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Adherence to Sorafenib Therapy Is Not Affected by Treatment-Related Side Effects or Demographic Characteristics of Iraqi Patients with Hepatocellular Carcinoma

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ABSTRACT

Introduction: Sorafenib is an orally active multiple kinase inhibitor for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma (HCC) patients. However, measuring the experience of patient-reported symptoms may provide additional information to compare the efficacy and toxicity of treatments.

Objective: The aim of the current study was to investigate the association between hepatocellular carcinoma patients' adherence to treatment and their demographic characteristics.

Patients and methods: An open-label cross-sectional study was conducted at the Oncology Teaching Hospital, Al-Amal Hospital, Imam Al-Kadhimin Medical City in Baghdad, Iraq, from November 2021 to July 2022. A total of 52 patients taking sorafenib for their HCC were recruited in our study. Adherence to treatment was assessed using Morisky Medication Adherence Scale. **Results**: A total of 52 patients were enrolled in current study. Fatigue was the most common adverse event as it was experienced by 90.4% of participants, followed by anorexia, anemia, nausea and diarrhea (71.2%, 67.3%, 65.4%, and 59.6%, respectively), while only 26.9% of participants had vomiting. In addition, all participants showed low-moderate adherence to treatment. Also, there was non-significant association between demographic data of patients or treatment-related adverse effects.

Conclusion: Patients with hepatocellular carcinoma on sorafenib treatment exhibit low-moderate levels of adherence. The latter had not affected by sorafenib-related adverse effects or demographic characteristics of patients.

Keywords: Adherence, Adverse effects, Hepatocellular carcinoma, Multikinase inhibitor, Sorafenib, Cross sectional study, University of Baghdad, Iraq.

INTRODUCTION

Liver cancer represents the sixth among all types of tumors globally [(1)]. Also, hepatocellular carcinoma (HCC) is the predominant primary liver cancer and the third largest cause of mortality [(2)]. Also, men are 2-3 times more likely than women to be affected [(3)]. According to epidemiological studies, both environmental and ethnic factors are key determinants of HCC [(4)]. The possible mechanisms involved in the pathogenesis of HCC are described in ***Figure 1***.

