A preclinical review of sunitinib, a multitargeted receptor tyrosine kinase inhibitor with anti-angiogenic and antitumour activities

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Sunitinib malate is an oral, multitargeted tyrosine kinase inhibitor that targets both angiogenic pathways (i.e., vascular endothelial growth factor receptor and platelet-derived growth factor receptor) and direct pro-oncogenic pathways (e.g., stem-cell factor receptor and FMS-like tyrosine kinase-3). Preclinical studies with this agent have indicated that it exhibits robust inhibitory activity against these targets. Clinical trial results have demonstrated the therapeutic potential of this agent and have implicated sunitinib targets in the pathophysiology of malignancies such as renal cell carcinoma and gastrointestinal stromal tumour. This paper reviews the preclinical data supporting the development of this agent and its translation from benchtop to bedside. It also highlights the importance of the multiple pathways that may be involved in cancer progression and the importance of these pathways in selected malignancies.

Key words: anti-angiogenesis, multitargeted, preclinical, sunitinib, TKI

introduction

Sunitinib malate (Sutent®, SU11248; Pfizer Inc.) is an oral, multitargeted receptor tyrosine kinase (RTK) inhibitor of vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), stem cell factor receptor (KIT), glial cell-line derived neurotrophic factor receptor (REarranged during Transfection; RET), FMS-like tyrosine kinase-3 (FLT3) and the receptor for macrophage colony-stimulating factor (CSF-1R). Sunitinib is approved multinationally for the treatment of advanced renal cell carcinoma (RCC) and imatinib mesylate-resistant or -intolerant gastrointestinal stromal tumour (GIST). Preclinical and/or clinical studies have implicated these RTKs as key factors in the progression of particular tumour types and linked the inhibitory effects of sunitinib on these RTKs with its antitumour activity. In particular, genetic dysregulation of KIT or PDGFR-alpha (PDGFR-α) has been associated with the pathogenesis of GIST and dysregulation of VEGFR- and PDGFR-dependent tumour angiogenesis with progression of clear-cell RCC.

Since angiogenesis is required for continued development of most solid tumours, sunitinib inhibition of VEGFRs and PDGFRs expressed by vascular or perivascular endothelial cells is predicted to produce anti-angiogenic effects on a wide variety of solid tumours. Sunitinib can also directly inhibit the growth or survival of selected tumour types with dysregulated or overexpressed RTK targets involved in regulation of cell proliferation or cell survival. This broad capacity of sunitinib for both anti-angiogenic and direct antitumour effects may be an important feature of its antitumour activity, at least for certain tumour types.

This review first examines the role of RTKs in different tumours before exploring the preclinical data supporting the multitargeted inhibitory activity of sunitinib and its relationship to its anti-angiogenic or antitumour activity. It then examines the data supporting the activity of sunitinib in the clinical setting, including an introduction of preliminary results from clinical biomarker studies that are consistent with the underlying mechanisms of the antitumour activity first demonstrated with sunitinib preclinically.

the role of RTKs in tumour progression

In recent decades, it has become clear that RTKs are linked to cellular signalling pathways that regulate critical processes important for cancer development and growth [1]. At least 60 of these transmembrane signaling proteins have been identified in humans. Structurally, RTKs consist of an extracellular domain that serves as the ligand-binding region, a transmembrane region that traverses the cell plasma membrane, and an intracellular domain possessing tyrosine kinase activity responsible for mediating downstream signal transduction. Ligand binding generally causes RTKs to dimerize or multimerize, which produces conformational changes that facilitate ATP binding and result in autophosphorylation or transphosphorylation of RTK kinase domains. The resulting phospho-tyrosine residues serve as...
Some examples include chromosomal translocations resulting in cell proliferation and survival, migration and metabolism, which are tightly regulated during normal tissue homeostasis and mammalian development.

