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Targeted Molecular Therapeutic Options for Hepatocellular Carcinoma

Swathi Sridhar[a], **Ishna Sharma**[a], **Umesh T. Sankpal**[a], **Bassam Ghabach**[b], **Kalyani Narra**[b], **Latha Neerukonda**[b], **Riyaz Basha**[a,*]

[a]Texas College of Osteopathic Medicine, University of North Texas Health Science Center at Fort Worth, Fort Worth, Texas

[b]JPS Oncology and Infusion Center, Fort Worth, Texas

Abstract

Liver cancer is the 6th leading cause of cancer related deaths in the US even though it ranks 14th in incidence. More men are diagnosed with liver cancer than women, and the number of projected deaths among men (20,020) is almost double that among women (10,140) in the US. Infections like hepatitis and metabolic conditions like obesity are believed to be major risk factors for the onset of liver cancer. Hepatocellular carcinoma (HCC), the most common type of liver cancer, accounts for 75% of all cases. Chemotherapy has not been effective in treating HCC. Targeted therapies are being used in advanced HCC patients due to a better survival and less side effects when compared to traditional chemotherapy. Therapeutic agents targeting the regulators of growth factor signaling pathways and the mediators of downstream signaling—for example, inhibitors of the tyrosine kinase receptor—are used as targeted molecular therapies. Kinase inhibitors that modulate growth signals, such as sorafenib and lenvatinib, are commonly employed in targeted molecular therapy for HCC patients. This review covers these agents, highlighting modes of action and providing details on clinical trials.

Keywords

Hepatocellular carcinoma; targeted molecular therapy; sorafenib; lenvatinib

I. INTRODUCTION

Liver cancer is a leading cause of cancer-related deaths worldwide.[1] It is also one of the cancers showing a recent increase in incidence and number of cancer-related deaths in the US.[2] At time of diagnosis, liver cancer may be categorized as primary (e.g., hepatocellular carcinoma, HCC; cholangio-carcinoma; sarcoma), originally arising from liver cells, or secondary, arising from metastases to the liver.[1,3] In the US and Europe, secondary liver cancer is more common than HCC whereas the opposite is true in Asia and Africa.

*Address all correspondence to: Riyaz Basha, PhD, Department of Pediatrics and Women's Health, Texas College of Osteopathic Medicine, University of North Texas Health Science Center at Fort Worth, Fort Worth, Texas 76107; Fax: +1-817-735-2563, Riyaz.Basha@unthsc.edu.

Several risk factors are associated with HCC, and their contribution to incidence varies based on educational, environmental, and genetic differences among various populations. In Asia, where the disease is endemic, vertical transmission of hepatitis B virus (HBV) and aflatoxin exposure are the most common causes of HCC development.[4-7] Further, Asian males are more affected than Asian females, showing earlier disease onset. In contrast, risk factors in Western countries include hepatitis C virus (HCV), cirrhosis, alcoholism, nonalcoholic fatty liver disease, obesity, and smoking.[5,6] Genetic disorders, such as tyrosinemia, hereditary hemochromatosis, and glycogen storage disease type Ia are also implicated in HCC development and progression.[1,3,8]

Because of variations in risk factor prevalence among populations, global incidence of HCC is also heterogeneous. In 2018, worldwide incidence was 841,080, with rates highest in East Asia and sub-Saharan Africa due to the previously listed endemic causes; incidence was lowest in the Americas.[1,9] Incidence in East Asia and sub-Saharan Africa is close to 20 per 100,000, while in the US it is 6.6 per 100,000.[1,2] Despite a global increase in HBV vaccination rates, aflatoxin exposure prevention, and general health education, the overall global incidence of HCC is expected to continue to increase.[1,2,10] In particular, the increase in the US correlates to an increase in environmental factors, such as HCV among adults born between 1945 and 1965, nonalcoholic fatty liver disease, and obesity. When factoring in ethnic variations, males have up to a threefold higher incidence than females.[2,10] Among different ethnicities, American Indians and Alaskan Natives have the highest incidence. Hispanics and blacks show an increasing incidence compared to non-Hispanic whites, who continue to have the lowest rates, partly due to greater awareness of what constitutes high-risk behaviors for HCC.[11-13]

