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Tolerance of sorafenib in patients with residual HCC post TACE

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Abstract---Background: Hepatocellular carcinoma (HCC) is among the most prevalent cancers and the second leading cause of cancer-related mortality globally. Objective: The aim was to investigate the sensitivity of sorafenib administration after TACE in advanced HCC patients. Methods: From June 2021 to June 2022, 36 patients from Hayatabad Medical Complex Peshawar were enrolled in this retrospective research. Based on the correct state of liver activity, sorafenib medication was started within two weeks of finishing TACE treatment. Throughout each follow-up, the liver and kidney function, adverse effects, and medicinal impact were assessed using the Modified response assessment criteria in solid tumors (mRECIST). Results: The mean overall survival (mOS) and mean time to progress (mTTP) were 11.5 months and 7.5 months, respectively. Patients with one or more localised hepatic lesions were respectively 18 months and 12 months old (□2 = 4.613, P = 0.0314). No patients had a full response, three had partial responses, 11 had stable disease (SD), and 22 had progressive illness (PD), as per the mRECIST. The disease control rate (DCR) was 38.89% (14/36) and the response rate was

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8.33% (3/36) for both. Hand-foot skin irritation (21 incidences, 58.3%), and diarrhoea (17 incidences, 47.22%) were the predominant adverse effects. Skin irritation and diarrhoea reduced from 58.3% to 50.0% and 47.22% to 27.79%, respectively, after therapy. Before combination treatment, the mean TACE interval was 48 days, and after, it was 90 days. Conclusion: Sorafenib medication after TACE might increase the time between TACEs, maintain the stable condition for longer, and increase the overall survival of patients with advanced HCC. The fact that the adverse effects are often manageable supports the combination's safety.

Keywords---sorafenib, hepatocellular carcinoma, transarterial chemoembolization, combination therapy.

Introduction

HCC ranks as one of the most prevalent malignancies and the second-leading cause of cancer-related mortality globally, and its prevalence is expected to rise in the coming years. Because of the low success rate of surgical intervention and higher incidence of postoperative recurrence, conventional radical surgery is ineffective for the therapies of unresectable or advanced phase HCC in the vast majority of instances of HCC linked with hepatitis B virus (HBV) disease at the time of the first diagnostic test [1-2]. HCC affects over than 711,000 people worldwide each year; 679,000 of them pass away. In clinical settings, a variety of medical and surgical techniques have been used, with over 50 percent of HCC patients displaying an unresectable or un-embolized state. Because of vascular invasion or extrahepatic metastases' limits, there are only palliative therapies accessible [3-6]. Sorafenib stimulates apoptosis by reducing tumor angiogenesis and growth. Restriction of VEGFR2-PDGFR- and Raf-kinase characteristics, signaling pathways found as a close reason in HCC research and offering survival advantages in advanced HCC, is how anti-angiogenic activity is achieved Patients receiving sorafenib have constraints in clinical settings, such as expensive costs that put a strain on finances, significant side effects (28–89%) that might restrict sorafenib intake and hamper treatment approaches, and a high rate of tumor progression with a single drug [7-14]. Sorafenib was used in combination treatment at a lower dose to get superior results in both in vitro and in vivo animals [15].

TACE is the prevailing standard treatment for transitional stage HCC (BCLC stage B) in medical settings, and a previous study found that sorafenib and TACE together were more efficient than either sorafenib alone or TACE alone for unresectable HCC. However, no information has been provided on the investigation of the impact of different sorafenib dosages with successive TACE before or following sorafenib discontinuation [16]. The aim was to investigate the sensitivity of sorafenib administration after TACE in advanced HCC patients.

