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Review Article

Adverse events of sorafenib in hepatocellular carcinoma treatment

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Abstract: Sorafenib is an oral multikinase inhibitor approved by the US Food and Drug Administration for treatment of the patients with surgically unresectable hepatocellular carcinoma (HCC). Sorafenib mitigates angiogenesis by targeting vascular endothelial growth factor receptors and platelet-derived growth factor receptors in endothelial cells and pericytes. Moreover, it suppresses cell proliferation via blockage of B-RAF and RAF1 of the mitogen-activated protein kinase pathway in tumor cells. Sorafenib has been the standard molecular targeted medication in the treatment of advanced-stage HCC patients ineligible for potentially curative interventional (radiofrequency or microwave ablation) or palliative trans-arterial chemoembolization (TACE) therapies for over a decade. However, it only increases overall survival by less than 3 months, and systemic exposure to sorafenib causes clinically significant toxicities (about 50% of patients). Given the high frequency and severity of these toxicities, sorafenib dose must be often reduced or discontinued altogether. In this review, we discussed the mechanism of sorafenib-associated adverse events and their management during HCC treatment.

Keywords: Adverse events, hepatocellular carcinoma, sorafenib, toxicity

Introduction

Hepatocellular carcinoma (HCC) remains the third-leading cause of cancer-related mortality worldwide, with the percentage of new deaths being 8.3% in 2020, following lung cancer (18.0%) and colorectal cancer (9.4%) [1-3]. Tyrosine kinase inhibitors are the standard molecular targeted drugs for the treatment of patients who are not suitable for surgical resection, interventional curative (radiofrequency or microwave ablation), or palliative trans-arterial chemoembolization (TACE) therapies [4, 5]. Sorafenib is a tyrosine kinase inhibitor approved by the US Food and Drug Administration in 2007 for the treatment of advanced HCC patients [6, 7]. It can inhibit angiogenesis by targeting vascular endothelial growth factor receptors (VEGFR) and platelet-derived growth factor receptors (PDGFR) in endothelial cells and pericytes, and also suppress cell proliferation via blockage of B-RAF and RAF1 of the mitogen-activated protein kinase (MAPK) pathway in tumor cells [8, 9]. As a result, sorafenib is capable of increasing overall survival (OS) by about 3 months compared with supportive care [10]. However, for the pharmaceutical form of oral administration, larger portion of sorafenib dosage undergoes either oxidation or glucuronidation, thus reducing efficacy and potency in the treatment of HCC patients [11]. Furthermore, clinical studies have shown that approximately 50% of an orally administered sorafenib dose is excreted without any alteration [12]. Low serum levels of sorafenib in some patients suggest that oral administration may not be adequate to elicit consistent and potent therapeutic responses [13]. Besides, similar to other tyrosine kinase inhibitors, systemically adminis-

tered sorafenib leads to clinically significant adverse events (AEs) e.g., diarrhea, hypertension, hand-foot skin reaction, and fatigue, for lacking tumor specificity [14-16]. Given the frequency and severity of these toxicities, dosage of sorafenib must be decreased frequently or discontinued altogether (>30% of patients) [17, 18], which diminishes therapeutic response and OS. Efforts have been taken to improve the safety of sorafenib administration in HCC therapy. Chen et al. and Poursaid et al. respectively used poly (D,L-lactide-co-glycolide) microsphere and silk-elastinlike protein polymer for localized release of sorafenib to reduce systemic exposures [19, 20]. Some researchers found that several derivatives of sorafenib got through structure modifications displayed higher bioavailability and fewer side effects [21]. Cumulative studies indicate that combination therapy with sorafenib may produce a better result in HCC treatment [22-25]. This review will briefly describe sorafenib's function, sorafenib-associated AEs, probable mechanism of toxicity, and methods for reducing toxicity-related AEs.

Hepatocellular carcinoma

Etiology

HCC, comprising 75%-85% of primary liver cancer cases, is a major health problem and accounted for more than 670,000 new cases and 620,000 deaths in 2020 worldwide [3]. The main risk factors for HCC include chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin-contaminated foods, excess body weight, type 2 diabetes, heavy alcohol intake, and smoking [26, 27]. A different spectrum of vital risk factors is observed depending on environmental and cultural behaviors. Vaccination against HBV, which has dramatically decreased the prevalence of HBV infection, incidence and mortality rates of HCC in high-risk countries in Eastern Asia, is proved to be a major public health success [28]. However, incidence rates in countries across Europe and America have increased or stabilized at a higher level than before, probably associated with the prevalence of excess body weight and diabetes [29, 30].

