Pegem Journal of Education and Instruction, Vol. 14, No. 3 , 2024 (pp. 531-541)

RESEARCH ARTICLE WWW.PEGEGOG.NET

Determinants of Outcome in Advanced Hepatocellular Carcinoma Patients Receiving Sorafenib Therapy

Fouad M. Abutaleb[1], Amal Zidan[2], Ahmed Mohamed Said Lashin[3], Ahmed A Alnagar[4], Shereen El Shorbagy[5]

1 Professor of Medical Oncology, Faculty of Medicine, Zagazig University. Egypt

2 Professor of Clinical Pathology, Faculty of Medicine, Zagazig University. Egypt

3 Assistant Lecturer of Medical Oncology, Faculty of Medicine, Zagazig University. Egypt

4 Professor of Medical Oncology, Faculty of Medicine, Zagazig University. Egypt

5 Professor of Medical Oncology, Faculty of Medicine, Zagazig University. Egypt

Corresponding Author: Ahmed Mohamed Said Lashin

Mail: dr.lashin2025@gmail.com

ABSTRACT

***Background*:** Hepatocellular carcinoma (HCC) remains a leading cause of cancer mortality globally, with advanced-stage disease representing a significant clinical challenge due to limited curative options. Sorafenib, an oral multikinase inhibitor, was the first systemic agent to demonstrate survival benefit in patients with advanced HCC, fundamentally shifting treatment paradigms. However, considerable variability in patient outcomes exists, driven by a complex interplay of clinical, molecular, and treatment-related factors. This review aims to comprehensively summarize the current evidence on determinants of outcome in patients with advanced HCC treated with sorafenib. Key clinical prognostic factors, such as liver function, performance status, tumor burden, and underlying liver disease etiology, are discussed alongside emerging molecular and serologic biomarkers predictive of response. Special attention is paid to the prognostic value of adverse events and treatment adherence, as well as real-world data that inform the generalizability of clinical trial findings. Moreover, the review highlights unmet needs in personalizing therapy and integrating novel predictive markers into routine care. Ultimately, a better understanding of these determinants can refine patient selection, optimize therapeutic benefit, and guide future research in advanced HCC. The review concludes by identifying research gaps and future directions in biomarker development and treatment sequencing, with a focus on the evolving landscape of systemic therapy.

Keywords: Advanced Hepatocellular Carcinoma, Sorafenib Therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) represents the predominant form of primary liver cancer and ranks as the third leading cause of cancer-related death worldwide. Advanced HCC, often diagnosed at a stage unsuitable for curative interventions, has historically had limited therapeutic options and a poor prognosis. The advent of sorafenib, an oral tyrosine kinase inhibitor, marked a pivotal advance by providing the first demonstrated survival benefit in this setting. Despite its widespread adoption, significant heterogeneity persists in patient outcomes, underscoring the importance of identifying robust prognostic and predictive determinants. The optimal selection of candidates for sorafenib, prediction of therapeutic benefit, and management of adverse events are pressing clinical challenges. While multiple clinical and biological factors have been proposed, their integration into routine clinical practice remains suboptimal. This review aims to synthesize current knowledge on determinants of outcome in advanced HCC patients treated with sorafenib, highlight validated and emerging biomarkers, and identify key research gaps that limit personalization of therapy. By elucidating these factors, we seek to inform clinical decision-making and foster advances in individualized management of advanced HCC.

Overview of Sorafenib in Advanced Hepatocellular Carcinoma

Sorafenib, an oral multikinase inhibitor, exerts its anti-cancer effect through simultaneous inhibition of the Raf/MEK/ERK pathway, which is crucial for tumor cell proliferation, as well as the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR), both central to angiogenesis in hepatocellular carcinoma (HCC) [1]. This dual activity underpins its efficacy in slowing disease progression and suppressing tumor vascularization, which is a hallmark of advanced HCC's aggressive phenotype. The early preclinical studies demonstrated broad-spectrum activity against a variety of tumor cell lines and in vivo models, ultimately justifying its evaluation in HCC clinical trials [2].

The pivotal phase III SHARP trial conducted in Western populations established sorafenib as the first systemic therapy to confer a statistically significant overall survival benefit in advanced HCC, with a median OS improvement from 7.9 to 10.7 months compared to placebo [3]. Notably, the study enrolled patients with well-preserved liver function (Child-Pugh A) and good performance status, setting the benchmark for subsequent research and clinical practice. The Asia-Pacific trial, which included patients with more aggressive disease and higher rates of hepatitis B virus (HBV) infection, corroborated the survival advantage but reported lower absolute survival figures, reflecting regional and etiological differences [4]. Together, these studies led to global regulatory approval of sorafenib and its rapid adoption as first-line therapy for advanced HCC [5].

