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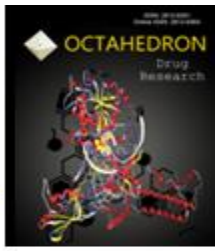

Indolin-2-one based scaffold for the development of multi-kinase inhibitor: Focus on sunitinib as an anticancer agent

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ABSTRACT

Indolin-2-one is a pharmacologically beneficial scaffold with several biological features. The role of oxindole may be recognized to be varied by various chemical groups to provide novel biological activities as a chemical scaffold for creating and developing biologically active drugs. Cancer treatment has advanced significantly in recent years. The oxindole multitarget kinase inhibitor sunitinib, which is taken orally, inhibits specific receptor tyrosine kinases. Sunitinib has shown potential anticancer impact in phase II trials of individuals with diverse cancers, including hepatocellular carcinoma, pancreatic neuroendocrine tumors, and renal cell carcinoma. The most frequent adverse effects of sunitinib, pharmacokinetic/pharmacodynamic studies, drug-drug interactions, and mechanism of action of sunitinib are also discussed. The review focuses on resistance developed in almost all responding patients, a significant cause of therapy failure. More studies are needed to investigate the mechanisms of antiangiogenic agent resistance to discover new analogs capable of circumventing antiangiogenic agent resistance with better therapeutic properties.

1. Introduction

Solid tumors require both proliferative and angiogenic signals, which are mediated by several molecular mechanisms. Angiogenesis is required for tumor development larger that are larger than 1-2 mm in diameter for giving nourishment while also eliminating waste products through blood vessels. Enhancing vascularity, particularly lymph angiogenesis, permits tumor cells to enter circulatory and lymphatic systems, allowing the tumor to spread [1]. Pro-angiogenic signals such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) induce tumor angiogenesis. The diversity of tumor development, which involves a variety of biochemical pathways, gives a specific rationale for multitargeted cancer therapy. Angiogenesis has been widely studied using animal cancer models. In model of the transgenic mouse, VEGF receptors (VEGFR) signaling suppression alone could prevent development of early-

stage islet tumors but was unable to stop the angiogenic transition in premalignant lesions. A VEGFR-2 inhibitor (SU5416) exhibited mild tumor regression or stable disease (SD) when paired with "metronomic" chemotherapy, indicating that combination targeted treatments may be more useful than a single targeted drug in causing the regression of more advanced cancers. In comparison to either drug alone, the combination of SU5416 and SU6668 was more effective against all phases of islet cell carcinogenesis. Through targeting pericyte receptors and breaking their interaction with endothelial cells, SU6668 impacted the tumor vasculature differently than SU5416, according to histological and other analyses, resulting in larger and deformed blood vessels. Drugs that can inhibit many molecular targets could be more effective than drugs that only inhibit one or two targets [2]. Kinases are a type of biochemical molecules that may transfer phosphate groups from adenosine triphosphate (ATP) as high-energy donor molecules to substrates as specified target molecules. This process is known as phosphorylation, and it eventually results in the target protein's changed biological activity. Inflammatory disorders, metabolic disorders, cancer, etc. are caused by the abnormal expression of many kinases [3]. As a result, kinases are very important therapeutic development targets. It had been a milestone in targeted cancer therapy when the food and drug administration (FDA) authorized imatinib in 2001 as the first commercial targeted tyrosine kinase (ABL) inhibitor for the treatment of chronic myelogenous leukemia. Up till 2021, 87 small-molecule kinase inhibitors had been approved for the treatment of a range of disorders, involving cancers [4]. Numerous publications have described 3-substituted indolin-2-ones or oxindole act as strong and specific inhibitors of various kinases [5]. Since sunitinib is the first small molecule with the oxindole template against various kinases, pyrrole-indoline-2-ones have been extensively studied for the inhibition of VEGFR, PDGFR, the stem cell factor receptor (KIT), the Fms-like tyrosine kinase-3 receptor (FLT3), and Colony-stimulating factor-1(CSF-1R) [6].