HCC therapeutic options

Early diagnosis of HCC through surveillance prompts the potential benefits of several types of treatment approaches [31]. Staging systems play a key role in predicting the prognosis of HCC patients, and Barcelona Clinic Liver Cancer (BCLC) staging system has been validated as capable of providing the best prognostic information with the highest discriminatory ability, and best suited for treatment guidance among many systems [32, 33]. According to this guideline, early-stage HCC patients are treated with surgical resection, transplantation, or image-guided loco-regional ablation. However, only 10%-15% of patients are suitable candidates for these potentially curative treatments [34-36]. Intermediate-stage HCC patients tend to be treated with TACE, yet OS benefits from current transcatheter approaches directed to the liver remain relatively modest [26, 37-40]. Systemic therapies can be utilized for patients with advanced HCC, but this type of drug offers little survival benefit, with the critical exception of multi-kinase inhibitor sorafenib [7, 41-43]. Notably, sorafenib has been available for advanced HCC patients for over a decade and is still used as first-line systemic therapy (**Figure 1**) [41, 44, 45].

Sorafenib already has a global assurance for HCC treatment [31]. In the western population, where the majority of cases are related to HCV infection or alcohol consumption, the use of sorafenib was validated by the sorafenib hepatocellular carcinoma assessment randomized protocol (SHARP) trial [10]. While most cases are related to HBV infection or alcohol consumption in the eastern population, the safety and efficacy of sorafenib were assessed by a multinational phase III trial in patients from the Asia-Pacific region with advanced HCC [46].

Sorafenib in HCC treatment

Sorafenib's tosylate is a solid nonchiral molecule with a carbamido in its structure [47]. In the molecular pathogenesis of HCC, both extracellular signaling pathway mediated by epidermal growth factor receptor (EGFR), VEGFR, PDGFR, and intracellular signaling pathway mediated by RAS/RAF/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK), phosphatidylinositol-3-kinase (PI3K)/phosphatase and tensin homolog deleted on chromosome 10 (PTEN)/AKT/mammalian target of rapamycin (mTOR) has been implicated [48-51]. Sorafenib exerts antitumor function by targeting various protein