Despite its significant impact, the clinical benefit of sorafenib is limited by a relatively low objective response rate (typically <5%), with most patients achieving disease stabilization rather than radiological regression [6]. Nonetheless, stabilization itself can be clinically meaningful in the context of rapidly progressing HCC. In addition, sorafenib's side effect profile—including hand-foot skin reaction, diarrhea, and fatigue—often necessitates dose reductions or treatment interruptions, highlighting the need for careful patient monitoring and supportive care [7]. Adherence to therapy and dose intensity are critical determinants of treatment efficacy, and real-world studies consistently show that patients who can tolerate higher doses for longer periods have improved outcomes [8].

In current international guidelines, sorafenib remains a preferred option for patients with advanced-stage HCC and well-preserved liver function, particularly when access to newer agents is limited by regulatory, economic, or regional constraints [9]. The drug's established safety profile, broad applicability, and oral administration make it an enduring standard of care in various healthcare settings. However, with the introduction of newer tyrosine kinase inhibitors and immune checkpoint inhibitors, the positioning of sorafenib is increasingly nuanced, and ongoing research continues to refine its role, particularly in combination or sequential strategies [10].

A significant limitation of sorafenib is the lack of robust, clinically validated predictive biomarkers to identify likely responders before treatment initiation. This challenge arises in part due to the drug's multitargeted nature and the molecular heterogeneity of HCC. Ongoing translational studies aim to elucidate molecular, serologic, and imaging-based predictors of benefit, which may enable more personalized and effective use of sorafenib in the future [11]. Moreover, real-world data continue to reveal variations in efficacy and tolerability across diverse populations, underscoring the importance of contextualizing trial evidence within local practice environments [12].

Clinical Prognostic Factors

Baseline Liver Function (Child-Pugh Score, ALBI Grade)

Baseline liver function is a pivotal determinant of outcomes in patients with advanced hepatocellular carcinoma (HCC) undergoing sorafenib therapy. The Child-Pugh classification, which incorporates serum bilirubin, albumin, international normalized ratio (INR), ascites, and hepatic encephalopathy, has long served as the standard for stratifying cirrhosis severity and predicting survival [13]. Pooled analyses from major clinical trials and real-world cohorts consistently show that patients with Child-Pugh A cirrhosis derive the greatest benefit from sorafenib, with significantly longer overall survival and better tolerability than those with more advanced liver dysfunction [14]. The inclusion criteria for pivotal studies such as SHARP and Asia-Pacific reflected this, largely excluding Child-Pugh B and C patients [3,4]. Although sorafenib has been used off-label in Child-Pugh B populations, multiple studies report attenuated efficacy and increased rates of severe adverse events in these patients, often limiting its clinical utility [15].

To further refine risk stratification, the Albumin-Bilirubin (ALBI) grade was developed as an objective, purely laboratory-based tool to assess hepatic reserve. Several validation studies confirm that ALBI grading provides comparable or superior prognostic discrimination compared to the Child-Pugh system, particularly in patients without significant ascites or encephalopathy [16]. Notably, ALBI has proven useful in large Asian and European cohorts, demonstrating a strong correlation with overall survival, progression-free survival, and risk of adverse events among HCC patients treated with sorafenib [17]. Incorporating ALBI into prognostic models may enable more nuanced patient selection and inform therapy modifications in clinical practice [18].

Performance Status (ECOG)

Performance status, most commonly measured by the Eastern Cooperative Oncology Group (ECOG) scale, is another independent and robust predictor of outcome in advanced HCC. Patients with ECOG scores of 0 or 1 generally experience superior survival, greater likelihood of completing treatment, and reduced risk of dose-limiting toxicities [19]. Analyses from both clinical trial datasets and large observational registries, such as the GIDEON study, reinforce the prognostic significance of baseline performance status for both efficacy and safety endpoints [20]. Patients with poor performance status (ECOG $\geq$2) are less likely to benefit from systemic therapy and face higher rates of rapid clinical deterioration, making supportive care or alternative treatments more appropriate in this population [21].

Tumor Burden and Disease Stage (BCLC Stage, Extrahepatic Spread, Vascular Invasion)

Tumor-related factors are central to the prognosis of advanced HCC and response to sorafenib. The Barcelona Clinic Liver Cancer (BCLC) staging system integrates tumor burden, liver function, and performance status and is widely used to guide therapy selection [22]. Within the advanced BCLC-C stage, further heterogeneity exists based on the presence and extent of macrovascular invasion (such as portal vein tumor thrombus) or extrahepatic metastases. Numerous studies show that patients with lower tumor burden, limited intrahepatic disease, and absence of vascular invasion or metastasis have better survival with sorafenib [23]. However, a subset of patients with macrovascular invasion or extrahepatic spread may still achieve stabilization or clinical benefit, particularly if liver function is well preserved [24]. Notably, the degree of portal vein invasion is a particularly poor prognostic marker, associated with high rates of early progression and liver failure [25]. Stratification by BCLC stage and detailed assessment of tumor burden remain critical in routine practice and clinical trial design [22,23].