2. Mechanism of action of kinases enzymes

Scientists had divided small-molecule kinase inhibitors into 4 categories based on their models of binding. Type I inhibitors target is ATP pocket of the kinase in its active state of which generally include a heterocyclic system and side chains occupying an adenine binding site and hydrophobic areas, respectively including anlotinib act as VEGFR2 kinase inhibitor. In the inactive state, drugs that bind to both the ATP-binding site and an extra rear hydrophobic pocket act as type II inhibitors such as axitinib act as VEGFR-2 inhibitors. Allosteric kinase inhibitors of type III, which do not compete with ATP for binding sites, bind to allosteric sites close to the ATP site including pexidartinib used for the treatment of tenosynovial giant-cell tumors, potently suppresses CSF-1R. Allosteric kinase inhibitors that bind to allosteric locations outside of the ATP pocket in the structural domain of the kinase act as type IV inhibitors. The first type IV inhibitors that bind to the c-Abl myristoyl pocket (CMP) site of Abl kinase are GNF-2 and GNF-5. Small-molecule allosteric kinase inhibitors are largely categorized into Type III and Type IV inhibitors according to how far they are from the allosteric site to the ATP-binding pocket [6].

3. Indolin-2-one as promising scaffold

Indolin-2-one or oxindoles are a family of endogenous chemical compounds that are found in fluids of body and tissue of mammals. Various sectors of academia and pharma industry had appeared great interest in designing new oxindole compounds with a distinct pharmacological profile and excellent efficacy. Utilizing synthetic routes, most current research on indolin-2-one derivatives had been slightly promoted the formulation of a newly drug, nintedanib (BIBF 1120) I, approved currently in March 2020 in the united states (US) for the treatment of interstitial lung diseases like idiopathic pulmonary fibrosis (IPF) and chronic fibrosis with a phenotype progression [7]. Also, BIBF 1120 effectively inhibits VEGFR, PDGFR and FGFR kinase activity in enzymatic tests. Endothelial cells, pericytes, and smooth muscle cells are three cell types involved in angiogenesis that are inhibited by BIBF 1120's suppression of the mitogen-activated protein kinase and Akt signaling pathways. This decreases cell growth and death. Other two more noted oxindole derivatives include sunitinib II and semaxanib III (Figure 1). Despite not being directly cytotoxic by itself, semaxanib is a synthetic molecule inhibitor of the TK domain of VEGFR-2, a robust competitive inhibitor of KIT, and a less effective inhibitor of the PDGFR (indirectly implicated in angiogenesis). Like sunitinib, toceranib phosphate IV is an orally accessible drug that has been anticipated to have both direct anti-tumor effect and significant inhibitory activity against numbers of the

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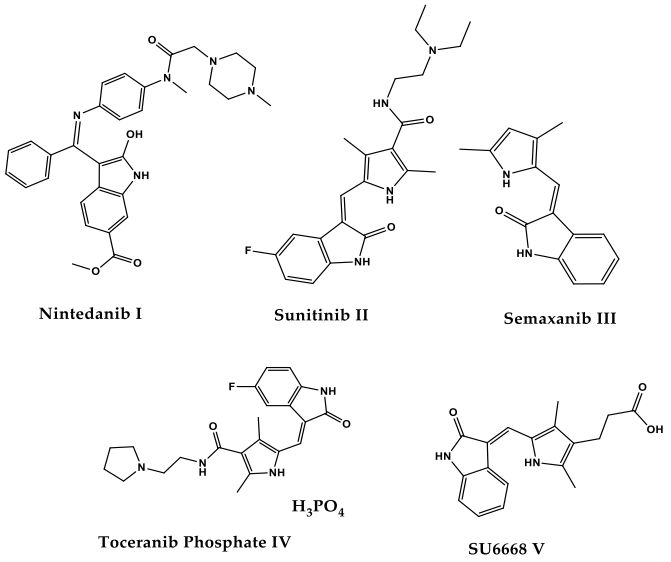

Figure 1. Structures of Nintedanib I, Sunitinib II, Semaxanib III, Toceranib Phosphate IV and SU6668 V

