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REVIEW ARTICLE

Combining Multi-kinase Inhibitors and Immune Checkpoints Blockade in Hepatocellular Carcinoma: A Pharmacotherapeutic Approach

Vothani Sarath Babu[1,*], P Bhavana Sree[2], C Pallavi[3], S Pavithra[2], P M Vasanth[2]

[1]*Faculty, Department of Pharmaceutics, S V U College of Pharmaceutical Sciences, Sri Venkateswara University, Tirupati, 517502, Andhra Pradesh, India*
[2]*S V U College of Pharmaceutical Sciences, Sri Venkateswara University, Tirupati, 517502, Andhra Pradesh, India*
[3]*Department of Biochemistry, S V U College of Sciences, S V U College of Pharmaceutical Sciences, Sri Venkateswara University, Tirupati, 517502, Andhra Pradesh, India*

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* *Corresponding author.*
Vothani Sarath Babu
sarathvothani@gmail.com

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ABSTRACT

Liver cancer, particularly hepatocellular carcinoma (HCC), represents a significant global health burden with limited treatment options and poor prognosis. This article provides a comprehensive overview of pharmacotherapy for liver cancer, focusing on both established and emerging drugs. Current standard-of-care treatments, including sorafenib and lenvatinib, target key pathways involved in tumor growth and angiogenesis. However, their efficacy is often limited, prompting ongoing research into novel therapeutic approaches. Emerging immunotherapies, such as immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapy, have shown promise in clinical trials, offering new avenues for personalized treatment strategies. Additionally, targeted therapies aimed at specific genetic alterations, such as FGFR inhibitors for FGFR-altered HCC, demonstrate potential for improved outcomes in select patient populations. These abstract highlights the evolving landscape of pharmacotherapy for liver cancer and underscores the need for further research to optimize treatment efficacy and patient outcomes.

Keywords: Multikinase Inhibitors; Immune Checkpoint Inhibitors; Hepatocellular Carcinoma (HCC); Sorafenib

INTRODUCTION

Liver is an organ, which is primarily responsible for the metabolism of carbohydrates, fats and proteins, also in detoxification and hormone production. Thus, diet has measurable biological impacts on key pathways hypothesized to be involved in liver cancer risk[1].

About 72 % of all liver cancer occurs in Asia, with China accounting for 47 %. Primary liver cancer is the third leading cause of cancer-related death worldwide Hepatocellular carcinoma (HCC) is the most common (>80 %) histological type of liver cancer[2].

Liver cancer, predominantly hepatocellular carcinoma (HCC), remains a formidable global health challenge with rising incidence rates and limited treatment options. Early diagnosis through imaging modalities and serum biomarkers enhances treatment success, although challenges persist in detecting liver cancer at early stages. Treatment options vary depending on tumor stage, liver function, and patient fitness. Surgical resection, liver transplantation, locoregional therapies (such as radiofrequency ablation and transarterial chemoembolization), and systemic therapies (including tyrosine kinase inhibitors and immunotherapy) constitute the mainstay of treatment.

Despite advancements, prognosis remains poor for advanced-stage disease, necessitating continued research efforts to identify novel therapeutic targets and improve patient outcomes. Collaboration between multidisciplinary teams, integration of precision medicine approaches, and ongoing surveillance are crucial in combating this complex disease.

LIVER CANCER

Different types of liver cancer are given in Figure 1.

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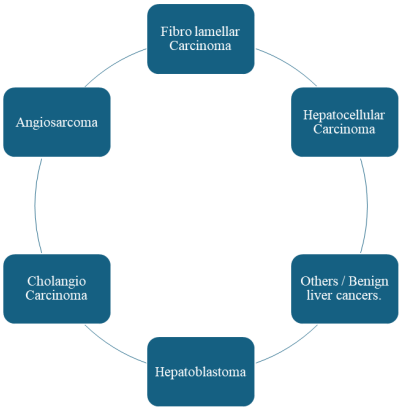


