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Review Article

Treatment Response to Sorafenib in Liver Cancer; A Comprehensive Review on Association with Single Nucleotide Polymorphisms

Saeed Khan*[1], Ayesha Akhtar[2], Muhammad Hanif Bangash[3]

[1]Molecuar Pathology, Dow University of Health Sciences, Karachi, Pakistan.
[2]Atta Ur Rehman School of Biological Sciences, National University of Science & Technology, Islamabad, Pakistan.
[3]Pakistan Institute of Nuclear Science and Technology Islamabad, Pakistan.
***Correspondence:** saeed.khan@duhs.edu.pk

Abstract

Liver cancer is one of the most challenging cancers to diagnose and treat. Sorafenib is a tyrosine kinase inhibitor (TKI) that is prescribed for advanced or unresectable liver cancer. While this drug is one of the already-limited choices for liver cancer treatment, sorafenib resistance and variation in therapeutic response add further to the difficulties in pharmacotherapy for liver cancers. There are various ways in which cancer cells can protect themselves from these drugs; genetic polymorphism is one of the ways through which the mechanisms of varied responses to sorafenib can be comprehended. Notably, studies including genes involved in pharmacokinetics of sorafenib like ATP binding cassette subfamily B member 1 (*ABCB1* rs2032582, rs1045642), ATP binding cassette subfamily G member 2 (*ABCG2* rs2231137, rs2231142, rs2622604), *ATP binding cassette subfamily C member 2 (ABCC2/ MRP2* rs3740066), UDP glucuronosyltransferase family 1 member A1 (*UGT1A1* rs8175347), UDP glucuronosyltransferase family 1 member A9 (*UGT1A9* rs17868320, rs72551330, rs6714486), Cytochrome p450 system (*CYP3A5*3* rs776746), (*CYP3A4* rs2740574), *(CYP26A1* rs7905939), Solute carrier organic anion transporter family member 1 B1 (*SLCO1B1* rs2306283, rs4149056), Solute carrier family 22 member 14 (*SLC22A14* rs149738, rs171248, rs183574), Solute carrier family 15 member 2 (*SLC15A2* rs2257212) in addition to genes involved in agiogenesis, like nitric oxide synthase 3 /endothelial NOS (*NOS3/eNOS* rs2070744, rs2070744, rs2070744, rs61722009, rs1799983), vascular endothelial growth factor A (*VEGF-A* rs25648, rs833061, rs699947, rs2010963), vascular endothelial growth factor C (*VEGF-C* rs4604006, rs664393), kinase insert domain receptor (KDR/VEGFR-2 rs2071559, rs2305948, rs1870377, rs4864950), hypoxia inducible factor 1 subunit alpha (*HIF-1A* rs1951795, rs10873142, rs12434438, rs12434438), fibroblast growth factor 2 (*FGF2* rs308379, rs308447) were analyzed in this article. Some of these SNPs were associated with favorable therapeutic outcomes, while others correlated with chemo-resistance or adverse events (AEs) after sorafenib administration. Some AEs showed counter-intuitive results i.e. association with improved overall survival (OS) and progression-free survival (PFS). This review article exhaustively covers and analyzes the pharmacogenomic mechanisms involved in the variation of sorafenib therapeutic response.

Keywords: Liver cancer, sorafenib, genetic polymorphism, treatment response, adverse effects

1. Introduction

Cancer is a disease in which cells grow uncontrollably and metastasize to other parts of the body. This abnormal and unregulated division of the cells can occur in any part of the body (National Cancer Institute 2021). According to the World Health Organization (WHO), cancer is one of the leading causes of mortality globally. This disease claimed nearly 10 million lives in 2020, or about one in six deaths occurred due to cancer during the year, globally (WHO 2022). However, liver cancer is the 6th most prevalent cancer worldwide. It is the 5th most common cancer among men and the 9th most common type of cancer in women population. There were more than 900,000 new cases of liver cancer in 2020, as reported by (World Cancer Research Fund International

2022). The highest rates of liver cancer are found in East and Southeast Asia and in Middle and Western Africa, whereas the incidence rates are low in the rest of Asia, as well as Eastern and Northern Europe (Jemal et al. 2011). We found that in countries with low income, hepatitis B virus (HBV) infection may be responsible for about 60% of total liver cancer, whereas hepatitis C virus (HCV) infection accounts for about 33% of total liver cancer cases (Parkin 2006). China accounts for over 50% of newly diagnosed hepatocellular carcinoma (HCC) cases worldwide, with nearly 700,000 new cases per year. Since China has a large number of HBV carriers (> 120,000,000), this makes chronic hepatitis-induced liver cirrhosis one of the major pathogenic factors behind hepatocellular carcinoma (HCC) (Maluccio and Covey 2012).

Liver cancer can be classified into two categories. One of them is primary liver cancer, which originates in liver tissue. There are two main types of primary liver cancer, HCC and intrahepatic cholangiocarcinoma (iCCA), which is cancer of the bile ducts (Yamashita and Kaneko 2016). The other type is called secondary metastatic liver cancer that involves the metastasis of cancer cells to the liver from other parts of the body (Li et al. 2021). It is noteworthy that if colorectal cancer spreads to the liver, the cancer cells in the liver are actually colorectal cancer cells. Oncologists refer to it as metastatic colorectal cancer, not liver cancer. The most common types of liver metastasis are colorectal cancers, gastrointestinal cancers, and melanoma (Hillman Cancer Center , Hoti and Adam 2008).

In order to determine the stage of liver cancer, diagnostic teams look at liver function, overall health, severity of symptoms, and whether the cancer has spread across the body (Hillman Cancer Center). However, the Barcelona Clinic Liver Cancer (BCLC) staging classification method, created in 1999, comprises four stages to select treatment strategies for the patients. Stage A or 'early stage' includes patients with asymptomatic early tumors that are suited for radical therapies-resection, percutaneous, or transplantation treatments. The intermediate stage (Stage B) is asymptomatic multinodular HCC. The advanced stage, also called Stage C, includes patients with symptomatic tumors and/or an invasive tumor pattern (vascular invasion or extra-hepatic spread). Palliative treatments as well as novel anticancer agents, in the setting of phase II investigations or randomized controlled trials, may be given in Stage B and C patients. However, due to an extremely grim prognosis, end-stage disease (Stage D) patients get symptomatic treatment only (Llovet, Brú, and Bruix 1999). Additionally, a sub-classification to BCLC stages B and C was also proposed in 2018, to update diagnostic and treatment guidelines for clinicians (Golfieri et al. 2018).

Another method for liver cancer staging was introduced (Okuda et al. 1985). In this method, the amount of ascites, serum albumin, and bilirubin levels are measured to determine the tumor size and severity of cirrhosis. However, this mode of cancer staging has drawbacks due to the non-inclusion of pathologic characteristics, such as vascular invasion or the presence or absence of nodal metastases. Patients staged according to this system mostly had unresectable HCC, thereby limiting its use as a clinical scoring system.

Cancer of the Liver Italian Program (CLIP) score is another tool for hepatic cancer staging (Llovet and Bruix 2000). It takes into account several factors: the severity of liver cirrhosis (Child-Pugh Stage), the appearance and spread of the tumor, the level of α-fetoprotein blood marker, and the presence of portal vein thrombosis. The score ranges from 0 to 6 and helps doctors classify patients with advanced HCC based on their expected outcomes. This stage-classification tool showed promise in studies conducted for comparing its prognostication accuracy with other staging methods (Cho et al. 2008, Huitzil-Melendez et al. 2010).

It should be kept in mind that there is no one-size-fits-all staging method for liver cancer. This is due to the heterogeneous nature of geographic factors, treatment approaches, and varying degrees of liver function. Further studies are needed for better understanding of liver cancer staging (Vauthey et al. 2010).

