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ROLE OF LENVATINIB FOR PATIENTS WITH HEPATOCELLULAR CARCINOMA

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ABSTRACT

AIM: The goal of this study is to learn more about the clinical features and efficacy of Lenvatinib, an orally active inhibitor of several receptor tyrosine kinases, in patients with hepatocellular carcinoma.

METHOD: 92 individuals with hepatocellular cancer were enrolled in a multicentre, randomised, non-inferiority trial. Lenvatinib (12mg orally once daily) was given to patients in a 1:1 ratio.

RESULTS: The majority of patients (67.8%) were men. Child-Pugh A was found in 44.6% of the population, whereas Child-Pugh B was found in 39.1 %. In 9 % of cases, dose decreases were noted. PFS and OS medians were not reached. The benchmark PFS and OS at 6 and 12 months were 85.1 and 64.9 %, respectively, and 91.8 and 72.6 %, respectively.

CONCLUSION: Lenvatinib therapy was shown to be effective and safe.

KEYWORDS: Lenvatinib, Hepatocellular carcinoma, Tyrosine kinase, Liver cancer, Multikinase inhibitor

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide [(1)] two major epidemiological facts characterize this cancer. It occurs in a previously diseased liver, and the causes of the underlying liver disease differ according to the geographical distribution [(2).]

The molecular pathogenesis of HCC differs depending on the genotoxic insults and etiologies involved. Hepatitis B and C viruses, diabetes, obesity, alcoholic fatty liver disease (AFLD), and non-alcoholic fatty liver disease (NAFLD) are all key risk factors for HCC (NAFLD). Tobacco smoking, food contaminants[(3,4)] such as aflatoxins, family or genetic factors, and different environmental pollutants that serve as carcinogens are all known to enhance the prevalence of HCC.

Surgical resection, tumour ablation, and liver transplantation are among current therapy options for early-stage illness [(5).] Intra-arterial chemotherapy, transcatheter arterial chemoembolisation, percutaneous ethanol injection, cryotherapy, thermotherapy, proton therapy, gene therapy, and a variety of their combinations are among the additional treatment options. However, the absence of conclusive data currently limits the usage of these medicines. Another possibility is gene therapy, which, while still in its early stages, could play a key role in the treatment of hepatocellular carcinoma in the future [(6, 7, 8)].

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that blocks the kinase activities of the VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4) vascular endothelial growth factor (VEGF) receptors [9]. In addition to their normal cellular functions, lenvatinib inhibits other RTKs that have been linked to pathogenic angiogenesis, tumour growth, and cancer progression, such as the fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; the platelet derived growth factor receptor alpha (PDGFR), KIT, and RET [10,11].

Lenvatinib has anti-tumor clinical activity in patients affected by differentiated thyroid carcinoma, renal cancer and hepatocellular carcinoma. Lenvatinib is a drug that is used to treat thyroid cancer in patients who are unable to receive radioactive iodine therapy. Used in the treatment of liver cancer that cannot be removed surgically. For the treatment of advanced renal cell carcinoma, lenvatinib is combined with Everolimus (kidney Cancer).

Over the past decade, Sorafenib, a multikinase inhibitor, has been considered the only first-line treatment for patients with HCC. Systemic therapies for patients with HCC are rapidly changing, with some new agents showing clinical efficacy in phase III trials [12]. The REFLECT trial compared Sorafenib to Lenvatinib and, having setting non inferiority criteria as analytical endpoints, found that the overall survival (OS) for those administered lenvatinib was similar to that for those administered sorafenib[13].

Therefore, we performed a multicentre retrospective analysis to evaluate the efficacy and safety of Lenvatinib for patients with advanced HCC.

MATERIALS AND METHODS

Study design and participants

This is a retrospective and multiregional study involving patients diagnosed with HCC. Participants were routinely attending multidisciplinary team consultations. All patients were fully informed about the objectives of this study and provided formal consent. Data were collected from patients during lenvatinib interventions for a period of one year from April 2019 to April 2020.

A total of 154 patients were initially deemed eligible. Each of these participants had received a confirmed HCC diagnosis using pathological assessment methods or through specific HCC imaging. The initial sample included participants who had not been recommended for hepatic resection, liver transplantation or any other radical ablation.

We excluded 28 patients who had been treated with lenvatinib combination therapies at the beginning of treatment. 23 patients were also excluded because they had received an additional antitumor therapy including systematic or locoregional therapy while receiving lenvatinib during this study.

