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Survey of Nivolumab and Lenvatinib for the Treatment of Advanced Hepatocellular Carcinoma

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The most common causes of hepatocellular carcinoma are hepatitis virus infection or cirrhosis of liver. Having on sixth position among all other cancers, hepatocellular carcinoma is one of the most fast-growing prognostic cancers over the world.
Objectives: The purpose of this study is to explore the clinical efficacy and side effects of Nivolumab combined with Lenvatinib.
Materials and Methods: This retrospective, observational study was done in Department of Hepatology, Lab-aid Specialized Hospital. The study was conducted during the period of Jan 2022 to Jan 2023. The total number of patients enrolled were 48. Patients were selected by purposive method of sampling. All the patients were suffering from advanced stage hepatocellular carcinoma. The data were obtained using a structured questionnaire by face-to-face interview and utilizing hospital records. Written, informed consent was obtained from each patient.
Results: The mean age of the patients were 55.8 ± 11.2 years. Regarding gender, males were more than females, which is 58.3%. With context to etiology, Hepatitis B was the major cause for development of the disease, which is 22 (45.8%) patients had this morbidity. Regarding all the patients, it was evident that, 35% patients showed Partial Response. Objective-Response Rate (ORR) was 40% and Disease-Control Rate (DCR) was 78%. With context to HBV-positive patients, 44% patients had Partial Response; the DCR was 82%. As per the HCV-positive patients were concerned, 40%, 30% and 30% demonstrated Partial Response, Stable Disease and Progressive Disease respectively. For HCV-negative patients, the DCR came out to be 84%. 38% patients suffered from dermatitis. Secondly, Grade 1-2 fatigue was seen in 23% patients. Lastly, pneumonitis and HFSR was found in minimal patients, that is 6% and 2% respectively.

Keywords: Lenvatinib; nivolumab; immunotherapy; hepatocellular carcinoma; liver.

ABBREVIATIONS

FGFR : Fibroblast Growth Factor Receptor
KIT : Member of type III Tyrosine Kinase Receptor family
PFS : Progression-Free Survival
REFLECT : Phase 3, multinational, randomized, non-inferiority trial
RET : Rearranged during transfection
VEGF : Vascular Endothelial Growth Factor

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related deaths across the world. Prognosis is poor in case of advanced HCC. Previously approved drug, Sorafenib, a multiple kinase inhibitor, has limited efficacy in terms of treatment concerned. In the recent times, several new drugs such as Nivolumab and Lenvatinib have received approval for the treatment of advanced HCC [1].

Nivolumab, the first programmed cell death protein-1 (PD-1) inhibitor is a human monoclonal antibody which prohibits the interaction of its ligand (PD-L1), restoring the immune response of T cells, and thereby enhancing the recognition of tumor cells by the immune system [2]. Lenvatinib, which is a multi-tyrosine kinase inhibitor, affects platelet-derived growth factor receptor-alpha (PDGFRa), RET and KIT. It reduces angiogenesis and suppresses tumor growth by inhibiting these pathways. Its potent blockage of FGFR pathway is considered the primary mechanism for the control of liver cancer. In REFLECT study, Lenvatinib was found to demonstrate an efficacious response and longer PFS and non-inferiority of survival than that of Sorafenib [3].

Currently, various evidences have demonstrated that VEGF pathway inhibitors have immunomodulatory effects. The amalgamation of VEGF pathway inhibitors and anti-PD-L1 improves treatment efficacy and therefore become the standard treatment for HCC. Multiple multi-kinase inhibitors that block VEGF pathway have been proved to have immunomodulatory effects, including Lenvatinib [4-6]. Lenvatinib, a potent FGFR inhibitor, acts in two ways, firstly

suppresses the progression of HCC and secondly activates the immune response in tumor microenvironment. Therefore, Lenvatinib is potential for the combination of anti-PD-1 drug [7].

The purpose of this study is to explore the clinical efficacy and side effects of Lenvatinib combined with Nivolumab.

2. MATERIALS AND METHODS

This retrospective, observational study was done in Department of Hepatology, Labaid Specialized Hospital. The study was conducted during the period of Jan 2022 to Jan 2023. The total number of patients enrolled were 48. Patients were selected by purposive method of sampling. All the patients were suffering from advanced stage hepatocellular carcinoma. The actual dose schedule given to the patients was Nivolumab 40 mg/kg/day for 6 cycles along with Lenvatinib 400 mg/day along with Tenofovir fumarate 25 mg/day. The data were obtained using a structured questionnaire by face-to-face interview and utilizing hospital records. Written, informed consent was obtained from each patient. Ethical approval was collected from Institutional Review Board of the hospital before commencing the study. At the baseline and at the end of treatment, relevant investigations were done as follows:

- CBC
- Liver function tests
- Alfa Feto Protein
- Serum Creatinine
- Ultrasonography of whole abdomen
- Magnetic Resonance Cholangio-Pancreatography (MRCP)

Primary end-points:

- Clinical profile of the patients.
- Treatment response of the patients as per mRECIST criteria.
- Toxic events encountered by the patients.

Inclusion criteria:

- Age above 20 years old.
- Malignancy limited to hepatobiliary system.

Exclusion criteria:

- Child Pugh score C.
- Pregnant or lactating mothers.
- Patients without effective assessment.
- Patients who did not give written informed consent.

Statistical analysis: Frequency analysis was performed as a descriptive analysis to observe the different variables involved. After the data were collected, they were compiled, edited and analyzed accordingly using Statistical Package for Social Sciences version 25.