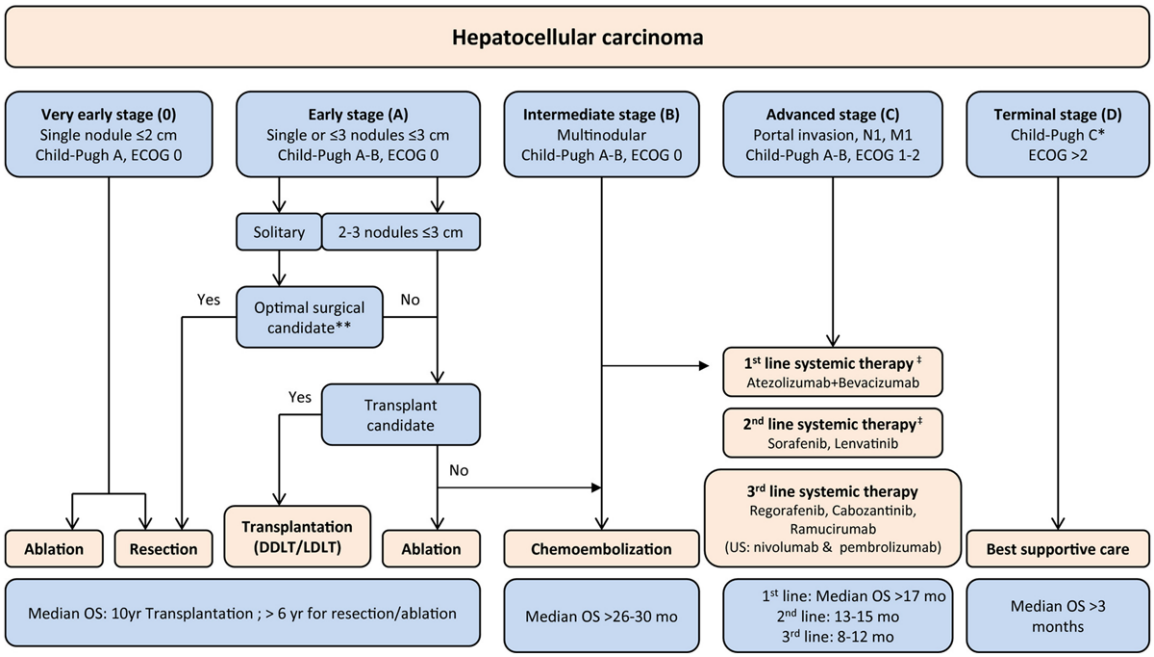

Figure 1. Modified BCLC staging system considering effective therapies in advanced stages (modified and updated from European Association for the Study of the Liver (EASL) guidelines). Management of patients with HCC is guided by the BCLC staging system, which takes into account both tumor extent and the severity of the underlying liver disease and defines 5 prognostic subgroups with respective treatments. Treatment for early-stage tumors is with curative intent, and options include RFA, hepatic resection, and liver transplantation. Patients with intermediate or advanced HCC are candidates for chemoembolization or systemic therapies, respectively. *Patients with end-stage liver disease if Child-Pugh class C should first be considered for liver transplantation. **Patients with preserved hepatic function Child-Pugh class A with normal bilirubin and no portal hypertension are optimal candidates for hepatic resection. ‡Atezolizumab plus bevacizumab has been approved as a new first-line treatment for advanced HCC. Nonetheless, sorafenib and lenvatinib are still considered first-line options when there is a contraindication for the combination treatment. Abbreviations: DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; M1, distant metastasis; N1, lymph node metastasis.

kinases and signal transduction pathways. It can mitigate angiogenesis by blocking the autophosphorylation of several tyrosine kinases receptors, e.g., VEGFR1/2/3 and PDGFRs in endothelial cells and pericytes [52]. Also, it can suppress cell survival and proliferation by directly inhibiting RAF/MEK/ERK signaling pathway in tumor cells. More specifically, as a unique electron-withdrawing chemical group in sorafenib, carbamido forms hydrogen bonds with B-RAF and RAF1 protein, thus interrupting signal transmission [21]. Additionally, sorafenib can regulate PI3K/AKT/PTEN signaling pathway, which might activate an escape pathway from the MAPK cascade and result in resistance to sorafenib [53, 54]. Furthermore, sorafenib can down-regulate the expression of myeloid cell leukemia sequence-1 (Mcl-1) and cellular inhibitor of apoptosis 2 (cIAP2), two anti-apoptotic proteins, by preventing nuclear factor-κB (NF-κB) from binding at the promoters of them, during which RAF signaling pathway is involved [55, 56]. Thus, sorafenib can inhibit the proliferation and angiogenesis of HCC and increase its apoptosis rate (**Figure 2**).

After oral administration, plasma level of sorafenib reaches a peak value in 3 hours, and its mean half-life varies from 25 hours to 48 hours. In vitro binding experiments indicated that human plasma proteins could bind 99.5% of sorafenib, and high-fat meal might decrease its bioavailability [57]. In the liver, sorafenib undergoes oxidative metabolism mediated by cytochrome P450 (CYP)3A4. At the same time, sorafenib also undergoes glucuronidation, which is mediated by uridine diphosphate (UDP) glucuronosyltransferase family 1 member A9 (UGT1A9). In plasma, sorafenib accounts for 70%-85% of the circulating analytes at the steady-state in which 5 metabolites of sorafenib have been detected. The main metabolite

