International Journal of Oncology Research

ISSN Print: 2664-665X
ISSN Online: 2664-6668
IJOR 2024; 4(1): 97-105
www.oncologyjournal.in
Received: 14-05-2024
Accepted: 21-06-2024

Noha Mohamed Azab
Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Rabab Mahmoud Abu-Sobaa
Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Mohamed Abd-Elhamed Alm Aldin
Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Fatma Zakria Hussein
Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Corresponding Author:
Noha Mohamed Azab
Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Tanta University, Tanta, Egypt

Evaluation of clinical and radiological response with antiangiogenic therapy in advanced hepatocellular carcinoma patients

Noha Mohamed Azab, Rabab Mahmoud Abu-Sobaa, Mohamed Abd-Elhamed Alm Aldin and Fatma Zakria Hussein

DOI: https://doi.org/10.33545/2664665X.2024.v4.i1b.22

Abstract
Background: Sorafenib represents the primary therapeutic option for people diagnosed with advanced hepatocellular carcinoma (HCC). Nevertheless, it is linked to a range of drug-related negative effects, impacting all cases having low objective response rates along with limited survival prolongation. This work was aimed at assessing the correlation between the early clinical response following a two-week period of Sorafenib therapy and the outcomes in patients with advanced HCC.
Methods: The prospective, observational and non-interventional study included 20 cases, with ages above 18 years, both sexes, developing typical HCC, hyper vascular HCC in the liver at baseline, Child-Pugh class A disease as regards liver function along with eastern cooperative oncology group performance status of 0 or 1. Triphasic-computed tomography (CT) images were obtained for all patients at baseline, within two and six weeks following Sorafenib administration, and then every 8 weeks till 6 months.
Results: Our prompt evaluation of Sorafenib treatment demonstrated a favorable overall survival rate (p<0.001) as well as progression free survival among cases whose arterial tumor enhancement disappeared on triphasic-CT, whose alpha fetoprotein (AFP) level decreased within the first two weeks following the dose and patients who had preserved liver function within a two-weeks following Sorafenib. These factors were all most significant and independent predictors of favorable overall survival rate (p<0.001) as well as progression free survival (p<0.001). They exhibited a significant correlation with a significantly reducred rate of disease progression at 6 weeks (p= 0.029).
Conclusions: For patients with advanced HCC, alterations as regards intra-tumor blood flow using triphasic-CT, AFP levels, as well as remnant liver function following a two-weeks period using sorafenib may be helpful in the outcome prediction as well as the anti-tumor effect of sorafenib therapy and can help identify patients should discontinue receiving it with early switch to second line therapy to avoid unnecessary toxicities and costs when sorafenib therapy is ineffective.

Keywords: Advanced hepatocellular, anti-angiogenic therapy, radiological response

Introduction
Hepatocellular carcinoma (HCC) represents a common type of cancer, associated with higher mortality rates globally. It is the fifth most prevalent malignancy type, being the second most significant contributor to cancer-related mortality. Annually, around 700,000 new cases are diagnosed, resulting in over 600,000 deaths [1].
Cases developing HCC at a late stage or those showing disease progression following loco regional treatment, usually exhibit an unfavorable prognosis, mostly because of the underlying liver disease along with the limited efficient treatments available [2].
Sorafenib stands as a potent inhibitor of multi-kinase, selectively blocking the signal transduction pathways responsible for tumor development as well as angiogenesis. It is presently the recommended first-line systemic therapy for advanced unresectable HCC [3].
Sorafenib therapy is subject to many limitations. Initially, it should be noted that it remains linked to a reduced objective response rate, only offering a modest survival prolongation [4]. Furthermore, Sorafenib therapy is linked to a wide range of drug-related side effects, impacting most cases who underwent treatment [5]. Ultimately, the sorafenib treatment's cost is still very high [6].

Hence, it is crucial to promptly identify individuals who are anticipated to get advantages from such a therapy. Also, this attempt might also aid in identifying people who are not a good fit for the medication, thus protecting these individuals from unnecessary side effects while saving expenses [7].

This work was aimed at assessing the correlation between the early clinical response following a two-week period of Sorafenib therapy and the outcomes in patients with advanced HCC.

Patients and Methods

The prospective, observational, non-interventional study included 20 cases, with ages older than 18 years, both genders, developing typical HCCs diagnosed clinically utilizing triphasic-computed tomography (CT) imaging, hyper vascular HCC in the liver at baseline that measured more than 10 mm in diameter, were contraindicated for surgical resection or loco regional therapy, child-Pugh (CP) class A disease as regards liver function, eastern cooperative oncology group performance status (ECOG PS) of 0 or 1, a serum alpha fetoprotein (AFP) level of at least 20 ng/ml, a haemoglobin (Hb) level of at least 8.5 g/dL, a platelet count higher than 65,000 /µL, a neutrophil count higher than 1500 /µL, a total bilirubin level below 2.0 mg/dL, serum aspartate aminotransferase and serum alanine aminotransferase levels below 5 times the upper limit of the study center's standard range, and a serum creatinine level below 1.5 times the upper limit of the study center's standard range. Our research was conducted within a timeframe between October 2022 and October 2023 after it got approved by the Ethical Committee Tanta University Hospitals, Tanta, Egypt. All participants were asked to sign an informed consent.

We excluded cases arranged to receive concurrent treatment on other anti-cancer drugs, prior systemic chemotherapy, active multiple tumors, contraindications for sorafenib treatment due to (brain tumors, dialysis, pregnant or those with high chances to be pregnant, poorly controlled hypertension, myocardial infarction, unstable angina, cardiac failure, or cerebrovascular disorder within the year prior to enrollment as well as contraindications for triphasic-CT against radiographic contrast media or other reasons.

Participants underwent a categorization into two groups: cases having an AFP ratio below 1.2 (the low AFP ratio group) as well as (2) cases having an AFP ratio above 1.2 (the high AFP ratio group).

Our team took a comprehensive medical history from all participants followed by lab testing as well as radiographs.

Sorafenib Therapy

The initial sorafenib standard dosage is 400 mg PO q12 hr. In our study the initial oral dose for 20 patients was 800 mg per day (400 mg PO q12 hr). We evaluated negative events based on the Common Terminology Criteria for Adverse Events (CTCAE) version 6.0

2 patients had dermatitis grade I (hand and foot syndrome) and treated with topical steroids. 3 patients had diarrhea grade I which treated with loperamide. Three patients had mild albuminemia with minimal ascites treated with diuretics. One patient had mild hyper bilirubinemia treated with liver support.