3. RESULTS

Table 1. Clinical profile of the patients (n=48)

Characteristics	Frequency (n)	Percentage (%)
Age (in years) (Mean ± SD)	55.8 ± 11.2	
Gender		
Male	28	58.3%
Female	20	41.67%
Etiology		
Hepatitis B virus infection	**28**	58.3%
Alcohol consumption	**18**	37.5%
Hepatitis C virus infection	**2**	4.2%
Child-Pugh score class		
A	34	70.8%
B	14	29.2%
BCLC staging		
B	**16**	33.3%
C	**32**	66.7%
PVT	**15/48**	31.25%

**SD: Standard Deviation; BCLC: Barcelona Clinic Liver Cancer; PVT: Portal Vein Thrombosis*

Table 1 demonstrates the clinical profile of the patients. It shows that, the mean age of the patients were 55.8 ± 11.2 years. Regarding gender, males were more than females, which is 58.3%. With context to etiology, Hepatitis B was the major cause for development of the disease, which is 22 (45.8%) patients had this morbidity. In addition, alcohol consumption was found in 14 (29.2%) patients. As per Child-Pugh score is concerned, 34 patients belonged to Class A and 14 patients were from Class B. Regarding BCLC staging, stage C was found in maximum patients which is 26 (54.17%). Lastly, portal vein thrombosis was seen in 15 patients.

Table 2 illustrates the treatment response as per mRECIST criteria. Regarding all the patients, it was evident that, 35% patients showed Partial Response. Objective-Response Rate (ORR) was 40% and Disease-Control Rate (DCR) was 78%. With context to HBV-positive patients, 44% patients had Partial Response; the DCR was 82%. In addition to this, among the HBV-negative patients, 42% patients had Stable Disease. As per the HCV-positive patients were concerned, 40%, 30% and 30% demonstrated Partial Response, Stable Disease and Progressive Disease respectively. For HCV-negative patients, the DCR came out to be 84%. Lastly, under the REFLECT criteria, for the fit patients, 48% patients showed Stable Disease with 92% DCR and unfit patients showed that 34% patients had Partial Response with 38% ORR and 75% DCR.

Table 3 shows adverse events experienced by the patients at the end of the therapy. It can be demonstrated that, 38% patients suffered from dermatitis. Secondly, Grade 1-2 fatigue was seen in 23% patients. Lastly, pneumonitis and HFSR was found in minimal patients, that is 6% and 2% respectively. Regarding laboratory tests, Grade 1-2 neutropenia, thrombocytopenia and anemia was seen in 20%, 15% and 10% patients respectively.

Table 2. Treatment response according to mRECIST criteria (n=48)

Patients	CR	PR	SD	PD	ORR	DCR
All patients	9%	35%	33%	23%	40%	78%
HBV						
Positive	5%	44%	31%	20%	45%	82%
Negative	9%	26%	42%	23%	28%	74%
HCV						
Positive	0%	40%	30%	30%	42%	78%
Negative	7%	39%	34%	20%	38%	84%
REFLECT criteria						
Fit	4%	41%	48%	7%	41%	92%
Unfit	8%	34%	26%	32%	38%	75%

**mRECIST: Modified Response Evaluation Criteria in Solid Tumors; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective-Response Rate; DCR: Disease-Control Rate; REFLECT: Phase 3, Multinational, Randomized, Non-Inferiority Trial; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus.*

Table 3. Distribution of the respondents according to the adverse events at the end of treatment (n=48)

Adverse events	Grade 1-2	Grade 3-4	All grades
Dermatitis	25%	13%	38%
Fatigue	23%	0%	23%
Diarrhoea	19%	0%	19%
Gastro-intestinal bleeding	0%	8%	8%
Pneumonitis	4%	2%	6%
HFSR	2%	0%	2%
Laboratory tests			
Neutropenia	20%	0%	20%
Thrombocytopenia	15%	0%	15%
Anemia	10%	0%	10%

**HFSR: Hand-Foot Skin Reaction*

4. DISCUSSION

To our knowledge, this is one of the few studies done regarding the combination of Lenvatinib and Nivolumab for the treatment of advanced stage HCC. Mean age of the patients was found to be 55.8 ± 11.2 years. Males were greater in number, which is 58.3%. Hepatitis B virus infection was found to be the most significant cause for HCC. Majority of the patients belonged to Child Pugh Score Class A and BCLC staging type C. A study done in China in 2022 showed similar findings in all mentioned aspects [3].

In terms of treatment response as per modified RECIST criteria, among all the patients 35% patients showed Partial Response. ORR was 40% DCR was 78%. For HBV-positive and HCV-positive patients the ORR 45% and 42% and DCR were found to be 84% and 78% respectively. Two studies done in China in 2021 and 2022 suggest similar findings [3,7].

Regarding adversities encountered by the patient at the end of 6 cycles of treatment with this drug regimen, it was found the patients suffered mainly from dermatitis, fatigue and diarrhea, which was seen in 38%, 23% and 19% of the patients. Laboratory findings revealed reduction of blood count in some aspects. A similar study in China done in 2022 revealed closer findings as well. Those enrolled patients complained of dermatitis, fatigue and diarrhea as well as pruritus, hypertension and dysphonia. As per as laboratory tests were concerned, hypothyroidism was one of the common problems encountered by those patients at the end of treatment [8-12].

The study has few limitations. Firstly, it was a retrospective study, therefore some information and selection bias may have existed. Secondly, it is not certain if these results will apply to Non-Asian residents as there are major differences in etiology of HCC in both the regions.

5. CONCLUSION

The study demonstrated promising efficacy and minimum toxicities with the proposed drug regimen for the treatment of advanced hepatocellular carcinoma. However, there are scopes of large-scale clinical trials to establish this regimen as a new modality of treatment.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard guideline, ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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