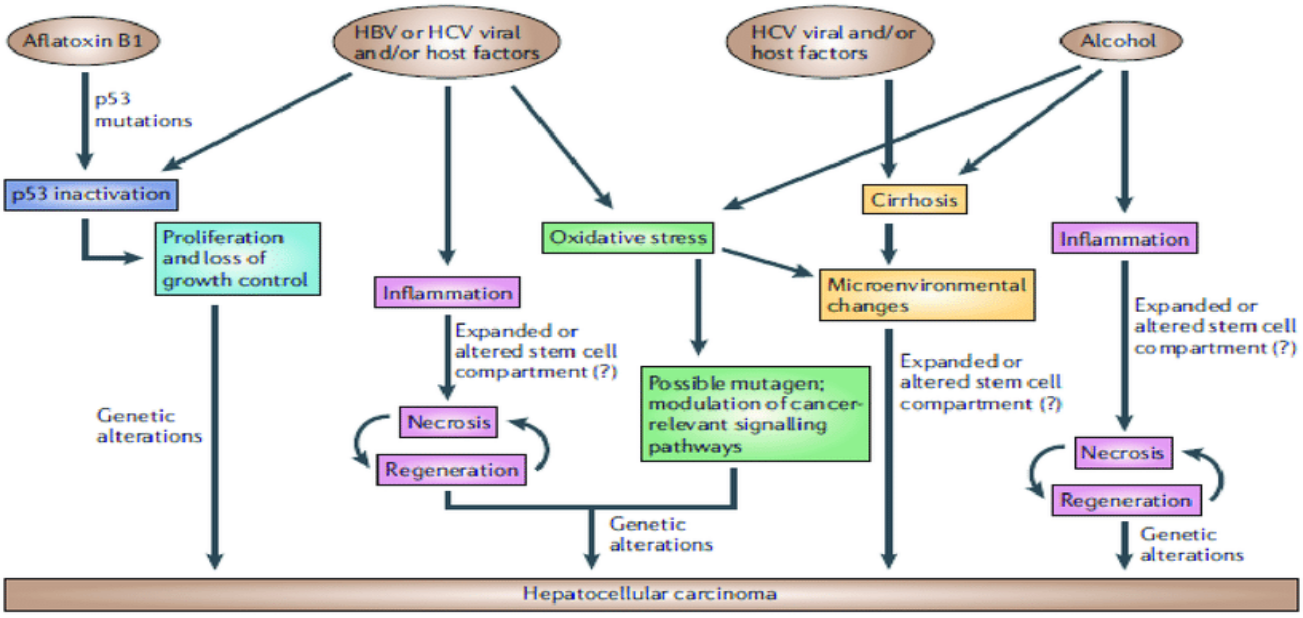

Figure (1). Mechanisms of hepatocarcinogenesis [(4)].

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However, hepatic tumors are diagnosed definitively via percutaneous biopsy and alpha fetoprotein (α-FP) in serum [5]. In addition, ultrasonography, magnetic resonance imaging, computed tomography, computed tomographic portogram, arteriographically-enhanced CT and hepatic arteriography are some of the imaging methods used to determine the size and location of tumors [3]. On the other hand, the overall goal of treatment is to slow the progression of the disease and reduce mortality [6].

Hepatocellular carcinoma had no standard treatment before 2007 and clinicians often utilized cytotoxic chemotherapy, but its effectiveness was debated due to a lack of high-quality evidence and concerns about toxicity in cirrhotic patients. Thus, Sorafenib was the first systemic treatment to show a survival benefit in a randomized controlled trial in 2007 [7]. Its mechanism of action is demonstrated in **Figure 2**.

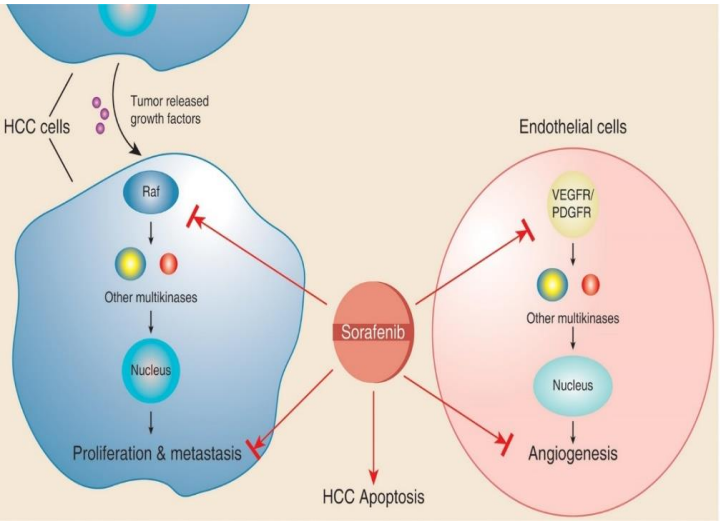

Figure (2). Mechanism of action of sorafenib [8].

Regardless of the fact that sorafenib is an effective treatment for HCC; it is accompanied with several side effects [9]. These include weight loss, fatigue, anorexia, diarrhea or constipation, abdominal pain, nausea, vomiting rash-desquamation, alopecia, hand-foot-skin reaction [10].

On the other hand, the advantages of effective drug use are based on taking the medication by patient as prescribed. This was previously referred to as "compliance". However, with a more patient-focused program of healthcare, the term "compliance" has evolved over time to "adherence" to represent medication taking behavior. Also, this change reflects a desire to emphasize the patient's active participation in decision-making [11].

The "Morisky Medication Adherence Scale (MMAS)" was created by Dr. Morisky and his colleagues and published in 1986. It is a simple, quick and practical instrument to use when encountering patients. However, it can be used both to identify patients who have adherence issues and also to evaluate adherence through the course of their treatment [12].

The aim of the current study was to investigate the association between hepatocellular carcinoma patients' adherence to treatment and their demographic characteristics.

PATIENTS AND METHODS

This is a cross-sectional, open-label study conducted at the Oncology Teaching Hospital, Al-Amal Hospital and Al -Imamein Al- Kadhimein Medical City in Baghdad, from November 2021 to July 2022.