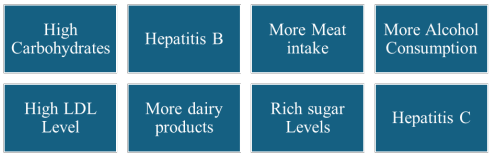
Fig. 1: Types of liver cancers

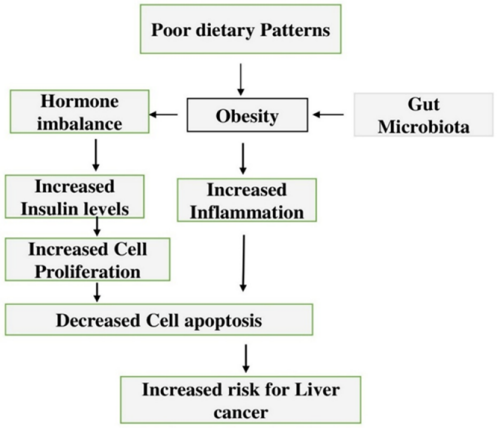
Symptoms of Liver Cancer

- Heavy loss of weight
- Loss of appetite
- Upper abdominal pain
- Abdominal swelling
- Yellow discoloration of the skin and eyes (jaundice)
- White or chalky stools[3].

Risk factors of Liver Cancer

Risk factors are discussed in following habits and caused by other disease associations.





Pathophysiology of Liver Cancer

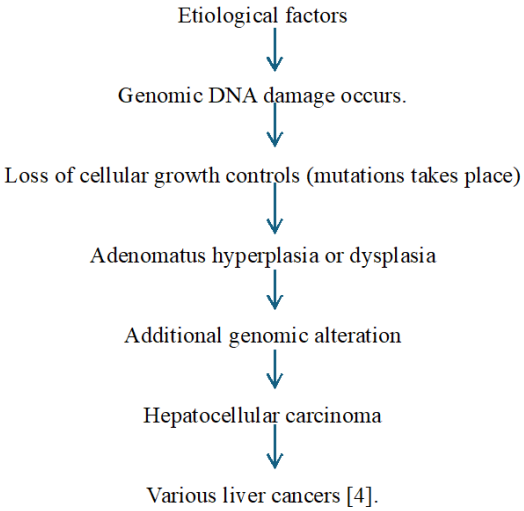


Fig. 2: Risk factors included in pathogenesis of liver cancer[4]

Classification of anti-cancer drugs on liver cancer

The drugs used for the treatment of liver cancer are classified based on mechanism of action as discussed in Table 1.