2. Pathophysiology of Liver Cancer

The most common primary liver cancers are HCC and iCCA, accounting for 75%–85% of all liver cancers (Sung et al. 2021). Much etiology has been linked to HCC development, the most prominent of which include chronic hepatitis B (HBV) and C (HCV) viral infection, chronic alcohol consumption, and aflatoxin-B1-contaminated food (Liu et al. 2012, Chu et al. 2017, Osna, Clemens, and Donohue Jr. 2005, Tokino et al. 1991, Lavanchy 2004). Almost all cirrhosis-inducing conditions carry the potential to cause HCC. It is widely accepted that lower expression of p53 participates in the development of HCC; however, p53 mutation contribution to cancer initiation, progression, or both remains under investigation (Ueda et al. 1995).

Generally, hepatocarcinogenesis is associated with the causative agents' induction of inflammation and, consequently, cycles of hepatocytic necrosis, regeneration, oxidative stress, and subsequently cirrhosis (Farazi and DePinho 2006). Host-virus interaction may also trigger oncogenic pathways, including viral integration into the host genome and subsequent DNA deletion. The excessive scar-tissue formation eventually results in liver cancer. Aflatoxin-B1-induced hepatocarcinogenesis is mostly associated with carcinogenic mutations. Moreover, Genomic instability like telomere erosion, chromosome segregation defects, and alterations in the DNA-damage-response pathways, in addition to tumor suppressor p53 inactivation, are considered among significant reasons behind liver cancer (Farazi and DePinho 2006).

In addition, genetic involvement in liver cancer pathophysiology is also making headways. Notably, *DNAJB1-PRKCA* fusion – due to a focal deletion in chromosome 19 – is identified in almost all fibrolamellar carcinoma and is considered to be highly specific (Honeyman et al. 2014, Graham et al. 2015, Cornella et al. 2015) but not pathognomonic, as it has been seen in certain cases of bile duct and pancreatic tumors as well (Vyas et al. 2020). The DNAJB1-PRKCA fusion causes constant activation of the protein kinase A pathway, leading to the transformation of normal liver cells into cancer cells (Gigante et al. 2021).

3. Current Treatment Regimens

Medical science has made numerous advances in cancer treatment. Extensive research into novel chemotherapeutic agents, radiation, and surgery has proven to be a boon for those debilitated by cancer. However, liver cancer remains one of the most difficult diseases to treat.

Broadly, liver cancer is managed according to the stage of cancer. The treatment plan for stage I and stage II can be partial hepatectomy, with the condition that the liver is relatively healthy and the cancer is in its early stages. Historically, the Child-Pugh score has been used to provide an estimate of hepatic function and to predict mortality rates after hepatectomy (Tsoris A 2023). For patients, who fail to qualify for surgical intervention, embolization of the portal vein (feeding the tumor) is done. Afterward, selective hypertrophy of the contralateral liver is induced, as demonstrated by Abulkhir and colleagues (Abulkhir et al. 2008). This procedure is not free of controversy as was observed by Schnitzbauer and fellows (Schnitzbauer et al. 2012). It was associated with a morbidity rate of 68% and a mortality rate of 12% despite reports of an 86% 6-month survival rate. Similarly, transarterial chemoembolization therapy (TACE) can also be used, as the blood supply to HCC is largely derived from the hepatic artery, and selective infusion of chemo-cocktail through

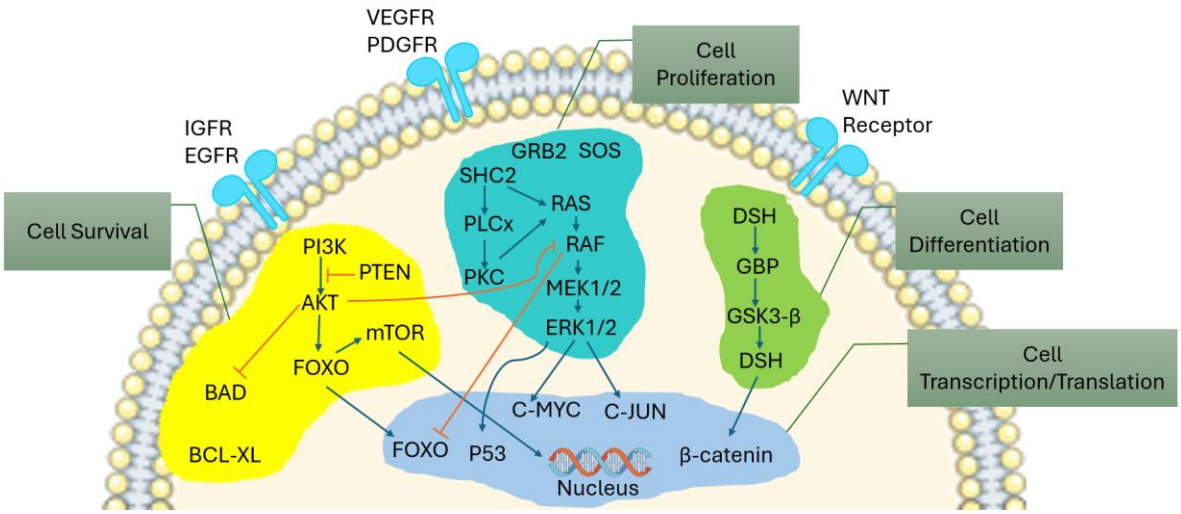

Figure 1: Cellular signaling pathways involved in the pathogenesis of HCC.

a catheter into the hepatic arteries induces tumor necrosis (Lo et al. 2002).

However, if a liver is not healthy, despite the early stages of cancer, a liver transplant is the preferred course of action. On the other hand, for unresectable and metastatic cancers, a combination of chemotherapy, radiotherapy, immunotherapy, and surgery can be used for cancer eradication (American Cancer Society 2021).

In treatment with curative intent, liver transplantation is more favored as it not only negates the fear of relapse due to undetectable hepatic tumors, but also avoids the bad prognosis of cirrhosis, and risk reduction for postoperative liver failure (Fong and Tanabe 2014).

Radiofrequency ablation (RFA) is another treatment option for liver cancer. RFA uses high-frequency electrical current for thermal destruction of HCC by inducing coagulative necrosis. RFA is used in the pre-transplantation management of unresectable HCCs and in some patients with resectable HCC (Goldberg et al. 2000). RFA is associated with significantly lower morbidity as compared to surgical resection (Mazzaferro et al. 2004). Advanced disease management is different from locally advanced and unresectable liver cancer. Patients who exhibit widely metastatic HCCs or portal vein invasion are referred for systemic therapy.

FOLFOX4 regimen is the systemic chemotherapy, which comprises fluorouracil, leucovorin, and oxaliplatin; however, its use in HCC is not as frequent as that of targeted therapies like soferanib and/or immunotherapy (Kim and Viatour 2020). Tyrosine kinase inhibitors (TKIs), like Sorafenib, are the standard first-line therapy in this case. It is a multiple kinase inhibitor (anti-angiogenic and anti-proliferative) that suppresses the activity of 'rapidly accelerated fibrosarcoma (Raf-1)' and other tyrosine kinases, such as vascular endothelial growth factor receptor 2 (VEGFR-2), VEGFR-3, platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor 1 (FGFR-1) (Liu et al. 2006). Novel TKIs like lenvatinib (Ikeda et al. 2017), donafenib (Liu et al. 2019), and regorafenib (notably for sorafenib-resistant cancers) (Finn et al. 2018) are also improving the survival rate in patients with liver cancers.

