have not been published, and it remains speculative whether side-effects of either drug could be aggravated by the other.

Impressive treatment responses have been reported in single case reports [41, 52]. Nonetheless, side-effects, especially hand-foot skin reactions, seem to be more severe in patients post liver transplantation, and dose adjustment may be necessary in the majority of patients [53, 54]. Therefore, dose titration with sorafenib in this group of fragile patients is mandatory. Larger case series are awaited in the near future.

Table 1 Recent trials assessing sorafenib during and after TACE for advanced HCC.

type of study	author	number of patients	schedule	outcome
retrospective	Sinakos [91]	14	sorafenib added after first TACE	median survival 15 mo
retrospective	Yoo [92]	10	not outlined	significant improvement of median survival for patients with TACE + sorafenib (20.5 mo) versus TACE + chemotherapy (9.8 mo)
retrospective	Martin [93]	30	sorafenib and doxorubicin-loaded beads	median overall survival 12 mo
phase II trial, START trial	Chung [55]	200 planned, 50 evaluable for efficancy	sorafenib and TACE	20/50 did not require more than 2 TACE, 18 achieved CR and 2 had progressive disease, remaining 30 patients had PR or SD
phase II, Socrates trial	Erhardt [56]	44	TACE combined with sorafenib	2 PR, 26 SD, PFS 242 d, OS 356 d
randomized Phase III trial	Kudo [58]	458	sorafenib after successful TACE	TTP 5.4 versus 3.7 months; HR 0.87 (0.7 – 1.09, p = ns)
phase II trial	Pawlik [16]	35	DEB-TACE in combination with sorafenib	100 % disease control rate; 58 % objective response rate (EASL-criteria)
phase II trial	Lencionie [57]	307	DEB-TACE + sorafenib	TTP 5.6 vs. 5.5 month

Sorafenib in Combination with Other Treatment Modalities

Transarterial chemoembolization

Transarterial chemoembolization (TACE) in advanced HCC is considered an effective and safe procedure with a significant improvement of progression-free and overall survival in HCC. Recent studies addressed the role of combination therapy of sorafenib with TACE (**Table 1**). Chung et al. [55] reported a promising disease control rate of 96 % in patients on combination therapy. Moreover, in 20 out of 50 patients, no more than two TACE procedures were necessary to achieve disease control. In 18 of these 20 patients, complete remission according to the EASL criteria was observed, and only 2 patients had progressive disease. The remaining 30 patients experienced partial remission and/or stable disease. The SOCRATES trial enrolled 44 patients, partial remission was observed in two cases, while 26 patients demonstrated stable disease by RECIST criteria. Progression-free and overall survival were 242 and 356 days, respectively [56]. In this study, 39 severe adverse events were observed, grade 3 or 4 adverse events were related to encephalopathy, renal insufficiency, liver abscess, and liver failure, in addition to the effects commonly observed with sorafenib treatment. Pawlik et al. [16] investigated the combination of DEB-TACE with sorafenib. Using the EASL criteria, a disease control rate of 100 % and an objective response rate of 58 % were achieved. A mean number of 2 TACE procedures were performed. At least one grade 3 or 4 toxicity occurred in the vast majority of patients during the first cycle (91 %). Although disease control rates seem promising in these trials, it is yet unclear, whether they will translate into better overall survival.

Based on these data, a prospective phase II trial (SPACE) was conducted in which more than 300 patients with advanced HCC were randomized to sorafenib or placebo during and after DEB-TACE [57]. The study met its primary end-point of progression-free survival (169 versus 166 days, HR 0.797, p = 0.072) but showed no benefit regarding overall survival (median not reached, 554 vs. 562 days HR 0.898, p = ns). In the subgroup of European patients, the number of embolizations was lower in patients on sorafenib, suggesting that toxicity led to early discontinuation of TACE.

