Review Article

# Deciphering the Complexities of Sunitinib Therapy: Molecular Mechanisms of Resistance, Associated Toxicities, and Strategies for Therapeutic Optimization

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**ABSTRACT**

Sunitinib is a small molecule multi-kinase inhibitor available in an oral formulation. This agent inhibits the vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit, along with other kinases while party of the function in biochemical or cell-based assays testing the effects of these agents very likely on-free. Sunitinib has shown clinical activity in the treatment of renal cell cancer and in patients with gastrointestinal stomal tumors who are no longer responsive to imatinib. Unfortunately, the effect of sunitinib is limited by resistance and toxicity. Resistance may develop through a number of mechanisms including signalling pathway activation, epithelial–mesenchymal transition, and changes in the tumor microenvironment, and together these may limit treatment success. The toxicities of the treatment include hypertension, impaired cardiac function, fatigue, or hematologic toxicities, may not be lethal, but decreased treatment adherence and decreased quality of life. Recent studies have tried to determine the best ways to enhance treatment efficacy and include rational multi-agent drug combinations, biomarkers to select patients, optimal dosing schedules, and novel VEGFR inhibitors with better toxicity profiles. This review summarizes the molecular considerations of resistance, clinical toxicities, and current knowledge with regards.

**Keywords:** Sunitinib, Tyrosine kinase inhibitor, Drug Resistance, Renal cell carcinoma, Therapeutic strategies.

## INTRODUCTION

Cancer represents a significant global health challenge, currently ranking as one of the leading causes of mortality worldwide. Heterocyclic compounds are of crucial importance in the development of novel anticancer agents. Targeted therapy has replaced radiation therapy and chemotherapy as the main treatment option due to the lack of significant efficacy with these conventional therapeutic regimens.[1,2]

Sunitinib, a multitargeted tyrosine kinase inhibitor, is effective in several cancers including these associated with renal cell carcinoma, gastrointestinal stromal tumours (GIST) and pancreatic neuroendocrine tumours (pNET).[3] It exerts antitumor effect primarily through preventing angiogenesis and proliferation of tumor cells, for inhibiting receptors as VEGFR, PDGFR, c-KIT. Although sunitinib is initially effective in therapy, long-term efficacy of sunitinib is largely reduced due to the development of acquired resistance, and it's a big challenge for APART from the human long-term therapy of tumor. The molecular mechanism of resistance to sunitinib is complicated and multi-factor.[4] Sunitinib frequently induces severe toxicities such as thrombocytopenia, anorexia, fatigue, hand-foot syndrome (HFS), and bleeding events. In addition, sunitinib induces rare, but potentially life-threatening events such as intestinal perforation, interstitial lung disease, and would healing complication.

### OVERVIEW OF SUNITINIB'S MECHANISM OF ACTION

An oral bioavailable small molecule known as a multitargeted tyrosine kinase inhibitor (TKI), sunitinib selectively inhibits a number of receptor tyrosine kinases (RTKs) implicated in angiogenesis and tumor growth.[5] The following receptor TKs have sunitinib-sensitive activity:

1) Vascular Endothelial Growth Factor Receptors (VEGFR-1, -2, and -3): These receptors are in charge of angiogenesis, the process by which tumor cells create new blood vessels in order to receive oxygen and nutrients. By inhibiting VEGFR signalling, sunitinib reduces endothelial cell proliferation and vascular permeability, effectively starving the tumor of its blood supply.[6]
2) PDGFR-α and β (Platelet-Derived Growth Factor Receptors): PDGFRs currently manage the recruitment of pericytes and the stabilization of vessels, as well as the proliferation of tumor cells. The interruption of these receptors breaks tumor vasculature and weakens stroma support for the development of cancer.[6-7]
3) KIT (c-Kit or CD117): Tumor survival and proliferation is promoted by KIT signalling in multiple lineages, including GISTs. The blocking of KIT results in decreased viability of the tumor cells.[8]
4) FLT3 (Fms-like Tyrosine Kinase 3): FLT3 is commonly associated with blood cancers. The FLT3 inhibition by Sunitinib has antileukemic effects. RET (Rearranged during Transcription) and CSF-1R (Colony Stimulating Factor 1 Receptor): RET is linked with some cancers of the thyroid and lung, whereas CSF-1R shapes the tumor microenvironment through the modulation of macrophage differentiation.[8-9]

Sunitinib has dual antitumor effects by targeting these RTKs simultaneously. Sunitinib directly antitumor by the

inhibition of cancer cell proliferation and survival. Sunitinib also indirectly antitumor by the inhibition of angiogenesis and remodelling of the tumor microenvironment [10]. Sunitinib's multitargeted mechanism of actions is why it is used for many cancer types; however, the broad range of cancer types it is used for also makes the resistance mechanisms more complex, as the tumors may activate bypass pathways directed at the RTKs that are being targeted by the sunitinib.[11-12]

**TYPES OF RESISTANCES TO SUNITINIB**

1. Primary (Intrinsic) Resistance:

Primary resistance has to do with the failure to respond to sunitinib therapy in the very beginning. A number of different biological and cellular elements cause this resistance.