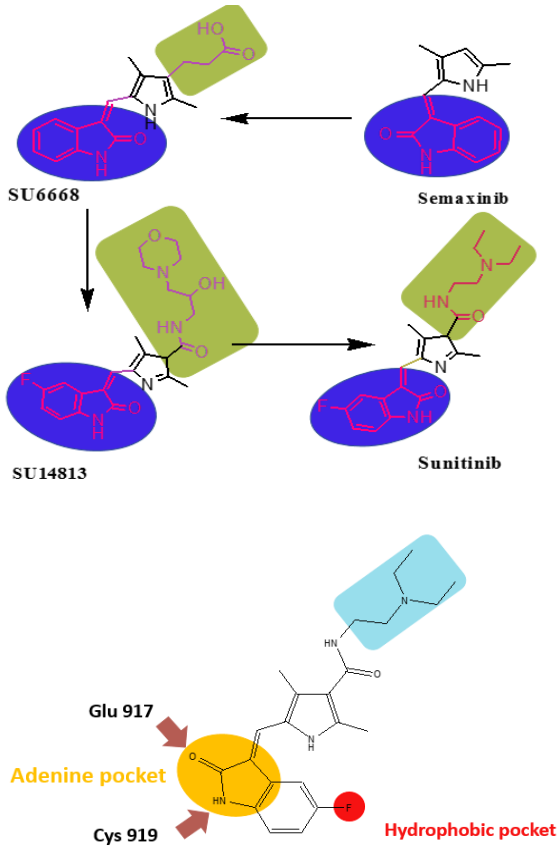

Figure 2. The design, SAR and interaction of sunitinib with ATP pocket.

family of split-kinase receptor. SU6668 V is a selective inhibitor of the VEGFR, PDGFR and FGFR1 receptors. After receiving daily oral medication, SU6668 significantly suppresses the development of tumor cell lines in culture and shows anti-tumor effect in xenografts.

4. Sunitinib as oxindole based drug

4.1. Sunitinib

Sunitinib targets many signaling pathways assumed to be included in the progress and spread of tumors act as oral small-molecule receptor tyrosine kinase (RTK) inhibitor. Several clinical trials have established that it offers impressive objective response rates and therapeutic useful when used as the first-line treatment of metastatic renal cell carcinoma and as the second-line treatment of unresectable/metastatic gastrointestinal stromal tumors (GIST) due to resistance after imatinib treatment. Additionally, studies have demonstrated that sunitinib increases progression-free survival in people with well-differentiated pancreatic neuroendocrine tumors (pNETs) that are undetectable, locally advanced, or metastatic [8]. Sunitinib has also showed potential anticancer efficacy in various different cancers, involving thyroid, lung, pancreatic, esophageal, and bladder carcinomas, gliomas and sarcomas [9]–[11].

4.2. Drug discovery

Sunitinib was created by Schlessinger and Ullrich. Early research identified sunitinib as a single agent as a powerful anticancer agent for cancers that depend on VEGF and VEGFR for angiogenesis. Before information demonstrating that the lack of selectivity may be taken as a benefit and serves as a unique paradigm for multitargeted drugs became available, sunitinib was first regarded as a "dirty medication.". Sunitinib has shown efficacy against both tumor cells and several non-cancerous cells in preclinical models, including endothelial cells, pericytes, and fibroblasts, which are frequently identified as stroma cells promoting the formation and maintenance of malignancies. In phase I first-in-man studies, the drug's human action was seen for the first time. Also, sunitinib was found in an indolin-2-one analogue screen because it can inhibit potently and selectively four RTKs: VEGFR-2, PDGFR, FGF and endothelial growth factor receptor (EGFR). Due to their low water solubility and protein-binding properties, three prototype compounds, (semaxinib) SU-5416, SU-6668, and SU-14813, are not acceptable for use in clinical trials. As a result, efforts were performed to modify the compounds. Side chains were added to the C4′ location of the modified compound SU-5416. The most potent and most water-soluble inhibitor of VEGFR and PDGFR was produced as a result of this called sunitinib (SU- 11248) [12]. This chemical is available as malate salt (sunitinib malate) (Figure 2). Additionally, sunitinib blocks the ATP pocket

through H-bond acceptor/donor interaction of the indolin-2-one core with the NH of Cys919 and the carbonyl of Glu917. The pyrrole moiety of sunitinib also forms hydrophobic interactions with the phenyl group of Phe918 in VEGFR-2.

4.3. Oral bioavailability of sunitinib

Sunitinib follows the four "rules of five" established by Lipinski for oral bioavailability. Most currently available oral effective medications share the four features. The applicable limitations are multiples of five, thus the name of the rules. Sunitinib achieves the first requirement, which states that a compound must have no more than five OH and NH groups as hydrogen bond donors. The second requirement is that the drug should only contain ten hydrogen bond acceptors (mostly N and O); sunitinib has two of these. The third requirement is that the molecular weight should be less than 500; sunitinib ($C_{22}H_{27}N_4FO_2$) has a molecular weight of 390. The fourth criteria states that the drug's log partition coefficient (log P), or its log ratio of solubility in octanol to water, should be less than 5. Sunitinib's log partition coefficient is 5.2. Because it affects a compound's capacity to cross cell membranes, particularly those of the intestine, the log of the partition coefficient, a measure of a compound's lipophilicity, is a crucial factor in oral absorption [13]. Compounds with a negative log P are too hydrophilic to pass through membranes. Drugs that are excessively lipophilic (log P more than 5) cannot be delivered to the target cells in physiological solutions [14].