The study was planned to recruit 50 patients, or more, who were taking sorafenib for their HCC. Patients were asked to participate voluntarily after an adequate explanation about the aim and method of the study. All participants were assured of anonymity and confidentiality of the information. Verbal consent was obtained from each participant.

A convenient sampling method was adopted to enroll the participants in current study. Their age should be ≥18 years and they should be able to provide an informed consent. Patients with other types of cancer, with chronic diseases (respiratory, renal, diabetes mellitus, hypertension, cerebrovascular and/ or cardiovascular disease), pregnant and/or nursing mothers were excluded from the study.

The data was collected using a validated questionnaire through interviews performed by the researchers with the participants, and included: Sociodemographic characteristics (gender, age, education, residence, and employment), adverse events associated with sorafenib treatment (liver function test, renal function test, and white blood cell count) and assessment of treatment adherence based on "Morisky Medication-Taking Adherence Scale (MMAS)" (**Table 1**) [12,13].

However, scores were categorized into the following 3 levels of adherence [14]:

- High adherence if the score = 8
- Medium adherence if the score = 6-8
- Low adherence if the score is < 6

Table 1. Morisky Medication-Taking Adherence Scale [12].

Q1. Do you sometimes forget to take your pills?
Q2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your medicine?
Q3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?
Q4. When you travel or leave home, do you sometimes forget to bring along your medication?
Q5. Did you take your medicine yesterday?
Q6. When you feel like your disease is under control, do you sometimes stop taking your medicine?
Q7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?
Q8. How often do you have difficulty remembering to take all your medications?

Ethical approval:

Ethical approval was obtained from the Scientific Research Ethics Committees at the Department of Pharmacology and the Department of Medicine at the College of Medicine, University of Baghdad. Written informed consents were obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical analysis:

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as means and SD, and independent sample t-test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

Demographic data of participants: A total of 52 patients were enrolled in current study, 34 were males (65.4%) and 18 were females (34.6%). Patients aged 51-60 years constituted the largest age group (34.6%). In addition, 67.3% of the patients were living in urban areas, 73.1% of them were unemployed and 40.4% had college or higher education (**Table 1**).

Table 1. Socio-demographic characteristics of participants.

Demographic characteristic		No.	%
Gender	**Male**	34	65.4%
	Female	18	34.6%
Age group	**≤40**	6	11.5%
	41-50	15	28.8%
	51-60	18	34.6%
	61-70	11	21.2%
	>70	2	3.8%
Education	**Primary school**	20	38.5%
	Secondary school	11	21.2%
	College or higher	21	40.4%
Residency	**Urban**	35	67.3%
	Rural	17	32.7%
Employment	**Yes**	14	26.9%
	No	38	73.1%

Adverse effects of Sorafenib experienced by participants: Fatigue was the most common adverse effect as it presented in 90.4% of participants, followed by anorexia, anemia, nausea and diarrhea (71.2%, 67.3%, 65.4%, 59.6%, respectively), while only 26.9% of the participants had vomiting (**Table 2**).

Table 2. Frequency of adverse effects of Sorafenib experienced by participants.

Adverse effects	No.	%
Fatigue	47	90.4
Anorexia	37	71.2
Nausea	34	65.3
Vomiting	14	26.9
Diarrhea	31	59.6
Constipation	19	36.5
Abdominal pain	24	46.2
Hand foot skin reaction	17	32.7
Weight loss	16	30.8
Anemia	35	67.3
Low WBC count	27	51.9
Abnormal Liver function	30	57.7%
Abnormal Renal function	24	46.1%

No.: Number of patients.

Participants' adherence to treatment:

Regarding adherence to treatment, 34.6% of the patients had low adherence, 65.4% had moderate adherence, while none of them had high adherence (**Figure 1**).

