Original Article ISSN (O):2395-2822; ISSN (P):2395-2814

The Effect of Sorafenib in Patients of Advanced Hepatocellular Carcinoma through Triphasic CT; A Cross-Sectional Study

Sana Kundi[1], Muhammad Omer Altaf[2], Mina Mariam[3], Salman Rafique[1], Ihsan ul Haq[4], Gurdeep singh[5]

[1]Consultant, Department of Radiology, Pakistan Kidney and Liver Institute and Research Center, Pakistan.
[2]FCPS Radiology, Registrar Radiology , Pakistan Kidney and liver institute and research center, Pakistan.
[3]Senior Registrar, Royal Commission Hospital, Jubail, Saudia Arabia, Pakistan.
[4]FCPS Hepatobiliary Surgeon, Department of Hepatobiliary surgery, Pakistan kidney and liver institute and research center, Pakistan.
[5]Epidemiologist, Department of Research, Pakistan Kidney and Liver Institute and Research Center, Pakistan.

Received: May 2020
Accepted: May 2020

ABSTRACT

Background: Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide. Around 30% of HCC patients can be offered curative treatment at the time of initial diagnosis. Objective: To study the effects of Sorafenib in patients of advanced HCC in our population to assess overall response, disease cure rate (DCR) and response towards specific characteristics of a tumor. **Methods:** We retrospectively studied all the patients treated with Sorafenib with a follow-up CT scan after 12 weeks of initiation of therapy. The association between pre-effects and post-effects of the Sorafenib among the study subjects according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria was calculated using SPSS V25. **Results:** Post-Sorafenib 6.25% patients demonstrated complete response, 15.6% had a partial response, 25% showed stable disease while 53% of patients showed disease progression. The overall disease cure rate (DCR) was 46.85 % patients. Almost 50% of patients showed complete response or stable disease in portal vein tumor thrombus who had portal vein invasion before start of Sorafenib (p-value < 0.001), similarly 75 % patients showed complete or incomplete response post-Sorafenib in hepatic vein tumor thrombus who had hepatic vein invasion before treatment. All patients who had an IVC invasion showed complete response post-Sorafenib (p-value<0.001) and those who had an extrahepatic disease in the form of nodal or organ involvement showed disease progression. **Conclusions:** Sorafenib is a favorable drug for patients with advanced hepatocellular carcinoma, especially in patients who had vascular invasion with an overall disease cure rate (DCR) of 46.85 %.

Keywords: HCC, Sorafenib, CT scan, m RECIST, DCR.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, with most deaths occur within 1 year of the diagnosis.[1] Approximately only 30% of HCC patients can be treated with curative modalities at the time of the initial diagnosis.[2] Therefore, more than half of HCC patients receive palliative treatments, such as trans-arterial chemoembolization (TACE), systemic chemotherapy, intra-arterial chemotherapy, radioembolization, radiation therapy, or combination of these modalities Sorafenib (Bayer, Leverkusen, Germany) is a newly-developed, molecular-targeted agent, and it is the first systemic agent that increases overall survival and the time to progression in patients with advanced HCC.[2-5] The treatment with Sorafenib is maintained until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.[6,7] In another study by Huan et al, patients with HCC showed complete clinical response after Sorafenib and there was no evidence of progression of the disease for 60 months after continuous treatment with Sorafenib.[8] In one of the studies done by Kim MJ et al. to evaluate the effect of Sorafenib on HCC, the size of the hepatic tumors was not significantly reduced; the tumor responses were stable disease or progressive disease on follow-up CT scans.[9] However, the median survival was better for the patients with the response of stable disease and the attenuation values of the tumors became lower after treatment, as compared to the baseline CT scans.[10] As there is a different outcome of different studies regarding the effect of Sorafenib on HCC and none of such study is conducted in Pakistan, where significant disease burden in the present. We have studied the effects of Sorafenib in patients of advanced HCC in our population to see not only an overall response but also to assess overall disease cure rate (DCR) and to see which component and characteristic feature of the tumor shows a better response to Sorafenib.