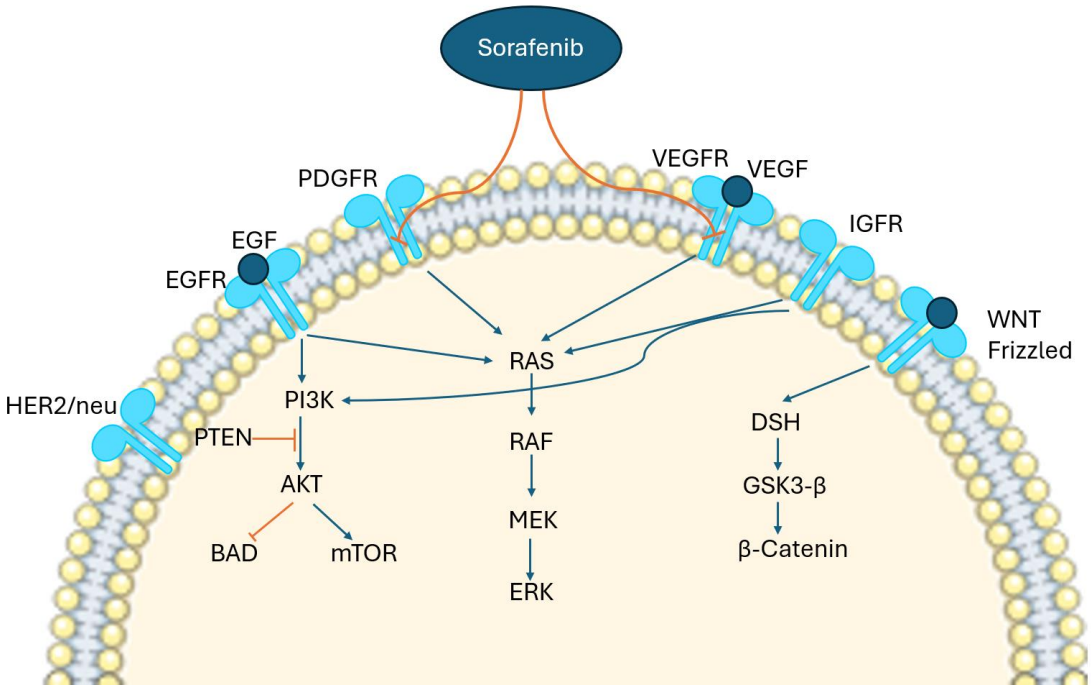

Figure 2: Sorafenib's molecular mode of action.

Non-tyrosine kinase inhibitors (NTKIs) like mesenchymal-epithelial transition (MET) inhibitors can also stop cell growth and bring about apoptosis. Tivantinib, a selective oral inhibitor of MET, has shown promising effects against HCC, as monotherapy and in combination with sorafenib (TKI) (Santoro et al. 2013). In addition to tivantinib, refametinib prevents cellular proliferation by specifically targeting Mitogen-activated protein kinase (MAPK) signaling pathway (Huynh et al. 2003, Weekes et al. 2013). It can also be used in combination with sorafenib (Lim et al. 2014).

Cytotoxic therapy is the next step in case the first line of treatment fails. However, there is no standard second-line agent, as HCC is considered to be a chemo-refractory kind of cancer (Llovet and Bruix 2003, Jonathan D Schwartz 2002). Moreover, systemic chemotherapy is not well received by patients with significant hepatic dysfunction. Nevertheless, for some individuals chemotherapy may still be administered, particularly in those with underlying non-cirrhotic liver. Single-agent doxorubicin has been the most studied agent for advanced HCC, of the available chemotherapeutic agents (Yeo et al. 2005). Various combination chemotherapy regimens have been tested to improve efficacy but the results have not been very encouraging (Treiber 2002, Simonetti et al. 1997). In general, cytotoxic chemotherapy should be kept for patients with adequate hepatic function, preferably administered within the safer setting of a clinical trial.

Interestingly, the ability to resist immunological-response-mediated extermination has emerged as a hallmark of cancer cells. These rogue cells not only evade detection and subsequent attack from the immune system but also thwart apoptotic programming (Douglas Hanahan 2011). By overcoming this resistance a hope for anticancer therapy emerges (Topalian et al. 2012). Immunotherapy can be used to treat advanced HCC, as it is considered to be immunogenic (Makarova-Rusher et al. 2015,

Hodi et al. 2010). This property aids with a targeted attack on the rapidly proliferating cells, particularly T-cell-based immunotherapy is considered to be promising (Ormandy et al. 2005, Mizukoshi et al. 2011).

In addition, by targeting immune checkpoints, like programmed cell death 1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1) which are immunoregulatory proteins, anticancer response may be achieved (Umemoto et al. 2015, Shi et al. 2011, Sznol and Chen 2013). Furthermore, by hitting the tumor microenvironment, like Treg cells that cause immunosuppression in the tumor cells, the immune system can better combat the cancer (Unitt et al. 2005).

Another method of treating HCC is by cytotoxic T-lymphocyte-associated Protein 4 (CTLA-4) monoclonal antibodies, such as ipilimumab and tremelimumab. CLTA-4 acts as a negative signal, to deactivate cytotoxic T cells, preventing autoimmune reactions in the body. However, by blocking CTLA-4's inhibitory signals, an immune response is unleashed on HCC cells (Larkin et al. 2015, Kelley et al. 2021, Vaja and Rana 2020).

4. Variability in Treatment Response: A Basis for Pharmacogenomic Exploration

The liver is one of the vital organs and is responsible for metabolizing a wide range of drugs (Vaja and Rana 2020). Any dysfunction in this organ will lead to variation in the pharmacokinetic and pharmacodynamic fate of a drug (Kocz. 2023, Zucman-Rossi et al. 2015). Since cancerous cells in the liver carry the potential to enhance or diminish a gene expression (Liedtke C 2009, Sultana et al. 2019); understanding the variability in treatment response through pharmacogenomic tools appears to be the next logical step for therapy optimization (Marin et al. 2020). Recent breakthroughs in precision medicine have the potential to significantly influence prescribing or contraindicating drugs in patients based on their genetic makeup. It can not only improve the outcome of treatments but also reduce the risk of toxicity and other adverse effects (Singh 2020). Notably, anticancer drugs usually have a narrow therapeutic margin, and genetic variations or polymorphisms play a pivotal role not only during cancer development but also progression, and therefore, represent targets for precision medicine (Yoon et al. 2018). Chemoresistance is one of the most concerning factors arising out of HCC that provides ground for studies, linking treatment response variety to genetic variability and the underlying mechanism governing these changes (Ain et al. 2023). However, while these SNPs and variations provide valuable insights into HCC risk factors and progression, they are not currently used as predictive markers in clinical practice due to their limited odds ratios. Further research can overcome this limitation and improve clinical practice regarding precision medicine (Stefano Caruso 2021).

5. Association of Genetic Polymorphisms with Soferanib Treatment Response in Liver Cancer Patients

Soferanib belongs to the class of TKIs, functioning as a targeted chemotherapeutic agent. It targets multiple molecular pathways that are involved in angiogenesis, tumor proliferation, and cell survival. However, the genetic heterogeneity of HCC poses one of the key challenges to sorafenib therapeutic success. The intra-tumor and inter-tumor genetic diversity in the same patient can, not only pose a poor prognosis but also make it harder to tailor an effective treatment plan (Zaki and Reeves 2016). While there are many mechanisms for sorafenib resistance, the process of comprehending the underlying mechanisms remains an evolving area of research (Tang et al. 2020). This review article will delve into genetic polymorphisms and aberrant gene expressions that are found to be influencing the fate of sorafenib outcome.

Figure 1: The table showing several SNPs and their association or lack thereof, with the efficacy and toxicity of Sorafenib.