4.4. Mechanism of action

Sunitinib suppresses cellular signaling by binding to several TK receptors. PDGFR, VEGFR types 1 and 2, c-KIT, FLT3 and RET are examples of receptor TKs which are included in both tumor angiogenesis and tumor cell growth. Furthermore, these receptors participate in the signaling and growth of several solid tumors. Inhibiting these TKs inhibits signal transduction, impacting several processes including in tumor metastasis and angiogenesis. Sunitinib binds to the adenosine triphosphate binding pocket of these kinases, acting as a competitive ATP inhibitor [15]. Sunitinib reduces fluorescent substrate efflux from cells expressing P-glycoprotein (P-gp) and ABCG2 transporters. Sunitinib decreased vascular permeability, stopped the growth of new blood vessels, and increase the regression of the tumor's existing vasculature. In biochemical and cell-based experiments, sunitinib inhibits several RTKs in addition to having potent anti-angiogenesis and anticancer effects in animal investigations. Sunitinib is thought to have anticancer properties because it inhibits myeloid-derived suppressor cell (MDSC) in vivo. The most striking activities of the 80 kinases examined in the first characterization were those against VEGFR-1, -2, and -3 (Ki=0.009 M), (Ki= 0.008 M) PDGFR-α, PDGFR-β, and (Ki=0.83 M) FGF. mouse fibroblasts' proliferation and Human endothelial cells in response to VEGF, FGF, and PDGF stimulation was decreased by sunitinib in generated cell lines [16].

4.5. Preclinical pharmacology and clinical efficacy

It has been demonstrated that the tyrosine kinase inhibitor sunitinib preferentially inhibits class III and IV split-kinase domain RTKs. sunitinib has many Targets including VEGFR-1, 2, and 3; PDGFR, KIT, FLT3 and RET. The effective inhibition of VEGFR or PDGFR in vivo requires a plasma level of at least 50 ng/ml, according to preclinical results from pharmacokinetic/pharmacodynamic studies in mice. Sunitinib was administered to the majority of responding patients with good tolerability at a dose of 50 mg once daily for 4 weeks, followed by 2 weeks off therapy (4/2 schedule). Phase II trials will continue using this regimen going forward. Patients receiving 50 mg once a day for sunitinib experienced total drug plasma concentration of more than 50 ng/ml which is in the dose range predicted by preclinical research to suppress phosphorylation of receptor and cause tumor regression [17].

4.6. Clinical trials

Sunitinib has been related to a long-term therapeutic use in almost 25% of 147 patients with advanced GIST who were imatinib resistant in phase II and III trials. Additionally, sunitinib has few side effects and is therapeutically advantageous for both advanced RCC and GIST that is resistant to imatinib. Sunitinib showed therapeutic efficacy in a patient with chemo-refractory adrenocortical carcinoma in a recent case report, signifying that it may be helpful in overexpression of Pgp tumor type. Additionally, to determine sunitinib's potential for interaction with (P-gp, ABCB1), multidrug resistance protein 1(MRP1, ABCC1), breast cancer resistance protein (BCRP, ABCG2), and lung resistance protein (LRP) in vitro that it totally reverses ABCG2 mediated drug resistance with a non-toxic dose of 2.5 M, according to study results by Dai CL et al. (2009), however it has no apparent reversal impact on ABCB1 and LRP mediated drug resistance [18]. Although combining sunitinib and conventional chemotherapeutic drugs had negligible synergistic effect on ABCB1 overexpressing

MCF-7/adr and parental sensitive MCF-7 cells. However, in overexpression of ABCG2 or parental susceptible cells, sunitinib does not affect the expression of ABCG2 mRNA or protein, nor does it prevent Akt and Erk1/2 phosphorylation [19].