Name & Address of Corresponding Author
Dr. Muhammad Omer Altaf,
FCPS Radiology,
Registrar Radiology , Pakistan Kidney and liver institute and research center,
Pakistan.

MATERIALS & METHODS

It was a retrospective cross-sectional study conducted at the Radiology department of Pakistan Kidney and Liver Institute and Research Centre.

All the patients from March 2018 to June 2019 of advanced HCC, treated with Sorafenib and got a follow-up CT scan after 12 weeks were included in the study. Newly diagnosed or follow up cases of advanced (unresectable or metastatic) hepatocellular carcinoma of both genders above 18 years of age who had not received previous systemic therapy, with Child-Pugh liver function classes A and B and a life expectancy of at least 12 weeks were included in this study. Only those patients were included who got pre Sorafenib CT scan done within 1 month prior to the start of therapy. All the patients with Child-Pugh liver function class C, previous or concomitant history of systemic or locoregional therapy, any history of organ allograft or with any other known malignancy were not included as it was not possible to interpret the effects of Sorafenib solely on Hepatocellular carcinoma which is the rationale of our study.

In this study after getting approval from Institutional Review Board, we retrospectively studied all the included patients who got treated with Sorafenib and had a follow up CT scan after 12 weeks of initiation of therapy. All the patients of advanced hepatocellular carcinoma discussed in MDT's who were put on Sorafenib and received standard 400 mg daily dose (200 mg B.D) in 1st week and increased to 800 mg daily from second week onwards till following up CT at 12th week provided the dose was well tolerated by the patient.[11] Primary outcomes were a response of a tumor to Sorafenib according to mRECIST criteria and to calculate overall disease cure rate (DCR) while the secondary outcomes were to assess the effect of Sorafenib on nontarget HCC and tumor thrombus.

Baseline dynamic triphasic CT scans of the patients were assessed, either performed in our hospital or from an outside facility. The follow-up dynamic triphasic liver CT findings were retrospectively assessed by two radiologists working in consensus with at least 5 years of radiology experience. CT Scans were performed on 128 slice GE Machine and the study comprised the following phases.

1. Late arterial phase taken according to smart prep method approximately between 33-38 seconds.
2. Venous phase 35 seconds after late arterial phase.
3. Delayed phase at 300 seconds from start of scan.

Contrast dose was calculated according to patient's weight and amount of iodine per ml of contrast.

Many patients had hepatic tumors that were immeasurable due to the infiltrative nature, and therefore, we needed another standard for response evaluation, rather than the simple measurement of tumor size. We adopted the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria for the analysis of the change in tumor burden in the liver.[12] The definitions of treatment response in these criteria were as follows.

For the target lesions, complete response (CR) was defined as the disappearance of any intratumoral arterial enhancement in all target lesions, and partial response (PR) was defined as at least 30% decrease in the sum of diameters of arterialized target lesions, taking as reference the baseline sum of the longest diameters of target lesions. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the longest diameters of arterialized target lesions, taking as reference the smallest sum of the longest diameters of arterialized target lesions recorded since treatment started, and stable disease (SD) was defined as neither sufficient reduction in arterialized component to qualify for PR, nor sufficient increase to qualify for PD.

For nontarget lesions complete response (CR) was defined as disappearance of any intratumoral arterial enhancement in all nontarget lesions, incomplete response or stable disease as persistence of arterial enhancement in one or more nontarget lesions and progressive disease is defined as the unequivocal increase in the size of nontarget lesions or appearance of new lesions. Disease Cure rate (DCR) is defined as the percentage of patients who achieved CR, PR and SD post sorafenib treatment.[13]