Adverse events (AEs) were analysed across the 103 remaining patients, of whom 92 patients provided complete information for further analysis. All 92 patients included were administered lenvatinib monotherapy until disease progression or until encountering an intolerant adverse event.

Treatment and Assessment

The standard dosing schedule of lenvatinib used in the REFLECT trial (8 mg/day to patients weighing <60 kg and 12 mg/day to those ≥60 kg) was recommended. However, modification of the starting dose was allowed depending on the clinical situation at the discretion of the attending physicians.

Dose interruptions or reductions were made according to the protocol of the REFLECT trial. Every 6–8 weeks, or anytime a sign or symptom suggested tumour progression, a CT or MRI scan was performed to examine the tumour. The Response Evaluation Criteria in Solid Tumors were used to determine the tumour response.

RESULTS

Patient Characteristics

Baseline patient characteristics are summarized in Table 1. From April 2019 to April 2020, 92 patients altogether who met the inclusion criteria were included in this analysis, out of the 99 total patients who received lenvatinib. The median age was 60 years (range 19–81 years), and 71 of the patients (77.2 %) were male. Hepatitis B virus was the most common etiology of HCC (n = 67, 72.8%). The majority of patients were classified as Child-Pugh A (n = 74, 80.4%) or BCLC stage C (n = 81, 88.0%), while 18 patients (19.6%) and 11 patients (12.0%) had Child-Pugh B or BCLC stage B, respectively, at the time of initiation of lenvatinib. Sixty-one patients (66.3%) had extra hepatic metastasis, with the most common metastatic site being the lungs (n = 46, 50.0%), followed by the lymph nodes (n = 29, 31.5%), and peritoneum (n = 12, 13.0%). Macro vascular invasion was noted in 37 patients (40.2%) and baseline serum AFP exceeded 200 ng/mL in 49 patients (53.3%). This study included 35 (38.0%) patients who did not meet the REFLECT inclusion criteria in terms of disease extent (bile duct invasion, n = 10; main portal vein invasion, n = 15; and tumor occupying ≥50% of the liver, n = 22).

Median age, years (range)	60 (19–81)
Male gender	71 (77.2)
Etiology	
Hepatitis B	67 (72.8)
Hepatitis C	12 (13.0)
Alcohol	6 (6.5)
Unknown	7 (7.6)
ECOG performance status	
0/1	58 (63.0)
2	34 (37.0)
BCLC stage	
B	11 (12.0)
C	81 (88.0)
Child-Pugh class	
A	74 (80.4)
B	18 (19.6)
Extrahepatic metastasis	61 (66.3)
Lung	46 (50.0)
Lymph nodes	29 (31.5)
Peritoneum	12 (13.0)
Macrovascular invasion	37 (40.2)
Main portal vein invasion	15 (16.3)
Baseline serum AFP >200 ng/mL	49 (53.3)
Maximum intrahepatic tumor size, mm (range)	46 (0–184)
Prior treatment	
Surgery	29 (31.5)
RFA	9 (9.8)
TACE	54 (58.7)
Prior systemic therapy	25 (27.2)
Multi kinase inhibitor	18 (19.6)
Sorafenib/regorafenib/atezolizumab + cabozantinib	18 (19.6)/10 (10.9)/1 (1.1)
Immune checkpoint inhibitors	15 (16.3)
Nivolumab/atezolizumab + bevacizumab/atezolizumab + cabozantinib	8 (8.7)/6 (6.5)/1 (1.1)
Treatment setting of lenvatinib	
First-line	67 (72.8)
Second-line	14 (15.2)
Third- or later-line	11 (11.9)

Values are expressed as *n* (%), unless otherwise indicated. ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; RFA, radiofrequency ablation; AFP, α-fetoprotein; TACE, transcatheter arterial chemo-embolization.

Table 1. Baseline characteristics of 92 patients

Lenvatinib was administered as first-line therapy to 67 (72.8%) patients, second-line therapy to 14 (15.2%), and third or fourth-line therapy to 11 (11.9%) patients. Of the 25 patients who had received prior systemic therapy, sorafenib and regorafenib were the drugs administered to 18 (19.6%) and 10 (10.9%) patients, respectively, and immune checkpoint inhibitors (ICIs) to 15 (16.3%, i.e., nivolumab to 8, atezolizumab + bevacizumab to 6, and atezolizumab + cabozantinib to 1). There was no significant difference in key baseline characteristics between patients who received lenvatinib as first-line and second- or later-line treatment.

