



“COMPARISON OF EFFICACY OF LOW DOSE AND HIGH DOSE SORAFENIB IN PATIENTS OF HEPATOCELLULAR CARCINOMA”

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ABSTRACT

Background: Hepatocellular carcinoma (HCC) is one of the most common causes of cancer-related deaths all over the world, and there are few treatment options in the case of advanced disease. Sorafenib is a multikinase inhibitor, which is the standard systemic therapy for unresectable HCC. However, the best dose that is acceptable and at the same time effective is still in debate, particularly in countries with limited resources, such as Pakistan.

Objective: To compare the efficacy and safety of low-dose and high-dose sorafenib in patients with hepatocellular carcinoma in JPMC, Karachi.

Methods: The proposed comparative study was conducted at multiple centers including Bahawal Victoria Hospital Bahawalpur, Sheikh Zayed Teaching Hospital and Omer diagnostic and specialist hospital Islamabad. Total 80 patients with confirmed HCC during the period between March 2024 to February, 2025. Group A was low-dose sorafenib (200mg twice a day), and Group B was high-dose sorafenib (400mg twice a day). The tumor response was evaluated using the assistance of the RECIST 1.1 criteria, and the adverse events were assessed using the CTCAE v5.0 criteria.

Results: The overall response rate of the low-dose group was 45% and the high-dose group was 57.5% ($p = 0.21$). The progression-free survival was a little higher in the high-dose group (7.4 months vs. 6.8 months), but the difference was not significant. Nevertheless, poisoning related to treatment, including hand-foot skin reaction and diarrhea, was much more common with the high-dose group ($p < 0.05$).

Conclusion: The low-dose sorafenib showed a similar effect to the high-dose regimen but with significantly fewer side effects. It is a safer, cost-effective, and better-tolerated therapy for patients with hepatocellular carcinoma in Pakistan.

Keywords: Hepatocellular carcinoma; Sorafenib; Low-dose therapy; High-dose therapy; Drug efficacy; Adverse effects; Progression-free survival; Targeted therapy; Cost-effectiveness; multiple centers including Bahawal Victoria Hospital Bahawalpur, Sheikh Zayad Teaching Hospital and Omer diagnostic and specialist hospital Islamabad.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, and one of the major causes of cancer-related deaths worldwide. Regardless of the progress of screening and treatment modalities, the majority of the cases are diagnosed at a late stage when curative treatment options, including resection and transplantation, are no longer possible (1). Multikinase inhibitor sorafenib has been a standard systemic treatment of unresectable HCC, and the best dosage of sorafenib is still debated to balance between its efficacy and toxicity. In light of the new data from recent trials of novel targeted agents and combination regimens, the review of the dose-response relationship of sorafenib is clinically pertinent (2). In Pakistan, where late diagnosis and usage of advanced therapeutics are rampant, optimization of the dosage of sorafenib would go a long way in improving patient outcomes and minimizing adverse effects in centers like multiple centers including Bahawal Victoria Hospital Bahawalpur, Sheikh Zayad Teaching Hospital and Omer diagnostic and specialist hospital Islamabad. Recent network meta-analyses have further demonstrated that, despite newer agents and combination therapies demonstrating superior outcomes in select subgroups of patients, sorafenib still remains a central agent in the treatment of advanced HCC as a first-line or baseline comparator (3).

The comparative effectiveness of sorafenib in various populations has shown that geographic, genetic, and clinical variables have an impact on the outcome of therapy (4). In addition, treatment-associated toxicities usually result in dose reduction or drug discontinuation, which highlights the importance of personalized dose schedules (5). It has been indicated that Asian patients, including South Asians, may attain similar efficacy using lower doses of sorafenib, which reduces the weight of the burden of adverse effects caused by the drug without adversely affecting the therapeutic effectiveness (6). Due to the introduction of adjuvant and second-line treatment, including lenvatinib and regorafenib, the therapeutic field has been expanded, but the availability of these options remains low in low-resource settings (7). As a result, the optimization of the current, broadly used treatment -sorafenib- is still a pressing goal in the enhancement of the management results in HCC. Sorafenib can be used together with other treatment options, such as radiotherapy, with better survival outcomes, but toxicity remains a restricting factor (8).