The prognosis for HCC is dependent on disease stage, demographics, and racial factors. The stage of HCC is a reliable predictor of patient prognosis, with earlier stages (e.g., 0, A) correlating with higher survival rates. Table 1 provides correlations between staging/Child-Pugh classification for liver cirrhosis (detailed further in Table 2) and associated survival rates. Moreover, variations in demographics and race are correlated with prognosis among US populations. For example, some studies report that younger patients have a poorer survival rate than older patients due to a greater tumor burden and cancer aggressiveness at diagnosis, and that men have a poorer prognosis than women.[14-16] Blacks are more likely to be younger at presentation and with a more advanced stage than non-Hispanic whites due to higher rates of viral hepatitis in blacks.[15,17,18]

Although HCC is the third most common cause of cancer-related deaths worldwide, HCC prognosis and survival continue to improve because of increasing avoidance of high-risk behaviors, accessibility of treatment, and treatment better tailored to genetic causes.[19,20] Depending on disease stage and other patient related factors, treatment options include complete resection via surgery, liver transplant, local ablation, systemic chemotherapy, and targeted therapy. Of these, oral targeted therapy can be used in many ways, such as in conjunction with local therapies for localized or locally advanced HCC, as a stand-alone therapy for metastatic HCC, and for a variety of patient populations.[21-23]

Despite increasing treatment options, racial and ethnic disparities remain an issue due to cost of treatment, access to care and lack of resources.[24]

II. MOLECULAR TARGET THERAPIES

As previously mentioned, using targeted molecular drugs in HCC therapy is advantageous for many reasons. Targeted therapy may be used in conjunction with other therapies. It can also treat patient populations with unresectable cancers. Many such therapies target the molecular pathways that are involved in HCC development and eventual metastasis.[21-23] Examples of these pathways are those that regulate growth factor signaling and downstream signaling mediators of the receptor tyrosine kinase.[24,25]

A. Regulation of Growth Factor Signaling

Cells control proliferation and temporary senescence via a variety of growth factor pathways. These pathways are generally stimulated by growth factors that bind to tyrosine kinase receptors, such as vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth (PDGFR) receptor, among others.[25] In malignant cells, regulation of these pathways at the receptor level is often lost, allowing for continuous cell proliferation. For example, constitutive activation of VEGFR encourages angiogenesis; an increase in the release of growth factors may stimulate other growth factor receptors.[25] Thus, it is advantageous to include molecular target therapy that directly inhibits receptors (Table 3).

B. Downstream Tyrosine Kinase Receptor Signaling Mediators

Activation of tyrosine kinase receptors stimulates downstream pathways that include Ras, Raf, mitogen-activated protein kinase (MAPK), and extracellular signal–regulated kinase (ERK). The receptors activate Ras, which in turn phosphorylates Raf serine threonine kinase. Raf eventually activates MEK (MAPK/ERK) to initiate inappropriate cell growth and angiogenesis while inhibiting the apoptosis pathway.[22,26,27] In addition, activation of the tyrosine kinase receptors may stimulate the PI3k/Akt/mTOR downstream pathways. In particular, the activated receptors work with phosphoinositide-3 kinase (PI3K) to activate phosphatidylinositol 4,5-bisphosphate (PIP2), which activates phosphatidylinositol 3,4,5-triphosphate (PIP3), which is negatively regulated by PTEN (phosphatase and tensin homolog detected on chromosome). PIP3 may then activate serine threonine kinase (Akt), which activates mTOR, a serine/threonine kinase. Ultimately, mTOR modifies gene transcription to favor cell proliferation and inhibits apoptosis. Because products of the PI3k/Akt/mTOR pathway participate in other regulation pathways, HCC targeted therapies designed to inhibit this pathway may be extremely efficacious.[23,28-30]