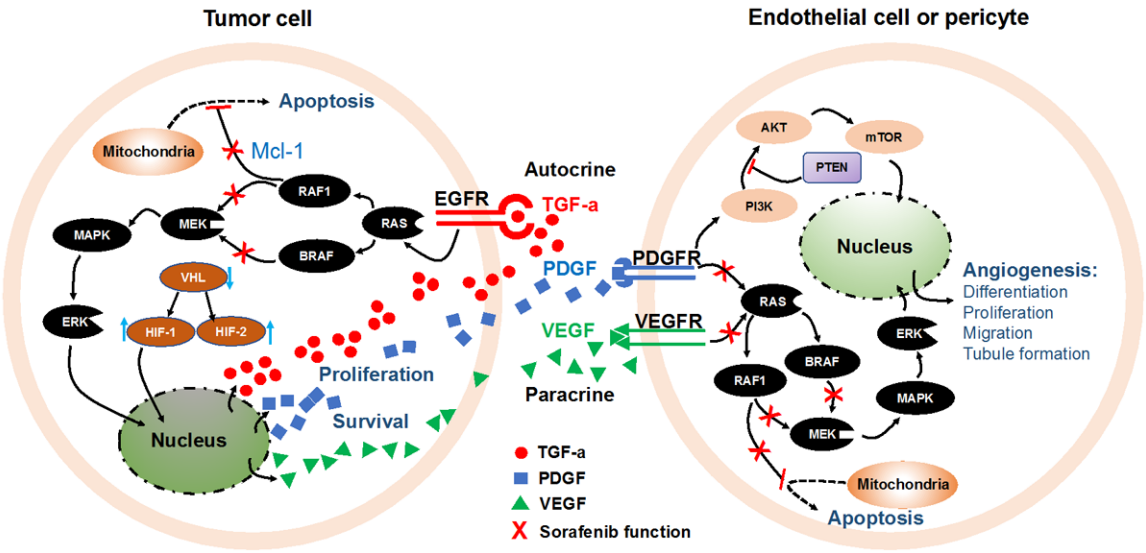

Figure 2. Mechanism of sorafenib functions by targeting tumor proliferation, apoptosis, and angiogenesis. AKT, serine/threonine-protein kinase; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal-growth-factor receptor; ERK, extracellular signal-regulated kinase; HIF, hypoxia-inducible factor; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; Mcl-1, myeloid cell leukemia sequence 1; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PI3K, phosphoinositol 3-kinase; PTEN, phosphatase and tensin homology deleted on chromosome 10; RAF, rapidly accelerated fibrosarcoma; RAF1, v-Raf-1 murine leukemia viral oncogene homolog 1; RAS, rat sarcoma virus; TGFα, tumor growth factor α; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; VHL, von Hippel-Lindau tumor suppressor gene.

of sorafenib in blood circulation is pyridine N-oxide M2, which possesses similar potency to that of sorafenib in vitro. After being taken orally, 96% of a sorafenib dose can be detected in blood circulation for up to 14 days, with 77% (of which 51% in the form of unchanged sorafenib) and 19% was excreted in feces and urine respectively as glucuronidated metabolites [12].

Toxicity

During the treatment of HCC with sorafenib, some drug-related AEs would occur [57]. Diarrhea, hand-foot skin reaction (HFSR), hypertension, fatigue, bilirubin elevation, thrombocytopenia, aspartate aminotransferase (AST) elevation, rash, anorexia, and alopecia are most frequently reported as dose-limiting toxicities (**Table 1**) [10, 58-60].

HFSR is frequently observed in treatments with sorafenib, which functions by targeting VEGFR. VEGFR is expressed not only on dermal endothelial cells but on hair follicles and keratinocytes [61]. In 2009, Kong et al. reported that blocking the VEGFR pathway in the vascular endothelium with sorafenib might result in HFSR development [62]. HFSR would exacerbate in frequency and severity if sorafenib is administrated in combination with bevacizumab, which is a humanized antibody against VEGF [63]. Furthermore, the incidence of HFSR is directly associated with the cumulative bevacizumab dose, which supports the deduction that inhibition of VEGF may be a critical factor in HFSR development. Inhibiting VEGFR can hamper the mechanisms of vascular repair from functioning properly, thus causing HFSR in such high-pressure areas as the palms and soles [64]. However, it is important to note that receptors besides VEGFR may also be associated with the induction of HFSR, and more studies are needed to elucidate the biological mechanisms of sorafenib-associated HFSR.

Hypertension is another side effect caused by sorafenib in HCC treatment. It is suggested that blocking the VEGF/EGFR signaling pathway with sorafenib would result in downregulation of vasodilatation, in that VEGFR is expressed on endothelial cells in blood vessels, and sorafenib functions via targeting VEGFR [65]. Also, the investigators of "VEGF in ischemia for vascular angiogenesis (VIVA)" found that giving

