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Original Article

Adverse Event Profile in Advance Hepatocellular Carcinoma treated with Sorafenib Presenting to CMH Rawalpindi

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ABSTRACT

Objective: To look for adverse event profiles in advance of hepatocellular carcinoma treated with Sorafenib presenting to CMH Rawalpindi and study associated socio-demographic factors

Study Design: Comparative cross-sectional study

Place and Duration of Study: Oncology Department, Combined Military Hospital, Rawalpindi Pakistan, from Dec 2020 to Nov 2021.

***Methodology*:** Three hundred patients with diagnosed hepatocellular carcinoma in advanced stage taking Sorafenib chemotherapy for more than three months and less than one year were included in the study. Each patient was assessed for relevant adverse effects in the follow-up outpatient visits by a consultant oncologist.

Results: Out of 300 cancer patients using Sorafenib for more than three months and less than one year, 212(70.7%) patients had at least one or more adverse effects, while 88(29.3%) did not experience any adverse effects. Diarrhoea 120(40%) was the most common adverse effect, followed by rash/desquamation 110(36.7%). Advancing age was statistically significantly associated (*p*-value-0.001) with adverse effects among the target population.

Conclusion: A significant number of patients suffering from hepatocellular carcinoma using Sorafenib had mild to moderate adverse effects. Physicians should keep an eye on patients with advancing age for adverse effects of this medication.

Keywords: Adverse effects, Hepatocellular carcinoma, Sorafenib.

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INTRODUCTION

All management options used to treat neoplastic diseases have specific adverse effects.[1,2] Multiple side effects have been reported by patients who have been managed with chemotherapeutic agents for malignant diseases.[3] Adverse effects related to skin, digestive system, nervous system, endocrine system, and various other organ systems of the body have been well documented in different populations of the world.[4,5]

Sorafenib has been related to several adverse effects in studies done in the recent past.[6] Flu *et al*. concluded that the incidence of adverse effects related to these medications was around 80%, but most of them were mild or moderate. Even the severe adverse effects could be tackled with a reduction in dose or cessation of treatment.[7]

Sorafenib is a commonly prescribed chemotherapeutic agent in patients suffering from advanced hepatocellular carcinoma in Pakistan.[8,9] A local study published investigated the use of Sorafenib tosylate, Ribavirn, and Sofosbuvir combination therapy for HCV virus-infected patients with decompensated liver cancer. Adverse effects were observed in 12 out of 30 patients but were not severe as lethal for life.[10] Limited epidemiological or interventional data has been available regarding the adverse effects of Sorafenib in our set-up. Therefore, we planned this study to look for adverse event profiles in advance of hepatocellular carcinoma treated with Sorafenib presenting to CMH Rawalpindi and study associated socio-demographic factors.

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METHODOLOGY

The comparative cross-sectional study was conducted at the Oncology Unit of Combined Military Hospital Rawalpindi from December 2020 to November 2021 after ethical approval from IERB (via letter 224/12/21). The sample size was calculated using the WHO sample size calculator using proportion of adverse effects with Sorafenib as 62.4%.[11] The non-probability purposive sampling technique was used to gather the sample.

Inclusion Criteria: Patients from 18 to 70 years of age, of either gender taking Sorafenib alone for

Hepatocellular carcinoma for more than three months and less than one year were included in the study.

Exclusion Criteria: The study did not include patients with uncontrolled DM, HTN, and IHD and taking any medications other than Sorafenib known to cause serious adverse effects. Patients using any alternative medications or those diagnosed with neurological, neuro-surgical or immunological illness were also excluded. Patients using any combination chemo-therapy or those using Sorafenib for early-stage HCC for any reason were also not made part of the analysis.

After taking written informed consent from all the potential participants. A consultant oncologist diagnosed advanced liver cancer based on clinical and radiological findings and TNM staging.[12] Sorafenib is a multi-kinase inhibitor used to treat various advanced solid and haematological malignancies. It was prescribed at a starting dosage of 400 mg per os twice daily.[13] Adverse effects were noted in patients after three months of Sorafenib use and recorded in a Performa specially designed for this study. Alpha-feto protein levels were performed on all the patients as part of the assessment before the start of Sorafenib. Comorbid conditions were inquired about via detailed history taking and checking all previous documents and hospital records.

Data was analyzed using the Statistical Package for Social Sciences version 23.0. The qualitative data were presented as frequency distribution, and quantitative data were presented as Mean±SD. Relationships of various variables like age, gender, presence of comorbid illness and alfa-feto protein levels at the start of treatment were associated with adverse effects in the study population using the Pearson Chi-square test. The *p*-value ≤0.05 was considered statistically significant to establish the association.