Evaluation of anti-tumor effect

Triphasic-CT scans were taken initially, two weeks and six weeks after Sorafenib was given, and subsequently every eight weeks until 6 months. The anti-tumor effects were assessed based on the Response Evaluation Criteria in Solid Tumors (RECIST1.1). Cases underwent a categorization into three categories based on their reaction: partial response (PR), stable disease (SD), as well as progression of disease (PD) [8]. The target lesions were determined to be detectable and hyper vascular HCCs with baseline sizes more than 10 mm. A maximum of four lesions were designated as target lesions. Two independent observers evaluated the anti-tumor effects of cases in a blinded manner. In our study the initial assessments of anti-tumor effects were within a Six-week period following sorafenib therapy so that there were no changes observed in the assessment at two weeks after Sorafenib administration.

Evaluation of changes in intra-tumor blood flow

We assessed the disappearance of arterial tumor enhancement on triphasic-CT at 2, 6, and every 8 weeks thereafter for 6 months to measure alterations in intra-tumor blood using the modified Response Evaluation Criteria in Solid Tumors (MRECIST) following Sorafenib. The cases were categorized into two groups: those whose arterial tumour enhancement faded on triphasic-CT (referred to as the DA group) as well as those whose arterial tumor enhancement persisted on triphasic CT (referred to as the non-DA group). The alterations as regards intra-tumor blood flow of all recruited cases were assessed utilizing two independent evaluators in a blinded manner.

We assessed the levels of serum AFP at the beginning of the study. Each patient's first HCC tumor marker was given a baseline AFP level of 1. We then assessed the ratios for AFP level at two and six weeks compared to the baseline AFP level following treatment initiation. This evaluation was repeated every 8 weeks until 6 months.

We assessed the variations in CP score as alterations in liver function. Liver function deterioration was defined as an increase of two or more points in the CP score at 2 and 6 weeks following Sorafenib treatment, and then every 8 weeks until 6 months. The participants were categorized into two groups: those whose CP scores had risen by two or more increments (the liver function deterioration group) as well as individuals who's CP scores had risen by less than two increments (the non-liver function deterioration group).

The primary outcome was aimed at assessing the clinical and radiological response within a two-week period following Sorafenib therapy, thus helping detect cases with potential resistance and preventing unnecessary toxicities, while evaluating the outcomes as well as anti-tumor response among cases developing advanced HCC. The secondary outcome involved progression free survival.

Statistical analysis

Our team analyzed data statistically with SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were showcased through mean and standard deviation (SD) and a comparison was conducted among the three groups utilizing ANOVA (F) test with post hoc test (Tukey). Qualitative variables were illustrated through frequency and percentage (%) then analysis was conducted utilizing the Chi-square test. A two tailed P value of below 0.05 was deemed

statistically significant. Univariate regression was employed for estimating the correlation between a dependent variable and one independent variable. Multivariate regression was also employed for estimating the correlation between a dependent variable and more independent variables.

Results

Patients' data for those undergoing Sorafenib, along with baseline characteristics were enumerated in Table 1.

Table 1: All cases undergoing Sorafenib as well as baseline characteristics

		N=103
Patients with active multiple cancers		8 (7.76%)
Patients with serum AF *p*< 20 ng/ml		58 (56.3%)
Patients with contraindication to radiographic contrast media		9 (8.73%)
Patients we couldn't contact them		8 (7.76%)
Patients enrolled in this study		20 (19.41%)
		N=20
Age (years)		60.3±7.2
Sex	Male	18 (90.0%)
	Female	2 (10.0%)
ECOG Performance Status	0	12 (60.0%)
	1	8 (40.0%)
CP score	5	14 (70.0%)
	6	6 (30.0%)
Number of tumors	1	10 (50.0%)
	2	6 (30.0%)
	3	2 (10.0%)
	4	2 (10.0%)
Tumor size (mm)	<30	3 (15.0%)
	>30	17 (85.0%)
Extrahepatic spread		8 (40.0%)
Portal vein invasion		9 (45.0%)
Serum AFP level (ng/ml)	<200	9 (45.0%)
	>200	11 (55.0%)

Data are presented as frequency (%). AFP: Alpha fetoprotein, CP: Child – Pugh, ECOG: Eastern cooperative oncology group.

Radiologic, biochemical, and clinical changes at different times of follow up after sorafenib therapy were enumerated in this table. Table 2.

Table 2: Radiologic, biochemical, and clinical changes at different times of follow up after Sorafenib therapy of the studied patients

		N=20
At 2 weeks	Stable disease	20 (100.0%)
At 6 weeks	Partial response	5 (25.0%)
	Stable disease	15 (75.0%)
At 14 weeks	Partial response	5 (25.0%)
	Stable disease	15 (75.0%)
At 22 weeks	Stable disease	20 (100.0%)
Intra-Tumor Blood Flow after Sorafenib		
	At 2 weeks	6 (30.0%)
	At 6 weeks	7 (35.0%)
	At 14 weeks	7 (35.0%)
	At 22 weeks	7 (35.0%)
The ratios for AFP level after Sorafenib		
At 2 weeks	<1.2	16 (80.0%)
	>1.2	4 (20.0%)
At 6 weeks	<1.2	16 (80.0%)
	>1.2	4 (20.0%)
At 14 weeks	<1.2	16 (80.0%)
	>1.2	4 (20.0%)
At 22 weeks	<1.2	15 (75.0%)
	>1.2	5 (25.0%)
Changes in Remnant Liver Function		
At 2 weeks	≥ 2 increments in CP score	4 (20.0%)
	<2 increments in CP score	16 (80.0%)
At 6 weeks	≥ 2 increments in CP score	2 (10.0%)
	<2 increments in CP score	18 (90.0%)
At 14 weeks	≥ 2 increments in CP score	4 (20.0%)
	<2 increments in CP score	16 (80.0%)
At 22 weeks	≥ 2 increments in CP score	1 (5.0%)

	<2 increments in CP score	19 (95.0%)
Prognostic score at 2 weeks	0	6 (30.0%)
	1	8 (40.0%)
	2	2 (10.0%)
	3	2 (10.0%)
	4	2 (10.0%)

Data are presented as mean ± SD or frequency (%). ECOG: Eastern cooperative oncology group, AFP: Alpha fetoprotein, CP: Child – Pugh.