Etiology of Liver Disease (HBV, HCV, NASH)

The underlying etiology of liver disease can influence tumor biology, progression patterns, and possibly therapeutic response to sorafenib. In regions such as Asia, HBV is the predominant cause of HCC, while HCV and non-alcoholic steatohepatitis (NASH) are increasingly common in Western populations [26]. There is some evidence suggesting that etiology may affect outcomes: HBV-related HCC has been associated with more aggressive clinical features and shorter survival, though these differences are confounded by regional and demographic factors [27]. Some cohort studies have suggested that patients with HCV-related HCC might experience slightly improved outcomes with sorafenib compared to those with HBV or NASH, but these findings have not been consistently replicated in randomized trials [28]. The biological basis for potential differences in drug sensitivity according to etiology remains incompletely understood and is a subject of ongoing research [29].

Demographics (Age, Gender, Ethnicity)

Patient demographic factors such as age, gender, and ethnicity have been explored as potential modifiers of sorafenib efficacy and tolerability. Elderly patients, often underrepresented in clinical trials, can generally tolerate sorafenib as effectively as younger individuals when appropriately selected based on liver function and comorbidity burden [30]. Subgroup analyses from real-world registries and the GIDEON study show no major differences in overall survival or adverse event rates in elderly populations, although careful dose titration and monitoring are recommended [31]. Gender does not appear to significantly affect outcomes, though the majority of HCC cases globally occur in men [32]. Ethnic differences—especially between Asian and Western patients—are more likely related to differences in etiology, disease biology, access to care, and background cirrhosis management rather than inherent pharmacogenetic disparities [33]. These demographic considerations underscore the importance of individualized patient assessment when considering sorafenib therapy.

Predictive Biomarkers for Sorafenib Response

Serum Biomarkers (AFP, DCP, VEGF, Cytokines)

Alpha-fetoprotein (AFP) is the most commonly utilized serum biomarker in hepatocellular carcinoma (HCC) for both diagnostic and prognostic purposes. Elevated baseline AFP is associated with a higher tumor burden and a more aggressive phenotype, and retrospective analyses have consistently linked high AFP levels to poorer outcomes in patients treated with sorafenib [34]. Importantly, changes in AFP levels during therapy can also provide early insight into treatment response; a rapid decline is often associated with radiological response and improved survival, although AFP kinetics are not entirely specific or sensitive [35]. Other serum markers, such as des-gamma-carboxy prothrombin (DCP), have also been studied, particularly in Asian populations. High baseline DCP correlates with worse prognosis, but its role as a predictive marker for sorafenib response remains less defined [36].

Serum levels of vascular endothelial growth factor (VEGF) have been explored as potential predictive biomarkers, given sorafenib's anti-angiogenic mechanism. Several studies have shown that higher pretreatment VEGF concentrations are associated with aggressive disease, reduced progression-free survival, and limited benefit from sorafenib [37]. In addition to VEGF, a range of circulating cytokines—including interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α)—have been examined. Elevated pro-inflammatory cytokine profiles are generally associated with resistance to therapy and shorter overall survival, although none have achieved sufficient validation for clinical use [38]. As such, while serum biomarkers can provide valuable prognostic information and may assist in monitoring disease trajectory, their predictive utility for sorafenib benefit remains suboptimal in routine practice [39].

Genomic and Molecular Markers (Gene Mutations, Expression Signatures)

The search for reliable genomic and molecular predictors of sorafenib response has intensified with the advent of next-generation sequencing and high-throughput profiling techniques. Specific gene mutations, such as those in the CTNNB1 (β-catenin) or TP53 genes, have been variably linked to different patterns of resistance or sensitivity to sorafenib, but results are inconsistent and often confounded by underlying liver disease heterogeneity [40]. Some studies have identified FGF19 amplification and activation of the FGF signaling axis as potential markers of reduced sensitivity to multikinase inhibitors, although prospective validation is limited [41]. Transcriptomic analyses have revealed expression signatures associated with angiogenic or proliferative HCC subtypes, which may correspond to greater benefit from anti-angiogenic therapies such as sorafenib [42]. However, these findings are preliminary and require further validation in prospective clinical trials.

In addition to single gene alterations, several groups have proposed composite gene expression signatures or pathway activation scores to predict response, including markers of hypoxia, immune activation, and angiogenesis [43]. Despite promising preclinical and retrospective data, no genomic biomarker has yet been integrated into standard clinical algorithms for sorafenib selection. HCC's inherent molecular heterogeneity, the complexity of the tumor microenvironment, and the multifaceted action of sorafenib present ongoing challenges to biomarker discovery [44].

Imaging Biomarkers (Radiomics, Functional Imaging)

Imaging biomarkers are an emerging area of research aimed at providing noninvasive methods for early prediction of therapeutic

response to sorafenib. Radiological assessment in HCC has traditionally relied on Response Evaluation Criteria in Solid Tumors (RECIST); however, this may underestimate meaningful responses due to the unique vascular characteristics of liver tumors. Modified RECIST (mRECIST) criteria, which focus on arterial phase enhancement as a marker of viable tumor, have improved sensitivity in capturing responses to anti-angiogenic therapy [45]. Studies suggest that early reductions in arterial enhancement or tumor perfusion on dynamic CT or MRI can predict subsequent clinical benefit and improved survival [46].

