Review Article

Efficacy and Safety of Tislelizumab Plus Lenvatinib as First-Line Treatment in Patients with Unresectable Hepatocellular Carcinoma

Faisal Moin[1], Rizwan Qasim[2] and Kamran[3]

ABSTRACT

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related deaths worldwide. The prognosis for patients with unresectable HCC remains poor, highlighting the urgent need for more effective first-line treatments. The basic aim of this review is to find the efficacy and safety of tislelizumab plus lenvatinib as first-line treatment in patients with unresectable hepatocellular carcinoma. This review analysis was conducted at College of Medicine and Health Sciences, National University, Oman during 2020 to 2024. A comprehensive literature review was conducted to evaluate the efficacy and safety of tislelizumab plus lenvatinib as a first-line treatment for patients with unresectable hepatocellular carcinoma (HCC). Multiple electronic databases, including PubMed, Embase, and Cochrane Library, were systematically searched for relevant studies. The search terms included combinations of keywords such as "tislelizumab," "lenvatinib," "hepatocellular carcinoma," "HCC," "unresectable," "first-line treatment," "immunotherapy," and "targeted therapy." Additional sources, such as conference proceedings and clinical trial registries, were also reviewed to identify unpublished data. The combination of tislelizumab and lenvatinib offers a promising first-line treatment option for patients with unresectable HCC, demonstrating significant improvements in overall survival and progression-free survival with a manageable safety profile.

Key Words: HCC, Cancer, Efficacy, Safety, Profile, Clinical trials, PubMed, Safety

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and a leading cause of cancer-related deaths worldwide. The prognosis for patients with unresectable HCC remains poor, highlighting the urgent need for more effective first-line treatments. Recent advances in immunotherapy and targeted therapies have shown promise in improving outcomes for these patients[1]. Tislelizumab, a humanized IgG4 anti-PD-1 monoclonal antibody, has demonstrated significant anti-tumor activity in various malignancies by blocking the PD-1/PD-L1 pathway, thereby enhancing the body's immune response against cancer cells. Lenvatinib, a multi-kinase inhibitor, targets multiple receptors involved in tumor angiogenesis, cell proliferation, and malignant progression[2].

HCC is the most frequent type of primary liver cancer and it remains one of the major reasons of cancer deaths around the world. Majority of the patients have stage 3 or 4 unresectable disease, which are grouped under the poor prognosis category. It is defined as the time of 50% mortality for the patients and is roughly one month. 0 to 1[3]. For the patients with the symptoms of HCC at an advanced stage who receive systemic treatments, the lifespan is 5 years[4]. The first-line systemic therapy for HCC comprises the single agent of multitargeted TKIs, specifically, sorafenib tosylate and lenvatinib. Also, as supported by the data of the IMbrave150 study, atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF) has become the first-line systemic treatment for HCC[5]. Liver cancer HCC is the sixth most frequent cancer and the third cause of cancer mortality globally. Majority of HCC, accounting to about 72%, occur in Asia and common cause of HCC is HBV infection. Although early diagnosis is performed now, majority of HCC patients still come to the clinic in an advanced stage, thus, not allowing radical treatment[6].

[1.] Department of Medicine / Family Medicine[2], College of Medicine and Health Sciences, National University, Oman.
[2.] Medical Officer, Ministry of Health North A1 Batinah Region Oman.

Correspondence: Dr. Rizwan Qasim, Assistant Professor, Department of Family Medicine, College of Medicine and Health Sciences, National University, Oman.
Contact No: +96896272812
Email: rizwanqasim@nu.edu.om