RESULTS

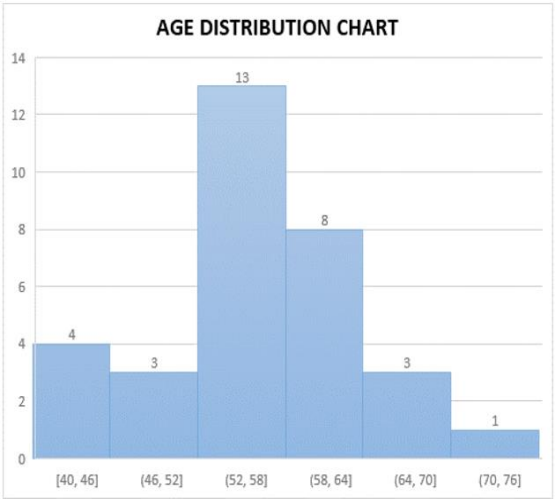

Chart 1: Representation of age distribution of HCC patients treated with sorafenib

All the analysis was done on SPSS 25, to see any hepatocellular carcinoma response pre and post Sorafenib. A total 32 patients' data was analyzed with mean age of 56.47 years, having a range of 40 years to 73 years. The age distribution is displayed in [Chart 1].

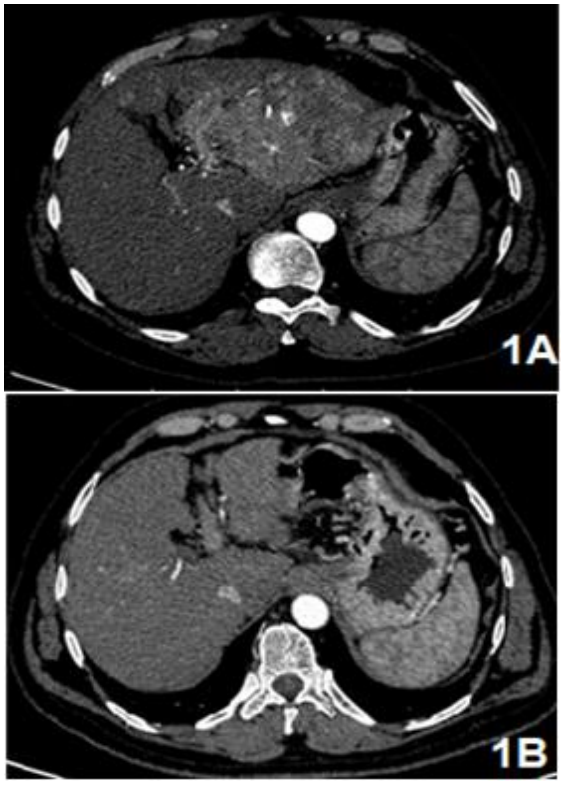

Figure 1: shows complete post-Sorafenib HCC response in a 54 years old female patient. 1A: Pre Sorafenib Axial slice through the triphasic CT scan in the arterial phase shows infiltrating left lobe HCC with arterialized tumor thrombus in left portal vein. 1B: Post sorafenib axial slice on the follow up triphasic CT scan at same level in arterial phase shows the disappearance of arterialization in left lobe tumor and adjacent left portal vein tumor thrombus.

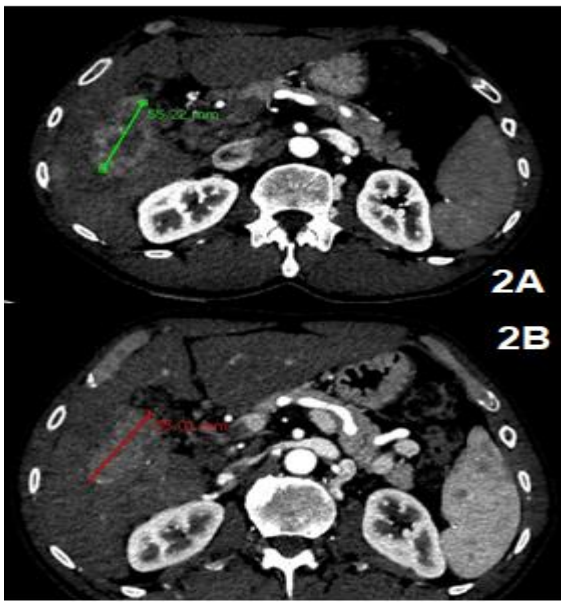

Figure 2: shows stable response of HCC in 42 years old female. 2A: Pre Sorafenib Axial slice through the triphasic CT scan in arterial phase shows arterialized HCC in segment V. 2B: Post sorafenib axial slice on the follow up triphasic CT scan at same level in arterial phaseshows no interval change in size of arterialized component.