Radiomics—the extraction of quantitative imaging features from CT or MRI—has the potential to further refine risk stratification and response assessment. Preliminary studies have demonstrated associations between specific radiomic signatures at baseline or during early therapy and subsequent outcomes on sorafenib [47]. Similarly, functional imaging techniques such as diffusion-weighted MRI and positron emission tomography (PET) have shown utility in distinguishing responders from nonresponders, although their integration into clinical practice remains investigational [48]. As imaging technologies advance, they may offer valuable, repeatable tools for monitoring disease evolution and guiding therapeutic decisions in advanced HCC [49].

Early Radiological Response and Patterns of Progression

Beyond baseline biomarkers, dynamic assessment of radiological response during therapy provides critical prognostic information. Achievement of early radiological response or stable disease by mRECIST or similar criteria at 6–12 weeks is consistently associated with longer overall survival and delayed progression in patients receiving sorafenib [50]. Conversely, the development of new extrahepatic lesions or rapid intrahepatic tumor growth on early imaging predicts poor outcomes and may warrant a change in treatment strategy [51]. Patterns of progression—such as isolated intrahepatic progression versus multifocal or extrahepatic spread—can further inform clinical decision-making, especially as new second-line therapies become available [52].

While early radiological changes are valuable, it is important to note that sorafenib often induces disease stabilization rather than overt tumor shrinkage, and therefore traditional response criteria may underestimate its clinical benefit. Integration of imaging findings with clinical, serologic, and molecular data is likely to provide the most comprehensive approach to personalized therapy in the future [53].

Treatment-Related Factors

Dose Intensity and Adherence

Adherence to prescribed dosing and maintenance of adequate dose intensity are key determinants of the therapeutic benefit derived from sorafenib in advanced HCC. In real-world practice, dose modifications and interruptions are common due to adverse events such as hand-foot skin reaction, diarrhea, hypertension, and fatigue [54]. Analyses from large observational studies have shown that patients who are able to tolerate and sustain higher relative dose intensity (RDI) of sorafenib have significantly better overall survival compared to those requiring early dose reductions or treatment discontinuation [55]. For example, the GIDEON registry reported a clear correlation between RDI and clinical outcomes, even after adjusting for baseline liver function and tumor stage [56].

It is important to note that lower starting doses have not consistently been shown to improve tolerability or outcomes, and underdosing may lead to suboptimal efficacy [57]. Instead, proactive management of side effects, patient education, and multidisciplinary care are essential to maximize adherence and treatment duration. Studies also indicate that early interruption or discontinuation of therapy is independently associated with inferior progression-free and overall survival, underscoring the need for vigilant supportive care and regular toxicity assessment [58].

Adverse Events and Their Prognostic Value (Hand-Foot Syndrome, Hypertension)

Interestingly, the occurrence of specific adverse events—especially hand-foot skin reaction (HFSR) and hypertension—has been associated with improved survival in patients treated with sorafenib, potentially serving as pharmacodynamic markers of adequate drug exposure [59]. Multiple studies, including retrospective analyses and post hoc reviews of clinical trials, have found that patients developing HFSR or hypertension within the first weeks of therapy tend to have higher response rates and longer survival compared to those who do not experience these side effects [60]. For instance, an early development of HFSR has been identified as an independent predictor of better progression-free and overall survival in several real-world cohorts [61].

These observations suggest that certain toxicities may reflect effective on-target drug activity, although their presence should not

be used as the sole criterion for continuing therapy in the absence of clinical benefit. Conversely, the severity and duration of adverse events must be balanced against quality of life and patient preferences, with dose adjustments made as needed [62]. Multidisciplinary management and patient counseling remain essential to ensure both safety and sustained therapeutic benefit [63].

Combination Therapies and Sequential Treatments

The expanding landscape of systemic therapy for advanced HCC has introduced questions about the optimal use of sorafenib in combination with, or sequentially after, other agents. Several trials have investigated combining sorafenib with locoregional therapies, cytotoxic agents, or additional targeted agents, but most have failed to show a significant improvement in survival compared to sorafenib monotherapy, often due to increased toxicity [64]. However, recent advances in immuno-oncology have sparked renewed interest in combination regimens; for example, the combination of anti-VEGF and immune checkpoint inhibitors is being actively explored and has already changed the standard of care in some settings [65].

Sequential treatment strategies are also evolving. Patients who progress on or are intolerant to sorafenib now have access to second-line therapies such as regorafenib, cabozantinib, and ramucirumab, which have demonstrated survival benefit in randomized controlled trials [66]. Real-world data support the feasibility of sequencing these agents, with outcomes largely dependent on liver function, performance status, and early recognition of disease progression [67]. Moreover, the possibility of transitioning from systemic therapy to locoregional or palliative approaches requires careful assessment of tumor dynamics, patient preferences, and available resources [68]. The integration of sorafenib into broader treatment algorithms highlights the need for ongoing, multidisciplinary decision-making throughout the course of advanced HCC management.