According to univariate analysis and based on the patients' parameters within a two-weeks period after starting sorafenib: Factors exhibited a significant correlation with OS and worse OS were ECOG performance status and AFP ratio of >1.2 (HR =4.138 and .416; 95%, CI, 1.268-13.506 and.222-.780; p = 0.019 and.006), presence of portal vein invasion as well as CP score increase of > 2 points (HR= 4.309 and .161; 95%, CI, 1.278-14.529 and.040-.647; p = 0.018 and .010) and prognostic score (HR = 3.102; 95% CI, 1.672-5.756; p = <.001). According to multivariate analysis ECOG performance status was independent and significant mortality predictors (HR = 7.829; 95% CI, 1.886-32.497; p = 0.005). Within a six-weeks following Sorafenib treatment, the anti-tumour effect on triphasic CT (HR = 5.452; 95%CI, 0.111-42.82; p = 0.046) and AFP ratio of >1.2 (HR = .514; 95% CI, .275-.959; p = 0.036), and CP score rise beyond > 2 points (HR = .045; 95% CI, .004-.512; p = .012) were significantly associated with worse OS. At 22 weeks, all parameter in the univariate analysis were non-significant. Table 3.

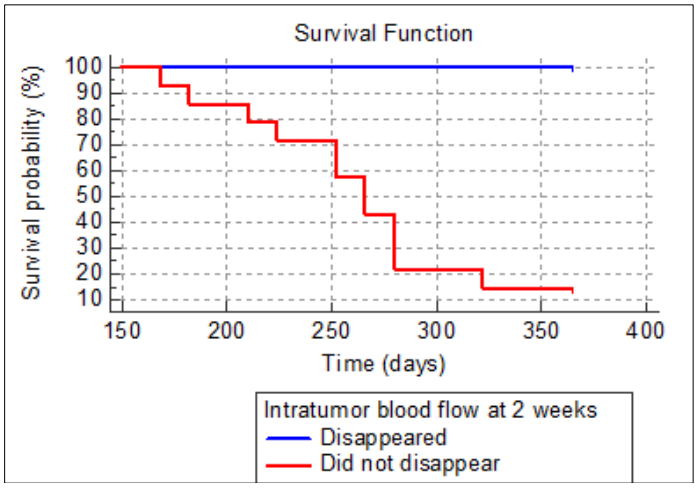
Table 3: Univariate and multivariate (forward stepwise) Cox regression analysis for survival analysis based on the pre-treatment baseline and patients' parameters at 2,6,14, and 22 weeks

		Univariate analysis		Multivariate analysis	
		HR (95% CI)	**P**	**HR (95% CI)**	**P**
Age (years)	<60	0.575 (0.172-1.915)	0.367	--	--
	≥ 60				
Sex	Male	0.827 (0.106-6.426)	0.856	--	--
	Female				
ECOG Performance Status	0	4.138 (1.268-13.506)	0.019*	7.829 (1.886-32.497)	0.005*
	1				
CP	5	0.920 (0.276-3.068)	0.892	---	---
	6			---	---
Number of tumors	<2	0.853 (0.186-3.868)	0.837	---	---
	≥2			---	---
Tumor size (mm)	<30	0.482 (0.128-1.821)	0.282	---	---
	>30			---	---
Extra hepatic spread		1.404 (0.442-4.462)	0.565	---	---
Portal vein invasion		(1.278-14.529) 4.309	0.018*	---	---
Serum AFP level (ng/ml)	<200	1.476 (0.466-4.672)	0.508	---	---
	>200			---	---
The patients' parameters at 2,6,14, and 22 weeks					
		Hazard ratio		**95% CI**	**P**
Anti-Tumor effect	At 2 weeks	--		--	--
	At 6 weeks	5.452		0.111-42.82	0.046*
	At 14 weeks	5.452		0.111-42.82	0.046*
	At 22 weeks	NA		NA	NA
Intra-Tumor Blood Flow	At 2 weeks	55.351		55.351-6613.132	.100
	At 6 weeks	75.874		.683-8426.495	.072
	At 14 weeks	75.874		.683-8426.495	.072
	At 22 weeks	75.874		.683-8426.495	.072
The ratios for AFP level	At 2 weeks	.416		.222-.780	.006*
	At 6 weeks	.514		.275-.959	0.036*
	At 14 weeks	.514		.275-.959	0.036*
	At 22 weeks	.663		.362-1.215	0.183
Changes in remnant liver function	At 2 weeks	.161		.040-.647	.010*
	At 6 weeks	.045		.004-.512	.012*
	At 14 weeks	.972		.212-4.462	.970
	At 22 weeks	.302		.035-2.558	.275
prognostic score at 2 weeks		3.102		1.672-5.756	<.001*

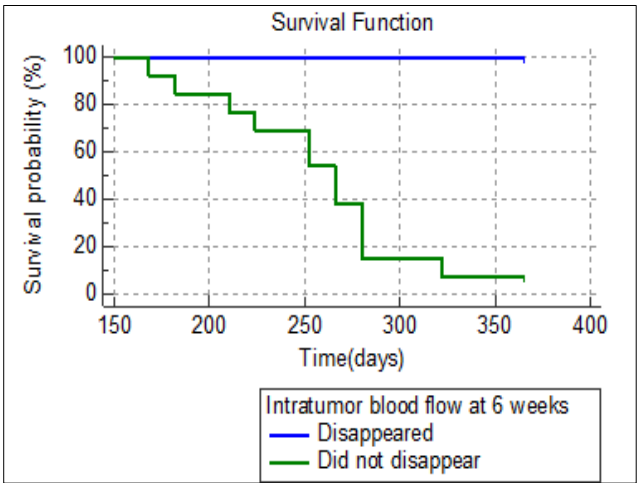
*Significant p value <0.05. OS: Overall survival, ECOG: Eastern cooperative oncology group, HR: hazard ratio, CI: confidence interval, CP: Child – Pugh, AFP: Alpha fetoprotein.

The mean patient OS exhibited significantly shorter values within (the non-DA group as opposed to the DA group) (265.143 days vs. 365 days; p = 0.002) and (257.46 days vs. 365 days; p<0.001) at 2 weeks and 6 weeks respectively and (within the high AFP ratio group and within liver function deterioration group than within low AFP ratio group as well as the non-liver function deterioration group at 2 weeks) (210 and 220.50 days, HR =30.25; 95% and 22.38; 95%, CI=3.68 to 248.51 vs. 316.37 days and 2.91 to 171.65 vs 313.75 days; HR =0.033; 95% and 0.044; 95% CI = 0.004 to 0.271 and 0.005 to 0.342 2.91) p 0.002 and 0.003 and at 6 weeks (234.50 and 196 days, HR =8.3578; 95% and 22.38; 95% CI= 1.382 to 50.525 vs. 310.25 and 2.91 to 171.65 vs306.11 days; HR=0.119; 95% CI=0.019 to 0.723 and 0.005 to 0.342) p =0.020 and <0.001 respectively. The Mean patient OS exhibited insignificantly variance between PR group (345.20 days HR =1.911; 95% CI, 0.056 to 0.641) and the SD group (278.40 days, HR = 5.233; 95% CI = 1.55 to 17.56). p<0.064. The Mean patient OS exhibited significantly shorter values within the high AFP ratio group