Existing mutations in downstream signaling pathways: There are mutations in fundamental pathways such as PI3K/AKT/mTOR, RAS/RAF/MEK/ERK, or JAK/STAT which are possible of bypassing receptor inhibition and causing continuous cell proliferation in the presence of sunitinib.[13-15]

Absence of target expression: Tumor tissues that do not express adequate domains of sunitinib's primary targets such as VEGFR, PDGFR or KIT, are sunitinib insensitive.[14]

Factors related to tumor microenvironment: Factors such as stroma cells, hypoxia, and paracrine signaling can cause tumor cells to escape the effect of RTK inhibition by providing alternative growth and survival signals.[15]

2. Acquired (Secondary) Resistance:

Using Sunitinib, acquired resistance starts developing after a certain period of clinical response, and is usually multifactorial, demonstrating tumor cellular and microenvironment plasticity.

Alternative pathway Activation: Tumor cells can potentially activate compensatory mechanisms, increasing expression of the FGFR, MET, or AXL pathways, in response to the inhibited RTKs.[14,16]

Genetic and epigenetic alterations: Epigenetic modifications and new mutations in target genes can lower drug access through binding or escalate survival signalling pathways.[14,15]

Drug Microenvironmental Adaptations: Recruitment of pro tumor immune cells, increase in the production of angiogenic factors, and the cascade of stromal remodelling can overcome the Drug's efficacy.[14]

Metabolism and Efflux of Drugs: Increased expression of transporters such as ABCB1/P-gp, which leads to the net active transport of the cell membrane, results in a decrease of the intracellular drug concentration and hence promotes resistance.[14]

**MOLECULAR MECHANISMS OF RESISTANCE**

**1. Activation of Alternative Angiogenic Pathways**

➢ Upregulation of FGF/FGFR Pathway

Mechanism of Resistance: The FGF family, and more importantly, FGF2, and their receptors (FGFR1–4) play a very important role in tumor angiogenesis.[17-18] Tumors can upregulate the FGF/FGFR pathway as a compensatory mechanism during the course of sunitinib treatment, which inhibits the VEGF receptors, to preserve angiogenesis and tumor growth.[19]

Key Findings

• Autocrine Activation: FGF2 was observed to induce VEGF-A expression, which promotes VEGFR signaling even in the presence of sunitinib. Autocrine loop is involved in resistance by maintaining the angiogenic signalling pathway.[20]

• Synergistic Inhibition: Synergistic inhibition of FGFR (e.g., BGJ 398) with sunitinib was observed to overcome resistance, wherein cross-talk between the VEGF and FGF pathways is highlighted.[20]

• Alternative Signaling Activation: FGF2 is able to activate downstream signals such as Ras-Raf-MEK-ERK and PLCγ/PKC, bypassing VEGFR inhibition and triggering proliferation of endothelial cells.[22]

➢ Ephrins and Eph Receptors

Mechanism of Resistance: The Ephrin/Eph receptor signalling pathway, i.e., EphrinB2/EphB4, is an opener door to vascular development and to angiogenesis. Upregulation of this pathway in resistance to sunitinib could offer alternative mechanisms of angiogenesis in evading VEGF-targeted therapy.[23-24]

Key Findings

•VEGFR Interaction: EphrinB2 is capable of modulating activation and internalization of VEGFR-2 and VEGFR-3 and induce angiogenic signaling despite VEGF pathway inhibition.[23,25]

•Tumor Angiogenesis: Overexpression of EphrinB2 is found in various forms of cancer, such as ovarian and renal cancer, with increased angiogenesis and possible resistance to anti-VEGF therapy.[26]

➢ Angiopoietins and the Tie2 Receptor

Mechanism of Resistance: Angiopoietin/Tie2 signaling pathway, and Angiapoietin-2 (Ang2) in particular, has a dual-edged contribution to angiogenesis. Under VEGF signaling deprivation (induced by sunitinib), Ang2 is capable of initiating vascular destabilization and sprouting for resistance.[27-28]