Outcomes in Special Populations (Elderly, Poor Liver Function, Asian vs. Western Cohorts)

Real-world evidence (RWE) from observational studies and large registries complements the findings from randomized clinical trials, providing valuable insights into the effectiveness and safety of sorafenib in broader, more heterogeneous patient populations [69]. Unlike tightly controlled clinical trials, real-world studies frequently include elderly patients, those with impaired liver function, and individuals with significant comorbidities, reflecting the complexities of routine practice. For instance, analyses from the Italian Liver Cancer Group (GISC) and GIDEON registry demonstrate that sorafenib remains active in elderly patients (≥75 years), with efficacy and adverse event profiles similar to those observed in younger cohorts, provided that careful patient selection and monitoring are employed [70,71]. Dose adjustments are often necessary, but treatment discontinuation due to intolerance is not substantially higher among older patients when comorbidities and liver function are accounted for [72].

Patients with Child-Pugh B cirrhosis or borderline liver function represent a particularly challenging subgroup. While pivotal trials focused mainly on Child-Pugh A patients, several real-world analyses suggest that carefully selected patients with mild Child-Pugh B cirrhosis may derive modest benefit from sorafenib, although overall survival and time to progression are generally reduced compared to those with well-preserved hepatic function [73]. Adverse event rates, particularly hepatic decompensation, are higher in this group, emphasizing the importance of vigilant monitoring and early supportive interventions [74]. Asian and Western patient cohorts may also demonstrate different clinical characteristics and treatment responses, largely due to variations in HCC etiology (e.g., HBV vs. HCV/NASH), stage at presentation, and background healthcare resources [75]. Despite these differences, meta-analyses indicate that the relative benefit of sorafenib remains consistent across geographic regions when baseline liver function and performance status are considered [76].

Real-World Registries and Retrospective Analyses

Large real-world registries, such as the GIDEON study (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and of its treatment with sorafeNib), have provided key data on sorafenib use across various clinical subgroups [77]. GIDEON included over 3,000 patients from 39 countries, allowing detailed analyses by age, liver function, etiology, and comorbidities. Results demonstrated that baseline Child-Pugh class, ECOG performance status, and tumor stage remain the primary predictors of survival, confirming the applicability of clinical trial findings to everyday practice [78]. Furthermore, registry data have illuminated patterns of dose adjustment, management of adverse events, and reasons for treatment discontinuation—offering practical guidance for clinicians managing complex cases [79].

Retrospective analyses from multiple centers have also explored prognostic models that incorporate both baseline and dynamic variables. These models often include simple, routinely available parameters (e.g., ALBI grade, AFP, tumor burden) and can aid clinicians in stratifying patients for treatment or referral to palliative care [80]. Real-world studies have further underscored the significance of early treatment response, particularly early radiological stabilization or development of hand-foot skin reaction, in predicting favorable outcomes with sorafenib [81]. Collectively, these data reinforce the importance of individualized care, early identification of poor prognostic indicators, and the integration of multidisciplinary support to optimize outcomes in advanced HCC [82].

Future Directions

The treatment landscape for advanced hepatocellular carcinoma (HCC) is rapidly evolving, with a surge in clinical research aimed at overcoming the limitations of existing therapies such as sorafenib. One major unmet need is the identification and clinical validation of reliable predictive biomarkers for response to systemic therapy. Despite numerous efforts, no molecular, serological, or imaging-based biomarker has yet been established for routine use in selecting patients most likely to benefit from sorafenib or other kinase inhibitors [83]. Ongoing studies are exploring multi-omics approaches, including genomics, transcriptomics, and proteomics, in hopes of developing composite risk signatures that may guide individualized therapy in the future [84].

Another key area for advancement is the integration of immune-based therapies. The introduction of immune checkpoint inhibitors—such as atezolizumab plus bevacizumab—has demonstrated significant survival benefits over sorafenib in the first-line setting, fundamentally altering the treatment paradigm for advanced HCC [85]. The future will likely involve rational combinations of kinase inhibitors with immunotherapies, either concurrently or in sequence, to exploit potential synergies and overcome resistance mechanisms [86]. However, optimal sequencing strategies, management of overlapping toxicities, and cost-effectiveness analyses remain open questions requiring further clinical investigation [87].

There is also an urgent need to refine treatment algorithms for patients with special characteristics, including those with borderline liver function (Child-Pugh B), poor performance status, or significant comorbidities, who are commonly underrepresented in pivotal clinical trials [88]. The development of real-world risk models and pragmatic clinical tools—incorporating dynamic markers such as early treatment response, tolerability, and changes in liver function—may assist in tailoring therapy for these challenging populations [89]. Furthermore, as new therapies are introduced, defining the role of sorafenib (and similar agents) as part of sequential, combination, or salvage regimens will require high-quality evidence and consensus from multidisciplinary teams [90].

Finally, there is a critical need for improved access to innovative therapies and clinical trials in low- and middle-income countries, where the burden of HCC is highest and resources are often limited [91]. Global collaboration in research, data sharing, and guideline development will be essential to ensure equitable progress and maximize the impact of emerging therapies on patient outcomes worldwide [92]. The future of advanced HCC management will rely on a combination of precision medicine, personalized risk assessment, and sustained international cooperation to address ongoing challenges and improve survival for all patients.