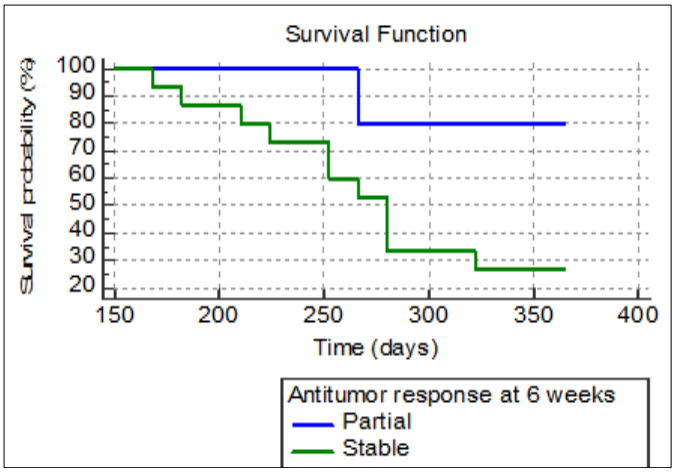
as opposed to the low AFP ratio group at 2 weeks (210 days, HR =30.25; 95% CI, 3.68 to 248.51 vs. 316.37 days; HR=0.033; 95% CI 0.004 to 0.271) p 0.002. And at 6 weeks (234.50 days, HR =8.3578; 95% CI, 1.382 to 50.525 vs. 310.25 days; HR =0.119; 95% CI, 0.019 to 0.723) p =0.020. The Mean patient OS exhibited significantly shorter values within the liver function deterioration group as opposed to the non-liver function deterioration one withat a two-weeks period (220.50 days, HR=22.38; 95% CI, 2.91 to 171.65 vs 313.75 days; HR =0.044; 95% CI, 0.005 to 0.342) p 0.003. And at 6 weeks (196 days, HR =22.38; 95% CI, 2.91 to 171.65 vs 306.11 days; HR =0.044; 95% CI, 0.005 to 0.342) $p<0.001$. The Mean patient OS exhibited significantly shorter values within the prognostic score 4 group (175 days HR=10.72; 95% CI, 0.065to 1748.31) as opposed to the prognostic score 3 group (266 days, HR =1.68; 95% CI 0.191to 14.89) than in the prognostic score 2 group (245 days; HR =1.83; 95% CI, 0.192 to 17.46) in comparison to the prognostic score 1 group (292 days; HR =0.093; 95% CI, 0.000 to 15.21) compared to the prognostic score 0 group (365 days) . $p<0.001$. Figure 1.



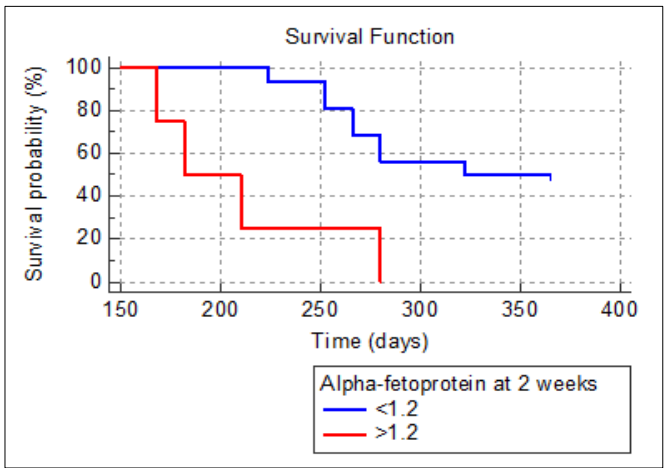
(A)



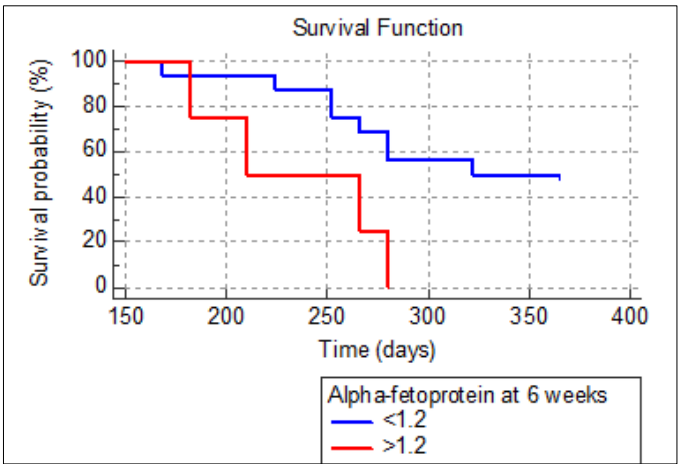
(B)



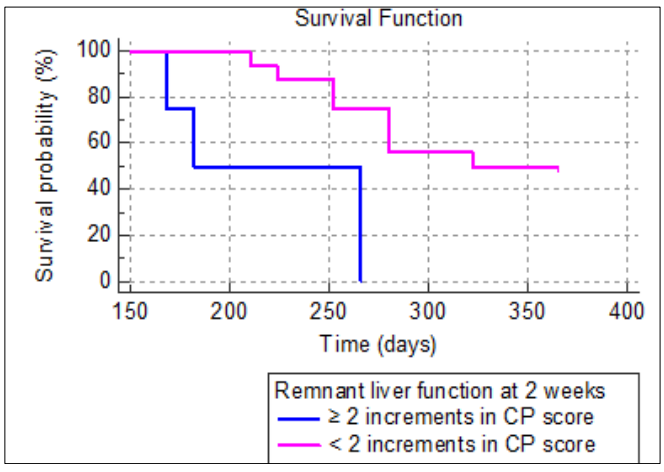
(C)