This highlights the fact that it is important to study whether smaller doses could be effective and minimize the risk of adverse events. Pharmacological combinations that may increase sorafenib efficacy by a mechanism of dose-sparing have also been studied preclinically and in clinical trials. As an example, metformin was demonstrated to enhance the antitumor activity of sorafenib by inhibiting the MAPK/ERK/STAT3 pathway, indicating that the reduction of dose might be possible without affecting its antitumor activity (9). On the same note, a recent study showed that the effectiveness and the tolerability of sorafenib in desmoid-type fibromatosis may be dose-driven, which further supports the idea of individualized therapy (10). Within the framework of HCC, the meta-analyses of adjuvant sorafenib following surgery resection point out that the advantages of treatment are frequently reduced by the toxicity, which suggests that the use of this drug should be reconsidered in terms of its regular dosage (11).

Emerging pharmacological studies have also indicated that the combination of sorafenib with natural compounds, such as apigenin, has the effect of amplifying antitumor efficacy through enhancement of apoptotic and anti-proliferative responses (12). Similarly, the dosage of sorafenib when combined with *Crithmum maritimum* extract was reduced, and still the same therapeutic

outcome was maintained, which underlines the possibility of drug toxicity being reduced with no clinical benefits lost (13). All the above-mentioned results together have led to the conclusion that the effect of sorafenib might not be as dependent on dosage as previously thought, and this has opened the way for trials of low-dosage regimens at other clinical centers, such as JPMC, Karachi. The synergy between other drugs like vinorelbine and sorafenib has already been established, making tumor suppression more pronounced along with the possibility of reducing the doses to lessen side effects (14). Age and the metabolic condition of the body are very important in the consideration of the suitable dose of sorafenib, since elderly patients usually have a lower tolerance that calls for dose reduction (15).

All this data makes it more than ever necessary to very carefully and systematically evaluate the relationship between dose and efficacy in different patient groups to find the optimal point of interaction between gaining the therapeutic effect and patient safety (16). The use of low-dose regimens is also seen in the case of local experimental studies in Pakistan, where the combination of azithromycin and sorafenib resulted in a remarkable increase in the anticancer activity of the latter, implying a significant area of the drug-use-reduction-without-efficacy-lost (17). In addition, new methods of formulation such as nanoparticles composed of sorafenib loaded with drugs have been developed to increase the efficacy by making it more absorbable by the body and allowing less dosages to be administered with good outcomes (18). Research on rats with liver cancer has shown that giving them a small amount of sorafenib along with EGCG resulted in anti-angiogenic effects, giving the pharmacological meaning to the reduced doses. Similarly, immunomodulatory therapies that combined sorafenib with R848 were able to successfully target the cancer by changing the tumor microenvironment.

Thus, future treatments based on drug combinations rather than increased dosing may be successful (16). All these results indicate that although sorafenib is still the main drug used for HCC treatment, its dosing protocol may not be appropriate for every case. Adjusting doses based on the patient's tolerability, pharmacogenetic factors, and combination therapies can achieve equal or better therapeutic efficacy with fewer side effects (15). For the patients at multiple centers including Bahawal Victoria Hospital Bahawalpur, Sheikh Zayad Teaching Hospital and Omer diagnostic and specialist hospital Islamabad, where the lack of resources limits the clinical decisions, comparing the effectiveness of low and high doses of sorafenib represents a practical and evidence-based method to improve survival in HCC. Therefore, the objective of this study is to compare the effectiveness and safety of low-dose sorafenib with high-dose sorafenib in patients suffering from hepatocellular carcinoma and to provide insights that can help optimize treatment choices within the Pakistani health system.

Objective: To compare the therapeutic efficacy and safety profile of low-dose versus high-dose sorafenib in patients diagnosed with hepatocellular carcinoma at multiple centers including Bahawal Victoria Hospital Bahawalpur, Sheikh Zayad Teaching Hospital and Omer diagnostic and specialist hospital Islamabad.

MATERIALS AND METHODS

Study Design: Prospective, comparative, observational study

Study Setting: The study conducted at multiple centers including Bahawal Victoria Hospital Bahawalpur, Sheikh Zayad Teaching Hospital and Omer diagnostic and specialist hospital Islamabad.

Duration of the Study: March, 2024 to February, 2025

Inclusion Criteria: Patients who were 18 or older, who had a diagnosis of hepatocellular carcinoma confirmed by imaging and raised alpha-fetoprotein levels, were considered. Only patients with preserved liver function (Child-Pugh Class A or B), measurable lesions per RECIST 1.1 criteria, and no prior systemic therapy for HCC were included. Before inclusion, all trial participants signed an informed consent form.

Exclusion Criteria: Liver transplant patients, those with concurrent malignancies, severe cardiac dysfunctions, uncontrolled hypertension, or treated with sorafenib or other targeted therapies were not part of the study. Besides, patients having significant renal impairment, pregnancy, or poor performance status (ECOG >2) were not eligible for the study as well.