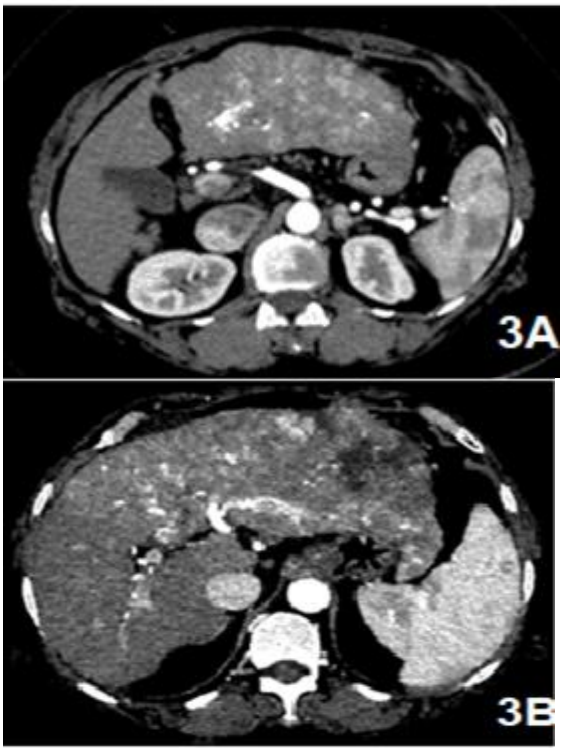

Figure 3: shows disease progression of HCC in 58 years old female. 3A: Pre-Sorafenib CT scan shows an arterialized infiltrating HCC in the left lobe left lateral segments with the involvement of left lateral branch of the portal vein. 3B: post sorafenib axial slice on the follow up triphasic CT scan at same level in arterial phase shows interval disease progression of HCC involving segment IV along with left lateral segments and in left portal vein.

Out of 32 patients 6.25% patients demonstrated complete response after getting Sorafenib for 3 months as can be seen in Figure 1.

About 25% of the patients showed stable disease on the Triphasic CT scan after 3 months of Sorafenib as depicted in Figure 2. Response evaluation on the basis of mRecist criteria of different morphological appearances of HCC is depicted in Table 1.

The overall disease cure rate (DCR) was calculated to be 46.85 %. There was mixed post-Sorafenib response in terms of tumor thrombus in which complete, partial and stable disease response was noted.

Almost 50% of patients showed complete response or stable disease in portal vein tumor thrombus who has portal vein invasion before start of Sorafenib (p-value < 0.001), similarly 75 % patients showed complete or incomplete response post-Sorafenib in hepatic vein tumor thrombus who had hepatic vein invasion before the study (p-value<0.001) and 100 % of patients who had IVC invasion showed complete response post-Sorafenib (p-value<0.001). All patients who had an extrahepatic disease in the form of nodal or organ involvement showed disease progression in locoregional lymph nodes (p value< 0. 001) and in extrahepatic metastatic disease (p-value < 0.001). Overall increase in the size of

arterialized tumor size (p-value < 0.004). The results are compiled in [Table 2].

Table 1: Showing pattern of post-sorafenib treatment response in different morphological appearances of HCC.

Hepatocellular Carcinoma Response Patterns to Sorafenib on Basis of mRecist Criteria						
		Complete Response	**Partial Response**	**Stable Disease**	**Progressive Disease**	**Total**
Tumor characteristics	Well Defined	0	3	2	5	10
	Infiltrative	1	0	4	7	12
	Both	1	2	2	5	10
Total		2	5	8	17	32
mRecist = modified Response evaluation criteria in solid tumors						

Table 2: Depiction of t-test, p value and confidence interval of individual variable as per study results.