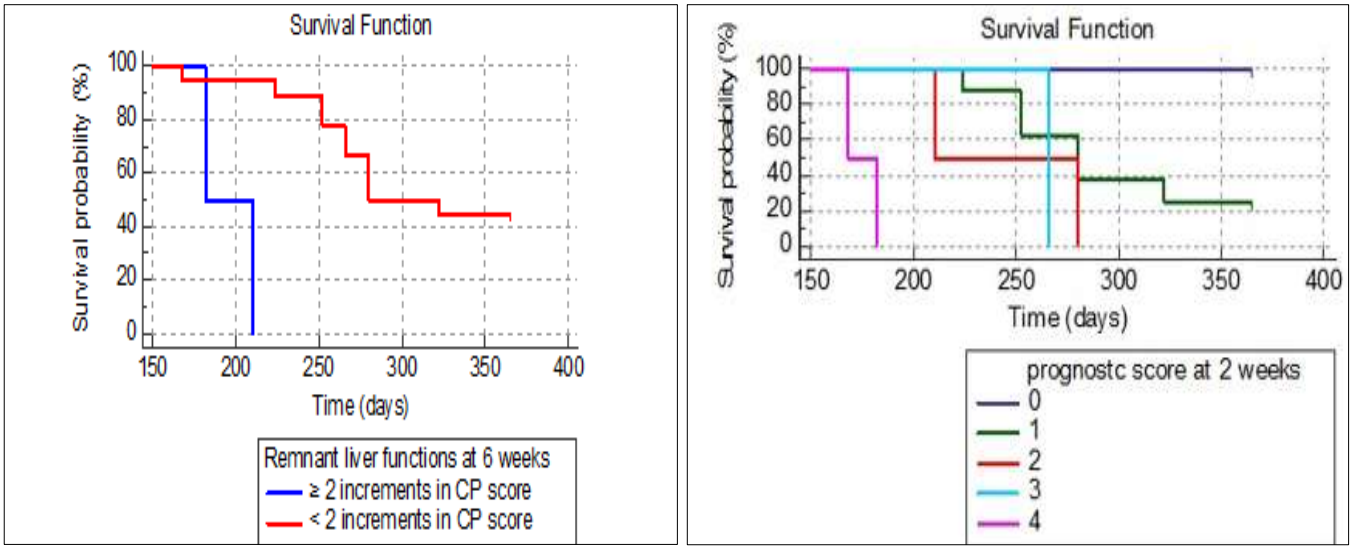
(D)



(E)



(F)



(G) **(H)**

Fig 1: Kaplan-Meier survival analysis for overall patients' survival according to the intratumor blood flow at (A) 2 weeks, (B) 6 weeks, (C) antitumor effect at 6 weeks, alpha fetoprotein ratio at (D)2 weeks, (E) 6 weeks, remnant liver functions at (F) 2 weeks, (G) 6 weeks, (H) prognostic score at 2 weeks

A prognostic score of 0 (n = 6) was observed within four PR cases and within two SD cases. A prognostic score of 1 (n = 8) was observed within zero PR cases and within eight SD cases. A prognostic score of 2 (n = 2) was observed within zero PR cases and within two SD cases. A prognostic score of 3 (n = 2) was observed within one PR case and within one SD case. A prognostic score of 4 (n = 2) was observed within zero PR and within two SD cases. The partial response rate among cases developing a prognostic score of 0 exhibited significantly greater values in comparison to that within cases developing a prognostic score of 4 (p = 0.029). Table 4.

Table 4: Correlation between prognostic score within a two-week period and the anti-Tumor Response at 6 weeks.

		Prognostic score at 2 weeks					Logrank test	
		0 (n=6)	1 (n=8)	2 (n=2)	3 (n=2)	4 (n=2)	X^2	P
Anti-Tumor effect at 6 weeks	Partial response	4 (66.7%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	---	0.029*
	Stable disease	2 (33.3%)	8 (100.0%)	2 (100.0%)	1 (50.0%)	2 (100.0%)		
	Total	6 (100.0%)	8 (100.0%)	2 (100.0%)	2 (100.0%)	2 (100.0%)		

*Significant p value <0.05. OS: Overall survival, HR: hazard ratio, CI: confidence interval, X2: chi-squared test, a: In comparison to 4, b: in comparison to 1, c: in comparison to 1, d in comparison to 1.

According to multivariate analysis based on the patients' parameters at 2 weeks, the prognostic score (2) and (3) (HR = 30.077; 95% CI 1.167 – 775.021; p = .040) and (HR = 31.088; 95%CI 1.129 – 856.302; p = .042) were independent and significant predictors of high mortality (p<0.001). At 6 weeks, all parameters were non-significant. Table 5.

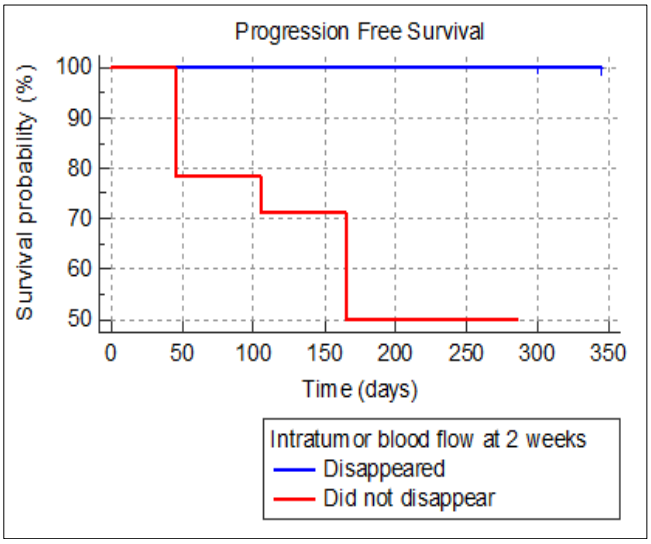
Table 5: Multivariate (forward stepwise) cox regression analysis for survival analysis based on the patients' parameters at 2 and 6 weeks

	B-coefficient	P	HR	95.0% CI for HR		P of model
				Lower	Upper	
Prognostic score (2)	3.404	.040*	30.077	1.167	775.021	<0.001*
Prognostic score (3)	3.437	.042*	31.088	1.129	856.302	
Anti-Tumor effect (SD versus partial response)	1.668	0.111	5.302	0.688	40.82	0.051

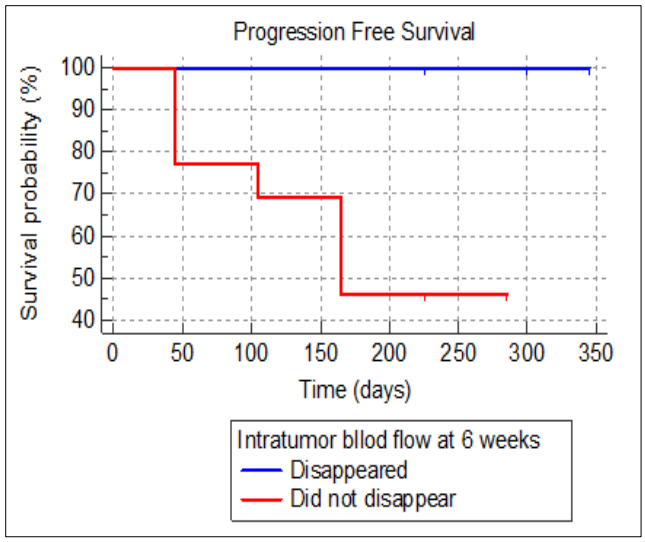
*Significant p value <0.05. HR: hazard ratio, CI: confidence interval, SD: stable disease.