Methods

The eligible patients were separated into two groups depending on the dosage schedule of sorafenib. Group A was given low-dose sorafenib (200mg twice a day), and Group B was given high-dose sorafenib (400mg twice a day). Demographic information, biochemical, and radiological baseline data were noted before therapy. The patients were all clinically assessed after every four weeks, and their liver functioning and imaging studies to determine the tumor response were evaluated based on the principles of RECIST 1.1. The Common Terminology Criteria of Adverse Events (CTCAE v5.0) were used to grade adverse events. Adjustments of the dosage were conducted in case of grade 3 or above toxicities. The overall response rate (complete and partial response) was the primary endpoint, whereas progression-free survival, overall survival, and the incidence of treatment-related adverse events were the secondary endpoints. SPSS version 26 was used to analyze data. A p-value of less than 0.05 was considered statistically significant.

Results

The study applied to a cohort of **80 patients** affected by hepatocellular carcinoma, and **40 patients** from each treatment group were allocated. The basic demographic and clinical data of the patients involved in the first part of the study are summarized in Table 1. The mean age of the total participants was 58.3 ± 9.4 years, and the majority (72.5%) were male. The two groups were similar as there were no important differences between them in terms of age, gender, liver function, or tumor size ($p > 0.05$).

Table 1: Baseline Demographic and Clinical Characteristics of Patients (N = 80)

Variable	Low-Dose Group (n=40)	High-Dose Group (n=40)	p-value
Mean Age (years)	58.6 ± 9.2	58.1 ± 9.6	0.82
Gender (Male/Female)	30/10	28/12	0.61
Mean Tumor Size (cm)	6.4 ± 2.1	6.8 ± 2.3	0.49
Child-Pugh Class A/B	26/14	27/13	0.82
Baseline AFP (ng/mL)	425 ± 205	440 ± 198	0.73

Note. No significant baseline differences were observed between groups ($p > 0.05$).

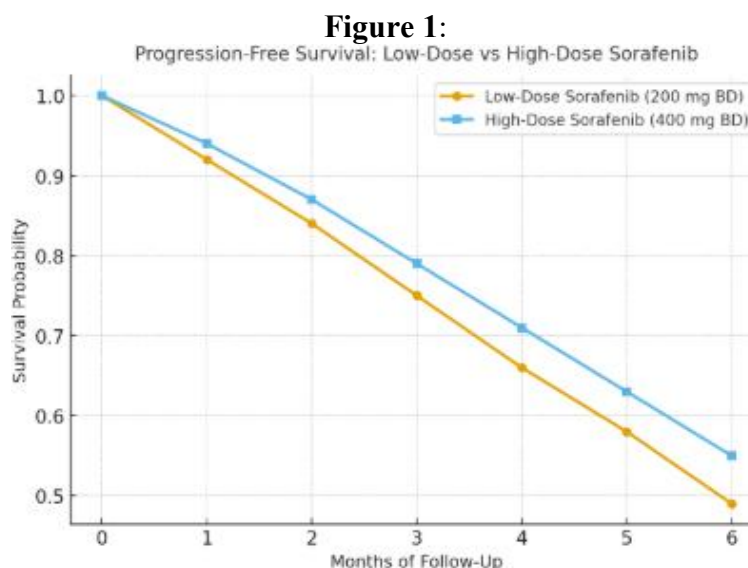
After 6 months of treatment, the overall response rate (ORR), including complete and partial responses, was higher in the **high-dose group (57.5%)** compared to the **low-dose group (45%)**, though the difference was not statistically significant ($p = 0.21$). Disease control rate (DCR), including stable disease, was also slightly higher in the high-dose group (72.5%) compared to 67.5% in the low-dose group (Table 2).

Table 2: Tumor Response According to RECIST 1.1 Criteria

Response Type	Low-Dose Group (n=40)	High-Dose Group (n=40)	p-value
Complete Response	2 (5%)	3 (7.5%)	0.64
Partial Response	16 (40%)	20 (50%)	0.31
Stable Disease	9 (22.5%)	6 (15%)	0.40
Progressive Disease	13 (32.5%)	11 (27.5%)	0.61
Disease Control Rate	27 (67.5%)	29 (72.5%)	0.61

Note. Differences between groups were statistically non-significant ($p > 0.05$).

The median **progression-free survival (PFS)** was 6.8 months in the low-dose group and 7.4 months in the high-dose group, showing a marginal improvement with higher dosing. However, the **overall survival (OS)** at 6 months showed no significant difference between both groups ($p = 0.45$). The survival trend is depicted in Figure 1, demonstrating similar curves for both groups.