RESULTS

Out of 300 cancer patients using Sorafenib for more than three months and less than one year included in the study, 197(65.7%) were male, while 103 (34.3%) were female. 212(70.7%) patients had at least one or more adverse effects, while 88(29.3%) did not experience any adverse effects (Table-I). Diarrhoea 120(40%) was the most common adverse effect, followed by rash/desquamation 110(36.7%). Out of the total 300 patients, 180(60%) patients had hepatocellular carcinoma secondary to hepatitis C, 104(34.7%) had secondary to hepatitis B, and 16(5.3%) had non-viral aetiology. Advancing age was statistically significantly associated (*p*-value-0.001) with adverse effects among the target population. In contrast, gender (*p*-value-0.459), presence of comorbidities (*p*-value-0.180) and alpha-feto protein levels (*p*-value-0.307) had no such relationship with the presence of adverse effects in patients managed with Sorafenib (Table-II).

Table-I: Characteristics of patients receiving Sorafenib (n=300)

Study Parameters	n(%)
Age (years)	
Mean±SD	46.98±7.967 years
Range (min-max)	21 years - 65 years
Gender	
Male	197(65.7%)
Female	103(34.3%)
Etiology of hepatocellular carcinoma	
Hepatitis C	180(60%)
Hepatitis B	104(34.7%)
Non-Viral	16(5.3%)
Presence of comorbidities	
No	205(68.3%)
Yes	95(31.7%)
Adverse effects	
Diarrhea	120(40%)
Rash/desquamation	110(36.7%)
Fatigue	92(30.7%)
Abdominal pain	79(26.3%)
Hand foot syndrome	78(26%)
Anorexia	76(25.3%)
Nausea	69(23%)
Hypertension	48(16%)
Others	04(1.3%)

Table-II: Relationship of Various Factors with different Parameters among the target population (n=300)

	No Adverse Effects	Presence of Adverse Effects	*p*-value
Age			
<50 years	55(62.5%)	87(41.1%)	0.001
>50 years	33(37.5%)	125(58.9%)	
Gender			
Male	33(37.5%)	70(33.1%)	0.459
Female	55(62.5%)	142(66.9%)	
Presence of comorbidities			
No	65(73.8%)	140(66.1%)	0.180
Yes	23(27.2%)	72(33.9%)	
Alpha feto protein level			
<400ng/dl	55(62.5%)	119(56.1%)	0.307
>400ng/dl	33(37.5%)	93(43.9%)	

DISCUSSION

Pakistan has a high burden of hepatocellular carcinoma, primarily secondary to hepatitis B and C.1 Underlying malignant disease and the use of various treatment options prone the patients towards various health-related problems. Different chemotherapeutic agents used to manage cancer have different

spectrums of adverse effects.[5,14] We planned this study to look for adverse event profiles before hepatocellular carcinoma was treated with Sorafenib presenting to CMH Rawalpindi and studying associated socio-demographic factors.

Lin *et al*.[15] concluded that drug-related adverse events (AEs) occurred in 89.4% of the patients. Hand-foot skin reaction, diarrhoea and hypertension were common adverse effects in patients in their study. Our results supported the findings generated by Lin *et al*., and a similar profile of side effects was also observed in our patients. An international cohort study by Hajiev *et al*.[16] revealed that elderly patients were more at risk of discontinuing medication due to toxicity than younger patients. Though the study design was different, our study results were in line with the results generated by Hajiev *et al*.

The efficacy and safety of Sorafenib in elderly patients with advanced hepatocellular carcinoma was studied by Marta *et al*. They came up with the conclusion that skin rash, diarrhoea and hypertension were the most common adverse effects and the age of the patient had no significant relationship with the incidence of all these adverse effects.[17] Our results were similar in aspects of the adverse effects profile but were different in the aspects that age was statistically significantly related with the presence of adverse effects in our study population. Ostwal *et al*. studied tolerance and adverse event profile with Sorafenib in Indian patients with advanced hepato-cellular carcinoma. They revealed that Common side effects seen were liver dysfunction (38.5%), hand-foot-syndrome-rash (HFSR) (Grade 2 and 3-25.6%), fatigue (Grade 2 and Grade 3-10.3%), and diarrhoea (7.7%).[18] Our profile of adverse effects was quite different in terms of frequency of various adverse effects. The reason may be that our sample size was almost ten times larger than that of Ostwal *et al*.

LIMITATIONS OF STUDY

Our study had a few limitations as well. A cross-sectional study design is not the best to determine the side effects of any treatment; therefore, we cannot generalize the study results. Long-term follow-up was not done in the patients, so the long-term effects of Sorafenib were not determined.

CONCLUSION

A significant number of patients suffering from hepatocellular carcinoma using Sorafenib had the presence of mild to moderate adverse effects. Physicians should keep an eye on patients with advancing age for adverse effects of this medication.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MM: & MN: Conception, drafting the manuscript, data interpretation, approval of the final version to be published.

AA: & TML: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AK: & AA: Study design, drafting the manuscript, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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