The mean patient progression free survival exhibited significantly shorter values within the non-DA group in comparison to the DA group at 2 weeks (195 days versus 345 days; p 0.044) and at 6 weeks (188.07 days vs 345 days; p 0.023). The mean patient progression free survival exhibited not significantly variance among the PR group (288.4 days HR =0.422; 95% CI, 0.081 to 2.185) and the SD group (228.66 days, HR=2.369; 95% CI, 0.457 to 12.267). p=0.383.The mean patient progression free survival exhibited significantly shorter values within the (high AFP ratio group as opposed to the low AFP ratio group) as well as (liver function deterioration group in comparison to the non-liver function deterioration group) at 2 weeks (75 and 90 days, HR =141.093 and 91.27; 95% CI, 12.10 to 1643.91 vs 307.50 and8.55 to 973.60 vs 303.75 days; HR =0.007 and0.010; 95% CI, 0.000 to 0.082 and0.001 to 0.116) p 0.001 and 0.0001. And at 6 weeks (90 and 45days, HR =91.27 and1138.01; 95% CI, 8.55 to 973.60 .91 vs 303.750 and21.10 to 61376.0 vs 285 days; HR =0.010 and 0.000; 95% CI, 0.001 to 0.116 and 0.000 to 0.047) p=0.0001 respectively. The Mean patient progression free survival exhibited significantly shorter values within the prognostic score 4 group (45 days hazard ratio [HR] = 21.13; 95% confidence interval [CI], 0.500 to 893.33) than in the

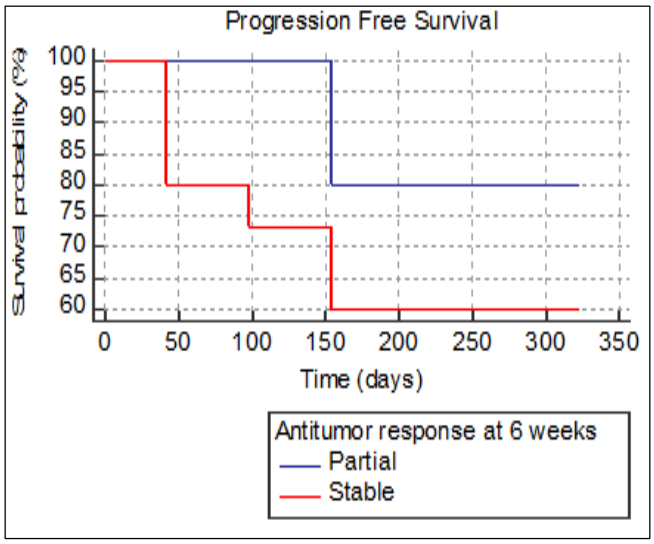
prognostic score 3 group (135 days, hazard ratio [HR] = 10.47; 95% confidence interval [CI], 0.670 to 163.83) than within the prognostic score 2 group (105 days; hazard ratio [HR] = 11.60; 95% confidence interval [CI], 0.657 to 204.94) than within the prognostic score 1 group (270 days; hazard ratio [HR] = 0.047; 95% confidence interval [CI], 0.001 to 1.99) than within the prognostic score 0 group (345 days) $p<0.001$. Figure 2.



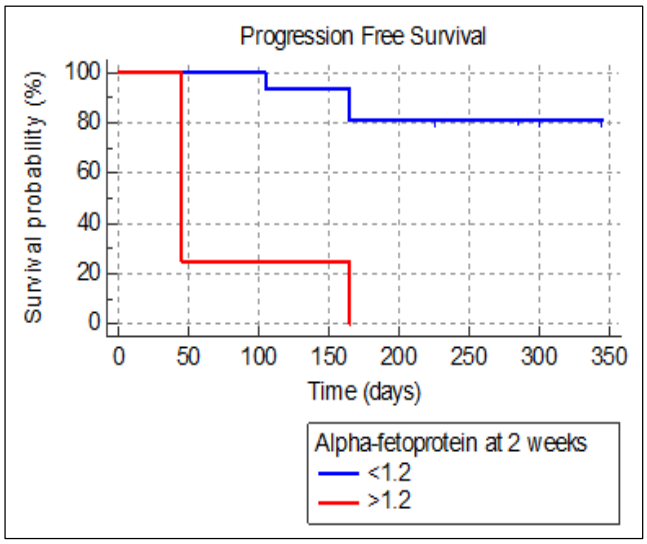
(A)



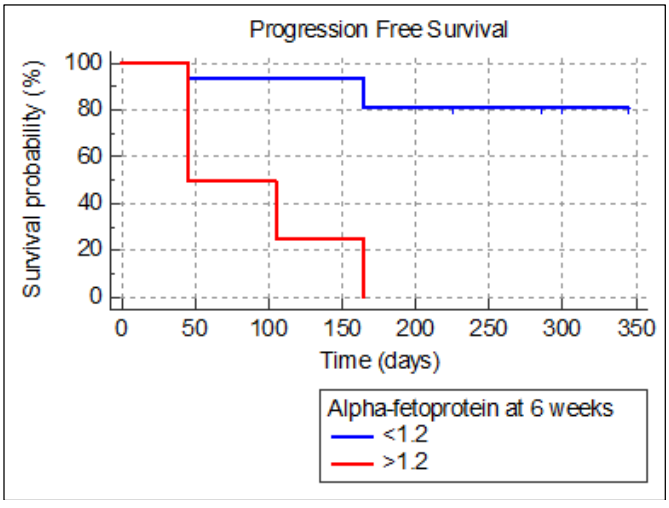
(B)



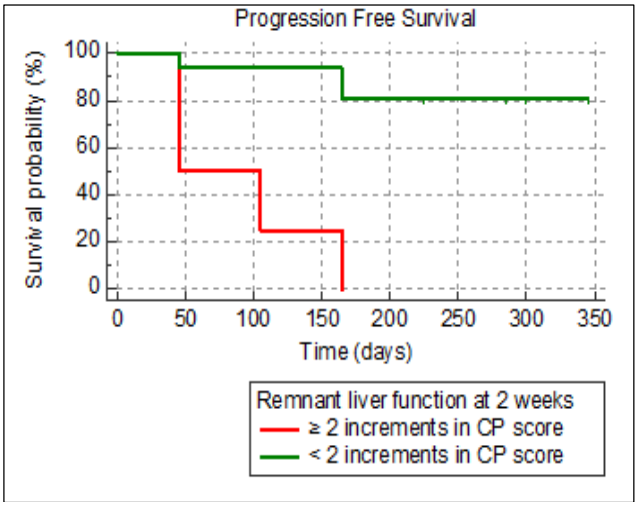
(C)