Key Findings

• Upregulation of Ang2: Sunitinib-resistant tumors have been shown to upregulate Ang2 levels, illustrating tumor progression and mechanisms for angiogenic escape.[29-30]

• Therapeutic Implications: Inhibition of the Ang/Tie2 pathway, in addition to VEGF inhibition, may be a strategy to overcome resistance by suppressing several angiogenic axes.[28,31] Sunitinib resistance is multi-factorial and involves upregulation of secondary angiogenic axes such as FGF/FGFR, ephrins/Eph receptors, and angiopoietins/Tie2. Understanding these mechanisms provides a basis on which therapy can be designed involving the inhibition of multiple angiogenic cues, potentially overcoming resistance and attaining maximum clinical benefit.[19,23,28]

**2. Upregulation of MET and AXL**

By preventing the 'vascular endothelial growth factor receptor' (VEGFR) and the 'platelet-derived growth factor receptor' (PDGFR), sunitinib focuses on the growth and vigorous spread of tumors and their blood vessels.[32] Unfortunately, adaptive resistance comes into play when tumors begin to activate other receptor-borne pathways, such as RTKs like MET and AXL, establishing other means to survive, grow, and spread, bypassing any form of restriction.[32,33]

**MET (Mesenchymal-Epithelial Transition Factor)**

**Activation Mechanism:**

All individual METs are activated through binding of the ligand HGF (Hepatocyte Growth Factor) to the MET's extracellular domain. HGF and other growth factors associated with it cause an increase in receptor dimerization and the autophosphorylation of numerous intracellular bonded and untethered tyrosine residues of various bounded ligands.[34,35]

Signaling Downstream:

- PI3K/AKT/mTOR Pathway: Promotes cell survival through an increase in proliferation and mild metabolic adaptation with resistance to apoptosis to sunitinib.[34,36]
- RAS/RAF/MEK/ERK Pathway: Promotes cell proliferation and increases cell motility.[34,36]
- Non-canonical STAT3 Pathway: Promotes immune evasion, increased contraction of the vasculature and angiogenesis, and increased stemness.[37]

Role in Resistance: With MET upregulation, the blockade of VEGFR and angiogenic signaling re-establishes. Even with sunitinib, the proliferation and invasion of tumor cells remain constant.[33,38]

**AXL (An RTK in the TAM Family)**

**Activation Mechanism:**

GAS6 activates AXL (AXL receptor tyrosine kinase) ligand. Receptor phosphorylation is also the result of dimerization in response to ligand, and leads to the latter signalling events.[37,39]

Signaling Activity:

- PI3K/AKT: Anti-apoptosis, survival and proliferation mediate.[40]
- MAPK/ERK: Induces neoplastic cell growth and migration.[40]
- NF-κB in EMT Programs: Inward to EMT which is pro-invading, pro-migratory, and metastatic.[41]

ROAXL enhances the adaptive phenotypic changes of the tumour and the cell resistance to sunitinib induced stress.

It promotes EMT, apoptosis-resistant cancerous cell phenotypes, and the mobile division.

Acts through MET to support angiogenesis and cell survival in the presence of TKIs.

**3. Tumor Hypoxia and HIF Activation**

Tumor hypoxia is a state of affairs in which areas of a solid tumor are underperfused by a sufficient amount of oxygen. This is because the tumor has grown too fast and expands beyond its source of blood and thus the inner areas of the tumor are underperfused and receive suboptimal amounts of oxygen. Anti-angiogenic treatments such as sunitinib can augment tumor hypoxia. Through vasoconstriction, tumors become hypoxic, thereby causing the activation of hypoxia-inducible factors (HIFs). HIF activation may cause adaptive resistance, where the tumors are rendered more malignant and can escape treatment.[42-44]

HIF (Hypoxia-Inducible Factor) is a transcription factor and master regulator of the cell's hypoxic response[45]. It is a heterodimer composed of:

• HIF-α (oxygen-regulated subunit: HIF-1α, HIF-2α, HIF-3α).

• HIF-β (also ARNT, constitutively expressed).[45,46]

Mechanism of Action

a) Sunitinib Inhibits Angiogenesis

- By inhibiting VEGFR and PDGFR signaling, sunitinib inhibits new blood vessel formation, depriving the tumor of oxygen.[43,47]
- This leads to hypoxia in the tumor microenvironment.[47]

b) HIF Activation in Hypoxia

- Under low oxygen, HIF-1α and HIF-2α become stabilized.[48]
- HIFs induce expression of survival genes in tumors, metabolic adaptation, and immune evasion.

c) Adaptive Resistance Mechanisms

d) HIF activation can result in overexpression of pro-angiogenic factors like VEGF to counteract the action of sunitinib.