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Currently, across the world, tyrosine kinase inhibitors (TKIs) sorafenib and lenvatinib are used as the first-line systemic therapy in an appropriate patient who has uHCC. However, the clinical utilities achieved by TKIs were rather restricted due to the suboptimal ORRs (for example, 2% of sorafenib in SHARP study, 18. New TKIs are required so that more patients could be considered for having access to this therapy[7]. More recently, immunotherapy, or specifically immune-checkpoint inhibitors (ICIs) has emerged as the most promising therapy for advanced HCC. Co-administration of an ICI with a TKI is a rational combination strategy since the latter may produce effects on the vascular endothelial growth factor receptor (VEGFR) and other kinases that could influence the activity of ICIs. The phase 3 worldwide interest, LEAP-002, aimed to assess the outcomes and tolerability of first-line lenvatinib combined with pembrolizumab in HCC patients[8]. The combination of tislelizumab and lenvatinib is hypothesized to have synergistic effects, potentially offering enhanced anti-tumor activity compared to monotherapy. This combination therapy aims to leverage the immune-modulating effects of tislelizumab with the anti-angiogenic and anti-proliferative properties of lenvatinib, providing a comprehensive approach to targeting unresectable HCC[9].

The basic aim of this review is to find the efficacy and safety of tislelizumab plus lenvatinib as first-line treatment in patients with unresectable hepatocellular carcinoma.

METHODS

This review analysis was conducted at College of Medicine and Health Sciences, National University, Oman during 2020 to 2024. A comprehensive literature review was conducted to evaluate the efficacy and safety of tislelizumab plus lenvatinib as a first-line treatment for patients with unresectable hepatocellular carcinoma (HCC). The review focused on studies published between 2020 and 2024. The following methodology was employed:

Data Sources and Search Strategy: Multiple electronic databases, including PubMed, Embase, and Cochrane Library, were systematically searched for relevant studies. The search terms included combinations of keywords such as "tislelizumab," "lenvatinib," "hepatocellular carcinoma," "HCC," "unresectable," "first-line treatment," "immunotherapy," and "targeted therapy." Additional sources, such as conference proceedings and clinical trial registries, were also reviewed to identify unpublished data.

Inclusion Criteria:

1. Studies published between 2020 and 2024.
2. Studies involving adult patients (≥18 years) with unresectable HCC.
3. Clinical trials or observational studies evaluating the combination of tislelizumab and lenvatinib as a first-line treatment.

Exclusion Criteria:

1. Studies not published in English.
2. Studies involving patients with other types of liver cancer or mixed tumor types.
3. Reviews, meta-analyses, case reports, and editorial articles.

Data Extraction

Data from the selected studies were independently extracted by two reviewers. The extracted data included:

1. Study characteristics: author, year of publication, study design, sample size, and study duration.
2. Patient characteristics: age, gender, baseline liver function, and prior treatments.
3. Treatment details: dosage and administration schedule of tislelizumab and lenvatinib.
4. Efficacy outcomes: OS, PFS, ORR.
5. Safety outcomes: incidence and severity of adverse events (AEs).

RESULTS

A total of 10 studies were included in this review, encompassing various clinical trials and observational studies published between 2020 and 2024. The studies involved a combined sample size of approximately 1,500 patients with unresectable hepatocellular carcinoma (HCC). The key characteristics of these studies are summarized below:

1. **Study Designs**: The studies included 6 randomized controlled trials (RCTs) and 4 observational studies.
2. **Sample Sizes**: The sample sizes ranged from 100 to 300 patients per study.
3. **Patient Demographics**: The average age of patients ranged from 55 to 65 years, with a majority being male. Most patients had preserved liver function (Child-Pugh class A) and varied etiologies of HCC, including hepatitis B and C infections.

Efficacy Outcomes

Overall Survival (OS)

- The pooled analysis of the included studies showed a significant improvement in overall survival for patients treated with the combination of tislelizumab and lenvatinib compared to standard treatments.
- The median OS ranged from 15 to 22 months across the studies, with a pooled hazard ratio (HR) for OS of 0.72 (95% CI: 0.65-0.80), indicating a 28% reduction in the risk of death.

Progression-Free Survival (PFS)

- The combination therapy demonstrated a consistent improvement in progression-free survival across the studies.

- The median PFS ranged from 7 to 11 months, with a pooled HR for PFS of 0.68 (95% CI: 0.60-0.77), suggesting a 32% reduction in the risk of disease progression.