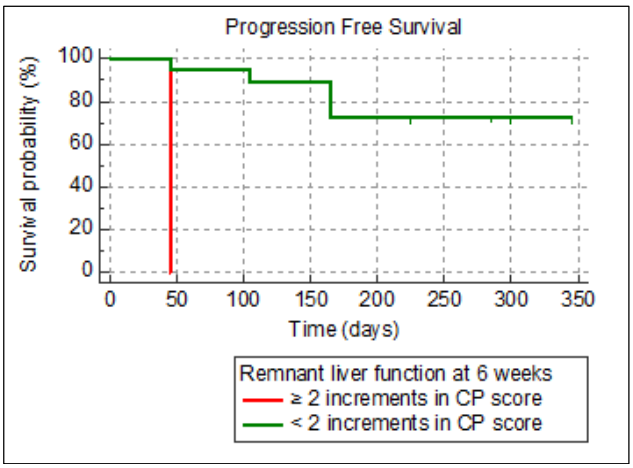
(D)



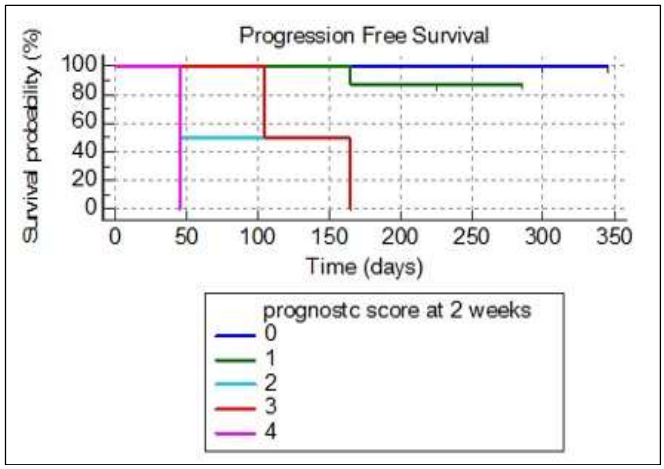
(E)



(F)



(G)



(H)

Fig 2: Kaplan-Meier survival analysis for progression free survival according to the (A) intratumor response at 2 weeks, (B) intratumor blood flow at 6 weeks, (C) antitumor effect at 6 weeks, (D) alpha-fetoprotein at 2 weeks, (E) alpha fetoprotein ratio at 6 weeks, remnant liver function at (F) 2 weeks, (G) 6 weeks and (H) prognostic score at 2 weeks

Discussion

In our research, as regards the timing to assess treatment response we focused on assessment of the early clinical and radiological response following a two-weeks period of Sorafenib therapy, thus helping us detect cases with potential resistance along with preventing unnecessary toxicity. This was matched with Hidaka *et al.* [9] and Kuzuya, *et al.* [10] they support the prompt assessment of the sorafenib's efficacy among cases developing advanced HCC. But, unlike to our study, Kim *et al.* [11] assessed radiological tumor response to sorafenib first at week 4 and every eight weeks thereafter.

Regarding intratumor blood flow assessment, we examined whether arterial tumor enhancement disappeared in a minimum of a single target lesion following two weeks receiving sorafenib therapy to assess the prompt radiological image therapeutic effects. We observed that 14 patients (70%) still had arterial tumor enhancement on triphasic -CT, and this finding was linked to a significant poor OS rate (265.143 days vs. 365 days) and significant differences in progression free survival (195 days vs 345 days). This supported a research published by Kuzuya, *et al.* [10] including 57 patients revealed that The median OS exhibited significantly shorter values among cases with non-disappearance of tumor blood flow following sorafenib treatment than among vases with disappearance of tumor blood flow following sorafenib treatment (212 days vs. 341 days; p = 0.0204). This was also matched with a research by Shiozawa *et al.* [12] proposed that the vascular architecture alterations inside a tumor could serve as an indicator of the sorafenib effectiveness.

As regards the prompt AFP response following sorafenib treatment, in our research, an AFP ratio of above 1.2 within a two-week period following the therapy in 4 patients (20%) was observed to be an independent and considerably poor prognostic factor following two weeks with sorafenib. According to Univariate analysis (p= .006) and exhibited a significantly correlation with a poor OS rate (210 days [HR] =30.25; 95% [CI], 3.68 - 248.51 vs 316.37 days \HR] =0.033; 95% [CI], 0.004 - 0.271) (p= 0.002) and progression free survival (75 days [HR] =141.093; 95% [CI], 12.10 - 1643.91 vs 307.50 days [HR] =0.007; 95% [CI], 0.000 - 0.082) (p= 0.001). This supported Kuzuya, *et al.* [10] demonstrated that The median OS exhibited significantly shorter values among cases developing AFP ratio > 1.2 as opposed to patients with AFP ratio< 1.2 (170 days vs. 340 days; p = 0.0098). A research by Plano *et al.* [13] showed that a reduction of over 20% in AFP levels following six to eight weeks as opposed to the initial measurement was a reliable indicator of a good response to sorafenib. In a multivariate analysis, the mean overall survival (MOS) for responding cases indicated 18 months, whereas for non-responding cases it indicated 10 months. The p-values associated with these results were 0.002 and 0.004, respectively. This was correlated with the study by He C *et al.* [14] founded that Following the treatment The response of AFP exhibited a strong correlation with overall survival (hazard ratio [HR] = 0.41, 95% confidence interval [CI]: 0.35-0.47, *P*<.001) as well as progression-free survival (HR = 0.46, 95% CI: 0.39-0.54, *p*<.001) among cases developing HCC.

Regarding the remnant liver function's prognostic effect within sorafenib therapy, In our research we found that the deterioration of remnant liver function within a two-weeks period following sorafenib that occurred in 4 patients (20%) exhibited an independent and significant mortality predictor based on univariate analysis (p= .010) and was associated with a worse OS rate (220.50 days, [HR] =22.38; 95% [CI], 2.91 - 171.65 vs 313.75 days; [HR] =0.044; 95% [CI], 0.005 - 0.342) (p= 0.003) as well as progression free survival (90 days, [HR] =91.27; 95% [CI], 8.55 to 973.60 vs 303.75 days; [HR] =0.010; 95% [CI], 0.001 to 0.116) (p= 0.0001). This supported Lee *et al.* [15] addressing that serum bilirubin, serum albumin, were independent predictive survival factors following sorafenib, which aligned with Vogel *et al.* [16] stating liver function to be a prognostic marker for HCC. Unlike our study and other studies using the CP system to evaluate remnant liver function there were some studies preferred evaluating remnant liver function by showed that the ALBI grade exhibited greater effectiveness as opposed to the CP score while predicting the HCC prognosis for cases developing normal liver function (CP A) who were treated with a combination of TACE as well as sorafenib.