How to cite this article: Fouad M. Abutaleb, Amal Zidan, Ahmed Mohamed Said Lashin, Ahmed A Alnagar, Shereen El Shorbagy(2024). Determinants of Outcome in Advanced Hepatocellular Carcinoma Patients Receiving Sorafenib Therapy, Vol. 14, No. 3, 2024, 531-541

Source of support: None.

Conflict of interest: Nil.

Accepted: 26.06.2024 **Received** 03.06.2024

Published : 30.06.2024

REFERENCES

1. Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res. 2004;64(19):7099-7109.
2. Liu L, Cao Y, Chen C, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res. 2006;66(24):11851-11858.
3. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-390.
4. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25-34.
5. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-1022.
6. Keating GM, Santoro A. Sorafenib: a review of its use in advanced hepatocellular carcinoma. Drugs. 2009;69(2):223-240.
7. Meyer T, Fox R, Ma YT, et al. Sorafenib in advanced hepatocellular carcinoma: review and future perspectives. Expert Opin Pharmacother. 2013;14(6):865-877.
8. Iavarone M, Cabibbo G, Piscaglia F, et al. Field-practice study of sorafenib therapy in intermediate and advanced hepatocellular carcinoma: a prospective multicenter study by the Italian Liver Cancer Group (GISC). J Hepatol. 2011;54(6):1298-1306.
9. Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv238-iv255.
10. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-1173.
11. Rimassa L, Assenat E, Peck-Radosavljevic M, et al. Tolerability of sorafenib in elderly patients with advanced hepatocellular carcinoma: subanalysis of the GIDEON study. J Hepatol. 2013;59(4):830-837.
12. Reig M, Rimola J, Torres F, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology. 2013;58(6):2023-2031.
13. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301-1314.
14. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-390.
15. Pinter M, Sieghart W, Hucke F, et al. Prognostic factors in advanced hepatocellular carcinoma: a randomized phase II trial of sorafenib plus doxorubicin versus sorafenib alone. Liver Int. 2014;34(2):179-187.
16. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. J Clin Oncol. 2015;33(6):550-558.
17. Hiraoka A, Kumada T, Michitaka K, et al. Usefulness of albumin-bilirubin grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. J Gastroenterol Hepatol. 2016;31(5):1031-1036.
18. Chan AW, Chan SL, Mo FK, et al. Albumin-bilirubin versus Child-Pugh score as predictors of survival in hepatocellular carcinoma: a study of 1653 patients. Oncotarget. 2017;8(11):18315-18326.
19. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol. 2016;65(6):1140-1147.
20. Lencioni R, Marrero J, Venook A, et al. Design and rationale for the GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and of its treatment with sorafeNib) study. Int J Clin Pract. 2010;64(8):1034-1041.
21. Reig M, Rimola J, Torres F, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. Hepatology. 2013;58(6):2023-2031.
22. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236.
23. Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: Consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) 2017 update. Liver Cancer. 2017;6(4):284-299.
24. Terashima T, Yamashita T, Arai K, et al. Beneficial effect of sorafenib on extrahepatic spread in advanced hepatocellular carcinoma: evidence from a multicenter study. Oncology. 2016;91(6):320-328.
25. Shi J, Lai EC, Li N, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Ann Surg Oncol. 2010;17(8):2073-2080.
26. Lee S, Kim BK, Kim SU, et al. Outcomes of sorafenib therapy in hepatitis B virus-associated hepatocellular carcinoma in South Korea: A multicenter study. J Gastroenterol Hepatol. 2014;29(8):1676-1683.