Finally, a phase III study from Japan and Korea evaluated sorafenib versus placebo after successful conventional TACE in 458 patients [58]. Sorafenib was started 9.3 weeks (median) after completion of TACE. In this setting, sorafenib showed no benefit in terms of progression free survival (5.4 versus 3.7 months, HR 0.87) or overall survival (29.7 months versus not reached, HR 1.06).

In summary, there is no clear evidence of a benefit of combining sorafenib with TACE. Factors to be considered are toxicity, which tends to be higher in combination treatment, as well as the timing of treatment. Sorafenib preceding TACE may lead to the reduction of hyperperfusion of HCC nodules required for successful TACE. On the other hand, the large trial by Kudo et al. [58] failed to show a benefit of sorafenib started after completion of TACE in Asian patients. It also remains unresolved, whether dosing should be continued or interrupted during TACE.

Radioembolization

Despite the lack of randomized trials demonstrating efficacy of intraarterial radiation therapy (SIRT) with yttrium-90 containing glass beads or resin microspheres, SIRT is gaining popularity. Retrospective cohort studies from the USA and Europe suggested that SIRT is a safe and effective treatment for patients with advanced stage HCC [59, 60]. Based on these cohorts, two studies assessed the synergistic effect of combining sorafenib with radioembolization (**Table 2**). Chaudhury et al. reported 21 HCC patients treated with yttrium-90 glass beads and sorafenib. All tumors exhibited necrosis following radioembolization, with 4 patients developing complete necrosis of the tumor [61]. Another multicenter phase II study was reported recently, in which patients with HCC received yttrium-90 microspheres and sorafenib. Complete remission was observed in 4/34 patients, partial remission in 7/34 patients, and stable disease in 16/34 patients. Only 7 patients progressed. Median overall survival was 47 weeks [62]. Again, it is too early to judge whether promising disease control rates will lead to increased survival. Currently, a prospective randomized study is ongoing to clarify the role of the combination sorafenib and SIRT (SORAMIC study) while studies investigating the effect of SIRT alone on overall survival are urgently needed.

Table 2 Efficacy of sorafenib and TACE/SIRT in hepatocellular carcinoma (sequential therapy not included) according to current phase I-II studies.[1]

author	year	phase	investigational drug	n	RR	DS	PFS/TTP	OS
Chow [62]	2010	II	sorafenib + SIRT	35	31.4	77.1	nr/nr	10.8
Chung[2] [55]	2010	II	sorafenib + TACE	50	nr[3]	96	nr/nr	nr
Dufour [95]	2010	I	sorafenib + TACE	14	nr[4]	nr[4]	nr[4]	nr[4]
Erhardt[2] [56]	2009	II	sorafenib + TACE	44	nr[5]	63.6	8.0/16.1	11.7
Pawlik [16]	2011	II	sorafenib + DEB-TACE	35	58	100	nr	nr
Lencioni [57]	2012	II	sorafenib + DEB-TACE	307	35.7	69.5	nr/5.6	18.5[7]

[1] DEB-TACE: Drug eluting beads-Transarterial chemoembolization; DS: Disease stabilization (%); OS: Overall survival (months); PFS/TTP: Progression free survival/Time to progression (months); RR: Response rate (complete + partial response [%]); SIRT: Selective internal radio therapy.
[2] Interim analysis.
[3] 20/50 patients received 2 cycles of TACE, only, and 18 of these 20 patients achieved complete response compared to 2 patients with progressive disease, and 30/50 patients received more than 2 cycles of TACE and achieved partial response or stable disease.
[4] Primary objective of this prospective trial was evaluation if safety and tolerability of a continuous regimen of sorafenib combined with TACE.
[5] According to 31 patients who received at least 1 cycle of TACE, 2/31 (6.5 %) showed complete response, 15/31 (48.4 %) showed partial response, and 11/31 (35.5 %) showed stable disease; PFS, TTP, and OS are given for all 44 patients enrolled at time point of interim analysis.
[6] Patients who completed DEB-TACE showed 100 % objective tumor response and 100 % partial response or stable disease according to EASL or RECIST criteria, respectively.
[7] Median overall survival not reached.