Starting doses of lenvatinib were: 12 mg (n = 32; 34.8%), 8 mg (n = 49; 53.3%), or 4 mg daily (n = 11; 12.0%) daily. The starting dose of lenvatinib was reduced in 22 patients (23.9%) because of a poor performance status (n = 14), old age (n = 6), or poor liver function (n = 2, both with a Child-Pugh score of 9).

Therapeutic efficacy and AEs during entire treatment period

Of all the study patients, 13 achieved a partial response (PR), graded by RECIST v1.1, but none achieved a complete response, resulting in an ORR of 14.1%. Stable disease (SD) and progressive disease (PD) were the best responses, observed in 60 (65.2%) and 19 (20.7%) patients, respectively, and the disease control rate (DCR) was 79.3%. The median follow-up duration was 6.6 months (95% confidence interval [CI] 4.9–8.4 months), median PFS was 4.3 months (95% CI 3.2–5.3 months), and median OS was 7.1 months (95% CI 5.5–8.7 months). In patients who received lenvatinib as second- or later-line therapy (n = 25), the median OS from the start of first-line systemic therapy was 15.5 months (95% CI 8.3–22.6 months).

Because of the heterogeneous nature of the population included in this study, efficacy outcomes were analysed after stratification according to the treatment line of lenvatinib, the Child-Pugh class, and the BCLC stage when lenvatinib was initiated in Table 2

	Overall (n = 92)	Child-Pugh A					Child-Pugh B (n = 10)	BCLC-B (n = 11)	BCLC-C (n = 81)
		all (n = 74)	1st-line (n = 57)	2nd–4th line (n = 17)	prior ICIs group (n = 11)	extensive tumor involvement in liver* (n = 28)			
Response according to RECIST 1.1									
Complete response, n (%)	0	0	0	0	0	0	0	0	0
Partial response, n (%)	13 (14.1)	12 (16.2)	12 (21.1)	0	0	3 (10.7)	1 (5.6)	4 (36.4)	9 (11.1)
Stable disease, n (%)	60 (65.2)	50 (67.6)	35 (61.4)	15 (88.2)	10 (90.9)	21 (75.0)	10 (55.6)	6 (54.5)	54 (66.7)
Progressive disease, n (%)	19 (20.7)	12 (16.2)	10 (17.5)	2 (11.8)	1 (9.1)	4 (14.3)	7 (38.9)	1 (9.1)	10 (22.2)
Objective response rate, %	14.1	16.2	21.1	0	0	10.7	5.6	36.4	11.1
Disease control rate, %	79.3	83.8	82.5	88.2	90.9	85.7	61.1	90.9	77.8
Median OS, months (95% CI)	7.1 (5.5–8.7)	7.4 (3.4–11.4)	10.7 (4.8–16.5)	6.4 (5.1–7.7)	7.1 (5.6–8.6)	6.0 (4.5–7.5)	5.3 (2.0–8.5)	7.0 (n.a.)	6.8 (4.7–8.8)
Median PFS, months (95% CI)	4.3 (3.2–5.3)	4.4 (3.0–4.9)	4.6 (3.1–6.1)	4.1 (3.1–5.1)	4.4 (3.0–5.8)	4.0 (3.5–4.5)	2.6 (0.6–4.6)	7.0 (n.a.)	4.3 (3.6–4.9)

ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; OS, overall survival; PFS, progression-free survival; n.a., not available.
* Tumor occupying ≥ 50% of the liver, bile duct invasion, and main portal vein invasion.

Table2: Clinical response to Lenvatinib

Of the 92 patients who continued to be treated with lenvatinib monotherapy, 92.86% (n = 85) developed AEs. The most common AEs encountered were hypertension in 44.64% (n = 41), decreased appetite in 23.21% (n = 21) and diarrhoea in 23.21% (n = 21). Proteinuria was encountered by 21.43% (n = 19) and fatigue by 17.86% (n = 16), followed by hand–foot skin reaction (n = 6), nausea (n = 5), abdominal pain (n = 4), rash (n = 4), decreased weight (n = 3), decreased platelet count (n = 3), hypothyroidism (n = 2), dysphonia (n = 1) and vomiting (n = 1). Complete AE data with percentages are shown in Figure 1