The dysregulation of RTK signalling caused by mutation or ectopic receptor or ligand expression has been implicated in various aspects of tumour progression, including cell proliferation, survival, angiogenesis and tumour dissemination. Some examples include chromosomal translocations resulting in BCR-ABL fusion proteins in chronic myeloid leukaemia, KIT and PDGFR-α mutations in GIST, and EGFR mutation/amplification in non-small-cell lung cancer (NSCLC).

Human epidermal growth factor receptor 2 (HER-2) amplification in metastatic breast cancer, FLT3 mutations in acute myeloid leukaemia, AML and RET mutations or translocations in thyroid tumours. Frequently, mutations within an RTK-encoding gene result in expression of a protein product with constitutive or ligand-independent kinase activity that drives tumour development. These are often referred to as activating or gain-in-function mutations and are commonly observed in KIT or PDGFR-α (the gene encoding PDGFR-α) in GIST cells, in which they are believed to be critical in the initiation and progression of these tumours.

As described above, the dysregulation of tyrosine kinases expressed directly by tumour cells is implicated as a key event in the pathogenesis of a number of tumour types. However, it has long been recognized that additional cell types also play critical roles in tumour progression and metastasis, including stromal, inflammatory and vascular endothelial cells and pericytes. RTKs located on these cells may play significant roles in cancer development and represent relevant targets for anticancer treatment. In particular, VEGFR-2 and PDGFR-β located on vascular endothelial cells and pericytes, respectively, have been shown to be important in tumour-related angiogenesis. Anti-angiogenic therapies focused on inhibition of the function of VEGFR-2 or its cognate ligand VEGF-A have demonstrated their utility as cancer treatment in a variety of indications either as single agents and in combination with chemotherapy. 'Proof of principle' of anti-angiogenesis as cancer therapy was first demonstrated with bevacizumab in patients with metastatic colorectal cancer (mCRC). Bevacizumab, a monoclonal antibody directed against VEGF-A, was shown to significantly prolong survival in patients with mCRC when added to 5-fluorouracil-based chemotherapy.

Clear-cell RCC represents a highly vascularized tumour strongly linked with dysregulation of VEGFR and PDGFR activity. Most clear-cell RCC tumours are associated with inactivation of the von Hippel–Lindau gene, leading to constitutively expressed hypoxia-inducible factor alpha and induction of VEGFs, PDGFs and other growth factors. Excess activity of VEGFR-2 and PDGFR-β due to up-regulation of their respective ligands at least partially accounts for the highly vascularized nature of these tumours and has been associated with RCC progression. Multiple preclinical studies of interest have demonstrated that more robust anti-angiogenic and antitumour effects resulted from inhibition of both VEGFR and PDGFR, compared with inhibition of either VEGFR or PDGFR alone.

In each of the cases mentioned, tumour initiation and progression has been linked with excessive tyrosine kinase activity, be it due to RTK overexpression, mutations leading to ligand-independent/constitutive kinase activity or overexpression of cognate ligands for particular RTKs. These data highlight RTKs (or non-receptor tyrosine kinases) as potential targets for anticancer therapy and RTK inhibition as an attractive therapeutic strategy. Furthermore, the existing data indicate that coordinated interaction of multiple cell types and multiple cellular processes is involved in tumour formation and progression, and therefore point to potential benefits of multigene-targeted anticancer therapy.

Sunitinib inhibition of RTK activity in vitro

Sunitinib was first identified in a drug discovery programme designed to prospectively identify potent and orally bioavailable small-molecule inhibitors of VEGF and PDGF receptors. Initial in-vitro biochemical kinase screening assays using recombinant proteins demonstrated sunitinib to be a potent inhibitor of VEGFRs (VEGFR-1, -2 and -3) and PDGFR-β, with IC50 ranging from 0.002 to 0.017 μM. It was demonstrated that sunitinib interacts with the ATP-binding pocket of these kinases and acts as a competitive inhibitor with ATP. In-vitro biochemical studies also showed SU12662, the major metabolite of sunitinib in vivo, to be an inhibitor of these RTKs with similar potency. Subsequently, sunitinib kinase inhibitory activity was characterized across broad panels of biochemical assays including more than 150 tyrosine kinases or serine–threonine kinases.