Radiofrequency ablation and surgery

Recurrent HCC occurs in 50 to 80 % of patients at 5 years after resection [63]. Local recurrence rates varied from 4 – 55 % by radiofrequency ablation [64]. Theoretically, sorafenib might prolong the progression-free survival. However, no data on the adjuvant use of sorafenib after ablation or resection in curative intent have been published. A randomized phase III trial (STORM), which has already completed recruitment, will clarify the role of sorafenib in the adjuvant setting. In the STORM trial, Sorafenib is given at 400 mg twice daily for the duration of 4 years. At present, the use of sorafenib in the adjuvant situation is not recommended.

Combination of sorafenib with other systemic agents

After the results from the SHARP trial were published, a number of initiatives were started to assess the role of combination therapy with sorafenib and other agents in the treatment of advanced HCC. Various chemotherapeutic agents have been combined with sorafenib in order to enhance the anti-tumor activity of sorafenib in advanced HCC (**Fig. 1**). The agents mainly include doxorubicin and fluoropyrimidines. The largest study was a phase II trial performed by Abou-Alfa et al., in which patients were randomized to treatment with sorafenib and doxorubicin versus placebo and doxorubicin. A total of 96 patients were randomized, combined therapy increased time to progression to 6.4 months, versus 2.8 months in the placebo arm. In addition, overall survival was significantly prolonged (13.7 months versus 6.5 months) [65].

A further approach aims to evaluate the combination of sorafenib and fluoropyrimidines in the treatment of advanced HCC. Several studies have been reported using different kinds of fluoropyrimidines, such as 5-FU [66], capecitabine [67], and tegafur/uracil [68]. Although some of these studies showed promising results, combination chemotherapy should not be considered outside of clinical studies.

Combining targeted agents with sorafenib is another strategy. A number of different trials have been conducted, investigating several agents, including octreotide, temsirolimus, antisense XIAP, and anti-IGF-1 R monoclonal antibody, among others. So far, most studies are evaluating dose-limiting toxicity in phase I designs. A phase III study combining sorafenib with erlotinib (SEARCH) has been recruited completely, and the results are awaited.

Management of Side Effects

Skin toxicity, diarrhea and fatigue are the most common and most incriminating side effects of sorafenib and will be discussed in detail.

Skin toxicity

Skin toxicity is among the most frequent side effects of sorafenib treatment. In the SHARP trial, skin toxicity occurred in the majority of patients treated with sorafenib. Hand-food skin reaction (HFSR) was the most frequent event occurring in 21 % of patients treated with sorafenib. Grade 3 events were rare and were reported in 8 % of the patients. Other skin toxicity signs included rash (16 %), alopecia (14 %), pruritus (8 %), and dry skin (8 %) [4]. In the Asia-Pacific study, HFSR occurred in 45 % of patients treated with sorafenib (10.7 % were grade 3 or 4), alopecia occurred in 24.8 %, and rash in 20.1 % [3]. In a study of 43 patients with RCC, 91 % experienced at least one skin reaction while on treatment with sorafenib, and 60 % suffered from HFSR [69].

It is unclear whether the development of skin toxicity correlates with response to sorafenib treatment as is the case in patients treated with EGF receptor antagonists [70]. Although some smaller, retrospective studies suggested this [71 – 73], compelling evidence is lacking.

HFSR seen with sorafenib, which usually develops in the first 2 – 4 weeks after initiation of treatment, is different from chemotherapy-associated hand-foot syndrome [74 – 76]. Patients with HFSR report paresthesia at the palms and soles that is described as tingling or burning. Erythrodermia, hyperkeratosis, desquamation or fissures follow paresthesia. Most severe symptoms occur at areas of pressure, trauma, or friction. Some patients report that contact with hot water exacerbates the pain [75, 76]. It is important to inform the patient before starting the treatment about the possibility and symptoms of HFSR and to encourage him to take preventive measures. These measures include wearing protective socks and gloves as well as loose shoes, if possible with padded insoles and to attend pedicure/manicure. The patient should also be advised to avoid hot water or vigorous work involving the hands as well as to carefully apply moisturizing lotions to his/her body and creams to his/her hands and feet. Addition of urea (5 – 10 %) to such creams helps to contain moisture in the skin. At the first signs of HFSR these measures should be intensified while no dose reduction is necessary at this point. In