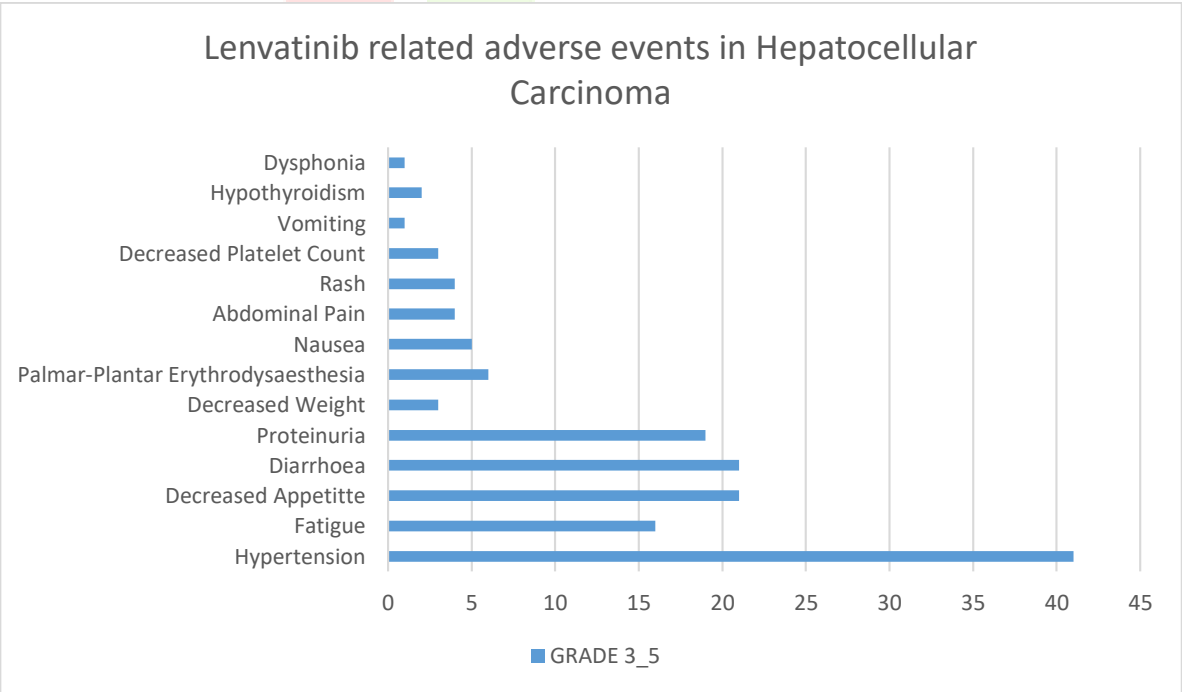

Figure1: Lenvatinib-related adverse events in patients with hepatocellular carcinoma

DISCUSSION

To date, sorafenib and lenvatinib have been approved as first-line treatments for HCC; however, in the near future, the TA regimen (i.e., atezolizumab plus bevacizumab), which has a positive effect, will also play an important role in first-line treatments. In this multicentre, retrospective analysis the efficacy and safety of lenvatinib were analysed from a variety of aspects. The objective was to develop a more comprehensive understanding of its effectiveness.

For patients with BCLC stage B disease participating in the REFLECT trial, found an ORR for lenvatinib of 61.3% with a PFS of 9.1 mo, which are higher than those achieved with any other known molecular targeted agent offered to HCC patients. Interestingly, of the patients with BCLC stage B disease, most were intolerant of chemoembolization or progressed despite previous TACE therapy. This means that most patients had good liver function and were therefore more likely to receive sustained lenvatinib treatment, which is also associated with a more favourable prognosis [14,15].

Lenvatinib showed favourable safety profiles, consistent with the results of the REFLECT trial and previous retrospective studies. There were no new safety-related events identified in this study. Most AEs were of grade 1 or 2 and were manageable with appropriate supportive care. AST elevation and fatigue, the most frequent AEs, occurred in 52.2 and 39.1% of patients, respectively, and hyperbilirubinemia (8.7%), AST elevation (6.5%) and diarrhoea (5.4%) were the most frequent grade 3–4 AEs.

These results may indicate the potential role of lenvatinib for the management of intermediate-stage HCC patients, in whom TACE is generally considered as an initial therapy. In future studies, the clinical relevance of lenvatinib should be further investigated for intermediate-stage HCC.

CONCLUSION

Lenvatinib is a promising agent for treating HCC. A well-preserved liver function and BCLC intermediate stage were key factors in achieving therapeutic efficacy.

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