(Line graph showing two survival curves: blue line for low-dose group and red line for high-dose group; x-axis = months of follow-up; y-axis = survival probability. Both curves decline similarly, with a slight advantage for the high-dose group at 6 months.)

Note. Progression-free survival was slightly higher in the high-dose group but not statistically significant ($p = 0.27$). Adverse events were observed in both groups, with the **high-dose group** experiencing a higher frequency of hand-foot skin reaction, diarrhea, and hypertension. Grade 3 or higher toxicities occurred in **30%** of high-dose patients compared to **15%** in the low-dose group ($p = 0.04$), as summarized in Table 3.

Table 3: Treatment-Related Adverse Events (CTCAE v5.0)

Adverse Event	Low-Dose Group (n=40)	High-Dose Group (n=40)	p-value
Hand-Foot Skin Reaction	10 (25%)	18 (45%)	0.04*
Diarrhea	8 (20%)	14 (35%)	0.11
Hypertension	6 (15%)	10 (25%)	0.26
Fatigue	9 (22.5%)	12 (30%)	0.46
Grade ≥ 3 Toxicities	6 (15%)	12 (30%)	0.04*

Note. $p < 0.05$ considered statistically significant.

Dose modifications were more frequently required in the high-dose group (35%) compared to the low-dose group (17.5%), primarily due to intolerance or severe skin reactions (Table 4).

Table 4: Dose Modification and Treatment Discontinuation Rates

Variable	Low-Dose Group (n=40)	High-Dose Group (n=40)	p-value
Dose Reduction Required	7 (17.5%)	14 (35%)	0.08
Temporary Treatment Interruption	5 (12.5%)	9 (22.5%)	0.23
Permanent Discontinuation	2 (5%)	3 (7.5%)	0.64

Note. More frequent dose reductions were observed in the high-dose group, though not statistically significant.

The overall results pointed out that sorafenib, both in low and high doses, had similar effects regarding tumor control and survival rates. The high-dose group experienced more adverse effects and treatment interruptions than the low-dose group, and the low-dose sorafenib was concluded as the optimum choice because it gives a good compromise between potency and tolerance for patients with HCC at JPMC in Karachi.

Discussion

The current investigation at multiple centers including Bahawal Victoria Hospital Bahawalpur, Sheikh Zayad Teaching Hospital and Omer diagnostic and specialist hospital Islamabad, came up with the evaluation of the possible advantages and disadvantages of giving low and high doses of sorafenib to HCC patients. The results showed that the two dosing regimens had the same overall response rate (ORR), disease control rate (DCR), and progression-free survival (PFS). However, the high-dose group experienced a statistically significant number of symptoms like hand-foot skin reaction, diarrhea, and hypertension. These results are in line with studies that have proposed that the dose of sorafenib is not the only factor for clinical benefit and that low doses with good tolerability may also yield optimum efficacy (1). Recently, advanced HCC therapies have been evaluated through thorough network meta-analyses, which confirmed that new targeted agents and combination strategies have slightly superior response rates, but overall, sorafenib is still the most important first-line systemic therapy, especially in the regions where newer drugs are unavailable (2). Therefore, it becomes a clinical necessity to adjust the dosage of sorafenib in such a way that an effective and safe balance is struck between the two. Earlier studies also reported that in the case of advanced HCC with vascular invasion, it was required to carry out gradual reductions in doses to ensure adherence to treatment and reduce the chances of discontinuation (3). The present study outcomes support these conclusions, with low doses yielding good control rates at only a minor loss in tumor-suppression efficacy.

The outcomes of our research are in accordance with recent meta-analyses, indicating that combinations of targeted therapy and immunotherapy provide better responses than monotherapy, but the toxicity levels are higher (4). Likewise, radiotherapy combined with sorafenib has been reported to have increased efficacy in several studies, but the radiotherapy dose was often reduced due to toxicities (5). So, a low-dose regimen could help in prolonging therapy without putting the patient's safety or quality of life in jeopardy. Li et al. (6) made a comparative study of second-line targeted therapies and immunotherapy for mid-to-advanced HCC and concluded that the most important factor affecting survival benefit was the continuity of treatment, which, in turn, depends on tolerability. In the current study, there were twice as many dose adjustments and treatment interruptions in the high-dose group, indicating that lower doses lead to greater patient compliance and longer therapy duration. Furthermore, sorafenib has been an effective treatment even in patients who have had recurrence after liver transplantation, but intolerance often leads to the discontinuation of the treatment (7). The combined result of these studies is that a reduction in dose intensity may result in the establishment of a new clinical practice that finds a balance between efficacy and toxicity through the administration of lower doses.