Consequently, our results suggest that when cases have three unfavorable prognostic factors within a two-week period following Sorafenib, Sorafenib therapy could be deened inefficient. Such poor prognostic factors could be

helpful in identifying patients who shouldn't continue receiving Sorafenib therapy.

The research was limited by its very modest sample size. The research only examined alterations in intra-tumor blood flow utilizing triphasic-CT among cases developing hypervascular tumours at baseline. Consequently, the study's findings cannot be extrapolated to cases who initially presented with hypovascular tumours before Sorafenib treatment. Finally, the research only examined the AFP levels alterations among cases who initially had abnormal AFP levels (namely, serum AFP>20 ng/ml) before starting Sorafenib treatment. Consequently, the findings of the research do not apply to individuals who have normal baseline AFP levels, namely those having serum AFP levels below 20 ng/ml.

Conclusions

For patients with advanced HCC, alterations as regards intra-tumor blood flow using triphasic -CT, AFP levels, as well as remnant liver function following a two-weeks period using sorafenib may be helpful in the outcome prediction as well as the anti-tumor effect of sorafenib therapy and can help identify patients should discontinue receiving it with early switch to second line therapy to avoid unnecessary toxicities and costs when sorafenib therapy is ineffective.

Financial support and sponsorship: Nil.

Conflict of Interest: Nil.

References

1. Shen H, Gu X, Li H, Tang M, Li X, Zhang Y, *et al*. Exploring prognosis, tumor microenvironment and tumor immune infiltration in *hepatocellular carcinoma* based on ATF/CREB transcription factor family gene-related model. Journal of Hepatocellular Carcinoma. 2023;10:327-345.
2. Allaire M, Bruix J, Korenjak M, Manes S, Maravic Z, Reeves H, *et al*. What to do about *hepatocellular carcinoma*: Recommendations for health authorities from the International Liver Cancer Association. Journal of Hepatology. 2022;40:600-620.
3. Huang A, Yang XR, Chung WY, Dennison AR, Zhou J. Targeted therapy for *hepatocellular carcinoma*. Signal Transduction and Targeted Therapy. 2020;5:146-150.
4. Huang KW, Lee PC, Chao Y, Su CW, Lee IC, Lan KH, *et al*. Durable objective response to sorafenib and role of sequential treatment in unresectable *hepatocellular carcinoma*. Therapeutic Advances in Medical Oncology. 2022;14:800-830.
5. Pang Y, Eresen A, Zhang Z, Hou Q, Wang Y, Yaghmai V, *et al*. Adverse events of sorafenib in *hepatocellular carcinoma* treatment. American Journal of Cancer Research. 2022;12:2770-12782.
6. Gupta N, Verma RK, Prinja S, Dhiman RK. Cost-effectiveness of sorafenib for treatment of advanced *hepatocellular carcinoma* in India. Journal of Clinical and Experimental Hepatology. 2019;9:468-475.
7. Personeni N, Pressiani T, Rimassa L. Which choice of therapy when many are available? Current systemic therapies for advanced *hepatocellular carcinoma*. Health Science Reports. 2020;3:100-160.
8. Siegel MJ, Ippolito JE, Wahl RL, Siegel BA. Discrepant assessments of progressive disease in clinical trials between routine clinical reads and formal RECIST 1.1 interpretations. Radiology Imaging Cancer. 2023;5:700-760.
9. Hidaka H, Nakazawa T, Fujii S, Yanagihara M, Minamino T, Takada J, *et al*. Early evaluation of response to sorafenib for *hepatocellular carcinoma* by duplex Doppler ultrasonography. Hepatology Research. 2015;45:976-985.
10. Kuzuya T, Ishigami M, Ishizu Y, Honda T, Hayashi K, Katano Y, *et al*. Early clinical response after 2 weeks of sorafenib therapy predicts outcomes and anti-tumor response in patients with advanced *hepatocellular carcinoma*. PLoS One. 2015;10:600-650.
11. Kim H, Yu SJ, Yeo I, Cho YY, Lee DH, Cho Y, *et al*. Prediction of response to sorafenib in *hepatocellular carcinoma*: A putative marker panel by multiple reaction monitoring-mass spectrometry (MRM-MS). Molecular & Cellular Proteomics. 2017;16:1312-1323.
12. Shiozawa K, Watanabe M, Ikehara T, Kogame M, Kikuchi Y, Igarashi Y, *et al*. Therapeutic evaluation of sorafenib for *hepatocellular carcinoma* using contrast-enhanced ultrasonography: Preliminary result. Oncology Letters. 2016;12:579-584.
13. Plano Sánchez AI, Velasco Roces L, Zapico García I, Lázaro López E, Calleja Hernandez MA, Baena Parejo MI, *et al*. Value of α-fetoprotein as an early biomarker for treatment response to sorafenib therapy in advanced *hepatocellular carcinoma*. Oncology Letters. 2018;15:8863-8870.
14. He C, Peng W, Liu X, Li C, Li X, Wen TF. Post-treatment α-fetoprotein response predicts prognosis of patients with *hepatocellular carcinoma*: A meta-analysis. Medicine. 2019;98:800-830.
15. Lee CU, Lee YS, Kim JH, Lee M, Kim S, Jung YK, *et al*. An analysis for survival predictors for patients with *hepatocellular carcinoma* who failed to sorafenib treatment in pre-regorafenib era. Journal of Liver Cancer. 2019;19:117-127.
16. Vogel A, Kelley RK, Johnson P, Merle P, Yau T, Kudo M, *et al*. Predictive and prognostic potential of liver function assessment in patients with advanced *hepatocellular carcinoma*: A systematic literature review. Liver Cancer. 2023;12:372-391.
17. Wang Z, Fan Q, Wang M, Wang E, Li H, Liu L. Comparison between *Child-Pugh* Score and albumin-bilirubin grade in patients treated with the combination therapy of transarterial chemoembolization and sorafenib for *hepatocellular carcinoma*. Annals of Translational Medicine. 2020;8:537.

How to Cite This Article
Azab NM, Abu-Sobaa RM, Abd-Elhamed MAA, Hussein FZ. Evaluation of clinical and radiological response with antiangiogenic therapy in advanced hepatocellular carcinoma patients. International Journal of Oncology Research. 2024; 4(1): 97-105.