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Tyrosine Kinase Inhibitors in the Treatment of Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma is the third leading cause of cancer-related mortality in the world. Locoregional therapy is used for early stage hepatocellular carcinoma. Tyrosine kinase inhibitors have been the mainstay of treatment for advanced hepatocellular carcinoma. Sorafenib was the first drug approved based on data from two pivotal phase III trials. Although sorafenib provided a survival benefit, development of adverse events limits its use in some patients. These adverse events, such as hand–foot syndrome and diarrhea, have a significant impact on the quality of life and, in some circumstances, are severe enough to prompt cessation of the drug. In recent times, a range of new therapeutic options have come on the scene including lenvatinib, regorafenib, and cabozantinib. Lenvatinibis now approved as an alternative first-line agent for hepatocellular carcinoma. Regorafenib and cabozantinib are both second-line agents. These medications provide a promising range of treatment options for patients who progress on sorafenib or are intolerant to it. This chapter provides an insight into the range of tyrosine kinase inhibitors available for the treatment of hepatocellular carcinoma.

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INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancer and is the third leading cause of cancer-related mortality in the world. Despite advances in treatment, 5-year survival rates are still poor at 18% (1). Unfortunately, up to 80% of patients present with advanced, incurable disease (2). The Barcelona Clinic Liver Cancer (BCLC) algorithm was published in 1999 and is the most widely used staging system. There are other staging systems in use such as the Hong Kong Liver Cancer staging system but these are not as commonly applied. BCLC guidelines classify patients with preserved liver function who have macrovascular invasion or extrahepatic spread of disease and Eastern Cooperative Oncology Group performance status (ECOG) 1–2 as having advanced stage disease (Stage C) (3) (Figure 1). In this group of patients, systemic therapy is recommended (3). Prior to 2007, there was a lack of effective treatment options for patients with advanced HCC. Traditional chemotherapeutic agents were non-targeted and resulted in significant side effects due to their widespread cytotoxic or cytostatic mechanisms of action. It was evident that therapies such as doxorubicin and FOLFOX (fluorouracil, leucovorin, oxiplatin) had insufficient antitumoral activity and caused excessive toxicity in the context of cirrhosis. As a result, the ongoing development of systemic therapies is centered on the development of more targeted systemic therapies. The realm of systemic therapy for HCC is rapidly evolving and encompasses a range of drugs such as tyrosine kinase inhibitors (TKIs), monoclonal antibodies (ramucirumab), and immune check point inhibitors (nivolumab and pembrolizumab). As the focus of this chapter is TKIs (Table 1), other systemic therapies will not be discussed here. The authors recommend referring to "Immune checkpoint

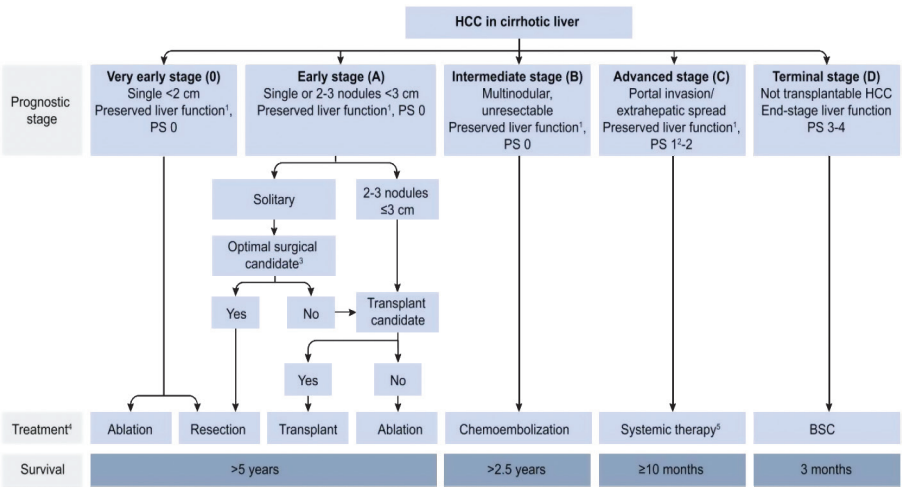

Figure 1 BCLC staging system and treatment strategy (3).