To further characterize and extend the understanding of sunitinib kinase activity, cellular kinase assays were utilized to examine its ability to inhibit ligand-dependent RTK phosphorylation in cells expressing these RTK targets. In particular, sunitinib was demonstrated to inhibit VEGF-stimulated VEGFR-2 phosphorylation and PDGFR-β phosphorylation in NIH-3T3 cells expressing these targets (IC50 ~0.01 μM) [26], stem-cell factor (SCF)-stimulated phosphorylation of KIT expressed in NCI-H526 human small-cell lung cancer (SCLC) cells (IC50 ~0.001–0.01 μM) [25], FLT ligand (FL)-dependent FLT3 phosphorylation in RS4;11 or OS-AML5 AML cells expressing FLT3 (IC50 ~0.25 μM) [27], and M-CSF-dependent phosphorylation of CSF-1R expressed in NIH-3T3 cells (IC50 0.05–0.1 μM) [28]. In addition to wild-type RTK targets, cellular assays also examined the ability of sunitinib to inhibit the tyrosine kinases in mutated RTKs with constitutive kinetic activity. Sunitinib was shown to inhibit...
constitutive FLT3 phosphorylation in MV4;11 AML cells expressing FLT-ITD (IC50 \sim 0.05 \mu M) [27] and constitutive RET phosphorylation in TT human medullary thyroid carcinoma cells expressing the RET C634W mutant (IC50 \sim 0.05 \mu M) [25].

Of particular note, sunitinib has also been shown to inhibit constitutive kinase activity associated with mutant forms of KIT or PDGFR-\alpha. This is of interest because more than 85% of GISTs harbour mutated and constitutively active forms of KIT or PDGFR-\alpha receptors, which are believed to be key factors in the pathogenesis of these tumours [29, 30]. In addition, sensitivity to imatinib (the current first-line treatment for GIST) varies for different mutant isoforms of KIT [29, 31], and acquisition of secondary KIT mutations is associated with acquired imatinib resistance [32–35]. Sunitinib has been shown to potently inhibit KIT autophosphorylation in isolated GIST cells or cells bioengineered to express constitutively active KIT exon 9 and exon 11 mutants commonly found in naïve GIST [36–38]. Similarly, Ikezoe and coworkers demonstrated that sunitinib not only inhibited KIT autophosphorylation in naïve GIST-T1 cells with activating mutations, but also inhibited phosphorylation of downstream effectors [39]. Importantly, sunitinib also potently inhibited exon 13 and exon 14 mutant variants of KIT (i.e., V654A and T670I), which are associated with reduced binding affinity and resistance to imatinib [36–38].

Sunitinib target inhibition has also been demonstrated in vivo in mice implanted with tumour cells that gave rise to established tumours expressing high levels of PDGFR-\beta or VEGFR-2. Orally administered sunitinib produced dose- and time-dependent inhibition of RTK autophosphorylation, as illustrated in Figure 1 [26]. Sunitinib also inhibited PDGFR-\beta activity in Colo205 tumour xenografts, which do not directly express PDGFR-\beta, suggesting that sunitinib was also effective in inhibiting PDGFR-\beta localized to stromal and perivascular endothelial cells, where this RTK is commonly expressed [26].

Other experiments also demonstrated the ability of orally administered sunitinib to inhibit RTK targets in vivo, including inhibition of KIT and PDGFR-\beta phosphorylation in athymic mice bearing NCI-H526 SCLC tumours [40] and FLT3 phosphorylation in athymic mice bearing MV4;11 AML tumours harbouring constitutively active FLT3-ITD [27]. KIT is also known to regulate hair pigmentation and further evidence of KIT inhibition by sunitinib was provided by the observation of dose-dependent decrease of hair pigmentation in mice treated with sunitinib [41].