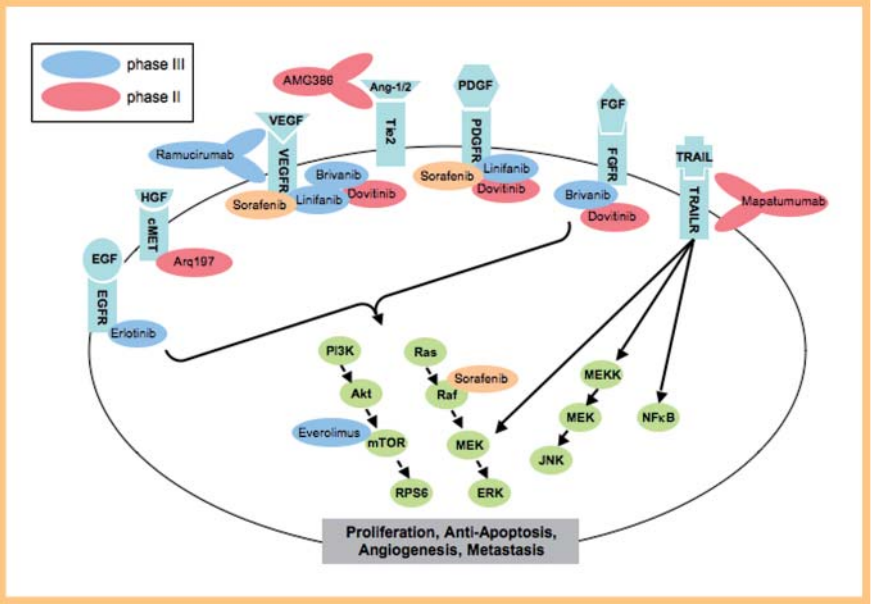

Fig. 1 Targeted agents in phase II and III development either as monotherapy or in combination with sorafenib in advanced HCC. Substances in phase III are shown as blue symbols, whereas those in phase II development are shown as red symbols. Currently there are mainly RTKIs (e. g., brivanib, linifanib, erlotinib, dovitinib), mTOR inhibitors (e. g., everolimus) and monoclonal anti- (e. g., ramucirumab and mapatumumab) or peptid-bodies (AMG386) tested in clinical trials. VEGF, vascular growth factor; FGF, fibroblast growth factor; Ang-1/2, angiopoetin-1 and -2; HGF, hepatocyte growth factor; TRAIL, tumor necrosis-related apoptosis-inducing ligand.

case of hyperkeratosis, keratolytics such as urea (10 – 40 %) or salicylic acid (6 %) can be applied. If necessary, analgetics should be prescribed, and topical application of anesthetizing gels or lotions (e. g., lidocain) may cause relief. Application of glucocorticoid ointments such as clobetasol 0.05 % should be considered in symptomatic patients. If HFSR worsens, the dose of sorafenib should be reduced or dosing should be interrupted to allow complete healing of the lesions before dose escalation or re-exposure to sorafenib. It is important to stop treatment before blistering or ulceration develops to spare the patient the discomfort associated with it and to avoid prolonged phases of sorafenib interruption. After the second occurrence of HFSR, the dose should remain reduced permanently [77].

Rash usually involves the face and upper thorax and has an erythematous aspect, frequently accompanied by slight desquamation, resembling seborrheic dermatitis. Some patients experience pruritus at the sites of the rash. Topical treatment with glucocorticoid ointments usually provides symptomatic relief and treatment can typically continue without dose modification. Colloid oatmeal lotion may be an alternative to glucocorticoids when an acneiform rash develops [78].