TABLE 1 Summary of tyrosine kinase inhibitors and relevant trials

Summary of tyrosine kinase inhibitors

TKI	Target receptors	Studies	Year	Type	No. of patients	Outcome	Current use
Sorafenib	VEGFR2, VEGFR3, PDGFR, c-kit, FLT-3, RET	SHARP Trial	2006–2008	Phase 3 randomized double-blind placebo-controlled trial (sorafenib vs. placebo)	602	Improved median OS (10.7 vs. 7.9 months, HR 0.69)	First-line agent for advanced HCC
		Asia Pacific Trial	2005–2007	Phase 3 randomized double-blind placebo-controlled trial (sorafenib vs. placebo)	226	Improved median OS (6.5 vs. 4.2 months, HR 0.68)	
Lenvatinib	VEGFR 1–3, FGFR 1-4, PDGF-alpha, RET, KIT	Ikeda et al	2010–2011	Phase 2 single-arm open label multicenter study	46	Improved median OS 18.7 months (95% CI: 12.7–25.1) TTP 7.4 months (95% CI: 5.5–9.4)	First-line agent for advanced HCC
		REFLECT Trial	2013–2015	Phase 3 open-label multicenter non-inferiority study (lenvatinib vs. sorafenib)	954	Improved median OS 13.6 months for lenvatinib versus 12.3 months for sorafenib (HR 0.92) TTP 7.4 months lenvatinib vs. 3.7 months sorafenib (HR 0.66)	
Regorafenib	VEGFR 1–3, oncogenic tyrosine kinase receptor	RESOURCE Trial	2013–2015	Phase 3 randomized double-blind parallel group (regorafenib vs. placebo)—previously treated with sorafenib	573	Improved median OS (7.8 vs. 10.6 months, HR 0.63) Improved PFS (1.5 vs. 3.1 months, HR 0.46)	Second-line agent for advanced HCC previously treated with sorafenib
Cabozantinib	MET, VEGF, AXL, RET, ROSI, TYRO3, MER, KIT, TRKB, FLT3, TIE2	CELESTIAL Trial	2013–2017	Phase 3 randomized double-blind placebo-controlled trial (cabozantinib vs. placebo)	707	Improved median OS (8 vs. 10.2 months, HR 0.76) Improved PFS (1.9 vs. 5.2 months, HR 0.44)	Second-line agent for advanced HCC previously treated with sorafenib

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTP, time taken to progression.

inhibition: Prospects for prevention and therapy of hepatocellular carcinoma" by Elsegood et al. for further information (4). Tyrosine kinases are involved in the activation of a wide range of proteins by phosphorylation. TKIs bind to the active site of tyrosine kinases, thus preventing phosphorylation and inhibiting downstream signal transduction of a range of growth factors. By blocking the key tyrosine kinase pathways in cancers such as the vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor 2(EGFR), and platelet-derived growth factor (PDGFR), tumor growth is halted.

SORAFENIB

Sorafenib was the first TKI to receive approval from the Food and Drug Administration (FDA) for systemic treatment of HCC in 2007 and remains the first-line therapy. It is an oral multi-kinase inhibitor that targets VEGFR2, VEGFR3, PDGFR, c-kit, FLT-3, and RET (5). This in turn prevents tumor angiogenesis and tumor cell proliferation, increasing the rate of apoptosis. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study and the Asia-Pacific trial were the two major trials which proved the efficacy of sorafenib.

The SHARP study was a phase III, randomized, double-blind, placebo-controlled trial carried out between 2006 and 2008 (5). It was conducted across multiple centers in North America and Europe. Child-Pugh (CP) A patients with advanced HCC who had not previously had any systemic treatment were recruited for the trial. For trial inclusion, the patients were required to have adequate hepatic, renal, and hematological reserve, and an ECOG of 0–2. 602 patients were included and randomized in a 1:1 ratio to oral sorafenib 400 mg twice a day versus placebo.

The Asia Pacific trial was also a multinational, phase III, randomized, double-blind placebo-controlled trial (6). It had similar inclusion criteria to the SHARP trial but was carried out in the Asia Pacific region; 226 patients were enrolled and randomized in a 2:1 ratio to sorafenib 400 mg twice a day versus placebo. Both trials permitted dose reductions in treatment interruptions in the event of drug toxicity.

The SHARP study demonstrated an improvement in overall survival of 2.8 months in favor of sorafenib (10.7 vs. 7.9 months, hazard ratio [HR] 0.69) (5). This effect was also seen in the Asia Pacific trial with sorafenib improving overall survival from 4.2 to 6.5 months (HR 0.68) (6). The difference in median survival between the two trials can be attributed to differences in the study populations. The patients in the Asia-Pacific trial were younger (51 years old vs. 65 years old), had predominantly Hepatitis B-related disease (75% vs. 18%), and had more advanced disease with more extrahepatic spread.