III. CURRENT TARGETED THERAPIES

Surgery for complete resection is the treatment of choice for patients with good liver function and/or localized tumors without metastasis or vascular expansion. Liver transplant is the ideal treatment to remove the tumor as well as the underlying liver disease.[29-32] For patients who cannot receive surgery, transplants or other therapies, local ablation (e.g.,

transarterial chemoembolization, TACE), and targeted molecular therapy are appropriate.[20] Here we focus on first-line targeted molecular therapies.

A. Sorafenib

Sorafenib is the first oral multikinase inhibitor to be used in the treatment of HCC. It is especially suitable for patients for whom localized therapy is not an option but who have advanced or intermediate HCC and preserved liver function. Its mechanism targets many crucial pathways involved in HCC tumorigenesis, including the targeted tyrosine kinase receptors VEGFR, PDGFR, and FGFR and downstream serine threonine kinases in the Raf/MEK/ERK pathways (Fig. 1). According to the double-blind, placebo-controlled SHARP trial, patients receiving sorafenib for systemic treatment of HCC had a 3-month increase in median survival rate (7.9 months to 10.7 months). A trial focusing on the Asia-Pacific region showed similar rates in the studied populations.[25,33-35]

B. Sorafenib versus Other Drugs

Monotherapy agents like brivanib, sunitinib, and linifanib have been studied and compared to sorafenib, but have not proved to be as efficacious. Brivanib, which inhibits VEGFR and FGFR, was compared to sorafenib in the BRISK-FL study. In this phase III trial, brivanib's overall survival (OS) did not meet its primary end point when compared to sorafenib (9.5 versus 9.9 months, respectively).[36] Similarly, a phase III study comparing sunitinib to sorafenib, in which the median OS was 7.9 months for sorafenib and 10.2 months for sunitinib, showed that sunitinib was neither equivalent nor superior to sorafenib. Sunitinib side effects and toxicity led to early termination of the trial.[33]

A phase III trial of linifanib versus sorafenib yielded the same conclusion as the previous ones: linifanib did not meet predetermined superiority or noninferiority OS boundaries. The median OS was 9.1 for linifanib and 9.8 for sorafenib.[37]

C. Combinations with Sorafenib

Erlotinib has been studied as conjunctive therapy with sorafenib. In a placebo-controlled trial, median OS between sorafenib plus erlotinib and sorafenib plus placebo was 9.5 and 8.5 months, respectively. Overall survival did not improve with erlotinib in patients with advanced HCC.[38] Doxorubicin has been used in combination with sorafenib as well, but the addition of doxorubicin did not significantly improve OS and had higher toxicity than sorafenib alone.[39]

Selective internal radiation therapy (SIRT) with yittrium-90 has been studied compared with sorafenib in patients with locally advanced or intermediate HCC. Median OS was 8 months and 9.9 months for SIRT and sorafenib, respectively, which was not considered a significant difference.[40]

IV. LENVATINIB AS FIRST-LINE THERAPY

Lenvatinib is an inhibitor of multiple proteins involved in angiogenesis and tumor growth. It competitively inhibits tyrosine kinase receptors VEGFR, FGFR, KIT, and RET, and

thus their respective downstream pathways.[41] Of note is lenvatinib's action on FGFR-4, which binds fibroblast growth factor 19. Overexpression of this ligand-receptor complex has been implicated in decreased formation of reactive oxygen species and apoptosis by sorafenib.[55,56] Lenvatinib's inhibition of signals generated by the FGF-19/FGFR4 complex is an important feature of its antitumor activity, as it overcomes a mechanism that leads to sorafenib's failure in slowing the development and spread of HCC (Fig. 1).[42,43]