Gene	SNPs	Sample Size	Population	Effect/Association	Reference
ABCB1	rs2032582	47	French	Not associated with lower sorafenib plasma levels	(Tandia et al. 2017)
	rs1045642			Significantly associated with lower plasma levels of sorafenib	
ABCG2	rs2231137	47	French	significant association with lower plasma sorafenib levels	(Tandia et al. 2017)
	rs2231142	47	French	significant association with lower plasma sorafenib levels	(Tandia et al. 2017)
		157	Taiwan	associated with unfavorable overall survival in sorafenib-treated HCC patients	(Huang et al. 2022)
	rs2622604	47	French	Significant association with the lower plasma level of sorafenib	(Tandia et al. 2017)
		20	French	Patients with 1143 TT exhibited a greater exposure compared to those with the 1143 CC	(Boudou-Rouquette et al. 2012)
MRP2/ ABCC2	rs3740066	49	Spanish	strong association with the pharmacokinetics of sorafenib and its metabolite	(Díaz-González et al. 2020)
UGT1A1	rs8175347	114	Dutch	associated with hyperbilirubinemia and treatment interruption	(Bins et al. 2016)
UGT1A9	rs17868320	92	French	associated with grade ≥2 diarrhea	(Boudou-Rouquette et al. 2012)
		49	Spanish	No association with the development of an ADR	(Díaz-González et al. 2020)
	rs72551330	49	Spanish	no clear-cut associations between SNP profile and the development of adverse events	(Díaz-González et al. 2020)
	rs6714486	49	Spanish	no clear-cut associations between SNP profile and the development of adverse events	(Díaz-González et al. 2020)
SLCO1B1	rs2306283	114	Dutch	associated with diarrhea	(Bins et al. 2016)
	rs4149056			associated with thrombocytopenia	
ANGPT2	rs1961222	135	Italian	No association with sorafenib outcomes	(Marisi et al. 2019)
	rs17063434			No association with sorafenib outcomes	
	rs3739392			No association with sorafenib efficacy	
	rs3739390			No association with sorafenib efficacy	
	rs3739391			No association with sorafenib efficacy	
	rs55633437			Associated with significantly lower median OS and PFS and sorafenib resistance	
		34	Italian	No significant association found	(Augello et al. 2023)
NOS3/ eNOS	rs2070744	135	Italian	Associated with sorafenib resistance identification	(Marisi et al. 2019)
	rs2070744	23	Italian	No significant correlation detected	(Augello et al. 2023)
	rs2070744	128	Italian	Associated with resistance to sorafenib treatment	(Casadei Gardini et al. 2016
	rs61722009			Associated with sorafenib resistance	
	rs1799983			No association was found with clinical outcomes of sorafenib	

CYP3A5*3	rs776746	600	Chinese	Associated with minimal sorafenib metabolism and consequent organ damage	(Guo et al. 2018)
CYP3A4	rs2740574	49	Spanish	No association with sorafenib metabolism	(Díaz-González et al. 2020)
CYP26A1	rs7905939	23	Italian	Significant association with lack of response to sorafenib	(Augello et al. 2023)
SLC22A14	rs149738	23	Italian	Significantly associated with sorafenib response.	(Augello et al. 2023)
	rs171248				
	rs183574				
SLC15A2	rs2257212	181	Korean	Associated with longer progression-free survival in sorefanib-treated HCC.	(Lee et al. 2015)
VEGF-A	rs25648	148	Italian	Significantly associated with PFS and OS	(Scartozzi et al. 2014)
	rs833061			Significantly associated with PFS and OS	
	rs699947			Significantly associated with PFS and OS	
	rs2010963	34		Significantly associated with sorafenib response	(Augello et al. 2023)
VEGF-C	rs4604006	148	Italian	Significantly associated with PFS and OS	(Scartozzi et al. 2014)
		34		No significant association	(Augello et al. 2023)
	rs664393	148		Significantly associated with PFS and OS	(Scartozzi et al. 2014)
KDR/VEGFR-2	rs2071559	148		Significantly associated with PFS and OS	(Scartozzi et al. 2014)
	rs2305948	148		Significantly associated with PFS and OS	(Scartozzi et al. 2014)
	rs2305948	78	Chinese	Significantly associated with a better response and longer time to progression	(Zheng et al. 2014)
	rs1870377				
	rs4864950	201	American, Italian	Associated with increased risk of grade ≥2 composite toxicity	(Quintanilha et al. 2022)
HIF-1A	rs1951795	210	Italian	Favorable association with PFS and OS for sorafenib-treated HCC patients	(Faloppi et al. 2016)
	rs10873142				
	rs12434438				
	rs12434438	20		Notably lower expression in HCC tissues of sorafenib-responsive patients	(Augello et al. 2023)
FGF2	rs308379	245	Korean	Associated with shorter OS	(KIM et al. 2019)
	rs308447			TT genotype was found to have shorter OS than patients with the CC or CT genotype	

5.1. ATP Binding Cassette Subfamily B Member 1 (*ABCB1*)

This gene encodes membrane-associated proteins. It belongs to the superfamily of ABC transporters, which transport materials in and out of a cell. As a member of the MDR/TAP subfamily of *ABC* genes, they are involved in multidrug resistance. The gene produces a protein that is an ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity. It is responsible for not only decreased drug accumulation in multidrug-resistant cells and is often responsible for the development of anticancer drug resistance (committee 2023c). (Tandia et al. 2017) analyzed *ABCB1* SNPs, including2677G>TA (rs2032582), and 3435C>T (rs1045642). The study, comprising 47 French HCC patients, found that *ABCB1* 2677G>TA (rs2032582) was not linked with pharmacokinetic variations of sorafenib levels in plasma. On the other hand, 3435C>T (rs1045642)

exhibited significant association with lowered plasma levels of the drug.

5.2. ATP Binding Cassette Subfamily G Member 2 (*ABCG2*)

ABCG2 encodes protein included in the superfamily of ATP-binding cassette (ABC) transporters. These proteins transport various molecules across the extra-cellular and intra-cellular barriers. It also functions as a xenobiotic transporter that may play a major role in multi-drug resistance (committee 2023e).

A study showed that patients with the *ABCG2*-1143 TT (rs2622604) genotype exhibited a greater susceptibility to sorafenib as compared to those with the 1143 CC genotype. It is noteworthy that the smaller size of the cohort (20 HCC patients on sorafenib) cannot paint a broader picture and more in-depth research is needed to develop a better understanding of the situation (Boudou-Rouquette et al. 2012).

Furthermore, a French study in 2017 also set out to find certain SNPs' association with sorafenib-treated HCC response. For this purpose, they enrolled 47 consecutive patients with advanced HCC treated with a single agent-sorafenib (Tandia et al. 2017). The researchers genotyped for *ABCG2* (rs2231137; rs2231142; rs2622604), and *ABCB1* (rs2032582; rs1045642). They found that *ABCG2* (rs2231137; rs2231142; rs2622604) carriers were more likely to have lower plasma levels of sorafenib, due to exposure and efflux transporters genotype polymorphisms. They also detected a propensity in the heterozygous groups, for the studied polymorphisms, to produce the best drug response. Further research is needed to confirm this by multicenter studies with more parameters and more patients.

ABCG2 rs2231142 polymorphism was found to be associated with poor survival outcomes in sorafenib-treated HCC patients, indicating its potential role as a prognostic factor. To establish this link, a study conducted in Taiwan, 97 patients with advanced HCC treated with sorafenib mono-therapy, were genotyped for *ABCG2* (rs2231142). The researchers recruited a total of 157 patients with advanced HCC, on sorafenib mono-therapy. These subjects were genotyped for specific SNPs, namely *VEGFR2* rs7692791, *WWOX* rs9926344, *CA9* rs1048638, *DICER* rs1057035, *ABCB1* rs2032582, *ABCG2* rs2231142, and *ABCG2* rs2231137. The results indicated *ABCG2* rs2231142 genotype "CC" association with poor survival outcomes (Huang et al. 2022).

5.3. ATP Binding Cassette Subfamily C Member 2 (*ABCC2*)

Like *ABCB1, ABCC2* also encodes protein which is a member of the superfamily of ABC transporters. They transport various molecules across cellular barriers. Due to it being a part of the MRP subfamily, it is also involved in multi-drug resistance. This protein is expressed in the canalicular (apical) part of the hepatocyte and functions in biliary transport. Moreover, its substrates include anticancer drugs, this protein appears to contribute to drug resistance in mammalian cells (Committee 2023d).

In a Spanish study, 49 patients were selected and genotyped. Nine SNPs, *CYP3A5* (cytochrome P450 3A5; rs776746); *CYP3A4* (cytochrome P450 3A4; rs2740574); *ABCC2 /MRP2* (multidrug resistance-associated protein 2; rs3740066); *UGT1A9* (UDP glucuronosyltransferase family 1 member A9; rs72551330, rs6714486 and rs17868320), and *UGT1A8* (UDP glucuronosyltransferase family 1 member A8; rs1042605, rs1042597 and rs17863762), were analyzed in this study. The study concluded that the sorafenib response was heterogeneous in HCC patients for different alleles of MRP2 (important in enterohepatic circulation), where the availability of the drug was related to SNP variations (Díaz-González et al. 2020).