Study Variables Pre And Post Sorafenib					
VARIABLES	**Mean ± SD**	**95% confidence interval of the difference**		**t-value**	**p-value**
		Lower	**upper**		
Exact size arterialized tumor (pre-and Post sorafinib)	0.00 (7.12)	-3.3	3.33	0	1
Involved portal vein response pre and post Sorafenib	-1.281 (1.57)	-1.848	-0.715	-4.615	<0.001
Involved hepatic vein response pre and post Sorafenib	-2.688(1.203)	-3.121	-2.254	-12.636	<.001
Involved IVC response pre and post Sorafenib	-2.906(0.734)	-3.171	-2.641	-22.387	<.001
Locoregional nodal involvement response post Sorafenib	-2.844(0.767)	-3.12	-2.567	-20.984	<.001
Extrahepatic disease response post Sorafenib	-2.844(0.767)	-3.12	-2.567	-20.984	<.001
Arterialized tumor size response post sorafenib	-0.531(0.950)	-0.874	-0.189	-3.164	<0.004
SD= Standard deviation IVC= Inferior venacava					

DISCUSSION

There are many different criteria being used to evaluate the response of hepatocellular carcinoma with Sorafenib. In one of the studies done to see which criteria is superior in response assessment of hepatocellular carcinoma by Juichi Takada et al, concluded that mRecist criteria is superior to RECIST in evaluating response assessment of hepatocellular carcinoma post-Sorafenib.[14]

We studied more than 100 patients who had advanced hepatocellular carcinoma and were decided to be given Sorafenib as per the above-mentioned criteria in the multidisciplinary weekly meetings. A board of hepatologists, gastroenterologists, hepatobiliary transplant surgeons in collaboration with radiologists prescribed the drug with consensus. Out of total of 100 patients, 23 patients were lost to follow up, 31 patients could not tolerate the drug well and discontinued the treatment, 9 patients were noncompliant to treatment and 5 patients expired due to general liver decompensation and advanced disease.

In the remaining 32 patients who continued treatment demonstrated following results on follow up after 4 weeks of Sorafenib.

17 patients showed progressive disease despite Sorafenib, 8 patients showed stable disease, 5 patients demonstrated a partial response and 2 patients showed complete response. Out of these 32 patients, 29 were infected with hepatitis C, 1 had hepatitis B and 2 patients had co-infection of hepatitis B and C. Out of these 32 patients, 12 patients had infiltrative HCC, 10 had well defined

measurable HCCs and 10 patients had a combination of infiltrative and well-defined components of HCC. There were 5 patients with solitary HCC and rest had a multifocal or infiltrative disease. Out of 32 patients, only one had IVC involvement before treatment which showed complete response; however, one patient with the progressive disease showed IVC involvement post-Sorafenib. Similarly, 20 patients had pre-Sorafenib portal vein invasive HCC in which 2 patients showed a complete response of tumor thrombus, 13 showed stable tumor thrombus/ incomplete response, 5 patients showed further progression of thrombus. There was interval development of portal vein invasion in 2 patients despite treatment. Only 4 patients had hepatic veins involvement pre-Sorafenib, out of which 2 patients showed complete response, 1 showed an incomplete response and 1 patient showed tumor thrombus progression in hepatic veins. There was interval development of tumor thrombus in hepatic veins in 3 patients. Only 4 patients had extrahepatic metastatic disease in the form of nodal and organ involvement which progressed post-Sorafenib and three patients showed new development of extrahepatic metastasis despite Sorafenib. The early disease control rate (DCR) which is defined as the percentage of patients who achieved CR, PR and SD after 4 weeks of Sorafenib, was 46.85%. In one of the studies done by Xiao-Chun et al,[13] in which the effect of

combination therapy of TACE with Sorafenib was assessed, the overall DCR was 63.2 %.