**functional consequences of sunitinib RTK inhibition**

The functional consequences of sunitinib target inhibition have been examined both in vitro and in vivo with a focus on exploring its anti-angiogenic and antitumour properties. Sunitinib demonstrated the ability to potently inhibit VEGF-A-stimulated proliferation of human umbilical vein endothelial cells (IC50 0.004 \mu M) [26] and serum-stimulated vascular tube formation of human microvascular endothelial cells (IC50 0.055 \mu M) in vitro [25, 42]. Since the ability of endothelial cells to proliferate and form tube-like structures is critical in the formation of new blood vessels, this data indicated that sunitinib potentially exhibited anti-angiogenic activity.

Sunitinib also potently inhibited VEGF-A-stimulated vascular permeability in mouse skin, a hallmark of VEGF-dependent angiogenesis, when orally administered to mice [26]. The inhibition of vascular permeability by sunitinib in vivo demonstrated a strong time- and dose-dependent correlation to inhibition of VEGF-2 phosphorylation and provided additional evidence of its anti-angiogenic properties.

Sunitinib was also assessed for its ability to inhibit cell growth and proliferation of a variety of tumour cell lines in vitro to provide insight into its ability to affect tumours through a direct antiproliferative mechanism. Although the majority of cell lines were not directly affected by sunitinib in these studies, there were several examples of its direct antiproliferative activity. Sunitinib was demonstrated to inhibit ligand-independent proliferation of primary GIST cells expressing KIT with activating mutations [37], MV4;11 cells expressing FLT3-ITD mutations [27], and TT human medullary thyroid carcinoma cells expressing RET (C634W) mutations [25]. In each case, the sunitinib IC50 for inhibition of proliferation was similar to the IC50 for inhibition of RTK autophosphorylation. The growth of an additional subset of other cell lines (e.g., melanoma, glioma and breast cancer) was also affected at pharmacologically relevant sunitinib

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Sunitinib dose- and time-dependent inhibition of PDGFR-\beta and VEGF-2 autophosphorylation in mouse tumour xenograft models. PDGFR-\beta or VEGF-2 was immunoprecipitated from tumour lysates from mice bearing (A) SF767T human glioblastoma tumours (where each lane represents a separate animal) or (B) A375 human melanoma tumours. Western blots were probed for phosphotyrosine (phospho-PDGFR-\beta) or phospho-VEGFR-2) or total PDGFR-\beta or VEGFR-2 protein (reproduced from Mendel et al., 2003 [26]).
Sunitinib at 40 mg/kg/day (HT-29) or 80 mg/kg/day (Colo205) was initiated when the tumours reached an average size of 400 mm³ (HT-29) or 300 mm³ (Colo205) and continued to the end of the experiment. Tumour volume was measured on the indicated days, with the mean tumour volume indicated for groups of 8 (treated) or 16 (vehicle control) animals (mean ± SEM) [25, 26].

Concentrations and the mechanism of growth inhibition is currently under investigation [25]. These data generally suggest that sunitinib can display direct antiproliferative activity against a subset of tumour cells and that antiproliferative activity is dependent upon presence of constitutively active RTK targets. Sunitinib has also been examined for antitumour effects in a series of rodent tumour xenograft models using cell lines derived from various human tumours, including lung (NCI-H460, NCI-H226, NCI-H526, NCI-H82), colorectal (Colo205, HT-29), melanoma (A375, WM-266-4), epidermoid (A431), renal (786-O) and glioblastoma (C6, SF763T) [25, 26]. In each of these models, orally administered sunitinib significantly inhibited tumour growth of established tumours, and in several of the models (Colo205, HT-29, WM-266-4, A431, 786-O, NCI-H226), sunitinib produced marked regression of large established tumours. Figure 2 illustrates regression of established HT-29 and Colo205 tumours during sunitinib treatment. Since several of the tumour cell lines examined in this series of studies do not express sunitinib targets, the antitumour effects of sunitinib in these models were presumably due to the anti-angiogenic mechanism. Orally administered sunitinib was also shown to produce marked regression of spontaneously arising and established tumours in the mouse MMTV-v-Ha-ras transgenic mammary model [43] and the DMBA rat carcinogenesis tumour model [25]. It is of note that the cytoreductive activity of sunitinib in at least some tumour models pointed to its potential for objective responses in human cancer patients.