5.4. UDP Glucuronosyltransferase Family 1 Member A1 (*UGT1A1*)

UGT1A1 encodes UDP-glucuronosyltransferase, an enzyme involved in the glucuronidation pathway that transforms small lipophilic molecules, such as bilirubin,

drugs, and hormones, into water-soluble, waste metabolites. Bilirubin is the preferred substrate of this enzyme; it also has moderate activity with simple phenols, flavones, and C18 steroids (committee 2023l).

In a research study, 114 HCC patients from the Netherlands were enrolled to comprehend the variation in the incidence of sorafenib-induced toxicity in the light of genetic polymorphism. The genotyped SNPs were for *SLCO1B1*, *SLCO1B3*, *ABCC2*, *ABCG2*, *UGT1A1* and *UGT1A9*. The study concluded that *UGT1A1* (rs8175347) was associated with various sorafenib-related side effects and toxicities (Bins et al. 2016). This toxicity was attributed to *UGT1A1**28 (rs8175347) as it leads to high sorafenib exposure, although the exact mechanism for this observation remains unclear (Peer et al. 2012).

5.5. UDP Glucuronosyltransferase Family 1 Member A9 (*UGT1A9)*

UGT1A9 also encodes UDP-glucuronosyltransferase. The enzyme encoded by this gene is active in phenols (committee 2023m). In order to understand the effects of *UGT1A9* polymorphism on sorafenib outcome in HCC patients, 20 subjects, undergoing sorafenib therapy, were recruited in France. The results highlighted that the risk of sorafenib-induced grade ≥2 diarrhea strongly increased when the T allele in *UGT1A9* 2152 C>T (rs17868320) was present. This severely impairs the bioavailability of sorafenib in the cancerous cells. In addition to large-scale replication of the study, they recommended *UGT1A9* genotyping before treatment initiation to identify patients at higher risk for grade ≥2 diarrhea, and subsequent priori dose reduction in order to avoid toxicity (Boudou-Rouquette et al. 2012).

On the other hand, the SNP rs17868320 was not found to be associated with any adverse outcome or side effect by Díaz-González and colleagues (Díaz-González et al. 2020). In this study in the Spanish population, cohort size of 49 HCC patients, genotyped for SNPs of *UGT1A9* (rs72551330, rs6714486, and rs17868320). A couple of SNPs were also found to have no association with any ADR development. Although the sample size and novelty of the study lend the findings more credence a broader level of study can bring forth more reliable results.

5.6. Solute Carrier Organic Anion Transporter Family Member 1B1 (*SLCO1B1*)

SLCO1B1 encodes a liver-specific member of the organic anion transporter family. This protein is a trans-membrane receptor, which mediates the sodium-independent uptake of numerous endogenous compounds including bilirubin. This protein is also involved in the removal of drug compounds such as statins, and rifampin from the blood into the hepatocytes. Genetic polymorphism for this protein is associated with impaired transporter function (committee 2023k). Another study genotyped 114 Dutch HCC patients, taking sorafenib treatment (Bins et al. 2016). In addition to *UGT1A1* polymorphism's influence on sorafenib outcomes, the study found *SLCO1B1* rs2306283 and *SLCO1B1* rs4149056 were associated with certain ADRs. The findings linked the SNP rs4149056 with thrombocytopenia, while rs2306283 was found to be associated with diarrhea in HCC patients on sorafenib therapy.

5.7. Angiopoietin 2 *(ANGPT2)*

ANGPT2 belongs to the angiopoietin family of growth factors. This gene encodes a protein which is an antagonist of angiopoietin 1. ANGPT2 is upregulated in multiple inflammatory diseases and is involved in the direct control of inflammation-related signaling pathways. The encoded protein affects angiogenesis during embryogenesis as well as tumorigenesis. It disrupts angiopoietin 1 vascular remodeling ability and may induce endothelial cell apoptosis (committee 2023b). In a 165-patient multicentre study in a similar population, with advanced HCC, when compared with the other genotype, there was no statistically significant association between

ANGPT2 rs55633437 TT/GT genotypes, with progression-free survival (PFS) (2.4 months vs. 5.7 months, HR = 1.93, P = 0.0833) and overall survival (OS) (15.1 months vs. 13.0 months, HR = 2.68, P = 0.55) (Casadei Gardini et al. 2016).

On the other hand, in an Italian study, 135 patients diagnosed with advanced HCC receiving sorafenib were enrolled. The aim of the study was to investigate the relationship between *ANGPT2* polymorphism and main sorafenib-associated toxicities like skin toxicity, asthenia, and diarrhea. *ANGPT2* genotyping was done ANGPT2 rs3739392, rs3739391, rs3739390, rs55633437, rs3020221, rs1961222, rs17063434, and rs2916747. In addition to being correlated with lower median OS and PFS (p-value: <0.001), *ANGPT2* rs55633437 polymorphisms could identify a group of patients more resistant to sorafenib. Moreover, *ANGPT2* rs1961222 and rs17063434 showed an association with late skin toxicity with grade ≥ 2 (Common Terminology Criteria for Adverse Events 4.0) (p = 0.030 and p = 0.003, respectively). No association could be established between other *ANGPT2* SNPs and sorafenib response (Marisi et al. 2019). Interestingly, early dermatologic adverse events (DAEs) development (within the first 60 days) after treatment initiation is associated with delayed tumor progression and improved survival. This phenomenon was observed in a Brazilian retrospective study conducted, involving 127 unresectable HCC patients (Branco et al. 2017). However, the study conducted by (Augello et al. 2023) in 34 Italians with advanced HCC found no association between *ANGPT2* rs55633437 and therapeutic outcomes of sorafenib in these patients.

5.8. Angiotensinogen (*AGT*)

AGT-encoded protein, pre-angiotensinogen or angiotensinogen precursor, is expressed in the liver. Renin enzyme cleaves it in response to lowered blood pressure, resulting in angiotensin I, which is then cleaved by angiotensin-converting enzyme to generate the physiologically active enzyme angiotensin II. The protein is involved in maintaining a balanced body fluid content, blood pressure, and electrolyte homeostasis. Mutations in this gene are associated with susceptibility to essential hypertension, renal tubular dysgenesis, non-familial structural atrial fibrillation, and inflammatory bowel disease (committee 2023f).

Furthermore, a clinical study conducted in Spain, also aimed to link *AGT* polymorphism with DAEs and eventually a better outcome in sorafenib-receiving HCC patients. A total of 82 patients were recruited, and genotyped, for this purpose. Genetic polymorphisms tested included *AGT, UGT1A8, CYP3A5, CYP3A4, UGT1A9,MRP2, IL23R, IL17, FOXP3, VEGF, PLA2G12A, IL-8,AT1R,ANGPT2, TNF-a, GNB3*, and *IL-6* genes. Only *AGT* M235T (rs699) was associated with early DAEs, with AA [prevalence: 32%] as the genotype used as the reference category, the HR (95%CI) was for AG [41%]: 0.34 (0.15–0.8) and for GG [27%]: 0.97 (0.41–2.31); p = 0.0335 (Reig et al. 2018).

Similarly, another study confirmed the association between *AGT* rs4762 SNP and eDAE occurrence, leading to better OS. In addition to better OS, *AGT* rs4762 could also predict therapy duration. The study was conducted in Italy and retrospectively evaluated 221 prospectively enrolled HCC patients on sorafenib. Just like the previously mentioned study, two SNPs, rs699 and rs4762, were studied. Later SNP was found to be a more useful biomarker than the former (Iavarone et al. 2019).

As previously mentioned, DAEs in patients with HCC have been associated with better treatment response, regardless of the anticancer agent being administered (Sapena et al. 2022, Shomura et al. 2014, Branco et al. 2017). AGT gene polymorphism, in recent studies, was found to be involved in influencing sorafenib treatment response in patients with advanced HCC.