Dose reductions due to adverse events (AE) were common across both trials (26% in SHARP, 30.9% in Asia Pacific trial) (5). The most common TKI-associated AEs and their relevant management strategies are discussed later in this chapter. The median duration of treatment was only 5.3 months in the SHARP trial (5). Unfortunately, tolerability of sorafenib impacted on the

duration of treatment and hence survival. A pooled analysis of the SHARP and Asia Pacific trials was undertaken to determine the predictors of sorafenib benefit. It was found that patients who developed early dermatological AEs (within the first 60 days) had a better median overall survival than those who did not (18.2 vs. 10.1 months) (7).

With the widespread usage of sorafenib, there is now real-world data available for comparison with the two phase III trials. The Global Investigation of Therapeutic Decisions (GIDEON) study was a large prospective observational registry with 3,371 patients to evaluate the safety and usability of sorafenib in the HCC population. This cohort demonstrated that a higher CP score and a higher BCLC stage were associated with a shorter median survival—CP A: 13.6 months, CP B: 5.2 months, and CP C: 2.6 months (8). It also showed that the overall incidence of AE was comparable between CP A and B patients (8). A Taiwan-based study by Huang et al. used sorafenib in a broader HCC population, including patients who were CP B and CP C. They reported median overall survival rates of 8 months (9).

As there is significant genetic heterogeneity in HCC, this can result in both primary and secondary loss of response to sorafenib. Other therapeutic options are required for patients who have lost response. The benefits of sorafenib in combination with other therapies are being investigated. There have been trials combining sorafenib with doxorubicin, and radioembolization with Yttrium90 and erlotinib. At present, none of these trials have shown an improvement in median overall survival (10–13). The STORM trial was a phase III study comparing adjuvant sorafenib to placebo after radiofrequency ablation or hepatectomy. The use of sorafenib did not result in an improvement in recurrence-free survival (14). Further research into combination therapies that include sorafenib is required to provide advanced HCC patients with more therapeutic options.

LENVATINIB

Sorafenib, which was shown to improve survival in the SHARP and Asia-Pacific trials, has been the standard first-line therapy for unresectable HCC since 2007. Since then, other molecular-targeted agents have been developed and tested in clinical trials. However, this has been marked by four failed phase III trials evaluating sunitinib, brivanib, linifanib, and erlotinib plus sorafenib that did not show non-inferiority or superiority to sorafenib in terms of overall survival in the first-line treatment of HCC (10, 15–17). These negative trials created a need to develop new drugs as first-line agents for the effective management of HCC.

Lenvatinib was discovered at Tsukuba Research Laboratory in Japan as a result of research on angiogenesis inhibitors. It is an oral multikinase inhibitor that targets VEGF receptors 1–3, FGF receptors 1–4, PDGF receptor α, RET, and KIT and is an extremely effective inhibitor of tumor angiogenesis (18). It has shown activity against a range of solid tumors. Lenvatinib monotherapy is approved for the treatment of radioiodine-refractory differentiated thyroid cancer (19). With everolimus, it is used as a combined treatment for advanced renal cell carcinoma following one previous antiangiogenic therapy (20). The studies proving efficacy of lenvatinib in advanced HCC are described below.

A phase II trial in patients with HCC conducted in Japan and South Korea confirmed the potent antitumor effect of lenvatinib and the feasibility of managing AEs in patients with HCC (21). It was a phase II, single-arm, open-label multicenter study which was conducted on 46 patients between July 2010 and June 2011 with advanced HCC who did not qualify for surgical resection or local therapies. The patients received a dose of 12 mg once daily in 28-day cycles. The median time to progression was 7.4 months (95% CI: 5.5–9.4). The median overall survival was 18.7 months (95% CI: 12.7–25.1). Seventeen patients (37%) had partial response and 19 patients (41%) had stable disease (20). The most common any-grade AEs were hypertension (76%), palmar–plantar erythrodysesthesia syndrome (65%), decreased appetite (61%), and proteinuria (61%). Dose reductions and discontinuations due to AEs occurred in 34 (74%) patients and 10 (22%) patients, respectively (20). Dose reductions were needed more often in patients with a low body weight. A later detailed analysis of the pharmacokinetics of lenvatinib in patients with HCC determined that the optimal dose was 8 mg/day for patients weighing less than 60 kg and 12 mg/day for patients weighing 60 kg or more. These findings paved the way for the phase III trial named the REFLECT study.