Lenvatinib was studied in phase I trials in patients with advanced HCC and Child-Pugh A and B. Optimal doses were determined to be 12 mg for Child-Pugh A and 8 mg for Child-Pugh B, with a tolerable side effect profile.[44] In a phase II study, Asian patients with advanced HCC not eligible for local therapy were given 12 mg of lenvatinib once a day in 28-day cycles.[45] Median time to progression was 7.4 months and median OS was 18.7 months. Lenvatinib was used in these patients for a median of 7.3 months, and the most common adverse event leading to discontinuation was proteinuria. Further analysis of these patients showed that 12 mg a day was optimal for Child-Pugh A patients weighing 60 kg or more and 8 mg a day for those weighing less than 60 kg.[45,46] In a phase III trial, patients with unresectable HCC were recruited from Asia-Pacific, Europe, and North America and randomly assigned to either lenvatinib or sorafenib treatments. Median survival for the lenvatinib group was 13.6 months, which was noninferior to that of sorafenib at 12.3 months.[47]

In addition to being as efficacious as sorafenib, lenvatinib may have an advantage in cost; it has been found to provide a 0.27 life year increase with a 0.23 quality improvement at a negative incremental cost compared to sorafenib.[47]

V. CONCLUSION

Various targeted therapies have been investigated for treatment of HCC. The most successful of these has been sorafenib, which is a multi–receptor kinase inhibitor. This standard-of-care treatment was one of the first to be approved as a first-line therapy to improve survival in patients with advanced disease. New first-line and second-line treatments have since been approved. Most of them (e.g., regorafenib, cabozantinib) are receptor tyrosine kinase inhibitors with different inhibition profiles. Cabozantinib has a profile that is partly similar to that of sorafenib, and it inhibits receptor tyrosine kinases including MET and AXL.[48] It is approved for use in patients who have previously been treated with sorafenib. In the CELESTIAL (Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma) phase III clinical trial involving HCC patients with advanced disease who previously received sorafenib, cabozantinib treatment increased both overall and progression-free survival compared to placebo treatment.[49]

Another drug, regorafenib, was the first to be approved for patients whose cancer had progressed on sorafenib.[50] Although structurally similar to sorafenib, it has a potent and distinct activity profile. Its approval as a second-line treatment was based on the outcome of the multinational phase III RESORCE (Regorafenib for Patients with Hepatocellular Carcinoma Who Progressed on Sorafenib Treatment) trial.[51] Regorafenib treatment resulted

in disease stabilization, which significantly improved overall and progression free survivals compared to placebo.[51,52]

VI. FUTURE DIRECTIONS

A tremendous increase in genetic and immunological understanding of HCC has recently gained momentum. Treatment options are rapidly expanding, with several agents undergoing clinical trials. Immunotherapy trials have had mixed results. A phase III trial (KEYNOTE-240, NCT02702401) with pembrolizumab, a single-agent immune checkpoint inhibitor, did not find this drug to be superior to placebo treatment in patients treated previously with sorafenib.[53] However, based on the overall response rate of 31% and the duration of response in a Check-Mate 040 trial in March of 2020 the FDA granted accelerated approval for the combination of immunotherapy drugs nivolumab and ipilimumab for patients with HCC who have been previously treated with sorafenib. There is optimism as well regarding other checkpoint inhibitors and therapy that combine these immune checkpoint inhibitors with receptor tyrosine kinases or antiangiogenic therapies (ClinicalTrials.gov; NCT03347292, NCT03755791, NCT03434379).[54] In addition to research focused on elucidating the molecular mechanisms of HCC, research is under way to better understand the association of environmental and other contributors in these populations. The results are urgently needed to address the disparities in HCC survival rates among different population groups.