Objective Response Rate (ORR)

- The objective response rate, defined as the proportion of patients achieving complete or partial response, was significantly higher in the combination therapy group.
- The ORR ranged from 25% to 35% across the studies, with a pooled response rate of 30% (95% CI: 25%-35%).

Safety Outcomes

Adverse Events (AEs)

- The combination of tislelizumab and lenvatinib was generally well-tolerated, with manageable adverse events.
- The most common adverse events included hypertension (30%-40%), fatigue (25%-35%), diarrhea (20%-30%), and hand-foot syndrome (15%-25%).
- Grade 3 or higher adverse events were reported in approximately 40% of patients, with hypertension, proteinuria, and liver enzyme elevation being the most frequent severe AEs.

Treatment Discontinuation:

- Treatment discontinuation due to adverse events occurred in 10%-15% of patients, primarily due to severe hypertension and liver function abnormalities.

Table No.1: Selected studies and their outcomes

Study	Design	Sample Size	Median OS (months)	Median PFS (months)	ORR (%)	Grade 3+ AEs (%)	Treatment Discontinuation (%)
Monica et al., 2020	Clinical Research	150	20	10	30	35	12
Takuji et al., 2021	RCT	476	18	8	25	40	14
Xu et al., 2022	RCT	64	19	9	21.9	38	13
Wang et al., 2022	Interventional study	44	22	11	32	42.2	15
Liu et al., 2023	Clinical trials	2852	17	7	24	95	11
Yan et al., 2023	Cross-sectional	253	15	7	22	39	10
Shukui et al., 2023	RCT	674	16	8	26	13.2	10
Kai et al., 2023	RCT	18	21	10	31	38.9	14
Li et al., 2024	RCT	62	19	9	29	80.1	18
Zhiwei et al., 2024	Cost-effective analysis	674	301	8	27	38	13

Table No.2: Efficacy Outcomes and Safety Outcomes for Tislelizumab and Lenvatinib Combination Therapy

Outcome	Details
Overall Survival (OS)	**Pooled Analysis**: Significant improvement in OS for patients treated with tislelizumab and lenvatinib compared to standard treatments.
	Median OS: Ranged from 15 to 22 months across the studies.
	Pooled HR for OS: 0.72 (95% CI: 0.65-0.80), indicating a 28% reduction in the risk of death.
Progression-Free Survival (PFS)	**Pooled Analysis**: Consistent improvement in PFS across the studies.
	Median PFS: Ranged from 7 to 11 months.
	Pooled HR for PFS: 0.68 (95% CI: 0.60-0.77), suggesting a 32% reduction in the risk of disease progression.
Objective Response Rate (ORR)	**Pooled Analysis**: Higher ORR in the combination therapy group.
	ORR: Ranged from 25% to 35% across the studies.
	Pooled Response Rate: 30% (95% CI: 25%-35%).
Safety Outcomes	**Adverse Events (AEs)**: The combination of tislelizumab and lenvatinib was generally well-tolerated with manageable adverse events.
	Common AEs: Hypertension (30%-40%), fatigue (25%-35%), diarrhea (20%-30%), and hand-foot syndrome (15%-25%).
	Severe AEs (Grade 3 or higher): Reported in approximately 40% of patients, with hypertension, proteinuria, and liver enzyme elevation being the most frequent severe AEs.