4.7. Drug-drug interactions

In general, pharmacokinetic interactions include a) medications that influence sunitinib's major biotransformation pathway (CYP3A4), or b) sunitinib hypothetically impacting the effects of other pharmaceuticals. Sunitinib plasma levels or systemic exposure may be decreased by anticonvulsants (phenytoin, phenobarbital, or carbamazepine), mitotane, or rifampin. Alternatively, co-administration of sunitinib may cause supratherapeutic trough levels with CYP3A4 enzyme inhibitors and a rise in the frequency or severity of toxicity. These medications involve clarithromycin act as macrolide antibiotic, itraconazole act as azole antifungal, nelfinavir act as HIV protease inhibitor, and citrus juice-based dietary supplements. In several clinical studies, interactions were observed. For instance, for extensive active antiretroviral therapy, ritonavir and efavirenz enhanced or reduced N-desethylsunitinib exposure, respectively. Greater plasma concentrations of sunitinib (+53%) have also been associated with co-administration of proton pump inhibitors and sunitinib. As a PgP inhibitor, sunitinib might enhance the toxicity of colchicine as PgP substrates. When used with a drug that has a strong affinity for albumin, sunitinib/N-desethylsunitinib displacement from plasma proteins may be significant. Several antiretroviral therapy regimens cannot demonstrate a substantial alteration in the unbound part of sunitinib and/or N-desethylsunitinib, even though no such interaction has been recorded [20]. Sunitinib may interact pharmacologically with drugs that affect the heartbeat, the immune system, the liver, and significantly, bisphosphonates, which might promote the hazard of osteonecrosis of the jaw. As a result, due to these adverse effects, sunitinib could be used carefully when combined with antiarrhythmics or medications that may extend the QT interval (such as some antipsychotics, 5-hydroxy tryptamine 3 (5-HT3) antagonists, vemurafenib, fingolimod, or nilotinib). Sunitinib can be used cautiously with medicines that are hepatotoxic or that might enhance levels of aspartate aminotransferase or alanine aminotransferase (such as leflunomide, or nimesulide), because it had been listed in the FDA's "black box warnings". Sunitinib should be taken cautiously when paired with amiodarone (proarrhythmic + thyrotoxic) due to the fact that it is also thyrotoxic [21].

4.8. Toxicity and Adverse effects

In combination with other targeted treatments for GIST and mRCC, sunitinib is tolerated at the prescribed dose, with most adverse effects being mild to moderate. The documented side effects (appearing in 20% of patients) were anemia, fatigue, skin discoloration, GIT issues (diarrhea, vomiting), stomatitis, reduced appetite, taste alteration, hypertension, hypothyroidism, and mucosal inflammation. Hypertension is common systemic adverse effect of VEGF-inhibitor medication, such as sunitinib [22]. One of the key contributing factors to the complex and poorly understood mechanism of hypertension is how VEGF-inhibitors affect nitric oxide (NO). By decreasing NO levels, VEGF-inhibitors decrease vasoconstriction and endothelial permeability, which in turn increases resistance of peripheral system in blood vessels and raises blood pressure (BP). Two further changes are a rise in extracellular volume and a reduction in vascular compliance. A decreasing in vascular density, an increase in baroreceptors, and thyroid dysfunction are further VEGF-inhibitor-induced features of hypertension. Hematological issues are among the most common side effects include neutropenia, thrombocytopenia, and anemia. Sunitinib may have serious but infrequent adverse effects, including hemorrhages, renal or cardiac failure, pulmonary embolism, and gastrointestinal perforation. Real-life patients have also reported hepatotoxicity, elevated creatinine, dysgeusia, anorexia, epistaxis, and mucositis in addition to these adverse effects [23].

4.9. Sunitinib and different types of cancer

4.9.1. Sunitinib and renal cell carcinoma (RCC)

In 2018, over 400,000 new instances of kidney cancer and roughly 175,000 fatalities globally appeared. Smoking and obesity, among other lifestyle and health-related issues, have been recognized in recent decades as risk factors for RCC. In its early stages, RCC has few or no symptoms. At approximately one-third of cases, the illness is detected in an advanced or mRCC due to a lack of symptoms. Currently, the majority of RCC cases are detected by chance [24]. Though the mechanism of this resistance to treatment is uncertain, RCC is assumed to be a chemotherapy-resistant cancer. Dai et al. (2009) reported that no medicine had a response rate more than 6% in trials for chemotherapy medications in RCC. Advanced RCC is being treated with anti-angiogenic therapies

including bevacizumab, antibodies that target VEGF receptors, and tyrosine kinase inhibitors that target VEGF receptors like sunitinib, pazopanib, and axitinib. Clear cell RCC (ccRCC) is the most frequent histologic type of RCC and may be identified by the absence of the von Hippel-Lindau (VHL) gene and an elevation of hypoxia inducible factor (HIF) and VEGF. Radical nephrectomy patients with early-stage RCC had a very high 5-year survival rate (92.6%). However, more than 20% of patients have metastatic disease when they are first diagnosed, and more than 30% of patients get metastases after surgery. Sunitinib and sorafenib, anti-angiogenic receptor TKIs, are the first-line therapy for mRCC. Both medications operate on the receptors for VEGF and PDGF. Niinivirta et al. (2017), patients who initially had tumors that expressed membranous cubilin benefited more clinically from sunitinib and sorafenib treatment, with a PFS that was doubled. Although cubilin is not known to play a function in cancer, extensive searches inside The Human Protein Atlas' internal protein database turned it up as a potentially significant protein. Due to its very specific immunohistochemistry and RNA expression patterns in healthy kidneys and renal cancers, it was chosen for further study. Since cubilin expression has been demonstrated to be highly specific for RCC, its absence is related to a poor prognosis. Sunitinib is also being investigated in RCC patients after failure treatment with bevacizumab [25].