Material and Methods

In accordance with the National Comprehensive Cancer Network regulations for Hepatobiliary Cancers, patients with advanced or intermediate-stage HCC were eligible for enrolment [17]. From June 2021 to June 2022, 36 patients from Hayatabad Medical Complex Peshawar were registered in this retrospective investigation**.** Patients with Child-Pugh class C liver function and those whose Eastern Cooperative Oncology Group performance scores (ECOG-PS) equivalent to or higher than 3 points, as well as those with tumors smaller than 3 cm, grade, coagulation issues, and other primary malignancies, were excluded from the study. Following were the criteria for inclusion: Patients should be in BCLC stages B or C. There was at least one detectable tumor, as determined by the updated response assessment criteria in solid tumors. Hepatectomy is not an option for the patient because they have at least three months to live. The ECOG-PS result was less than 2 points.

Doctors with more than five years of TACE expertise performed the treatment. In short, the patient was pierced under local anesthetic with 2% lidocaine, and an arterial catheter was intubated using the Seldinger technique at the base of the main artery. A super selective micro catheter was put into the tumors' feeding artery while a catheter was introduced into the hepatic vein under the direction of digital subtraction angiography. After hepatic angiography, epirubicin (20 mg) was introduced into the tumor together with 5-fluorouracil (750 mg) and oxaliplatin (150 mg) in a mixed emulsion that also contained 15–30 ml of hyper-liquefying iodide oil. Each patient received a specific dosage according on their embolization situation. The supplying arteries were fully blocked using easily absorbed gelatin sponge nanoparticles. Iodine tablets were eventually acquired to verify the total embolism of the feeding arteries.

As the lipiodol accumulation decreased and remaining lesions appeared, more TACE would be advised if contrast-enhanced MRI revealed viable lesions or intrahepatic recurrence within six weeks of TACE treatment. Based on the correct state of liver function, sorafenib medication was started within two weeks of finishing TACE treatment. Two times per day, 400 mg of sorafenib was taken orally, and every three weeks, 3 mg/kg of nivolumab was given intravenously. All patients received routine follow-up care and rechecks. Within six weeks of starting TACE administration, an abdominal MRI and hematological reexamination were performed for the first time. Subsequent reexaminations were advised to be done every one to three months while undergoing care. Reconsideration intervals for stable lesions were extended after 3-6 months. During each follow-up, the hepatic and renal function, adverse effects, and therapy impact were assessed using mRECIST. The statistical programme SPSS 24.0 was used to analyses this research. Categorical variables are described as quantities or percentages whereas continuous variables are given as averages and extremes. The chi-square test was used to assess categorical variables. The Student's t-test was used to evaluate continuous variables. Using the log rank test, differences between several survival curves were evaluated. P value less than 0.05 on a two-tailed test was used to determine statistical significance for variations.

Results

A total of 73 patients' data were collected, of which 36 patients met the inclusion criteria. Of them, 28 patients (77.79%) were man and 8 patients (22.21%) were female. Table 1 compares the basic characteristics of the two groups, comprising age, gender, Child-Pugh score (CPS), BCLC stage, alpha-fetoprotein (AFP) level, hepatitis, sorafenib injection, and TACE treatment. Also, 27 patients had entire TACE operations prior to the treatment of sorafenib, with a sample mean of 4 TACEs per patient (4-6 times). The average duration among TACEs was 48 days. In the first week following the first TACE, nine patients started taking sorafenib. All 36 patients had TACE operations with a mean number of three TACEs per patient following combination treatment (1–6 times). The average time between TACEs increased to 90 days.

The most common adverse effects in this group were those related to TACE, which included nausea, fever, vomiting, and stomach discomfort. These symptoms often subsided or were relieved after one week of symptomatic therapy. Skin sensitivity (21 incidents, 58.3%), diarrhea (17 incidents, 47.22%), tiredness (15 incidents, 41.67%), hypertension (10 incidents, 27.78%), hair loss (3 incidents, 8.33%), and oral ulceration (4 incidents, 11.10%) were adverse effects linked to sorafenib. Sorafenib adverse effects often started 1 week to 15 days after starting. Symptomatic therapy and dose adjustments allowed for the majority of them to be relieved (table 2).