Table 1: Classification of anti-cancer drugs on liver cancer

S. NO	Details	Multi Kinase inhibitors	Immune check point inhibitors
1	List of drugs	Sorafenib, Lenvatinib, Cabozatinib, Infigratinib phosphate, Futibatinib Pegaptanib, Regorofinib.	Atezolizumab, Bevacizumab, Durvalumab, Pembrolizumab, Ramucirumab, Tremelimumab, Ipilimumab, Nivolumab.
2	Drug targets/drug profile	Protein kinases are intracellular enzymes that regulate cell growth & proliferation as well as triggering & regulation of immune responses. Protein kinase play a crucial role in cancer by regulating signaling pathways that control cell growth survival & proliferation. Targeting these kinases with specific inhibitors can disrupt these pathways. Offering potential therapeutic avenues to inhibit cancer progression & promote cell death in malignant cells. Protein kinases are enzymes that catalyze the transfer of phosphate groups from ATP to specific amino acids on target proteins, there by regulating their activity. **Kinases associated with liver cancer:** **1. Epidermal growth factor receptor (EGFR):** overexpression or activation EGFR is observed in a subject of HCC cases, promoting cell proliferation and survival **2. Fibroblast growth factor receptor (FGFR):** FGFR signaling is implicated in HCC progression, promoting cell growth, angiogenesis, and metastasis. **3. Vascular endothelial growth factor receptor (VEGFR):** activation of VEGFR promotes angiogenesis in HCC, facilitating tumor growth and metastasis. **4. Hepatocyte growth factor receptor (c-Met):** Dysregulation of c-Met signaling contributes to HCC development and progression, promoting cell proliferation, migration, & invasion. **5. Pl3K/AKT/m TOR pathway:** Kinases within this pathway, including phosphatidylinositol-3 kinase (Pl3K), AKT, & mammalian target of rapamycin [m TOR], are frequently dysregulated in HCC, promoting cell survival, proliferation, & metabolism. **6. MAPK pathway:** components of the mitogen-activated protein kinase (MAPK) pathway, such as Ras, Raf, MEK, & ERK, are often activated in HCC, driving cell proliferation, survival, & metastasis. **7. Checkpoint kinases:** checkpoint kinases like CHK1 & CHK2 are involved in cell cycle regulation & DNA damage response. Dysregulation of these kinases can contribute to genomic instability and tumor development in HCC. **8. CDKs:** Cyclin-dependent kinases (CDKs), such as CDK4 & CDK6, regulate cell cycle progression & are frequently dysregulated in HCC, promoting uncontrolled cell proliferation.	Immunity plays a significant role in liver cancer, particularly in the context of Hepatitis B & Hepatitis C virus infections, which are major risk factors for development of liver cancer. Immune checkpoint pathways such as the PD-1, PD-L1 axis, play a crucial role in regulating the immune response in liver cancer. Overexpression of PD-L1 on tumor cells can inhibit T-cell function, allowing cancer cells to evade immune destruction. Immune check point inhibitors are drugs that enhances the immune system's ability to recognize and attack cancer cells. Immune checkpoint inhibitors (ICIs) have emerged as a promising treatment option for liver cancer, particularly hepatocellular carcinoma (HCC). ICIs work by blocking inhibitory checkpoints on T cells, such as PD-1 (programmed cell death protein 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), thereby enhancing the immune response against cancer cells. Several clinical trials have investigated the efficacy and safety of ICIs in patients with advanced HCC. Drugs like nivolumab, pembrolizumab, and atezolizumab have shown promising results in some patients. Pembrolizumab was the first ICI to receive FDA approval for the treatment of patients with HCC who have previously been treated with sorafenib, based on the results of the KEYNOTE-224 trial. ICIs are often studied in combination with other systemic therapies, such as tyrosine kinase inhibitors (e.g., sorafenib) or anti-angiogenic agents, to enhance their efficacy. Biomarkers like PD-L1 expression and tumor mutational burden (TMB) are being investigated to predict response to ICIs in HCC. However, there is currently no consensus on their utility in guiding treatment decisions. While ICIs have shown efficacy in some patients, they can also lead to immune-related adverse events (irAEs) that affect various organs. Close monitoring and management of these side effects are essential during treatment. Ongoing research is focused on identifying predictive biomarkers, optimizing treatment strategies (including combination therapies), and exploring the role of ICIs in earlier stages of HCC. Overall, immune checkpoint inhibitors represent an important therapeutic avenue in the management of liver cancer, offering new hope for patients with advanced disease.

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Table 1 continued

3	Mechanism of actions	Sorafenib, Lenvatinib, Cabozatinib, infigrinatib Phosphate, futibatinib, Pemigatinib, regorafenib. ↓ Targets multiple kinases ↓ Inhibition of kinases EGFR, FGFR, VEGFR, CDKs, RAF, PDGFR, KIT, RAT ↓ Downstream effects Anti-angiogenesis, cell growth inhibition, apoptosis induction ↓ Clinical effects anticancer activity, tumor regression.	Atezolizumab, bevacizumab, durvalumab, pembrolizumab, ramucirumab, tremelimuma, ipilimumab, nivolumab. ↓ T-cell activation. These inhibitors primarily target T- cells, a type of white blood cell involved in the immune response. ↓ PD-L/PD-L1 pathway: Most immune checkpoint inhibitors block the interaction between programmed cell death protein 1 on T-cells and programmed death ligand-1 on cancer cells or other immune cells. ↓ CTLA-4 Pathway: Some inhibitors target cytotoxic T-lymphocyte associated protein 4, which regulates T-cell activation. ↓ Inhibition of checkpoint proteins Blockade of PD-1 / PD-L1 pathway and CTLA-4 pathway ↓ Enhanced antitumor immunity. ↓ Clinical effects – anti cancer activity, tumor regression
4	Polymers	Polymers (MKls)- PLGA (poly D, L lactide co glycolide), PCL (poly e caprolactone), PLA (poly lactic acid) are the polymers which are mostly used in the formulation of tyrosine kinase inhibitors. Hydrogels are complex structures of cross-linked polymeric chain, which are used in formulation to control the release rate of drug. Oils such as captex 300 are used in formulation of low soluble drugs. Surfactants such as kolliphor RH 40, transcutol HP are used. HPMC K4M is used as precipitation inhibitor.	Polymers (lCls)- No polymers are used in formulation of immune check point inhibitor drugs (as they control and expands the time of drug release). Most of the drugs which of the immune check point inhibitors are administered through lV infusion for immediate release.