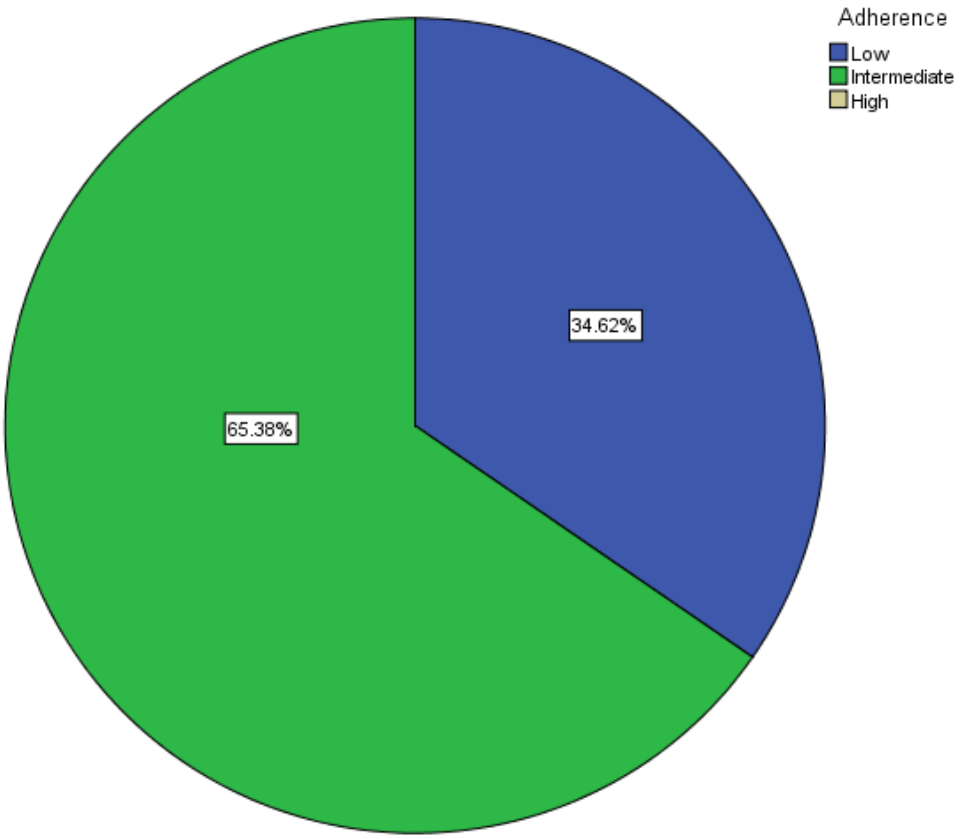

Figure 1. Participants' adherence according to Morisky Medication-Taking Adherence Scale.

Association between participants' adherence to treatment and their demographic characteristics: There was no significant association between the adherence level and demographic characteristics of participants, including gender, age, residency, education, and occupation (**Table 3**).

Table 3. Association between participants' adherence to treatment and their demographic characteristics.

Demographic characteristic		Adherence						P-value
		Low		Intermediate		High		
		No.	%	No.	%	No.	%	
Gender	Male	12	35.3%	22	64.7%	0	0.0%	0.888
	Female	6	33.3%	12	66.7%	0	0.0%	
Age (year)	<=40	2	33.3%	4	66.7%	0	0.0%	0.883
	41-50	5	33.3%	10	66.7%	0	0.0%	
	51-60	5	27.8%	13	72.2%	0	0.0%	
	61-70	5	45.5%	6	54.5%	0	0.0%	
	>70	1	50%	1	50%	0	0.0%	
Education	Primary school	9	45%	11	55%	0	0.0%	0.320
	Secondary school	2	18.2%	9	81.8%	0	0.0%	
	College or higher	7	33.3%	14	66.7%	0	0.0%	
Residency	Urban	9	25.7%	26	74.3%	0	0.0%	0.068
	Rural	9	52.9%	8	47.1%	0	0.0%	
Occupation	Yes	5	35.7%	9	64.3%	0	0.0%	0.919
	No	13	34.2%	25	65.8%	0	0.0%	

Chi-squared test. No.: Number of patients.

Association between participants' adherence to treatment and the experienced adverse effects: There was no significant association between the adherence level and the adverse effects including fatigue, anorexia, nausea, vomiting, diarrhea, constipation, abdominal pain, hand foot skin reaction, weight loss, anemia, low WBC counts, abnormal Liver function test, abnormal Renal function (**Table 4**).

Table 4. Association between participants' adherence to treatment and the experienced adverse effects.