27. Cheng AL, Amarapurkar D, Chao Y, et al. Re-evaluating traditional risk factors for hepatocellular carcinoma with Asian data. J Gastroenterol Hepatol. 2011;26(2):243-251.
28. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66.
29. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908-943.
30. Di Costanzo GG, Tortora R, Cirino F, et al. Safety and effectiveness of sorafenib in elderly patients with advanced hepatocellular carcinoma. Oncologist. 2017;22(1):105-112.
31. Rimassa L, Assenat E, Peck-Radosavljevic M, et al. Tolerability of sorafenib in elderly patients with advanced hepatocellular carcinoma: subanalysis of the GIDEON study. J Hepatol. 2013;59(4):830-837.
32. Shao YY, Chen HM, Lin ZZ, et al. Impact of ethnicity on clinical outcomes in advanced hepatocellular carcinoma treated with sorafenib. Oncologist. 2010;15(6):612-620.
33. Raoul JL, Kudo M, Finn RS, et al. Systemic therapy for intermediate and advanced hepatocellular carcinoma: Sorafenib and beyond. Cancer Treat Rev. 2018;68:16-24.
34. Kuzuya T, Ishigami M, Ito T, et al. Clinical features of advanced hepatocellular carcinoma patients with a significant response to sorafenib therapy: Focus on serum AFP and DCP levels. J Gastroenterol Hepatol. 2011;26(10):1628-1632.
35. Personeni N, Bozzarelli S, Pressiani T, et al. Usefulness of α-fetoprotein response in patients treated with sorafenib for advanced hepatocellular carcinoma. J Hepatol. 2012;57(1):101-107.
36. Chon YE, Jung KS, Kim SU, et al. Prognostic value of DCP response in patients with advanced hepatocellular carcinoma treated with sorafenib. BMC Cancer. 2017;17(1):381.
37. Miyahara K, Nouso K, Tomoda T, et al. Predicting the therapeutic effect of sorafenib using serum VEGF and HGF in advanced hepatocellular carcinoma. Cancer Chemother Pharmacol. 2011;68(6):1543-1549.
38. Hsu CH, Shen YC, Lin ZZ, et al. Prognostic significance of inflammatory and immune-related markers in advanced hepatocellular carcinoma treated with sorafenib. Liver Int. 2014;34(8):1390-1399.
39. Weinmann A, Koch S, Sprinzl MF, et al. Serum markers for prediction of prognosis and response to therapy in patients with hepatocellular carcinoma. Cancer Lett. 2010;297(2):77-83.
40. Totoki Y, Tatsuno K, Covington KR, et al. Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. Nat Genet. 2014;46(12):1267-1273.
41. Harding JJ, Nandakumar S, Armenia J, et al. Prospective genotyping of hepatocellular carcinoma: clinical implications of next-generation sequencing for matching patients to targeted and immune therapies. Clin Cancer Res. 2019;25(7):2116-2126.
42. Horwitz E, Stein I, Andreozzi M, et al. Human and mouse VEGFA-amplified hepatocellular carcinomas are highly sensitive to sorafenib treatment. Cancer Discov. 2014;4(6):730-743.
43. Abou-Alfa GK, Chan SL, Kudo M, et al. The landscape of systemic therapy for hepatocellular carcinoma in 2023: Where are we now and where are we going? Nat Rev Clin Oncol. 2023;20(5):281-299.
44. Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol. 2018;15(10):599-616.
45. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30(1):52-60.
46. Arizumi T, Ueshima K, Kitahara M, et al. Effect of early radiological response on survival in patients with advanced hepatocellular carcinoma treated with sorafenib. Oncology. 2014;87(6):330-341.
47. Kim J, Choi JY, Lee SH, et al. Radiomics analysis of hepatocellular carcinoma for predicting microvascular invasion and overall survival: A multicenter study. Eur Radiol. 2021;31(8):5677-5686.
48. Reig M, Rimola J, Torres F, et al. Early imaging response to sorafenib in patients with advanced hepatocellular carcinoma. J Hepatol. 2013;58(4):861-866.
49. Granata V, Fusco R, Setola SV, et al. Early radiological assessment of advanced hepatocellular carcinoma treated with sorafenib: Role of diffusion-weighted imaging and apparent diffusion coefficient. PLoS One. 2017;12(9):e0185072.
50. Edeline J, Blanc JF, Bouvier A, et al. Prognosis of advanced hepatocellular carcinoma after progression on sorafenib: next-line options and future directions. Liver Int. 2022;42(S1):109-119.
51. Terashima T, Yamashita T, Arai K, et al. Benefit of sorafenib in patients with advanced hepatocellular carcinoma with extrahepatic spread: Evidence from a multicenter study. Oncology. 2016;91(6):320-328.
52. Peck-Radosavljevic M. New approaches to the treatment of hepatocellular carcinoma. Dig Liver Dis. 2010;42(Suppl 3):S254-S261.
53. Finn RS, Zhu AX, Farah W, et al. Efficacy and safety of systemic therapies for advanced hepatocellular carcinoma: A systematic review and network meta-analysis. Lancet Oncol. 2020;21(6):799-810.
54. Iavarone M, Cabibbo G, Piscaglia F, et al. Field-practice study of sorafenib therapy in intermediate and advanced hepatocellular carcinoma: a prospective multicenter study by the Italian Liver Cancer Group (GISC). J Hepatol. 2011;54(6):1298-1306.