The REFLECT trial was an open label phase III, multicenter non-inferiority trial which enrolled patients with unresectable HCC who had not received prior systemic chemotherapy. This was conducted at 154 sites across 20 countries. Stratification factors included region (Asia or non-Asia), macroscopic portal vein involvement and/or extrahepatic spread, ECOG performance status (0 or 1), and body weight (<60 kg or ≥60 kg); 954 eligible patients were randomized in a 1:1 ratio to lenvatinib (12 mg daily for body weight ≥60 kg, and 8 mg daily for body weight <60 kg) or sorafenib (400 mg twice daily for all patients) arms. Treatment was continued until disease progression or occurrence of intolerable adverse event. The primary endpoint was overall survival, measured from the date of randomization until the date of death from any cause (22).

Secondary endpoints included evaluation of progression-free survival, time to progression, objective response rate, quality-of-life measurements, and plasma pharmacokinetics lenvatinib exposure parameters.

Lenvatinib was non-inferior to sorafenib revealing that the median survival time for lenvatinib was 13.6 months (95% CI 12.1–14.9), and for sorafenib, it was 12.3 months (95% CI 10.4–13.9). The objective response rate for lenvatinib was higher (24% vs. 9%), and the median time to progression was longer (7.4 vs. 3.7 months, HR = 0.66, 95% CI 0.57–0.77) (22).

From the AEs point of view, the rate of grade 3 or 4 hypertension was higher with lenvatinib (23% vs. 14%), while the hand–foot skin reaction was more frequent with sorafenib (52% vs. 37%any grade, and 11% vs. 3% grade 3 or worse), as was alopecia of any grade (25% vs. 3%) (22).

Based on the REFLECT study, lenvatinib was approved in Japan in March 2018 for the treatment of unresectable HCC. In August 2018, it received approval in the United States adding another agent to the arsenal of medications used as the first-line treatment of HCC. Consensus-based guidelines from the National Comprehensive Cancer Network (NCCN) suggest limiting the use of lenvatinib to individuals with CP A cirrhosis. Therapeutic combinations involving lenvatinib with an immune checkpoint inhibitor have potential as future treatment strategies (23).

REGORAFENIB

Regorafenib is an oral diphenylurea multikinase inhibitor that targets kinases involved in tumor angiogenesis, cell proliferation, and survival (24, 25). Its chemical structure is similar to that of sorafenib, differing only in the presence of an extra fluorine atom. This change in structure is theorized to provide a wider range of targets to inhibit (25). Regorafenib was initially used for the treatment of metastatic colorectal cancer and gastrointestinal stromal tumors. In 2017, regorafenib received FDA approval for the treatment of patients with advanced HCC who had previously been treated with sorafenib. Despite this, regorafenib is currently not approved by the Therapeutic Goods Administration in Australia.

The RESORCE study was the first successful randomized, double-blind, parallel group, phase III trial for regorafenib. It was a multicenter trial conducted across 152 sites in 21 countries; 573 patients were enrolled and randomized in a 2:1 ratio to regorafenib 160 mg or placebo for the first 3 weeks out of every 4-week cycle. Both groups received best supportive care (26). The study included CP A patients with BCLC stage B or C disease who had documented progression of their disease on imaging despite sorafenib. Patients must have been able to tolerate sorafenib at a dose of at least 400 mg daily for 20 out of 28 days (26). Exclusion criteria were intolerance of sorafenib and failure of previous systemic therapy.

The study's primary endpoint was overall survival, defined as time from randomization to death from any cause. Secondary endpoints were progression-free survival (based on radiological or clinical data), time to progression, objective response (complete or partial response), and disease control rate (defined as complete response, partial response, or stable disease for >6 weeks based on mRECIST criteria). Treatment was continued until progression, death, or unacceptable toxicity from the drug.

The RESORCE trial showed that regorafenib increased survival, as compared with placebo, from 7.8 to 10.6 months (HR = 0.63, $P < 0.0001$). Progression-free survival in patients on regorafenib also increased from 1.5 to 3.1 months (HR = 0.46, $P < 0.0001$); 54% of patients had stable disease with 23% experiencing a progression in their disease (26). Subanalysis showed that patients treated with sorafenib and regorafenib had a longer survival time of 26.0 versus 19.2 months in patients who had sorafenib and placebo (27).