- Cancer cells will adapt to glycolytic metabolism, tending to their survival under hypoxia.

- Immune responses are also manipulated by HIF-mediated mechanisms, tending to tumor drug resistance.

Ways to Avoid Resistance

Drug-resistant can be avoided by certain measures. One of them is combination therapy, in which sunitinib is given in combination with HIF inhibitors to avoid resistance through hypoxia or immune checkpoint inhibitors to boost the immune effect. Replacement of sunitinib with other tyrosine kinase inhibitors (TKIs) avoids resistance accumulation. Metabolic dysfunctions are also controlled by one such method, e.g., inhibition of serine synthesis or mTOR pathway, both of which are associated with resistance. Hypoxia-activated prodrugs like TH-302 selectively target hypoxic tumor areas and therefore improve the treatment.[43,49]

**4. Genetic and Epigenetic Changes**

**Genetic Changes**

Genetic changes are changes in the DNA structure, e.g., mutations, deletions, or chromosomal rearrangements, inherited from the parents or due to the environment. Genetic changes directly influence gene function, leading to disease or variation of traits.[50]

Mechanism of Genetic Changes

a) Mutations

•Alteration in the DNA structure, e.g., point mutations, insertions, deletions, and chromosomal rearrangements, may result in loss of gene function.[51]

•Oncogene or tumor suppressor mutations (e.g., RAS, EGFR, MYC or TP53, BRCA1) are the direct basis for cancer formation.[52]

b) Copy Number Variations (CNVs)

•Gene copy number variation can lead to loss of gene expression or overexpression and affect cell behavior.[52]

c) Genomic Instability

•Genetic instability can result in chromosomal abnormalities with enhanced disease susceptibility.[52]

**Epigenetic Alterations**

Epigenetic changes regulate gene expression but not sequence. They are made up of DNA methylation, histone modification, and noncoding RNA binding, and they control genes to be on or off. Epigenetic changes may be caused by environmental influences like diet, stress, and toxins, and therefore in some cases, they may be reversible.[53]

Mechanism of Epigenetic Changes

a) DNA Methylation

Methylation of DNA group suppresses gene expression, typically against tumor suppressor genes in cancer.[53]

b) Histone Modifications

Chemical alterations (e.g., methylation, acetylation) regulate chromatin structure, with implications for accessibility and gene transcription.[53]

c) Regulation by Noncoding RNAs

Small RNAs (e.g., microRNAs) modulate gene expression by suppressing or degrading messenger RNA (mRNA).

Epigenetics refers to a gene regulation system without altering the DNA sequence. Genes of treatment-treated proliferating tumors may become resistant to sunitinib by epigenetic modification through processes like DNA methylation and histone modifications. VHL gene hypermethylation (an oxygen-sensing gene) has been reported in renal cancer, reduced efficacy of sunitinib following.[54]

**ADVERSE EFFECT OF SUNITINIB**

Sunitinib is generally well-tolerated; however, it also carries numerous adverse effects that can collectively affect the quality of life (QOL) and patient's adherence to the medication, both requires proper monitoring and treatment at right.[55,56] In clinical practice, the most common adverse effects of sunitinib treatment tend to be fatigue/asthenia, hand-foot syndrome, hypertension, hypothyroidism, and diarrhoea.[57]

1) Fatigue

The impact of fatigue in patients consuming Sunitinib is greater than that estimated during the Phase III clinical trials. It was given less importance in clinical trials because of the selection biases followed, the patients included were patients with better performance and less comorbidities. But due to its subjective nature it is one of the most challenging adverse effects to deal with.[56,57]

Management:

a) Conservative approach: ensuring a consistent sleep-wake cycle, adequate fluid and nutritional intake, avoiding excessive use of caffeine and alcohol.[56]

b) Schedule change: doe reduction (four weeks on/ two weeks off to two weeks on /onw week off).[56]

2) Hand-foot syndrome

It is one of the common side effects during targeted therapy especially for MTKIs. It is associated with the indirect inhibition of proangiogenic pathways VEGF and PDGF. This inhibition prevents the vascular repair mechanisms this results in HFS in high pressure areas such as palms and soles and it can be due to frictional trauma.[56,57]

Management:

a) Performing a full-body skin exam prior to treatment majorly at palms and soles or hyperkeratotic areas.[56]

b) Patients are asked to avoid exposure of their hands and feet to hot water it might accelerate the symptoms.[56]

c) Avoid using constrictive footwear and avoid excessive friction on skin.[56]

d) Vigorous exercise during the first month of medication should be avoided.[56]