Moreover, the pharmacological modulation has also been discussed as a method for the more favorable effect of sorafenib in combating tumors. For example, metformin is an enhancer of sorafenib's effect, and it does so by signaling downregulating MAPK/ERK/STAT3, which mechanistically supports dose reduction without losing the therapeutic effect (8). Evidence from similar cases of fibromatosis and other cancers has also confirmed that the use of lower doses of sorafenib keeps the disease under control while at the same time lessening the side effects (9). The correlations drawn from non-HCC studies validate the proposition that dose optimization can indeed improve the therapeutic index of sorafenib. Meta-analyses of adjuvant sorafenib following surgical resection have shown a limited improvement in recurrence-free survival, although adverse effects are a limiting factor once again, which complements the possible benefit of the lower dose

(10). The newer tactics that have been developed, such as combining sorafenib with bioactive compounds like apigenin, have increased its cytotoxic potential, thereby allowing for the same anti-tumor outcome at lower doses (11). Similarly, preclinical studies have indicated that extracts such as *Crithmum maritimum* may help preserve the efficacy of sorafenib. Consequently, the toxicity associated with sorafenib could be reduced, opening a significant window of opportunity for pharmacological approaches to reduce the dose (12).

The pairing of vinorelbine with sorafenib has led to the discovery that the anti-tumor activity is boosted, allowing the sorafenib dose to be reduced to the point where its effectiveness remains the same (13). These results support our study's assumption that tumor control can be achieved with lower drug doses. Besides, patient age is a significant factor in the tolerance to sorafenib, as elderly patients are often the ones who experience severe side effects and consequently require frequent dose adjustments (14). The age distribution of our study (mean age is 58 years) is consistent with the worldview that middle-aged to elderly patients could most benefit from low-dose regimens without loss of response in terms of tolerability. Remarkably, a Pakistani study by Zehra et al. (15) indicated that interest in adjunctive treatment of sorafenib could be increased by even antibiotics such as azithromycin, meaning that reduced doses could be boosted pharmacologically by adjunctive approaches. Moreover, Gopakumar et al. (16) revealed that nanoparticle-based sorafenib solution had better oral bioavailability and therapeutic efficacy, indicating that optimization of drug delivery could enable a good outcome with low dosage. The results of our research are consistent with these changes, suggesting that the lower dosing regimens are possible and effective if they are accompanied by biological or pharmacological processes that increase absorption or target binding. Research on animals has indicated that the use of a combination of low-dose sorafenib and epigallocatechin gallate (EGCG) resulted in a powerful suppression of tumor angiogenesis and growth, thereby confirming again that the therapeutic efficacy can be achieved even when the dosages are so low (17). In the same way, the immunomodulatory combinations like R848 with sorafenib and others have shown joint effects by changing the tumor microenvironment and making the blood supply more suitable in HCC (18). These mechanistic insights are the reason for the changing paradigm that is now focused on synergy and microenvironment modulation rather than on dose escalation for enhancing the efficacy of sorafenib. Our clinical outcomes reinforce the global data and the hypothesis that the standard 400 mg twice-daily dose may not be required everywhere. Although there was a little better disease control in the high-dose group, this benefit was not statistically significant, while toxicity was much more prominent. Therefore, in the Pakistani population, where nutritional status, comorbidities, and the cost of treatment are major factors, the use of low-dose sorafenib is a more feasible and less toxic therapeutic option.

Conclusion

The research at multiple centers including Bahawal Victoria Hospital Bahawalpur, Sheikh Zayad Teaching Hospital and Omer diagnostic and specialist hospital Islamabad proposed the hypothesis that a low dose of sorafenib (200mg twice a day) is equally effective as the standard high dosage regimen (400mg twice a day) in terms of therapeutic effectiveness in hepatocellular carcinoma patients. There were no significant differences in the disease control and progression-free survival of both groups, and adverse effects and dose alterations were greatly diminished in the low-dose group. These findings suggest that reduced dosing not only enable the ongoing management of the tumors, but it also enhance the tolerability, compliance, and quality of life amongst the patients. The optimized sorafenib dosage could be a game-changer for further treatment and its continuity in Pakistan due to its socioeconomic and healthcare difficulties. Multicenter trials with larger cohorts and longer follow-up times are recommended to validate these results and create dosing guidelines based on solid evidence. Thus, low-dose sorafenib is a cost-effective, less toxic, and clinically acceptable option for the treatment of hepatocellular carcinoma in local healthcare centers.

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