Desquamation of the oral mucosa or blistering of the lips or oral mucosa may develop and should prompt dose reduction or interruption if the lesions do not respond to topical treatment such as dexpanthenol or hexetidine mouth wash.

Besides these frequent skin toxicities, yellow discoloration of the skin can occur, although much less frequently then observed with sunitinib [79]. In patients with renal cell carcinoma, squamous cell carcinoma and keratoacanthomas were observed with increased frequency [80] in patients receiving sorafenib.

Diarrhea

Diarrhea is the second most frequent adverse event occurring with sorafenib treatment, however symptoms are usually mild.

In the SHARP trial diarrhea was reported in 39 % of the treated patients (8 % grade 3) and in 11 % of patients receiving placebo treatment (2 % grade 3) [4]. Thus, the presence of diarrhea was significantly more frequent in sorafenib patients. Although diarrhea was the second most frequent reported grade 3 adverse events, most patients only suffered from mild diarrhea. Nevertheless, the most frequent adverse event leading to dose reductions in the sorafenib group was diarrhea (8 %), followed by hand-foot skin reaction (5 %) and rash or desquamation (3 %).

Diarrhea is also frequently reported in patients with extrahepatic cancer. Especially in patients with RCC a number of studies have assessed the frequency of diarrhea during sorafenib treatment. In this tumor entity, diarrhea was observed in up to 43 % of patients, but most patients had mild symptoms. The incidence of diarrhea treated with sorafenib was comparable to treatment with sunitinib in patients with RCC (53 %) [81]. In a recent report on the extended access program of sorafenib in RCC, gastrointestinal events, including diarrhea, were the second most common adverse events (4.4 %) leading to dose reductions and interruptions, respectively [82]. Diarrhea of grade 2 and 3 and higher was reported in 2 – 6 % of patients of first-line and previously treated RCC patients.

Although the pathophysiology of diarrhea in patients receiving sorafenib or any other RTKI is still incompletely understood, small intestinal bacterial overgrowth was suggested as a possible mechanism [83]. It was diagnosed in 60 % of HCC patients with CP-A cirrhosis during sorafenib treatment. Diarrhea during sorafenib treatment developed in 78 % of patients with small intestinal bacterial overgrowth compared to 50 % without bacterial overgrowth. Rifaximin treatment led to bacterial decontamination in 71 % of patients and was associated with a clinically relevant reduction of symptoms. Thus, small intestinal bacterial overgrowth may have a synergistic effect with sorafenib on the onset of diarrhea. Hilgard et al. reported diarrhea in 27 of 61 HCC patients treated with sorafenib [84]. After concomitant treatment with 100 mg daily E. coli Nissle a dose reduction of sorafenib was necessary in only one single patient.

In summary, diarrhea is a frequent side effect of sorafenib treatment, however, most patients suffer from mild to moderate diarrhea, which can be managed with loperamide.

Food that may aggravate diarrhea (spicy or fatty foods, caffeine), as well as stool softeners, and fiber supplements should be avoided. Furthermore, oral rehydration with fluids containing water, salt and sugar is recommended. In severe cases treatment with loperamide is the best option. The standard dose of loperamide is 4 mg, followed by 2 mg every 4 h or after every loose stool. A

more aggressive approach can be performed by giving 4 mg initially, then 2 mg every 2 h. In patients with severe diarrhea, other drugs such as codeine or octreotide may be considered.

Fatigue

Many patients with cancer, but also those with liver cirrhosis, suffer from fatigue. It is often hard to discriminate whether fatigue is caused by the underlying disease or a side-effect of a drug such as sorafenib.