3) Hypertension

Classic effect of drugs that target VEGFR and angiogenesis. Patients with Grade 1 or 2 hypertension can generally be maintained on sunitinib treatment and their hypertension managed with a calcium antagonist, such as amlodipine, or an angiotensin-converting enzyme (ACE) inhibitor, such as ramipril. Non-dihydropyridine calcium channel blockers, such as diltiazem, should be avoided in patients taking sunitinib.[58]

4) Cardiotoxic effects of sunitinib

Left ventricular (LV) dysfunction and overt heart failure; in fact, some patients had to discontinue medication due to congestive heart failure. Sunitinib was thought to cause cardiotoxicity due to its ability to block platelet-derived growth factor receptors (PDGFRs) resulting in decreased myocardial pericytes and microvascular density. Sunitinib impair the angiogenic response necessary to overcome the effects of HTN-induced pressure overload to the heart, thus resulting in an increased incidence of cardiac dysfunction and HF.[59,60]

5) Mucosal side effects

Such as stomatitis and oral mucositis, occur more frequently with Sunitinib, which can cause significant discomfort and impair a patient's ability to eat and speak.[61,62]

STRATEGIES OF THERAPEUTIC OPTIMIZATION

For therapeutic optimization combination therapy can be used.

Combination therapy

**1) The combination of sunitinib and mTOR inhibitors**

Mechanistic target of rapamycin kinase (mTOR) is a protein that plays a role in mediating normal cellular processes, such as cell proliferation, apoptosis, and autophagy. The activation of the PI3K / Akt pathway by receptor tyrosine kinase, cytokine receptors and other stimuli, phosphorylates mTOR at amino acid residue S2448, which activates the enzyme, p70S6 kinase (p70S6K), which increases the translation of hypoxia inducible factor-1a (HIF-1a). In cells that have a high concentration of HIF-1a, hypoxia-induced genes, including the genes that code for VEGF and PDGF, are transcribed and translated, creating a microenvironment conducive to the growth of tumor cells [63]. In in vitro experiments, temsirolimus was shown to overcome sunitinib resistance. These results suggested that the combination of temsirolimus and sunitinib restored the efficacy of sunitinib - mediated apoptosis in RCC cells.[64]

It is worth noting that several phase I clinical trials involving the administration of temsirolimus and sunitinib (15 mg temsirolimus, i.v., once per week and 25 mg, orally, of sunitinib orally) have shown that the toxic effects produced by this combination were greater than that of sunitinib alone, reducing the toxicity of combination therapy is also one of the directions for future research.[65]

2) **Sunitinib and trebananib**

There are data from animals and humans indicating that the overactivation of angiopoietin-Tie2 signaling induces resistance to sunitinib.[64] Thus, it may be hypothesized that treatments which decrease the levels of angiopoietin and / or block the activation of Tie2 could be used to treat sunitinib - resistant RCC. Trebananib is a recombinant peptide-Fc fusion protein that binds to angiopoietin-1 and angiopoietin-2, preventing their binding to Tie2, thereby decreasing tumor angiogenesis.[66] Results suggests that trebananib and sunitinib when given as a combination produced a significant pharmacological effect. But the toxicity level was found to be greater in the combination than the individual drug alone.[65,66,69]

**3) Sunitinib and nivolumab**

Sunitinib plus nivolumab is an active scheme with manageable toxicity in the treatment of selected patients with advanced soft tissue sarcoma and studies proved that almost half of the selected population was free of progression at 6 months.[67] Nivolumab is a PD-1 immune checkpoint inhibitor antibody that increases T cell function and induces anti-tumor efficacy in certain cancers, by selectively blocking the binding of PD-L1 / PD-L2 to PD-1 on tumor cells.[67]

**4) The combination of sunitinib and certain natural product compounds**

In recent years, due to the adverse and toxic effects caused by clinically approved drugs to treat RCC patients, researchers have gradually turned their focus to certain natural products, due to their potential anticancer efficacy and lower incidence of toxicity. Hispidulin, a flavonoid has positive allosteric effect on $GABA_A$ receptor and due to lipophilic activity is can cross blood brain barrier easily. The results of some in vivo and in vitro experiments showed that hispidulin can decrease survival rate of certain RCC cell lines. The combination use of sunitinib and hispidulin increased apoptosis.[68]

## CONCLUSION

Sunitinib is a very powerful multitargeted agent, but its application is limited due to resistance mechanisms and adverse effects. Resistance develops because of alternative pathways, adaptation to hypoxia, and genetic or epigenetic changes. Combination treatment or personalized approaches potentially have a better chance to overcome these limitations with increasing patient benefit and limiting toxicities.

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