Adverse effect		Adherence						P-value
		Low		Intermediate		High		
		No.	%	No.	%	No.	%	
Fatigue	Negative	1	20.0%	4	80.0%	0	0.0%	0.648
	Positive	17	36.2%	30	63.8%	0	0.0%	
Anorexia	Negative	6	40.0%	9	60.0%	0	0.0%	0.749
	Positive	12	32.4%	25	67.6%	0	0.0%	
Nausea	Negative	4	22.2%	14	77.8%	0	0.0%	0.227
	Positive	14	41.2%	20	58.8%	0	0.0%	
Vomiting	Negative	11	28.9%	27	71.1%	0	0.0%	0.197
	Positive	7	50.0%	7	50.0%	0	0.0%	
Diarrhea	Negative	4	19.0%	17	81.0%	0	0.0%	0.076
	Positive	14	45.2%	17	54.8%	0	0.0%	
Constipation	Negative	11	33.3%	22	66.7%	0	0.0%	0.515
	Positive	7	36.8%	12	63.2%	0	0.0%	
Abdominal pain	Negative	8	28.6%	20	71.4%	0	0.0%	0.388
	Positive	10	41.7%	14	58.3%	0	0.0%	
Hand foot skin reaction	Negative	13	37.1%	22	62.9%	0	0.0%	0.758
	Positive	5	29.4%	12	70.6%	0	0.0%	
Weight loss	Negative	12	33.3%	24	66.7%	0	0.0%	0.763
	Positive	6	37.5%	10	62.5%	0	0.0%	
Anemia	Negative	7	41.2%	10	58.8%	0	0.0%	0.544
	Positive	11	31.4%	24	68.6%	0	0.0%	
Low WBC count	Negative	8	32.0%	17	68.0%	0	0.0%	0.776
	Positive	10	37.0%	17	63.0%	0	0.0%	
Liver function	Abnormal	11	36.7%	19	63.3%	0	0.0%	0.775
	Normal	7	31.8%	15	68.2%	0	0.0%	
Renal function	Abnormal	12	32.4%	25	67.5%	0	0.0%	0.749
	Normal	6	40.0%	9	60.0%	0	0.0%	

Chi-squared test. No.: Number of patients.

DISCUSSION

Males older than 50 years old made up more than half of the HCC patients who participated in the current study. Comparatively, a Japanese study revealed similar results as men are more likely than women to get HCC overall, particularly among those who are older than 70 years [15]. Also, ***Brunocilla et al.*** [16] reported the same findings in their study as most of the participants were males with a median age of 67 years. Moreover, the results of current study were compatible with those of a Japanese study that involved a total of 465 patients, 219 males and 51 females, with a median age of 71 years [17]. Moreover, two recent studies involved Iraqi patients with colorectal and pancreatic carcinomas reported that 52% and 73.3% of participants were males, respectively [18,19].

According to some significant research conducted in the United States, sex may be involved in the development of HCC. The latter is more common in men than in women, with a ratio of 2:1-4:1. However, compared to women, men are more likely to have a viral hepatitis infection, drink more alcohol, smoke more cigarettes, and have a greater body mass index. Additionally, higher testosterone levels or the use of anabolic steroids have been linked to a higher incidence of HCC in males [20].

The positive association between age and HCC incidence might be due to the effects of alcohol consumption and HCV on the development of HCC as it becomes stronger with advancing age. This conclusion may be partially explained by the likely increased prevalence of alcoholic HCC in older patients in Korea [21].

Regarding the Residency, those diagnosed in urban communities represented the majority of patients in current study. The same results were obtained in the United States from another study that included a percentage (75.8%) of patients with HCC receiving sorafenib who were diagnosed in an urban community [22]. Also, a study conducted in Iraq revealed that 77.1% of breast cancer patients came from urban areas [23].

Regarding the adverse events, fatigue was the most common adverse event, followed by anorexia, anemia, nausea and diarrhea. In comparison, another study that was done in Italy by ***Brunocilla et al.*** [16] also concluded that fatigue was the most prevalent adverse event; a total of 66.7% of patients experienced fatigue during treatment while 52.8 % of patients experienced other adverse effects during treatment. Of the latter, the most common events were anorexia hand–foot skin reaction, abdominal pain, nausea and vomiting. In addition, diarrhea and fatigue were the most prevalent adverse reactions (39% and 22%, respectively), followed by hand–foot skin reaction (21%), anorexia (54.8%), in another study [7].