4.9.2. Sunitinib and hepatocellular carcinomas (HCC)

A primary liver cancer that is frequent is HCC. One of the leading causes of cancer-related deaths globally is HCC. HCC has a complex pathophysiology, and the development of the cancer and tumor are influenced by several signal transductions. HCC, however, is difficult to detect in its early stages. Patients who are unable to have surgery frequently utilize transcatheter arterial chemoembolization (TACE), radiofrequency ablation, and other treatments, although most patients use chemotherapy and targeted therapy. Currently, cytotoxic drugs like gemcitabine and fluorouracil, which have severe side effects and are not reproducible, are the main chemotherapeutic drug options for HCC treatment. Multi-kinase inhibitor targeted drugs have drawn a lot of attention as HCC therapeutic possibilities. For HCC, currently available targeted medicines include somatonin, sunitinib, and others. According to Response Evaluation Criteria In Solid Tumors, sunitinib developed necrosis in more than 30% of tumors, demonstrating that sunitinib had an anti-hepatocarcinogenic effect After 1-1.5 months of treatment [26]. Non-coding RNA, long non-coding RNA (lncRNA), had been extensively studied as a marker of tumor prognosis. According to research by ang et al., increased expression of the lncRNA HOTAIR in HCC patients is related to tumor recurrence followed by liver transplantation and may be act as an independent prognostic marker. Additionally, lncRNA HOTAIR can be act as an independent prognostic marker for sunitinib in the treatment of advanced HCC. In the most recent clinical study, patients with hepatitis B had similar survival benefits with sunitinib as those with sorafenib, while those with hepatitis C did not. Sunitinib can activate p53 in the SK-hep-1 p53-wild-type cell line, moderately decrease proliferation in the Huh7.5 cell line and improve the S-phase and sub-G1 component of the cell cycle in the Hep3B cell line. Necroptosis has recently received attention as a possible cancer therapeutic target. Systemic chemotherapy, which includes the use of cisplatin and multi-targeted receptor tyrosine kinase inhibitors like sunitinib, is typically fatal and has little therapeutic benefit. Cisplatin's effects on cytotoxicity, oxidative stress, apoptosis, necroptosis, and MAPK pathways were changed by sunitinib. Sunitinib decreased necroptosis while increasing oxidative stress and cisplatin-induced apoptosis. Treatment of advanced HCC with cisplatin and sunitinib may be efficient [27].

4.9.3. Sunitinib and bladder cancer

Bladder cancer is anticipated to account for 81,190 new cases in 2018 and 17,240 fatalities, making it the most common cause of cancer deaths in the country. About 70% of those that have just been diagnosed are non-muscle invasive tumors. The main therapy for non-muscle invasive bladder cancers is endoscopic resection. Recurrence rates are reduced by 30–40% with conventional therapy by TURBT followed by intravenous therapy, frequently using Bacillus Calmette Guerin (BCG), enhancing bladder preservation and avoiding major surgery. Few treatment options are available to patients with high-risk non-muscle invasive diseases who develop a recurrence or persistent disease following first BCG therapy. Additionally, it is well-known that angiogenesis has a key part in the survival, growth, and potential for metastatic spread of a variety of malignancies, including urothelial carcinoma. Patients with urothelial carcinoma exhibit elevated levels of many angiogenesis markers, most notably VEGF, which is associated with a poor prognosis [28]. These results inspired research on anti-VEGF drugs for bladder cancer. Discovering sunitinib to be therapeutically effective in urothelial cancer preclinical