A combined study involving the Italian population was conducted to establish a link between *AGT* polymorphism and DAEs. The

study was conducted in 2 HCC cohorts, with 2 groups in each cohort. One cohort (290 sorafenib-treated advanced HCC subjects) was genotyped for 2 SNPs of the *AGT* gene, namely *AGT1* (rs699) and *AGT2* (rs4762). The study concluded that DAE development in HCC patients receiving sorafenib could be explained by the *AGT2* (rs4762) gene variant. One theory behind this outcome is that tissue renin-angiotensin system (tRAS) (in skin and liver) activation is associated with tissue regeneration, inflammation, and fibrosis; these are key components in tumorigenesis. So, DAE development in subjects with rs4762 AA genotype may be considered a consequence of tRAS activation at the skin level (Sapena et al. 2022).

5.9. Nitric Oxide Synthase 3 (*NOS3*)/Endothelial NOS (*eNos*)/ Constitutive NOS (*cNOS*)

The *NOS3* gene encodes the NOS3 enzyme, which is responsible for the production of the small molecule nitric oxide (NO). It is predominantly expressed in the endothelial tissue, lining the circulatory system and heart, where it plays an important role in the regulation of NO (committee 2023j).

In another Italian study, 165 advanced HCC subjects were recruited and genotyped. *NOS3* (rs2070744) was one of the SNPs under evaluation, it showed that *NOS3* rs2070744 CC/CT genotypes were significantly associated with a higher median PFS (5.9 months vs. 2.4 months; HR = 0.43; P = 0.0007) and OS (15.7 months vs. 8.6 months; HR = 0.38; P < 0.0001), as compared to TT genotype. The study named *NOS3* an independent prognostic factor for PFS and OS after multivariate analysis (Casadei Gardini et al. 2016).

However, another study was conducted on Italian HCC patients. About 128 subjects were enrolled and divided into two cohorts, one was a training cohort (n=41) and the other was a validation cohort (n=87). Patients on sorafenib treatment with advanced or intermediate-stage HCC (either histologically proven or diagnosed) were eligible candidates for this study. Subjects were genotyped for *eNOS*-786 T>C (rs2070744), eNOS+894G>T (rs1799983), and *eNOS* VNTR 27bp 4a/b (rs61722009). The primary objective was to evaluate the prognostic value of *eNOS* polymorphisms and the resulting clinical outcome (PFS and OS) in advanced HCC patients on sorafenib therapy (training cohort). The other objective was to identify if *eNOS* polymorphisms were related to the objective response. The prognostic value of *eNOS* polymorphisms in patients with advanced HCC was then confirmed in an independent cohort (validation cohort). The Multivariate analysis confirmed the *eNOS* haplotype as the only independent prognostic factor predicting PFS (HR 11.17, 95%CI 3.71-33.63, P < 0.0001) and OS (HR 7.03, 95%CI 1.86-26.55, P = 0.004). It means that patients with the *eNOS* haplotype (HT1: T-4b at *eNOS*-786/*eNOS* VNTR) had significantly shorter PFS and OS compared to those with other haplotypes. This effect was consistent in both the training and validation sets and the HT1 haplotype was identified as the only independent predictor of prognosis when considering multiple variables (Casadei Gardini et al. 2016).

Additionally, a clinical evaluation aimed at connecting *NOS3* polymorphism with sorafenib outcome was conducted in Italy. For this study, 133 advanced HCC patients (receiving sorafenib) were genotyped, including for *NOS3* rs2070744. The univariate analysis of PFS and OS in relation to NOS3 polymorphisms showed that patients with at least one copy of the minor allele C for *NOS3* rs2070744T > C polymorphisms had a significantly better outcome, with higher median PFS (7.03 vs. 3.5 months, HR 0.43, 95% CI 0.30–0.63; p < 0.001) as well as OS (15.6 vs. 9.1 months, HR 0.65, 95% CI 0.44–0.97; p = 0.036), as compared to those with homozygous for the T allele. However, patients with the *NOS3* rs2070744 TT genotype showed a worsening prognosis than patients with other genotypes.

The study also reported that *NOS3* rs2070744 SNP could be used to identify patients more resistant to sorafenib. In addition, *NOS3* rs1799983 was found to be associated with late DAE (Marisi et al. 2019).

However, in a recent study in Italy, a total of 34 advanced HCC patients, who had undergone sorafenib treatment, were enlisted and divided into two groups i.e. responders and non-responders. The patients who showed partial response or stable disease for more than 6 months were classified as responders. On the other hand, patients with a progressive disease were considered non-responders. SNPs in angiogenesis-related genes, including *NOS3* (rs2070744), were investigated. The study found no significant influence of this SNP on sorafenib clinical outcomes(P value: T=0.724, CT= 0.15, TT= 0.289) (Augello et al. 2023).

5.10. P450 Genes (CYP)

These genes have been estimated to be relevant for 10–20% of all drug therapies. Notably, out of the genes encoded in the human genome, most drugs in clinical use are metabolized by eight enzymes (CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5)of the cytochrome system (Zhou and Lauschke 2022). In the microsomal fraction of the smooth endoplasmic reticulum, these enzymes facilitate the metabolism of various endogenous and xenobiotic compounds.

Due to the extensive polymorphic nature of CYP genes, they should be used as an added predictive biomarker/pharmacokinetic measure during drug prescription (Bhatia, Mahesh, and Bhatt 2023), as it is an important source of interindividual variability of drug response (Ahmed et al. 2020).

To find a link between *CYP450* polymorphism and sorafenib toxicity in the Chinese population, a study was done on a total of 600 subjects. About 300 of those subjects belonged to a group of patients diagnosed with HBV/HCV-associated HCC, to collect peripheral blood samples, while the remaining samples were taken from the healthy recruits. Subjects were genotyped for polymorphisms of *CYP3A4*, *CYP3A5*, *CYP2D6*, and *CYP2C19*. Of all the mutations identified in that population, *CYP3A5**3 (rs776746) demonstrated minimal sorafenib metabolism, leading to drug accumulation, and consequently to severe hepatic and renal damage. This finding was empirically confirmed by the high levels of ALT, AST, BUN, and Cr in peripheral blood samples (Guo et al. 2018).

Furthermore, (Díaz-González et al. 2020) also studied the influence of CYP polymorphism on sorafenib pharmacokinetics, adverse events, and OS. The researchers selected 9 SNPs in 5 genes related to sorafenib metabolism and transport to identify the best point for starting the combination therapy of tyrosine kinases and checkpoint inhibitors. 49 HCC Spanish patients, initiating or on sorafenib therapy, were enrolled and genotyped for *CYP3A5* (rs776746), and *CYP3A4* (rs2740574). The study failed to establish a significant link between these SNPs and sorafenib clinical response. However, one of the key findings was that sorafenib pharmacokinetic values varied across patients and this heterogeneity affected the development of adverse events and the outcome in recruited patients.

However, *CYP26A1* (rs7905939) was found to be a significant influencer on sorafenib response, since *CYP26A1* is seen to be commonly involved in the signal transduction pathways that are usually dysregulated in HCC, resulting in uncontrolled cell division and metastasis (Malik and Catherino 2007). The study selected a subgroup of 23 patients, diagnosed with HCC, and genotyped them for absorption, distribution, metabolism, and excretion (ADME) genes. *CYP26A1* (rs7905939) was identified to be one of the 10 polymorphic ADME genes. With a p-value of 0.027, a significant association with a lack of response to sorafenib was observed (Augello et al. 2023).

5.11. Solute Carrier Family 22 Member 14 (*SLC22A14*)

SLC22A14 is a protein-coding gene. The encoded transmembrane protein is thought to transport small molecules. It is reported to have a fundamental role in mammalian systems. This gene encodes a member of the organic-cation transporter family and anions (OATs), whose expression is high in the liver. An important paralog of this gene is SLC22A13.

As previously mentioned, a study genotyped 34 HCC patients (9 sorafenib responders and 25 non-responders), both angiogenesis-related and ADME-related genes and their SNPs were studied (Augello et al. 2023). One of the ADME genes, *SLC22A14* (rs149738 (AA), rs171248 (TT), and rs183574 (AA)) was found to be strongly associated with the responder cohort with a p-value of 0.001.