In the SHARP trial fatigue was observed in 22 % of patients treated with sorafenib and 16 % of patients in the placebo arm. Although fatigue was less frequently reported in the placebo arm, this difference was not statistically significant. This finding argues for the contribution of the underlying disease to the presence or aggravation of fatigue in this patient cohort. In patients without liver disease who are treated with sorafenib, e. g., in RCC, fatigue was reported in 29 % of patients, with 3 % of grade 3 or 4 events [85]. In a further RCC study, fatigue was present in approximately 37 % of patients treated with sorafenib, in 58 % of patients treated with sunitinib, and in 51 % patients treated with temsirolimus [81]. In a recent report on the extended access program of sorafenib in renal cell cancers, fatigue was among the most commonly observed moderate and severe adverse events [82].

In summary, fatigue is a frequent symptom in HCC patients treated with sorafenib. Generally, the available data indicate that sorafenib aggravates pre-existing fatigue due to cancer or chronic liver disease, rather than being solely based on drug toxicity.

Treatment of fatigue in cancer patients is often difficult. Evidence for a benefit of supportive measures on fatigue is either limited, e. g., a positive effect of increased physical activity, or has been disproved, e. g., carnitine supplementation. Most importantly, coexisting morbidity that may aggravate fatigue, e. g., hypothyroidism, anemia and depression, should be carefully evaluated and effectively treated. The use of psychostimulants such as methylphenidate should be discussed although results from studies show mixed results. A large phase III study suggested that patients with severe fatigue may benefit most [86]. Likewise, a cochrane meta-analysis found a benefit for methylphenidate [87]. Another psychostimulant, modafinile, also proved effective for the treatment of severe fatigue [88], while selective serotonine re-uptake blockers demonstrated no benefit [89, 90].

Psychosocial interventions, nutritional consultation, and behavioral counseling including recommendation of activity enhancement constitute the mainstay of care for all patients with cancer associated fatigue.

Hypothyroidism, anemia, and depression should be ruled out. Since physical activity helps to cope with fatigue in other cancer patients, patients with HCC should be motivated for at least light physical activity. If severe fatigue interfering with daily activities occurs, treatment should be interrupted. Besides psychosocial interventions, the psychostimulant methylphenidate is an option.

Hypertension

Hypertension is a class-type side effect of anti-angiogenic drugs and has been reported in the SHARP trial in 5 % and in the Asian-Pacific trial in 19 % of patients [3, 4]. In both pivotal trials the incidence of hypertension grade 3 was 2 %. Sorafenib-induced hypertension generally responds to standard antihypertensive treatment.

Since management of hypertension rarely causes difficulties, hypertension will not be discussed in greater detail here.

Before the initiation of sorafenib, patients should control preexisting hypertension either by dose modification of current antihypertensive medications or by initiation of combination treatment according to standard medical practice. In case of new-onset hypertension, prompt treatment should be initiated according to standard medical practice.

Quality of life during sorafenib treatment

Adverse events observed during sorafenib treatment might also affect the quality of life. In the pivotal SHARP trial the quality of life under treatment with sorafenib was estimated with the FACT Hepatobiliary Symptom Index (FHSI-8) [4]. This questionnaire is a validated patient-oriented outcome instrument, which might be influenced by both the presence of drug-related toxicity and the effect of the response to tumor-related symptoms. In the SHARP trial there was no significant difference in responses to this questionnaire in patients in the sorafenib and the placebo groups, indicating that the quality of life is not negatively influenced by sorafenib. This indicates that disease stabilization induced by the treatment with sorafenib might overcome potential side effects. In unselected patients with advanced liver cirrhosis, the quality of life, especially with a starting daily dose of 800 mg, is affected negatively. A step-up approach, as discussed above, may be beneficial.

Abbreviations

BCLC:	Barcelona Clinic liver cancer
CP:	Child-Pugh
ECOG:	eastern cooperative oncology group
HCC:	hepatocellular carcinoma
HFSR:	hand-foot skin reaction
RCC:	renal cell carcinoma
RECIST:	response evaluation criteria in solid tumors
RFA:	radiofrequency ablation
RTKI:	receptor tyrosine kinase inhibitor
SIRT:	selective intraarterial radiation therapy
TACE:	transarterial chemoembolisation

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