models. Sunitinib has showed minimal effect in clinical studies investigating its function in metastatic urothelial carcinoma, either alone or in combination. Another study looked at the efficacy of sunitinib as a maintenance medication for patients with metastatic UC to help maintain the response to chemotherapy and limit progression of disease. While anti-angiogenic therapy and systemic chemotherapy do not have a recognized impact on the treatment of non-muscle invasive bladder cancer, they may raise concerns as a potential alternative to radical cystectomy, especially in patients with high-risk BCG resistant illness. Due to this, it has been suggested to combine VEGF inhibitors with immune checkpoint inhibitors (ICI), which is the basis for several ongoing trials in solid tumors, such as urothelial carcinoma. It has been demonstrated in prior research that sunitinib decreases MDSC levels and increases regulatory T cells (Treg), reversing tumor-induced immunosuppression. Recent research has also demonstrated that sunitinib increases BCG-mediated cytotoxicity through the apoptosis pathway, which may provide another combination strategy for enhancing result. In conclusion, Sunitinib monotherapy did not seem to be clinically appreciable efficacy in the treatment of non-muscle invasive TCC of the bladder that is BCG-refractory. Preliminary data from this trial's correlative analyses show that sunitinib may treat MDSC-derived immunosuppression, which provides a justification for combining VEGF inhibitors with novel immunotherapeutic in the treatment of refractory non-muscle invasive illness [29].

4.9.4. Sunitinib and colorectal cancer (CRC)

The fourth most prevalent malignancy overall are CRCs. Overall, 64% of people survive five years. Stage IV cancer patients only had a 14% 5-year survival rate, despite a small percentage of patients with circumscribed stage IV illness being able to reach long-term remission by surgical excision or ablation of liver metastases. Sunitinib recommended for the treatment of adjuvant RCC, and pancreatic neuroendocrine tumors. Sunitinib has previously shown minimal effect in individuals with advanced molecularly unrestricted CRC patients with advanced FLT-3-amplifed metastatic colorectal cancer, sunitinib failed to show a clinically meaningful single-agent anticancer effect in this patient group in this phase II research. Because FLT-3 mutations are found in 30% of acute myeloid leukemia (AML) patients, the role of FLT-3 in AML has received the most attention effectiveness of sunitinib in FLT-3-mutated AML had before established. Sunitinib reduced FLT-3 phosphorylation in all five of the patients with internal tandem duplication (ITD) or tyrosine kinase domain mutations (TKD) mutations in phase I clinical trials. In patients with refractory AML, especially those with FLT-3 ITD and TKD mutations, sunitinib produced short PRs. In a phase I/II research, sunitinib and conventional chemotherapy were given to older patients with FLT-3-mutated AML. The largest dose of sunitinib that could be tolerated on days 1 to 7 due to myelosuppression and hand-foot syndrome was 25 mg. With approved dose regimens, sunitinib inhibits VEGFR and PDGFR and reduces FLT-3 ITD-mediated signaling in vivo. Also, to promote prolonged drug release, sunitinib maleate may be effectively integrated into poly lactic-co-glycolic acid (PLGA) polymeric nanoparticles. The improved sunitinib loaded PLGA nanoparticles better than the free drug in terms of cytotoxicity against HT-29 cell lines. These nanoparticles have the potential to efficiently transport and deliver anticancer medicines for colon cancer treatment [30].

4.9.5. Sunitinib and gastrointestinal stromal tumors

The most prevalent form of gastrointestinal sarcoma is GIST. With a median survival of 19 months, metastatic disease affects more than half of GIST patients. In 80–85% of cases, constitutively active KIT kinase is the consequence of activating KIT mutations, which have been linked to the pathogenesis of GISTs. Up to 12% of GISTs might have KIT and PDGFR-α wild-type mutations, and about 7% of GISTs could have PDGFR-α activating mutations [31]. As the initial line of defense against metastatic disease, imatinib mesylate, an inhibitor of mutant KIT and PDGFR-α, is employed. But after range of two years of imatinib treatment, 12–14% of patients develop early or primary resistance, and > 40% do so because of secondary resistance. After the illness progressed or became intolerable to imatinib therapy, more than 50% of GIST patients treated with sunitinib showed therapeutic benefit (response and stability). Also, in patients with GIST, High-grade neutropenia and hematologic toxicities are also rather common side effects of sunitinib. Appropriate prevention and management appear essential. Additionally, a crucial mechanism of imatinib progression in GIST is the development of polyclonal KIT secondary mutations. Regorafenib and sunitinib, both approved KIT inhibitors, exhibit complimentary action against KIT resistant mutation [32].