Continued on next page

Table 1 continued

5	Therapeutic activity (Pharmacokinetics)	Multi-kinase inhibitors are typically administered orally and undergo absorption in the gastrointestinal tract. Factors such as solubility, formulation, and food intake can affect their absorption rates. In patients with liver cancer, alterations in gastrointestinal function due to liver dysfunction or other comorbidities may influence drug absorption. **Distribution:** Once absorbed, multi-kinase inhibitors are distributed throughout the body, including to the liver tumor tissue. However, distribution may be influenced by factors such as protein binding, tissue perfusion, and the presence of efflux transporters. In liver cancer patients, altered hepatic blood flow and potential liver metastases may affect drug distribution to the liver. **Metabolism:** Multi-kinase inhibitors undergo hepatic metabolism primarily via cytochrome P450 enzymes, particularly CYP3A4. Liver dysfunction associated with liver cancer can affect drug metabolism, leading to altered plasma concentrations and potentially increased risk of adverse effects. Additionally, drug interactions with other medications metabolized by the same enzymes should be considered. **Excretion:** Multikinase inhibitors and their metabolites are primarily eliminated through hepatic and renal routes. Liver dysfunction can impair drug clearance, leading to prolonged drug exposure and increased risk of toxicity. Renal impairment may also affect drug excretion, although it is less common with most multi-kinase inhibitors.	**Absorption:** ICIs are typically administered intravenously, leading to rapid and complete absorption into the bloodstream. Distribution: They distribute widely throughout the body, reaching tumor sites as well as peripheral tissues. However, the distribution may be limited by factors such as protein binding and tissue penetration. **Metabolism:** ICIs, such as monoclonal antibodies targeting PD-1, PD-L1, or CTLA-4, are primarily metabolized by proteolytic degradation or catabolism, like endogenous immunoglobulins . **Elimination:** The elimination half-life of ICIs varies but can be relatively long, ranging from weeks to months. They are eliminated via proteolysis and clearance by the reticuloendothelial system. **Factors affecting PK:** Factors such as renal or hepatic impairment, patient's immune status, and concomitant medications may influence the pharmacokinetics of ICIs.

Comparative analysis

A comparative analysis of various levels of the current available anti-cancer drugs on liver cancer was discussed in Table 2 and different graphical representations (Graphs 1, 2 and 3).

Table 2: Comparative analysis of liver cancer drugs

Name of the drug	BCS classification	Mechanism of action	Half-life	Bioavailability	Therapeutic efficacy / Overall response rate
Sorafenib	Class 2	Multikinase inhibitors	20-48 hours	38-49%	56.8%
Lenvatinib	Class 2	Multikinase inhibitors	28 hours	85%	81%
Cabozatinib	Class 2	Multikinase inhibitors	99 hours	25-77%	32%
Infigratinib phosphate	Class 4	Multikinase inhibitors	33.5 hours	1.5-51%	-
Futibatinib	Class 2	Multikinase inhibitors	2.3 hours	11.2%	13.7%
Pemigatinib	Class 2	Multikinase inhibitors	5 hours	14-41%	36%
Regorafenib	Class 2	Multikinase inhibitors	20-30 hours	69-83%	9%
Atezolizumab	-	Immune check point inhibitors	27 days	Subcutaneous 30%	24%
Bevacizumab	-	Immune check point inhibitors	4.8 days	Subcutaneous 1%	73.2%
Durvalumab	-	Immune check point inhibitors	18 days	Intravenous administration	42.9%
Pembrolizumab	-	Immune check point inhibitors	26 days	Intravenous administration	20-50%
Ramucirumab	-	Immune check point inhibitors	10 days	Intravenous administration	9.1%
Tremelimumab	-	Immune check point inhibitors	22 days	Intravenous administration	25%
Ipilimumab	-	Immune check point inhibitors	14.7 days	Intravenous administration	28%
Nivolumab	-	Immune check point inhibitors	20 days	Intravenous administration	82.9%