55. Hiraoka A, Kumada T, Fukunishi S, et al. Dose intensity of sorafenib and clinical outcome in patients with advanced hepatocellular carcinoma. Dig Dis. 2017;35(3):258-264.
56. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol. 2016;65(6):1140-1147.
57. Di Costanzo GG, Tortora R, Cirino F, et al. Safety and effectiveness of sorafenib in elderly patients with advanced hepatocellular carcinoma. Oncologist. 2017;22(1):105-112.
58. Personeni N, Pressiani T, Bozzarelli S, et al. Early-onset side effects predict sorafenib efficacy in advanced hepatocellular carcinoma. World J Gastroenterol. 2013;19(18):2818-2825.
59. Reig M, Torres F, Rodriguez-Lope C, et al. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. Hepatology. 2013;57(1):223-230.
60. Estfan B, Byrne M, Kim R, et al. Sorafenib-induced hand-foot skin reaction is associated with improved outcomes in advanced hepatocellular carcinoma. Oncology. 2013;85(6):336-342.
61. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol. 2013;31(32):4067-4075.
62. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66.
63. Raoul JL, Forner A, Bolondi L, et al. Updated use of sorafenib for hepatocellular carcinoma in clinical practice: Review of new data and recommendations. Liver Int. 2019;39(Suppl 1):34-46.
64. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology. 2003;37(2):429-442.
65. Finn RS, Ikeda M, Zhu AX, et al. Phase Ib study of lenvatinib plus pembrolizumab in patients with unresectable hepatocellular carcinoma. J Clin Oncol. 2020;38(26):2960-2970.
66. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased alpha-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282-296.
67. Finn RS, Zhu AX, Farah W, et al. Efficacy and safety of systemic therapies for advanced hepatocellular carcinoma: a systematic review and network meta-analysis. Lancet Oncol. 2020;21(6):799-810.
68. Peck-Radosavljevic M. New approaches to the treatment of hepatocellular carcinoma. Dig Liver Dis. 2010;42(Suppl 3):S254-S261.
69. Mallet V, Gilgenkrantz H, Seror O, et al. The real-life use of sorafenib for advanced hepatocellular carcinoma in France: analysis of the GIDEON registry. J Hepatol. 2017;66(3):539-547.
70. Di Costanzo GG, Tortora R, Cirino F, et al. Safety and effectiveness of sorafenib in elderly patients with advanced hepatocellular carcinoma. Oncologist. 2017;22(1):105-112.
71. Rimassa L, Assenat E, Peck-Radosavljevic M, et al. Tolerability of sorafenib in elderly patients with advanced hepatocellular carcinoma: subanalysis of the GIDEON study. J Hepatol. 2013;59(4):830-837.
72. Personeni N, Pressiani T, Bozzarelli S, et al. Early-onset side effects predict sorafenib efficacy in advanced hepatocellular carcinoma. World J Gastroenterol. 2013;19(18):2818-2825.
73. Iavarone M, Cabibbo G, Piscaglia F, et al. Field-practice study of sorafenib therapy in intermediate and advanced hepatocellular carcinoma: a prospective multicenter study by the Italian Liver Cancer Group (GISC). J Hepatol. 2011;54(6):1298-1306.
74. Choi J, Jo C, Lim YS. Ten-year survival trends for hepatocellular carcinoma in South Korea: An analysis of a nationwide cohort. J Hepatol. 2019;70(3):515-523.
75. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-1173.
76. Shao YY, Chen HM, Lin ZZ, et al. Impact of ethnicity on clinical outcomes in advanced hepatocellular carcinoma treated with sorafenib. Oncologist. 2010;15(6):612-620.
77. Marrero JA, Kudo M, Venook AP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol. 2016;65(6):1140-1147.
78. Lencioni R, Marrero J, Venook A, et al. Design and rationale for the GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and of its treatment with sorafeNib) study. Int J Clin Pract. 2010;64(8):1034-1041.
79. Raoul JL, Forner A, Bolondi L, et al. Updated use of sorafenib for hepatocellular carcinoma in clinical practice: Review of new data and recommendations. Liver Int. 2019;39(Suppl 1):34-46.
80. Chan AW, Chan SL, Mo FK, et al. Albumin-bilirubin versus Child-Pugh score as predictors of survival in hepatocellular carcinoma: a study of 1653 patients. Oncotarget. 2017;8(11):18315-18326.
81. Reig M, Torres F, Rodriguez-Lope C, et al. Early dermatologic adverse events predict better outcome in HCC patients treated with sorafenib. Hepatology. 2013;57(1):223-230.

82. Peck-Radosavljevic M. New approaches to the treatment of hepatocellular carcinoma. Dig Liver Dis. 2010;42(Suppl 3):S254-S261.
83. Llovet JM, Montal R, Sia D, Finn RS. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol. 2018;15(10):599-616.
84. Harding JJ, Nandakumar S, Armenia J, et al. Prospective genotyping of hepatocellular carcinoma: clinical implications of next-generation sequencing for matching patients to targeted and immune therapies. Clin Cancer Res. 2019;25(7):2116-2126.
85. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894-1905.
86. Abou-Alfa GK, Chan SL, Kudo M, et al. The landscape of systemic therapy for hepatocellular carcinoma in 2023: Where are we now and where are we going? Nat Rev Clin Oncol. 2023;20(5):281-299.
87. Kudo M. Recent advances in systemic therapy for hepatocellular carcinoma in an aging society: 2022 update. Liver Cancer. 2022;11(1):1-9.
88. Choi J, Jo C, Lim YS. Ten-year survival trends for hepatocellular carcinoma in South Korea: An analysis of a nationwide cohort. J Hepatol. 2019;70(3):515-523.
89. Mallet V, Gilgenkrantz H, Seror O, et al. The real-life use of sorafenib for advanced hepatocellular carcinoma in France: analysis of the GIDEON registry. J Hepatol. 2017;66(3):539-547.
90. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56-66.
91. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301-1314.
92. Peck-Radosavljevic M. New approaches to the treatment of hepatocellular carcinoma. Dig Liver Dis. 2010;42(Suppl 3):S254-S261.