4.9.6. Sunitinib and Pancreatic neuroendocrine tumors

Pancreatic endocrine cell-derived tumors, or panNETs, are

comparatively uncommon. Surgery is the greatest therapeutic choice for patients with locally developed or oligometastatic illness that can be surgically resected; however, there are few treatment alternatives and a poor prognosis for patients with advanced disease that cannot be surgically resected. The abnormal regulation of angiogenic factors, such as VEGFRs and PDGFRs, promotes the development of highly vascularized panNETs. Currently, there are several therapies for panNETs (TKIs), including somatostatin analogues, cytotoxic chemotherapy, mammalian target of rapamycin inhibitors, peptide receptor radionuclide therapy, and TKIs. The only TKI directed for the treatment of metastatic or advanced panNETs in clinical studies is sunitinib. Through the targeting of numerous receptors, including VEGFR 1-3 and PDGFR-α and β, it prevents angiogenesis and the growth of tumors. Sunitinib exhibited to extend progression-free survival (PFS) in patients with progressive, well-differentiated panNETs compared to placebo in an important phase III clinical research (A6181111, NCT00428597) [33]. Sunitinib's efficacy and safety in treating patients with well-differentiated advanced/metastatic panNETs were established in an open-label, phase IV research (A6181202, NCT01525550) to satisfy post-approval regulatory requirements. Because of recent studies showing that ORR is a crucial first objective for efficacy in panNET treatments. In both trials, ORR was formerly a supplemental endpoint. To provide a more thorough understanding of sunitinib's efficacy in the treatment of panNETs, OS, the PFS, and analysis of safety data for this combined sunitinib cohort were also performed [34].

4.10. Resistance mechanisms

There is frequently overlap between the primary and secondary resistance mechanisms. Molecular variants with an immunosuppressive microenvironment may be the main cause of sunitinib resistance. Inadequate target inhibition, which may result from single-nucleotide polymorphisms (SNPs) in genes regulating the pharmacokinetics or pharmacodynamics of sunitinib, or from lysosomal sequestering, is another major resistance mechanism. Sunitinib can generate both SNPs and lysosomal sequestering, making them secondary resistance mechanisms. The following categories describe secondary resistance routes to sunitinib: Pro-angiogenic signaling pathways, changes to the tumor microenvironment, increased cancer invasion and metastasis, resistance mediated by microRNA activity, and activation of alternative signaling pathways. Challenge of sunitinib is justified on the basis that preclinical research has further shown the significance of the microenvironment in secondary resistance. Concerns have been raised concerning sunitinib's capacity to increase the metastatic potential of RCC and other malignancies treated with anti-angiogenics, in contrast to its anticancer effects. concentrating on sunitinib resistance in RCC patients. Long non-coding RNAs (lncRNAs) have been connected to the development, growth, metastasis, and recurrence of tumors, according to growing data. Sunitinib resistance was shown to be caused by lncARSR sponging miR-34/miR449 increasing AXL and c-MET expression. In RCC, Chen *et al*. reported that the expression of the microRNA miR942 and the lncRNA LINC00461 was associated with a poor clinical outcome [35]. Elgendy *et al*. (2019), it was found mutations in genes whose loss of function caused sunitinib resistance to tumor cell lines in culture and xenografted in mice by evaluating successive tumor biopsies from an mRCC patient who developed resistance to sunitinib. Additionally, mRCC had a substantial phenotypic dependency on Y-box binding protein 1(YB1) and erythropoietin-producing hepatocellular (EphA2), and sunitinib resistance was mediated by increased expression of the RTK family's YB1 and EphA2 receptors. Furthermore, it was showed that YB1 increases ccRCC invasion, metastasis, and sunitinib resistance via modulating the EphA2 signaling pathway. Furthermore, TRAF (tumor necrosis factor receptor-associated factor) overexpression enhances sunitinib resistance via altering apoptotic and angiogenic pathways through methyltransferase like 14 (METTL14) [36].

Conclusion

Sunitinib is an example of a multitargeted agent. Sunitinib had potent anticancer action in a variety of tumor types while also being highly angiogenic. Patients taking sunitinib should get counseling on possible adverse effects and how to avoid them. Renal cell carcinoma, activity of sunitinib was seen in tumors that were resistant to conventional cytotoxic therapies. Although safety was the major priority. As with other anticancer medications, some patients have developed primary or secondary resistance to sunitinib. Many trials are being conducted to investigate the mechanisms of antiangiogenic agent resistance, which may lead to the discovery of new analogues capable of circumventing antiangiogenic agent resistance. Many trials are being conducted to investigate the mechanisms of antiangiogenic agent resistance, which may lead to the discovery of new analogues capable of

circumventing antiangiogenic agent resistance.

Ethical consideration: All the participants in this study gave their informed permission.

Conflicts of Interest: No conflicts of interest are disclosed

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