Table 1
Basic characteristics of research participants

Different factors	Number of patients (n) and percentage (%)	
	Male	Female
Age	49 ± 10.21 years	
Gender	28 (77.79)	8 (22.21)
AFP	21 (58.35)	15 (41.65)
CPS (stage A/B)	31 (86.11)	5 (13.89)
Hepatitis/no hepatitis	29 (80.56)	7 (19.44)
BCLC (B/C)	5 (13.89)	31 (86.11)
Three or more TACEs preceding combination treatment	27 (75.0)	
Sorafenib therapy within a week of the first TACE	9 (25.0)	
* alpha-fetoprotein * Child-Pugh score *BCLC=Barcelona Clinic Liver Cancer *TACEs=Transarterial chemoembolization		

Table 2
With sorafenib therapy, research participants had adverse effects

Adverse Effects	Preceding Therapy					After Therapy				
	L 1	L 2	L 3	L 4	Total	L 1	L 2	L 3	L 4	Total
Hair loss	3	0	0	0	3	0	0	0	0	0
Oral ulceration	4	0	0	0	4	0	0	0	0	0
Hypertension	5	3	2	0	10	5	3	2	0	10
Fatigue	12	2	1	0	15	10	1	1	0	12
Diarrhea	8	6	3	0	17	6	2	2	0	10
Skin Reaction (Hand/Foot)	9	11	0	0	21	16	1	1	0	18
*L= Levels										

In this research, the mOS was 11.5 months and mTTP was 7.5 months (95% confidence intervals [CI]: 9-15 months and 7-13 months, correspondingly) (figure 1 and 2). Patients with Child-Pugh types A and B had mOS of 12 months and 9 months (95% CI: 9-18 months and 6-23 months) correspondingly. There was little variation among them ($\chi 2$ = 0.0632, P = 0.8756). Participants with or without vessels had mOS of 10 months and 13 months (95% CI: 9-14 months and 9-18 months) correspondingly. There was little variation among them ($\chi 2$ = 1.7439, P = 0.3293). The mOS for participants with a single or multiple hepatic focal lesions was 18 months (95% CI: 6-32 months and 9 -13 months), correspondingly, and there was a major distinction between the two ($\chi 2$ = 4.613, P = 0.0314). No patients had a full response, three had partial responses, 11 had SD, and 22 had PD, according to mRECIST. The DCR was 38.89% (14/36) and the response rate was 8.33% (3/36) for both.