Table 1. Common adverse events occurred in HCC treatment with sorafenib

Adverse Event	Reference	All grades [% (x/n)]	Grade ¾ [% (x/n)]
Hand-foot skin reaction	[10]	20.87% (62/297)	8.08% (24/297)
	[46]	44.97% (67/149)	10.74% (16/149)
	[58]	65.71% (46/70)	15.71% (11/70)
	[59]	52.42% (249/475)	11.37% (54/475)
	[60]	48.08% (75/156)	8.33% (13/156)
	Average	43.51% (499/1147)	10.29% (118/1147)
Rash	[10]	16.16% (48/297)	1.01% (3/297)
	[46]	20.13 (30/149)	0.67% (1/149)
	[58]	30.00% (21/70)	0% (0/70)
	[59]	16.00% (76/475)	0.42% (2/475)
	[60]	17.31% (27/156)	2.56% (4/156)
	Average	17.62% (202/1147)	0.87% (10/1147)
Hypertension	[10]	4.71% (14/297)	2.02% (6/297)
	[46]	18.79% (28/149)	2.01% (3/149)
	[58]	47.14% (33/70)	15.71% (11/70)
	[59]	30.32% (144/475)	14.32% (68/475)
	[60]	24.36% (38/156)	12.18% (19/156)
	Average	22.41% (257/1147)	9.33% (107/1147)
Diarrhea	[10]	39.06% (116/297)	8.08% (24/297)
	[46]	25.50% (38/149)	6.04% (9/149)
	[58]	47.14% (33/70)	7.14% (5/70)
	[59]	46.32% (220/475)	4.21% (20/475)
	[60]	49.36% (77/156)	5.13% (8/156)
	Average	42.20% (484/1147)	5.75% (66/1147)
Fatigue	[10]	21.89% (65/297)	4.04% (12/297)
	[46]	20.13% (30/149)	3.36% (5/149)
	[58]	28.57% (20/70)	1.43% (1/70)
	[59]	25.05% (119/475)	3.58% (17/475)
	[60]	18.59% (29/156)	3.21% (5/156)
	Average	22.93% (263/1147)	3.49% (40/1147)
Anorexia (Decreased appetite)	[10]	14.14% (42/297)	1.01% (3/297)
	[46]	12.75% (19/149)	0% (0/149)
	[58]	20.00% (14/70)	2.86% (2/70)
	[59]	26.74% (127/475)	1.26% (6/475)
	[60]	24.36% (38/156)	3.85% (6/156)
	Average	20.92% (240/1147)	1.48% (17/1147)
Alopecia	[10]	14.14% (42/297)	0% (0/297)
	[46]	24.83% (37/149)	NA
	[58]	20.00% (14/70)	0% (0/70)
	[59]	25.05% (119/475)	0% (0/475)
	[60]	14.10% (22/156)	0% (0/156)
	Average	20.40% (234/1147)	0% (0/1147)
AST elevation (Aspartate aminotransferase increase)	[10]	NA	NA
	[46]	NA	NA
	[58]	27.14% (19/70)	8.57% (6/70)
	[59]	16.84% (80/475)	8.00% (38/475)
	[60]	16.67% (26/156)	5.13% (8/156)
	Average	17.83% (125/701)	7.42% (52/701)

Bilirubin elevation (Blood bilirubin increase)	[10]	NA	NA
	[46]	NA	NA
	[58]	54.29% (38/70)	20.00% (14/70)
	[59]	13.26% (63/475)	4.84% (23/475)
	[60]	14.10% (22/156)	6.41% (10/156)
	Average	17.54% (123/701)	6.71% (47/701)
Thrombocytopenia (Decreased platelet count)	[10]	NA	NA
	[46]	NA	NA
	[58]	51.43% (36/70)	15.71% (11/70)
	[59]	12.21% (58/475)	3.37% (16/475)
	[60]	11.54% (18/156)	1.28% (2/156)
	Average	15.98% (112/701)	4.14% (29/701)

VEGF to humans could induce dose-dependent vasodilation, which would result in hypotension, tachycardia, and a decreased cardiac output [66, 67]. Vasodilation is mainly mediated by nitric oxide and prostacyclin (also called prostaglandin I2, PGI2), which are produced by endothelial cells predominantly through a signal pathway involving the receptor of VEGFR2. Technically, nitric oxide is produced through endothelial-type nitric oxide synthase via the calcium-independent PI3K/AKT pathway under the condition of VEGF binding to VEGFR2 [67-70]. Additionally, VEGF is an inhibitor for the secretion of endothelin 1, which is a potent vascular constrictor that plays a crucial part in vascular remodeling [71]. These findings indicated that hypertension induced in treatment with sorafenib might have a relationship to VEGFR2 signaling pathways inhibition. Blocking of the VEGF/EGFR signaling pathway leads to decreased production of nitric oxide, PGI2, and endothelin 1, and finally elevation of blood pressure as a result.