Of note, 93% of patients on regorafenib experienced an adverse event with up to 50% having a severe (Grade 3 or 4) adverse event. This would have resulted in interruption to treatment and dose reduction. As the duration of dose interruption and degree of dose reduction were not formally reported in the results of the trial, it is difficult to ascertain its effect on the results.

Real-world data are available since the RESORCE trial. A retrospective multicenter study in Japan by Ogasawara et al. has verified the safety and efficacy of the medication in advanced HCC. The median progression-free survival is comparable to that of the RESORCE trial. The Japanese study did have a significantly longer median overall survival of 17.3 months (28). However, this difference may be attributable to the use of other systemic therapies such as lenvatinib in the patients who discontinued regorafenib.

Based on the existing data, regorafenib is a suitable second-line therapy for advanced HCC in patients who tolerated sorafenib, even if they experienced progression. It is yet unclear if it would be appropriate to use in a sorafenib naïve population.

CABOZANTINIB

Cabozantinib is another oral multikinase inhibitor targeting multimodal pathways. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2 (29, 30). MET and AXL genes are associated with poor prognosis and development of resistance to VEGF inhibition. Thus, developing inhibitors that simultaneously inhibit VEGF and other pathways involved in tumor invasion and metastasis may confer broad and potent antitumor efficacy. Cabozantinib was initially indicated for the treatment of advanced renal cell carcinoma in treatment naïve adults with intermediate or poor risk or in adults following prior treatment with VEGF-targeted therapy.

Efficacy of cabozantinib in treating advanced HCC was shown in phase III CELESTIAL trial (31). It was a randomized double-blind multicenter study conducted across 95 centers in 19 countries. A total of 707 patients were enrolled and randomized in 2:1 ratio to cabozantinib 60 mg or placebo. Eligible patients had received previous treatment with sorafenib, had evidence of disease progression after at least one systemic treatment, and could have received up to two previous systemic treatments for advanced HCC. The patients were 18 years of age or older who had received a pathological diagnosis of HCC not amenable to curative treatment and had CP A cirrhosis. Furthermore, patients were required to have an ECOG score of 0 or 1. Exclusion criteria included previous treatment with cabozantinib and uncontrolled clinically significant illness.

The trial's endpoint was overall survival defined as the time from randomization to death from any cause. Secondary endpoints were progression-free survival defined as the time from randomization to radiographic progression or death from any cause whichever occurred first and objective response rate (the percentage of patients with a confirmed complete or partial response). Tumors were assessed by computed tomography or magnetic resonance imaging at baseline and every 8 weeks after randomization.

CELESTIAL trial showed that cabozantinib increased the median overall survival as compared to placebo from 8.0 months to 10.2 months (HR = 0.76, *P* 0.005) (31). The difference was more pronounced when the analysis was limited to patients whose only prior therapy was sorafenib (median overall survival: 11.3 vs. 7.2 months). The median progression-free survival was also higher on cabozantinib, 5.2 months as compared to 1.9 months on placebo (HR = 0.44, *P* <0.001). The most common grade 3 or 4 AEs with cabozantinib were palmar–plantar erythrodysesthesia (17% vs. 0% in the placebo group), hypertension (16% vs. 2%),

increased aspartate aminotransferase (12% vs. 7%), fatigue (10% vs. 4%), and diarrhea (10% vs. 2%) (31).

The success of the clinical trial for cabozantinib expands the agents available for HCC therapy as second-line treatment. Based on these findings, in January 2019, cabozantinib was approved for treatment of patients with HCC who have been previously treated with sorafenib. Consensus-based guidelines from the NCCN recommend considering cabozantinib only for patients with CP A cirrhosis.

ADVERSE EFFECTS AND MANAGEMENT

Within clinical trials, AEs were graded according to severity—Grade 0 (none), grade 1(mild), grade 2(moderate), and grade 3 (severe). Grade 0 to grade 2 AEs did not require any change to the treatment regime. Grade 3 AEs necessitated an interruption to treatment until improvement in symptoms. Patients with grade 3 AEs were also given reduced doses if the event re-occurred on recommencing the medication.

Across the four sentinel phase III trials done for sorafenib, regorafenib, lenvatinib, and cabozantinib, a significant proportion of patients reported drug-related AEs. The incidence of grade 3 AEs ranged from 45% to 75% (5, 6, 26, 31). This indicates that a majority of patients would have experienced an interruption to their treatment or dose reduction because of AEs. The most common AEs and their management recommendations are detailed below.