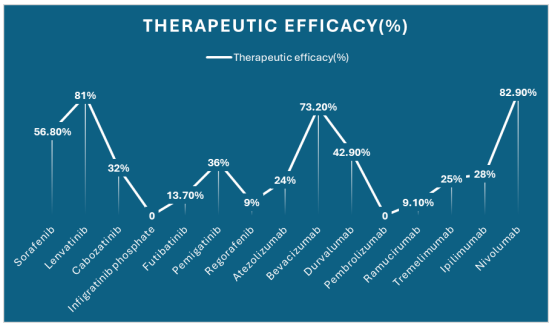
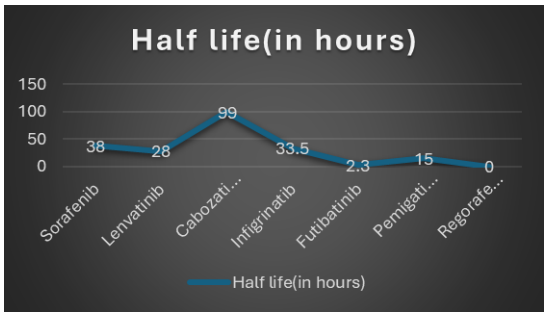
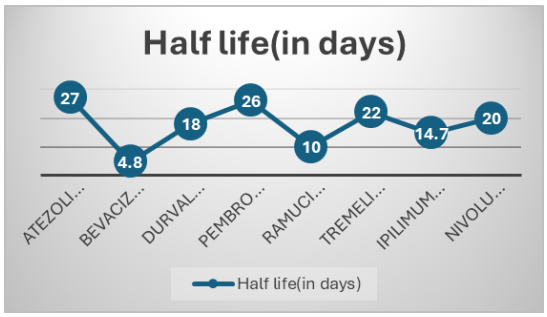


Fig. 3: Therapeutic Efficacy (%) [5]

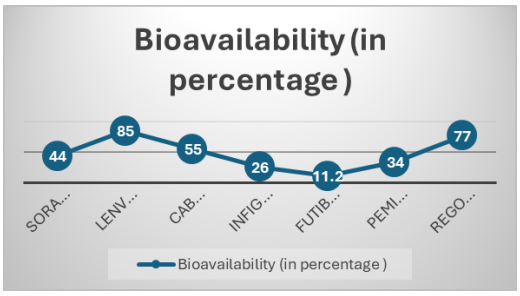
Graphical analysis: [6]



Graph 1: **Half-life of multikinase inhibitors**



Graph 2: **Half-life of immune check point inhibitors**



Graph 3: **Bioavailability of multikinase inhibitors**

SUMMARY AND CONCLUSION

From the above analysis, it is concluded that multi-kinase inhibitors, such as sorafenib, lenvatinib are mostly used as a first line approach for the treatment of liver cancer. Whereas immune checkpoint inhibitors are prescribed during advanced disease conditions. Economically multi-kinase inhibitors are cost effective, compared to immune checkpoint inhibitors. Multi-kinase inhibitors exhibit low bioavailability, when compared to immune checkpoint inhibitors (as they are administered through iv infusion). Nivolumab and pembrolizumab are best immune checkpoint inhibitors used for the treatment of liver cancer. Half-life and bioavailability may vary from different individuals, based on disease state food intake, age, gender etc. Multi-kinase inhibitors may fail in the treatment in some cases, due to low bioavailability. So, it necessary to include, some polymers, which controls the drug release, solubility, and dissolution rates and Immune checkpoint inhibitors exhibits best pharmacokinetic properties than multi-kinase inhibitors. Therapeutic efficacy and overall response rate best for immune checkpoint inhibitors. So, immune checkpoint inhibitors are used for advanced liver cancer[7–10].

Conflict of Interest

No conflict of interest.

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