Symptoms and management of AEs

Although these sorafenib-associated AEs are considered to be positively correlated with the survival rate of patients, and therefore can be used as clinical biomarkers for efficacy appraisal [72], efforts should be made to prevent and manage AEs with a final aim to increase patient compliance and improve clinical benefit.

Dose modification is the first consideration of management for any kind of sorafenib-related AEs. According to BCLC recommendations, dose modification should be made conforming to AEs severity. For mild AEs (grade 1), no dose modification is needed but only symptomatic treatment; for moderate AEs (grade 2), dose reduction should be made; for severe AEs (grade 3/4), dose interruption must be carried out [73]. Yet for each kind of AEs, there should be more specific management strategies. Here, we describe the symptoms and related management methods of the following types of common AEs.

Diarrhea: Diarrhea is one of the most frequently observed AEs associated with sorafenib therapy, and the incidence rates of it in all grades range from 39% to 58% [10, 74]. Because the severity of diarrhea ranges from mild to severe, a thorough assessment of severity should be undertaken before making recommendations for diarrhea management. Patients should be reminded to report symptoms of diarrhea to their healthcare team immediately since early intervention can reduce the severity and improve both therapy efficacy and life quality. The primary aims of diarrhea management are to alleviate symptoms, prevent complications and restore normal bowel movements.

Dehydration may be caused by under-estimated or inadequately managed diarrhea. An imbalance in electrolytes can result in fatigue. In this case, maintaining hydration by orally intaking extra electrolyte-containing fluids is critical. Patient education is also very helpful in handling diarrhea symptoms, such as advising them to prefer a low-fiber diet, avoid foods with high insoluble fiber, and take some anti-diarrheal medicines e.g., loperamide if necessary [75].

HFSR: HFSR is another kind of widely reported AEs associated with sorafenib. According to our analysis of several milestone trials involv-

Table 2. Information on the trials involving sorafenib included in **Table 1**

Reference	[10]	[46]	[58]	[59]	[60]
Trial keyword	SHARP	Asia-Pacific	Japanese	REFLECT	IMbrave150
Trial arms	Sorafenib VS placebo	Sorafenib VS placebo	Safety profile of sorafenib, HCC VS RCC	Lenvatinib VS sorafenib	Atezolizumab plus bevacizumab VS sorafenib
Number of patients in sorafenib group	297	149	70	475	156
Year of data publish	2008	2009	2014	2018	2020
Trial phase	III	III	Real-life conditions	III	III
Trial number	NCT00105443	NCT00492752	-	NCT01761266	NCT03434379
Patients enrolled	121 centers, 21 countries in Europe, North America, South America, Australasia	23 centers in China, South Korea, Taiwan	Japanese HCC patients	154 sites in 20 countries throughout the Asia-Pacific region, Europe, North America	Asia excluding Japanese v.s. the rest of the world

ing sorafenib administration (**Table 2**), the incidence of HFSR for all grades is about 21%-66% (with the mean value being 43.5%) (**Table 1**). HFSR poses the most significant impact on a patient's life quality, especially for individuals with grades 3/4, who frequently need dose reduction or treatment withdrawal. Also, HFSR is a dose-dependent side effect and it will regress rapidly if sorafenib is discontinued.

For different grade HFSR, management strategies are mainly empirical. For grade 1, the clinical goal is to provide supportive measures, continue treatment with sorafenib, control hyperkeratotic areas, maintain skin moisture, and educate patients with skincare and protection knowledge. For grade 2, the clinical goal is to control hyperkeratosis, cushion callused areas, moisturize the skin, control symptoms and relieve discomfort. For grades 3/4, the clinical goal is to reduce symptoms and prevent further progression. Specific approaches may include administering some reagents, like salicylic acid, urea-based products, nonsteroidal anti-inflammatory drugs (NSAID), and corticosteroids [76].

Rash: A rash is frequently reported during many studies, with the incidence of all grades being 16%-40% [10]. The severity of the rash should be appraised together with clinical features such as fever, mucosal injury, enlargement of organs, and biological abnormalities to detect hypersensitivity reaction. For grade 1/2 rash, treatment can be continued under the monitoring of related clinical and biological markers to verify the favorable outcomes.