In another Randomized phase II trial of sequential hepatic arterial infusion chemotherapy and Sorafenib versus Sorafenib alone as initial therapy for advanced hepatocellular carcinoma: SCOOP-2 trial, done by Kondo M et al,[15] the DCR was reported as 45.7 and 45.5% respectively.

CONCLUSION

Sorafenib is a favorable drug for patients with advanced hepatocellular carcinoma especially in patients with vascular invasion with an overall disease cure rate (DCR) of 46.85 %.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J. Clin. 2005; 55: 74–108.
2. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology. 2002;35: 519–24.
3. Dimitroulis D, Damaskos C, Valsami S, Davakis S, Garmpis N, Spartalis E, Athanasiou A, Moris D, Sakellariou S, Kykalos S, Tsourouflis G. From diagnosis to treatment of hepatocellular carcinoma: An epidemic problem for both developed and developing world. World journal of gastroenterology. 2017;23(29):5282.
4. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. SHARP Investigators Study Group. N Engl J Med. 2008; 359(4):378-90
5. Hwang YH, Choi JY, Kim S et al. Over-expression of c-raf-1 proto-oncogene in liver cirrhosis and hepatocellular carcinoma. Hepatol Res 2004; 29: 113–21.
6. Wilhelm S, Carter C, Lynch M, et al. Discovery and development of Sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov. 2006; 5: 835–44
7. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359: 378–90.
8. Huan HB, Lau WY, Xia F, Ma KS, Bie P. Complete response to Sorafenib in a patient with recurrent hepatocellular carcinoma. World J Gastroenterol. 2014;20(39):14505-9.
9. Kim MJ, Choi JI, Lee JS, Park JW. Computed tomography findings of sorafenib-treated hepatic tumors in patients with advanced hepatocellular carcinoma. J Gastroenterol Hepatol. 2011;26(7):1201-6.
10. Anne Helene Køstner, Morten Sorensen, René Krøjgaard Olesen, Henning Grønbæk, Ulrik Lassen, and Morten Ladekarl, "Sorafenib in Advanced Hepatocellular Carcinoma: A Nationwide Retrospective Study of Efficacy and Tolerability," The Scientific World Journal, vol. 2013, Article ID 931972, 6 pages, 2013.
11. Kim TS, Kim JH, Kim BH, et al. Complete response of advanced hepatocellular carcinoma to Sorafenib: another case and a comprehensive review. Clin Mol Hepatol. 2017;23(4):340-346.
12. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52-60.
13. Meng Xiao-Chun, Chen Bing-Hui, Huang Jing-Jun, Huang Wen-Sou, Cai Ming-Yue, Jing-Wen Zhou Jing-Wen et al. Early prediction of survival in hepatocellular carcinoma patients treated with Transarterial chemoembolization plus Sorafenib: World J Gastroenterol. 2018; 24(4): 484–493.
14. Takada J, Hidaka H, Nakazawa T, Kondo M, Numata K, Tanaka, et al. Modified response evaluation criteria in solid tumors is superior to response evaluation criteria in solid tumors for assessment of responses to Sorafenib in patients with advanced hepatocellular carcinoma. BMC Research Notes volume 8, Article number: 609 (2015).
15. M Kondo, M Morimoto, S Kobayashi, S Ohkawa, H Hidaka,T Nakazawa and et al. Randomized, phase II trial of sequential hepatic arterial infusion chemotherapy and Sorafenib versus Sorafenib alone as initial therapy for advanced hepatocellular carcinoma: SCOOP-2 trial. BMC Cancer. 2019;19(1):954.

How to cite this article: Kundi S, Altaf MO, Mariam M, Rafique S, Haq IU, Singh G. The Effect of Sorafenib in Patients of Advanced Hepatocellular Carcinoma through Triphasic CT; A Cross-Sectional Study. Ann. Int. Med. Den. Res. 2020; 6(4):RD01-RD05.

Source of Support: Nil, **Conflict of Interest:** None declared