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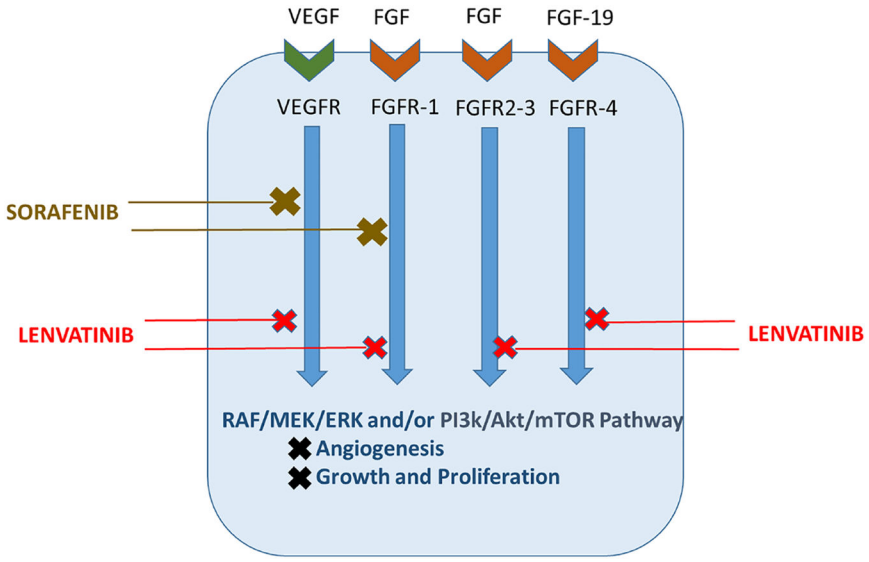

FIG. 1:

Mechanism of action for first-line HCC targeted molecular therapies. Current targeted therapies affect molecular pathways important in HCC development and metastatic ability. Shown are sorafenib, which competitively inhibits VEGFR and FGFR1 signaling at the receptor level and at their respective downstream signaling pathways, and lenvatinib, a preferred first-line targeted therapy due to its inhibition at multiple receptors and their associated downstream signal cascades. A primary target of lenvatinib is the receptor FGFR4, which has been shown to decrease the apoptotic ability of sorafenib if overexpressed.

TABLE 1:

Hepatocellular carcinoma staging, classification, and survival rate

Stage	Lesions	Child-Pugh class	Survival rate with therapy	Ref.
0	Single lesion, < 2 cm	A or B	86% (5 yr)	20
A	Single lesion or ≤ 3 lesions ≤ 3 cm	A or B	69% (5 yr)	25
B	Multinodular	A or B	50% (5 yr)	55
C	Vascular invasion and hepatic spread	—	13% (3 yr)	56
D	Extrahepatic and vascular spread	C	8% (3 yr)	57

TABLE 2:

Child-Pugh classification system for liver cirrhosis (based on the results of Clarke and Hurwitz[58])

Criteria	1 point	2 points	3 points
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Ascites	None	Mild-moderate; diuretic responsive	Severe; diuretic refractory
Bilirubin (mg/dL)	< 2	2–3	> 3
Encephalopathy	None	Grade 1–2	Grade 3–4
INR	< 1.7	1.7–2.3	> 2.3
Total Points	5–6 = Class A	7–9 = Class B	10–15 = Class C

TABLE 3:

Targets of HCC molecular therapy

Agent	Molecular targets	Efficacy compared to sorafenib	Status	Refs.
Sorafenib	VEGFR, PDGFR, c-KIT, RET, Ras/Raf, MEK/ERK	—	Approved 1st line	23,26,27,33,59
Lenvatinib	VEGFR, PDFGFR, FGFR-4, RET	Equivalent	Approved 1st line	58
Cabozantinib	VEGFR, KIT, MET AXL	Superior (compared to placebo)	Approved later lines (after sorafenib)	58
Regorafenib	VEGFR, PDGFR, FGFR	Superior (compared to placebo)	Approved later lines (after sorafenib)	51
Brivanib	VEGFR2, FGFR1	Inferior	Completed clinical trial 2013	22,36
Linifanib	PDFGF-Rs, VEGF-R	Inferior	Completed clinical trial 2012	37

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