Ostwal et al. [24] revealed that hand–foot skin reaction, abnormal liver function tests and fatigue were the most frequent adverse events. Additionally, current study found a number of adverse events including abnormal liver function tests, low WBCs counts, abdominal pain, abnormal renal function tests, respectively, according to their prevalence. The patient's age, gender, existence of other disorders, interactions with other medications and other clinical and demographic variables, may have an impact on the variations of the incidence of adverse events. Moreover, sorafenib may inhibit multiple tyrosine kinases by a several various paths, including the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, and epidermal growth factor receptor (EDGR), making it challenging to pinpoint a single mechanism to account for the drug's side effects. For instance, some studies have shown that the hand-food syndrome might be caused by inhibiting VEGFR, which may hinder vascular healing, while other researchers suggested that this reaction was caused by direct skin toxicity [25]. Furthermore, ***Bins*** [26] found new correlations between genetic polymorphisms for drug transporters in genes encoding and various kinds of sorafenib toxicity. Genetic polymorphisms in *UGT1A1 and SLCO1B1* are correlated with numerous sorafenib side effects.

The majority of patients in the current study reported moderate adherence, followed by low adherence while none of participants showed high adherence.

Morisky-Green test in an earlier study conducted in Brazil showed that 81.8% of patients had high adherence to sorafenib in clinical practice, 18.2% had moderate adherence, and none of the subjects presented low adherence. However, another study also carried out in Brazil revealed that the proportion of patients who adhered well to their treatment was a little more than a half (55.0%) [27]. Moreover, another study conducted in the Switzerland showed that the adherence to oral antineoplastic treatment was generally high [28]. However, non-adherence was recorded by 30% of patients receiving oral sorafenib therapy to treat HCC in a study conducted in the United States [29].

Factors linked to non-compliance or poor adherence level can be classified as health system related factors, patient and treatment related factors and patient-healthcare provider interactions such as the duration of treatment, forgetting to take the medication, drug adverse events, misunderstanding instructions, besides, the awareness about the illness and its management.

The current study showed that there was non-significant association between adherence level and the demographic characteristics of the participants. ***Krolop et al.*** [30] revealed the same results in their study in Germany as there is non-significant correlation between oral antineoplastic agent and demographic characteristics of

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the patients. However, sociodemographic variables of adherent patients did not differ statistically from those of non-adherent patients [31]. Another study revealed that some demographic characteristics were associated with oral antineoplastic treatment adherence level (e.g., age and educational level) [32]. The adherence to oral antineoplastic treatment in a study carried out in Australia was associated with age [33].

The current study showed that there was non-significant association between the treatment adherence level and the experienced adverse effects by participants. However, a recent study involved Iraqi patients with colorectal carcinoma revealed the existence of an association between patients' adherence to treatment and their experience of treatment-related adverse effects [34].

Gebbia et al. [35] revealed the same results in their study in Italy as there was statistically non-significant relationship between adherence to oral antineoplastic drugs and the experienced adverse effects.

A study with 2546 patients from 63 countries undergoing oral antineoplastic agents found that the presence of side effects did not have a high effect on adherence. In the latter study findings were mixed; while some evidence suggested that 50% of patients altered the doses of oral antineoplastic medications intentionally (without consulting the treatment provider), there was also evidence that there was only a weak relationship between the frequency of side effects and treatment adherence. This discrepancy may be explained by the likelihood that inadequate side effect management will have a greater influence on treatment compliance than the mere existence of side effects in patients [33].

A systematic review conducted in Germany stated that one study demonstrated that patients who experienced nausea or vomiting were less adherent. Moreover, side effects were analyzed by another five studies, only one of them was statistically significant and the directions of the effects were conflicting [32].

In current study, the main problem is the limited number of patients who are participating and losing their follow up due to death for some of them. Moreover, treatment adherence was recorded at a specific time of treatment, so it might change later to better or worse depending on the severity of the illness and the individual's factors.

CONCLUSION

Patients with hepatocellular carcinoma on sorafenib treatment exhibit low-moderate levels of adherence. The latter is not affected by sorafenib-related adverse effects or demographic characteristics of patients.

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Author contribution: Authors contributed equally in the study.

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