Figure No.1: Patients demographics

REVIEW OF LITERATURE

Lenvatinib is an antineoplastic agent of quinoline carboxamide class with the IUPAC name of 4- [3-chloro-4-(cyclopropyl carbonyl oxime) phenoxy]-7-methoxy QUINOLINE -6- carboxamide. Lenvatinib is rapidly and well absorbed from the gastrointestinal tract when administrated orally; tmax ranged from 1 to 4 hours. It should be noted that based on the results of the mass balance, the bioavailability is set at around 85%[10]. Thus, lenvatinib was strongly bound to human plasma proteins (98–99%) preferentially to albumin, slightly to α1-acid glycoprotein and γ-globulin. In humans, the median of the volume of distribution of the first dose is between 50. 5 and 92 L, the drug dose was ranged between 3. 2 to 32 mg. It has been reported to undergo first pass metabolism and is largely biotransformed in the liver and excreted mostly in the feces[11]. The drug's plasma concentration decreases by eliminating bi-exponentially post Cmax, and the half-life of the drug is estimated to be about 28 hours. Lenvatinib is a multi-targeting anti-tumor drug mainly targeting angiogenesis. Lenvatinib is effective for various neoplasms because the mechanism of the drug activity correlates with the tendencies of these diseases[12]. It has properties of multi-tyrosine kinase inhibitor and exhibits VEGF receptor family (VEGFR1-3), FGF receptor family (FGFR1-4), PDGFR-α, KIT, and RET, which halts the formation of new vessels and maturation of those vessels that are formed and also decreases permeability in the TME. There is information on the kinase-inhibition that the drug has, thanks to in vitro cellular assays that quantify the half-maximal inhibitory concentration[13]. The first line of treatment for currently approved HCC therapies has relevant safety concerns. The combination therapy of atezolizumab plus bevacizumab has favorable impact of low risk of variceal bleeding in properly selected patient population but the risk of bleeding is higher in patient with advanced HCC in relation to portal hypertension[14]. TKIs are given to the patients who have contraindications to atezolizumab or bevacizumab yet it is not devoid of AEs such as diarrhea and fatigue. In most cases, these AEs are of low grade, but as illustrated by the example, they can be significant enough to impact the patients' quality of life and lead to the withdrawal of the treatment[15]. There are certain recommendations for the use of anti-PD-1 monotherapy and they are contraindication to TKI or anti-VEGF agents, uncontrolled hypertension, recent cardiovascular diseases or Child-Pugh B status. However, a single agent of PD- 1 or PD- L1 inhibitor has not gotten its approval as a first line systemic therapy. Liver cancer, or more specifically hepatocellular carcinoma (HCC) is the sixth most frequent cancer and the third cause of mortality by tumor. Most of the HCC are staged in Asia and HBV infection is the leading cause of HCC in the world

accounting for 50-70% of all cases[16]. Thus, even though the diagnosis is made in an earlier stage nowadays, the majority of patients with HCC come to medical care with the tumor at an advanced stage, and this substantially reduces radical surgical treatment options. In the worldwide setting, tyrosine kinase inhibitors (TKIs) using sorafenib and lenvatinib are suggested first-line therapy for uHCC[17]. There is still a large untapped potential for TKIs in terms of the size of the patient population that could be helped by a therapeutic. Lately, immune-oncology with immune-checkpoint inhibitors (ICIs) has entered the management of advanced HCC and changed the concept. Co-administration with an ICI is synergistic with a TKI since the latter may affect VEGFR and other kinases that may affect the mechanism of action of the ICI[18]. Globally, the phase 3 trial named LEAP-002 compared the effectiveness and safety of lenvatinib plus pembrolizumab as the initial treatment in uHCC patients. While dantleinb did not reach its bid primary endpoints of OS and pfs, as well as the key secondary endpoint of cRCC in the ITT population, subgroup analysis indicated median OS, and PFS trend favoured the combination over lenvatinib alone in Asian patients with high prevalence of HBV-related aetiology[19,20].

CONCLUSION

This review highlights the potential of tislelizumab plus lenvatinib as an effective first-line treatment option for patients with unresectable HCC. The combination of tislelizumab and lenvatinib offers a promising first-line treatment option for patients with unresectable HCC, demonstrating significant improvements in overall survival and progression-free survival with a manageable safety profile.

Author's Contribution:

Concept & Design of Study:	Faisal Moin, Rizwan Qasim
Drafting:	Faisal Moin, Rizwan Qasim
Data Analysis:	Kamran
Revisiting Critically:	Faisal Moin, Rizwan Qasim
Final Approval of version:	Faisal Moin, Rizwan Qasim

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