Management of the general rash is similar to that of HFSR in which anti-inflammatory therapies such as corticosteroid ointments and creams can be used topically for symptom relief [77, 78]. For minimization of skin irritation, thick and alcohol-free moisturizers can be used regularly. Moreover, antihistamines e.g., diphenhydramine or hydroxyzine can be taken orally for some relief if necessary [79].

Hypertension: Hypertension with an incidence of all grades ranging from 5% to 47% is observed during HCC treatment with sorafenib (**Table 1**). For early detection of hypertension, frequent monitoring of blood pressure by medical personnel is essential. Also, patients can be trained to monitor and record their blood pressure for medical personnel.

For the management of hypertensive patients, we can follow Joint National Committee (JNC) guidelines for prevention, diagnosis, appraisal, and treatment of high blood pressure. Hypertension can be easily managed with 5 classes of drugs validated in blood pressure control (calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin 2 receptor blockers (ARBs), thiazide diuretics, and beta-blockers) alone or combination. If preexistent hypertension can be well controlled with a certain agent, patients should remain on that treatment. However, it should be noted that sorafenib can compete with calcium channel blockers such as diltiazem or 1,4-dihydropyridine in the CYP3A4 pathway, which may increase the plasma exposition of these medications [80].

Fatigue: Fatigue is the most common side effect with a frequency of between 18.6% and 29% for all grades and 1%-4% for grades 3/4 (**Table 1**). For the management of fatigue, mul-

tifactorial causes should be investigated carefully. At first, patients should be informed regarding multifactorial causes of fatigue such as hypohydration, depression, anorexia, diarrhea, and pain. Second, patients need to be advised to better management of their routine movements by working effectively around occurrences of fatigue. Third, encouraging patients to report fatigue symptoms and keep in contact with their medical team is crucial. Specifically, patients should be reminded to remain hydrated in case of fatigue resulting from dehydration. For patients with diarrhea, increasing hydration is especially important. At the same time, energy management techniques, such as adding resting periods as needed in the daytime, lowering body movements, and beginning a strength-training exercise program before sorafenib treatment, can also be employed for fatigue management [81, 82].

Future

Currently, sorafenib remains the first-line drug for advanced HCC treatment according to BCLC guidelines, especially in case of contraindication for atezolizumab plus bevacizumab treatment strategy. Therefore, awareness of the AEs induced in HCC treatments is essential.

There are several recommendations and suggestions for the administration of sorafenib at a higher safety level, including modification of sorafenib's molecular structure, transformation of pharmaceutical dosage forms, and optimization of drug delivery systems. Among these options, dose modification is the first consideration for the management of any kind of sorafenib-related AEs. Many reports have revealed that the efficacy of sorafenib under a modified dosage could be maintained. Two Japanese studies found comparable progression-free survival (PFS) and OS in HCC patients who started on full or half-dose sorafenib [83, 84]. Also, a multivariate analysis made by Korean scientists indicated that a decreased dosage of sorafenib provided significantly better PFS and OS than another dosing [85]. Similarly, a research group from Canada revealed that starting sorafenib at a full and lower dose did not affect OS, and patients receiving half-dose sorafenib for 70% of their treatment had a better OS than those who maintained full dose for 70% of the treatment period [15]. Based on feasibly administrating sorafenib at a lower dosage level, combination therapy is gaining the attention of the research community. Because the tumor microenvironment of HCC is complicated by various kinds of immune cells, such as immune-stimulating cells like dendritic cells (DCs), $CD8^+$ T, natural killer (NK), gamma delta T, and immune-suppressive cells like regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC), it is reasonable to make a consideration of administrating sorafenib in combination with adoptive cell therapy [86, 87]. Indeed, sorafenib can both decrease immune-suppressive cell populations and enhance immune-stimulating cell groups in the tumor microenvironment of HCC. Sorafenib can improve NK cell function in a low-dose manner without leading to exhaustion, thus paving the path to developing a rationale for using it in combination with NK cell-based adoptive immune therapy [88, 89]. In conclusion, combination therapy with a consideration of orchestrating diverse types of treatment strategies to produce a synergistic antitumor effect and lower related AEs of each type of monotherapy method is emerging as the best possible option for the treatment of advanced HCC.

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Disclosure of conflict of interest

None.

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