Hand–foot syndrome (HFS)

Hand–foot syndrome is also known as palmar–plantar erythrodysesthesia. It is a common reaction to TKIs which can occur within days of commencing the drug. In some cases, presentation is delayed and can commence several months after the initiation of the drug. It is most commonly seen with regorafenib, occurring in 53% of patients (26). It was also the most prevalent AE in sorafenib, lenvatinib, and cabozantinib trials, occurring in 21%, 27%, and 46% of patients, respectively (4, 5, 30). The hands and feet are frequently involved. Symptoms include altered sensation (numbness and tingling), stiffness, and pain. Erythema is often seen with some patients also experiencing hyperkeratosis or onycholysis. HFS can affect patients' ability to perform activities of daily living, impairing the quality of life (32).

Diagnosis is made clinically. Recommendations for the management of HFS are largely derived from clinical experience rather than trials. Prophylactic use of emollients and urease-based creams three times a day results in decreased incidence of HFS (33). Other strategies include avoiding mechanical trauma to hands and feet in the form of friction or extreme temperatures. This entails wearing well-fitting shoes with padded insoles and using non-foaming cleansers (33).

If HFS develops, topical corticosteroid cream and topical lignocaine are recommended for symptomatic relief. Oral analgesics can be used with caution. Cessation or dose reduction of the drug leads to improvement in symptoms but this is not ideal from a HCC perspective. Temporary cessation and re-introduction of the drug when symptoms have completely resolved is recommended. If severe symptoms recur, a dose reduction or discontinuation may be necessary.

Diarrhea

Diarrhea is the second most common AE. It is strongly associated with sorafenib and cabozantinib, occurring in 55% and 54% of patients, respectively (33). Initial management includes cessation of lactulose and making dietary changes to avoid food triggers. Sufficient fluid intake should be emphasized to ensure patients do not become dehydrated. When the above strategies are insufficient to manage symptoms, loperamide is recommended, with a maximum dose of 16 mg per day.

Hypertension

Hypertension is a common side effect of all TKIs. Patients taking lenvatinib and regorafenib had the highest incidence of hypertension (42% and 31%, respectively) and the largest number of patients with grade 3 hypertension (23% and 15%). In comparison, only 5% of sorafenib-treated patients reported hypertension. Of these, 2% of patients had grade 3 hypertension (33).

It is recommended that all patients have their blood pressure checked prior to commencing TKI treatment and be monitored throughout their treatment course. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta blockers are all appropriate choices for the management of hypertension.

Fatigue

It is difficult to differentiate whether the fatigue reported by patients is due to TKIs or may be a symptom of advanced HCC and cirrhosis. Fatigue may also be associated with malnutrition caused by other TKI-associated AEs. Physical exercise has been shown to reduce fatigue in patients with advanced malignancy (33). Management is largely supportive in the form of encouraging adequate rest and nutrition.

Nausea and vomiting

Nausea, vomiting, decreased appetite, and weight loss are the common side effects of TKIs. The prevalence of nausea was highest in patients on cabozantinib (31%) and sorafenib (24%). Although relatively common, nausea and vomiting were rarely severe with less than 2% of patients across all studies experiencing grade 3 nausea and vomiting (33). Antiemetics can be utilized for symptom control. Ondansetron can cause QT prolongation and should be used with caution in combination with sorafenib, cabozantinib, and lenvatinib, as these agents can also cause QT prolongation.

CONCLUSION

TKIs have been the mainstay of systemic treatment for advanced HCC since 2007. Although AEs limit their usage, patients who can tolerate TKIs do have a survival benefit. The landscape in the management of advanced HCC has been changing

rapidly over the past few years. With the new arsenal of therapies available for advanced HCC, sorafenib is no longer the sole therapeutic option. Lenvatinib, the new first-line agent for unresectable HCC patients, though non-inferior to sorafenib in terms of overall survival, did demonstrate significantly improved progression-free survival and objective response rates, while also being generally well tolerated. Either option is reasonable for selection by the treating physician. Similarly, second-line options are also available now. While these agents provide a multitude of additional therapeutic options, some questions remain to be addressed. The data on second-line agents have been reported in patients who had prior sorafenib and not lenvatinib. The choice of second-line agents may be based on various factors including physicians' comfort, familiarity with using a particular agent, and patient choice after education regarding safety profile. Finally, the impact of various combination therapies on advanced HCC is currently being investigated. Combination therapies with TKIs and PD-1 inhibitors are currently in their early phase and are being evaluated in terms of safety and tolerability. These ongoing developments will certainly go a long way. Although great strides have been made, ongoing progress is still needed and yet to come.

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