5.12. Solute Carrier Family 5 Member 12 (*SLC15A2*)

SLC15A2 is a member of the same gene family as *SLC15A1*, the proton-coupled peptide transporter found in the small intestine. Its associated processes include glial cell carnosine metabolism and the transport of inorganic cations, anions, amino acids, and oligopeptides (HUGO gene nomenclature committee 2023).

A study in Korea was carried out to investigate genetic variations associated with sorafenib responsiveness in patients with advanced HCC. After whole-genome analysis of blood samples from 2 extreme, 2 strong, and 3 poor responders to sorafenib, the findings were validated in 174 HCC patients. Furthermore, validation genotyping corroborated the sequencing results and revealed patients with *SLC15A2* rs2257212 showed longer PFS (HR = 2.18). Notably, the T allele of the rs2257212 (Leu350Phe) was associated with a significantly longer PFS than the CC genotype. This can potentially act as a biomarker for identifying sorafenib-sensitive patients (Lee et al. 2015).

5.13. Vascular endothelial growth factor A (*VEGFA*)

VEGFA encodes a heparin-binding protein, which exists as a disulfide-linked homodimer. This factor is essential for angiogenesis, as it induces proliferation and migration of vascular endothelial cells, in both physiological and pathological scenarios. In many known tumors this gene is up-regulated and its expression correlates with tumor stage and progression (committee 2023a).

A clinical study was conducted in a cohort, recruited from the Italian population, diagnosed with HCC. The objective of this study was to associate *VEGF* and *VEGFR* polymorphisms with the clinical outcome of HCC patients receiving sorafenib. For this purpose, 148 samples (tumor or blood samples) of these patients were tested for *VEGF-A, VEGF-C,* and *VEGFR*-1,2,3 SNPs. At univariate analysis, VEGF-A alleles C of rs25648, T of rs833061, C of rs699947, and C of rs2010963 were significant predictors of PFS and OS. At multivariate analysis, rs2010963 was found to be one of the independent factors influencing PFS and OS. After prospective validation, the analysis of *VEGF* and *VEGFR* SNPs may represent a clinical tool to identify HCC patients more likely to benefit from sorafenib. Interestingly, a statistically significant difference in terms of PFS and OS was found between patients in B (45 patients) or C (103 patients) stage of BCLC classification (PFS: 7.6 stage B vs. 4.5 stage C, $p = 0.0346$; OS: 21.0 stage B vs. 10.7 stage C, $p = 0.0033$) (Scartozzi et al. 2014).

In another study in the same population, 34 HCC patients (9 sorafenib responders and 25 non-responders) were enrolled and genotyped for, *VEGF-A* (rs2010963), *VEGF-C*(rs4604006), HIF-1α (rs12434438), *ANGPT2* (rs55633437), and *NOS3* (rs2070744), genes involved in angiogenesis, in this case tumor microvascularization. They concluded that only *VEGF-A* (rs2010963) C allele and CC genotype ($p = 0.004$) and ($p = 0.046$), respectively)were

significantly associated with good therapeutic outcomes for sorafenib. This study suggests that these genetic variants in the *VEGF-A* gene may influence the level of circulating VEGF, a protein involved in angiogenesis. This could, in turn, affect how well patients respond to sorafenib (Augello et al. 2023). This finding is in line with the SHARP Trial findings, which reported that a low baseline level of VEGF-A in the blood could predict sorafenib outcomes in advanced HCC patients, even for those in the placebo cohort. This indicates that VEGF-A levels are an important prognostic factor for HCC (Llovet et al. 2008).

5.14. Vascular Endothelial Growth Factor C (*VEGFC*)

The protein encoded by this gene is a member of the VEGF family. This protein is involved in angiogenesis and endothelial cell growth, and can also affect the permeability of blood vessels. The pro-protein is then further cleaved into a form that activates VEGFR-2 and VEGFR-3 receptors (committee 2023n).

In addition to VEGF-A, a study also genotyped *VEGF-C* alleles T of rs4604006 and G of rs664393 (Scartozzi et al. 2014). They found that *VEGF-C* rs4604006 T>C was significant in PFS (10.1 months for T vs. 4.3 for C; p = 0.0043; Fig. 2c) and OS (22.0 months for T vs. 13.0 for C; p = 0.0334) in Italian HCC cohort (n=148). It was suggested that this could be instrumental in identifying HCC patients who are more likely to benefit from sorafenib therapy.

On the other hand, when (Augello et al. 2023) studied *VEGF-C* rs4604006 in a 34-HCC-diagnosed subjects cohort (9 sorafenib sensitive and 25 non-responders), the SNP was not found to be significantly associated with sorafenib response.

5.15. Kinase Insert Domain Receptor *(KDR) /VEGFR-2*

This gene encodes one of the receptors of the VEGF. KDR receptor is a type III receptor tyrosine kinase. It serves as the main mediator of VEGF-induced endothelial proliferation, survival, migration, tubular morphogenesis, and sprouting. The signaling and trafficking of this receptor are regulated by multiple factors, including Rab GTPase, P2Y purine nucleotide receptor, T-cell protein tyrosine phosphatase, etc. (committee 2023i)

KDR/VEGFR-2 SNPs (rs2071559, rs2305948, rs1870377, and rs7667298) were also studied by Scartozzi and fellows, in an attempt to understand their association with sorafenib therapeutic response. The results showed that rs2071559 C>T was significant in PFS (6.1 months for C vs. 3.3 for T; p = 0.043) and OS (15.0 months for C vs. 8.6 for T; p = 0.0049), whereas rs2305948 C>T was also significant in PFS (5.7 months for C vs. 3.8 for T; p = 0.037) and OS (14.7 months for C vs. 8.1 for T; p = 0.0059). These SNPs were associated with better therapeutic response in HCC patients (Scartozzi et al. 2014)

Another study was conducted in the Chinese Han population, over the span of 3 years, aiming to understand whether SNPs in the *KDR* gene are associated with clinical outcomes after first-line sorafenib therapy in advanced HCC. 78 subjects, diagnosed with advanced HCC, were selected and genotyped for SNPs of interest (rs2305948, rs1870377, rs34231037, and rs34038364) that code for a non-synonymous amino acid change in the KDR, and a functional SNP (rs2071559). AA genotype rs1870377 and AA genotype rs2305948 were found to be significantly associated with a better response and longer time to progression (TTP) (5.8 vs. 4.0 months, P = 0.001; 5.8 vs. 4.5 months, P = 0.016, respectively). While those with AA genotype in rs1870377 and TT/TC genotype in rs2071559 had a longer OS (15.0 vs. 9.6 months, P = 0.001; 13.0 vs. 9.0 months, P = 0.007, respectively). After multivariate analysis, rs1870377 was one of the independent factors in TTP and performance status, whereas, rs1870377 and rs2071559 were independent factors in OS. This study suggested that SNPs in KDR could predict the clinical outcome of sorafenib (Zheng et al. 2014).

On the other hand, a recent study aimed to identify markers of toxicities induced by sorafenib with the aid of a discovery-validation approach. The discovery set included 140 sorafenib-treated HCC patients. The results were validated in another cohort of 201 patients, receiving sorafenib. The study showed that KDR rs4864950 predisposed the subjects to the risk of grade ≥2 composite toxicity (meta-analysis p = 6.79 × 10−4, OR = 2.01, 95% CI 1.34–3.01). This finding could be used as a prediction tool for VEGFR- TKIs- induced toxicities (Quintanilha et al. 2022).

5.16. Hypoxia Inducible Factor 1 Subunit Alpha (*HIF1A*)

HIF-1 protein, encoded by the *HIF-1A* gene, functions as the main regulator of cellular and systemic homeostasis, triggered in response to hypoxia, by activating transcription of many genes. This includes genes that are involved in metabolism, angiogenesis, and apoptosis, as well as genes that encode proteins that elevate oxygen delivery or facilitate metabolic adaptation to hypoxia. Additionally, HIF-1 plays an essential role in tumor vascularization (committee 2023h). It accomplishes that by triggering the transcription of various genes, like VEGF. The over-expression of *HIF-1A* in HCC is associated with tumor vascularization, invasion, metastasis, and treatment resistance, all of which lead to a grim prognosis (Faloppi et al. 2020).