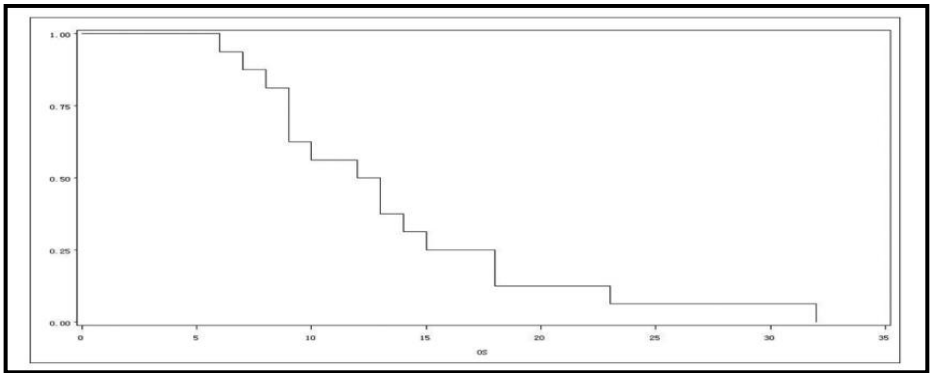

Figure 1. Month-over-month survival curve

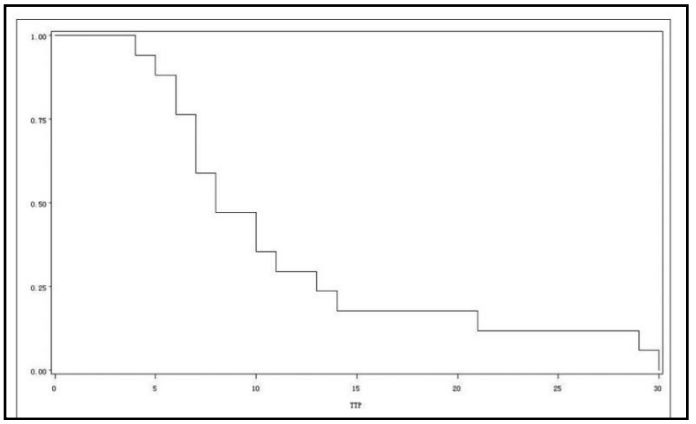

Figure 2. Duration of improve curve month

Discussion

One of the most prevalent malignant tumors in the globe is HCC. TACE has been established as the primary palliative therapy technique for unresectable HCC because to the well-documented short-term impact. Nevertheless, the brief outcome is disappointing, particularly for tumors with poorly margins and many lesions, since TACE was unable to physically block the feeding veins, preventing 100% death from occurring [18]. The first and only molecular target drug to be licensed for the treatment of mid- and delayed HCC is sorafenib [19]. Several intracellular threonine kinases are also inhibited by sorafenib. According to the two renowned phase III clinical trials, SHARP and Oriental, the treatment of sorafenib to people who have advanced-stage HCC can increase overall survival by 44% or 47%, shorten time to progression by 74% and reduce cancer risk by 31% respectively. In various recommendations, sorafenib has been suggested as the preferred therapy for late-stage HCC [20]. Nevertheless, it has been discovered that using sorafenib by itself has relatively modest impact in clinical settings. Combo treatment has drawn the interest of several researchers in recent years.

According to Pericleous *et al.,* (2016), late stage HCC was successfully treated. In their investigation, 18 individuals received TACE and sorafenib combined treatment. The 27 more patients received just sorafenib therapy. The combined group's OS and TTP were 16 months and 5.3 months, while the single therapeutic group's was 11 months and 4.5 months. Both variations were statistically meaningful ($P < 0.01$). According to the findings, TACE and sorafenib combination treatment for late stage HCC may increase the participant's survival [21]. The DCR, mOS, and mTTP in this trial, which coincided with previous domestic studies, were 38.89%, 11.5 months, and 7.5 months, respectively [22]. The findings of this study weren't very encouraging. We speculate that the majority patients in this group were in advanced stages, which may be the cause. A percentage of 86% of them were in BCLC C stage. During a week of the first TACE, only nine patients started taking sorafenib. Since they were resistant to TACE, 75% of patients started taking sorafenib after three TACEs. The combo therapy served solely as a corrective measure for them. Nonetheless, the combo treatment resulted in a respectable DCR for them. Patients in Stages A and B of the Child-Pugh classification had mOSs of 12 months and 9 months,

correspondingly. The mOS was 18 months for individuals with a single hepatic lesion and 12 months for those with multiple hepatic lesions. The findings imply that TACE and sorafenib combined treatment, particularly for patients with single lesions, may effectively limit tumour development, enhance the patient's life, and lengthen survival rate. The combined treatment with TACE and sorafenib has shown good outcomes in the trial by Rapicetta *et al.,* (2015).

The average period among TACE and combo treatment in this study was 48 days. It was extended to 90 days but after combination, which was comparable with the Beginning results. Increasing the gap might lessen the adverse effects of drugs on the liver and relieve patients' financial as well as mental burdens. The most frequent adverse effects in this sample, experienced by the majority of the participants, were skin reactions and diarrhea. Using cotton gloves and periodically rubbing the affected area with Vaseline ointment will help to reduce skin sensitivity (Hand/Foot). When using sorafenib, individuals who have diarrhea are advised to avoid eating or drinking anything cold, raw, or irritative two hours prior to take the drug. The majority of patients' symptoms might be reduced or eliminated by following the aforementioned recommendations.

Conclusion

By giving sorafenib following a TACE, patients with advanced HCC may live much longer generally, maintain a stable condition longer, and go longer among TACEs. Typically, the adverse effects are manageable. The combo treatment is therefore efficient and secure.

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