In an Italian study, the researchers enrolled 210 patients with advanced HCC with the aim of investigating *HIF-1A's* association with sorafenib outcomes. Tumor samples were taken from the recruited subjects and studied for 8 HIF-1A SNPs. Post-univariate analysis, it was concluded that TT > CC+CT of rs10873142, CC > AA+AC of rs1951795, AA+AG > GG of rs12434438 HIF-1A SNPs were significant for PFS and OS, statistically (Faloppi et al. 2016).Interestingly, the presence of GG rs12434438 in the HIF-1A gene was found to be associated with a particularly poor outcome, i.e. shorter TTP and OS. (TTP: 2.6 months, HR: 0.54, p = 0.0374; OS: 6.6 months, p = 0.0061, HR: 0.43) (Faloppi et al. 2020).

In order to investigate the association of HIF1A polymorphism with variation in sorafenib therapeutic response, a study in Italy by (Augello et al. 2023) genotyped 34 advanced HCC patients for *HIF1A* rs12434438. *HIF-1A* expression was notably lower in HCC tissues of sorafenib-responsive patients (n = 20, p value= 0.0015). So, *HIF1A* may potentially be used as a prognostic tool correlated to HCC patient response to sorafenib therapy.

5.17. Fibroblast Growth Factor 2 (*FGF2*)

FGF -2 encoded protein is a member of the fibroblast growth factor (FGF) family. They possess numerous mitogenic and angiogenic activities. This protein has been implicated in various biological processes including tumor growth (committee 2023g).

A recent study was conducted in Korea about *FGF2* SNP's influence on sorafenib outcome. For this purpose, 245 HCC patients were enrolled and genotyped nine SNPs in the *(FGFR)-2, Flt-1,* and *c-MET* genes. Patients carrying the *FGF2* rs308447 TT genotype were found to have shorter OS than patients with the CC or CT genotype (p=0.016). Moreover, *FGF2* rs308379 A allele carriers had shorter OS than patients with the TT genotype (p=0.020). Multivariate analysis showed that the *FGF2* rs308379 A allele (hazard ratio(HR)=1.663, p=0.004) and advanced tumor stage (HR=3.430, p<0.001) were independent prognostic factors for OS in patients with HCC (KIM et al. 2019).

6. Discussion

Liver cancer remains one of the most challenging cancers to treat. The cancerous cells not only hijack numerous physiological mechanisms to proliferate but they can also become resistant to the actions of chemotherapy. Sorafenib is still one of the most important anticancer drugs for cancer like HCC; however, in addition to being an expensive drug, it is effective in a few patients, and may even cause significant ADRs.

Therefore, an accurate selection of patients is needed but the success rate is unfortunately low due to the various ways it develops resistance and toxicity (Jing et al. 2023).

This article focused solely on sorafenib and many of its interactions with polymorphic genes, particularly the genes involved in ADME and angiogenesis/tumor microvascularization, which can act as a tool to identify patients who are likely to benefit from its treatment as well as those who will suffer from treatment failure due to toxicity or resistance. An interesting phenomenon of early DAE as a favorable indicator and delayed DAE being a toxic effect shows that further investigation is needed to develop a more reliable scale for when to keep going with the treatment plan and when to switch (Branco et al. 2017).

Fortunately, there are studies that are developing a scoring system for the effective utilization of this drug. De Costanzo et al. first developed a scoring system for determining sorafenib efficacy in HCC patients and later conducted another study to validate these findings. The validation part of the study was done by retrospective analysis of clinical records of 279 outpatients treated with sorafenib in eight Italian centers. The adverse effects taken into account to calculate the score were skin toxicity, diarrhea, and arterial hypertension, occurring during the first month of therapy. The scale ranged from 0 to 3, with 1 point for each point for each AE. As the score increased, both OS and TTP increased progressively. This suggests that patients with higher scores had better OS and longer TTP ($p < 0.001$). Moreover, with the rise in the score, the disease control rate also increased, with score 3 patients having the highest disease control rate (96.3%) ($p < 0.001$)(Di Costanzo et al. 2017).

Studies also elaborated that it is not only the SNP but also the allelic distribution that influences the therapeutic response to sorafenib. The limited number of studies in this area despite more than a decade-long usage of this drug demands more attention. Furthermore, the studies are more concentrated in the Western, particularly the Italian population. This lack of representation in clinical studies on one of the most crucial anticancer drugs may potentially be the reason behind the misuse and treatment failure of sorafenib.

7. Recommendations and Future Perspective

From an evolutionary perspective, cancer cells, particularly chemo-resistant cells, will have far better survival capability than normal cells. It is important to understand not only how resistance is developed but also how to tackle it when presented with the issue (Cabral, Tiribelli, and Sukowati 2020). Pharmacogenomics is one of many explanations behind this phenomenon. The multiple targets of sorafenib also make it prone to a wide range of genetic polymorphisms, which lead to either therapy failure or positive association with better therapeutic response. Moreover, getting insights into sorafenib resistance in HCC from the perspective of non-coding RNAs, liver cancer stem cells, MET, exosomes, autophagy, ferroptosis, and the tumor microenvironment will further help with developing resistance-proof therapy regimen (Jing et al. 2023). In addition, studies inclusive of epigenetic factors will also aid in decoding the complexity of sorafenib resistance (Tang et al. 2020). An in-depth study of polymorphisms and their influence on sorafenib therapy will help with dealing with dose calibration as well as designing combination therapy with other chemotherapeutic agents like immune check-point inhibitors, or substituting it with other agents of TKIs like regorafenib (Bruix et al. 2017). Additionally, Identifying predictive biomarkers of drug response is of key importance to improve therapy management and drug selection in cancer therapy (Boudou-Rouquette et al. 2012). The dearth of investigative studies regarding sorafenib resistance calls for more attention and studies on this topic, the absence

of diversity in pharmacogenomic studies should also be rectified. The Asian population, due to HBV and HCV, is more vulnerable to developing HCC and other liver cancers which is why there should be more clinical studies from this region (Maluccio and Covey 2012). Sorafenib remains one of the most important anticancer agents for those with unresectable HCC; scoring systems and broad-scale replication of studies mentioned above, as well as making pharmacogenomics a part of prescribing practice (E. Caudle et al. 2014). This can also help with improving sorafenib therapeutic outcomes, which is not really impressive at this point (Colagrande et al. 2015).

8. Conclusion

From the studies mentioned above it can be concluded that sorafenib interaction with the body is quite complex. While the data dictates that a drug causing AEs should be discontinued, the early onset of these effects is a sign of the efficacy of this drug. Furthermore, the genetic polymorphism, particularly of ADME and angiogenesis genes is also quite convoluted. While some SNPs produce favorable responses in one population, they lead to treatment failure in other groups. This further adds to the intricacies of sorafenib's use as an anticancer agent. The research literature on this topic should be expanded, and be studied extensively in other populations as well, especially those in the global south. Precision oncology can not only improve therapeutic outcomes but can also reduce the cost of cancer treatment, which remains notoriously expensive and inaccessible to many. The ability of sorafenib to target multiple points for treating cancer favors its utilization but also predisposes it to a wide array of genetic polymorphisms, identifying favorable SNPs and other predictive biomarkers can highlight patients who will benefit from this drug. This practice can not only save the precious time of an advanced liver cancer patient but also save valuable resources. Pharmacogenomics has the potential to do just that and proper resource allocation for these studies is a need of the hour.

Competing Interests

The authors declare no competing interests.

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Ethics Approval

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Consent Forms

Not Applicable

Author Contributions

SA supervised the project, AA & MHB searched the literature and wrote the initial draft, however, the idea was conceptualized by SA, who also wrote the final manuscript.

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