Because its RTK targets are also implicated in the metastatic progression of cancer, sunitinib was evaluated for its ability to inhibit tumour cell dissemination and metastatic progression in mouse models of experimental metastasis. To evaluate the ability of sunitinib to inhibit growth of established tumour metastases in the bone, the MDA-MB-435HAL-Luc (435/HAL-Luc) mammary carcinoma model, in which bone metastases can be evaluated by optical imaging, was utilized [28]. Similarly, sunitinib also significantly inhibited formation of metastatic colonies of disseminated tumour cells in mouse lung in the B16-F1 melanoma lung colonization model [25]. Collectively, these data suggest that sunitinib may be effective in treating bone metastases and metastatic progression of certain human cancers.

Human tumour xenograft models were also utilized to explore the antitumour mechanism of sunitinib and the role of its therapeutic targets. Microvessel density (MVD) in sunitinib- and vehicle-treated animals has been used to assess sunitinib inhibition of angiogenesis in a variety of tumour xenograft models [22, 26]. As can be seen in Table 1, sunitinib treatment reduced vascular density in established tumours by roughly 70% or more in most models, and only the C6 glioma model failed to show significant inhibition with sunitinib versus vehicle. Tumours were grown as subcutaneous xenografts in athymic mice to mean sizes of 300–400 mm³. When optimal tumour size was established, vehicle or 40 mg/kg sunitinib was administered once daily until the end of the study as indicated. Furthermore, Osusky and coworkers employed the tumour vascular window model to look at sunitinib impact on in-vivo neoangiogenesis in C57BL6J mice implanted with Lewis lung carcinoma cells [42]. Sunitinib reduced vascular permeability, inhibited new blood vessel formation and demonstrated regression of existing vasculature compared with vehicle-treated mice.

Studies were also initiated to determine the relative contributions of individual RTK targets of sunitinib antitumour and anti-angiogenic activity in various tumour xenograft models [22]. This was accomplished by investigating the anti-angiogenic and antitumour effects of agents that inhibit VEGFR, PDGFR and KIT (sunitinib); PDGFR and KIT only (imatinib); or VEGFR only (SU10944) at dose levels associated with complete inhibition of intended targets. Strikingly, in all solid tumour models evaluated, the reduction of microvessel density and antitumour efficacy of SU10944 combined with imatinib was similar to that of single-agent sunitinib and was greatly superior to that of each compound alone. These data suggest that inhibition of VEGFR, PDGFR and KIT contribute in a cooperative fashion to the antitumour

Figure 2. Regression of large established (A) HT-29 and (B) Colo205 tumour xenografts in athymic mice by sunitinib. Daily oral administration of sunitinib at 40 mg/kg/day (HT-29) or 80 mg/kg/day (Colo205) was initiated when the tumours reached an average size of 400 mm³ (HT-29) or 300 mm³ (Colo205) and continued to the end of the experiment. Tumour volume was measured on the indicated days, with the mean tumour volume indicated for groups of 8 (treated) or 16 (vehicle control) animals (mean ± SEM) [25, 26].
and anti-angiogenic effects of sunitinib, at least in the tumour models examined.

A recent non-clinical study by Yao and coworkers [23] also supports the conclusion that dual inhibition of VEGFR and PDGFR with sunitinib is associated with greater anti-angiogenic effects compared with selective inhibition of VEGFR or PDGFR alone. Yao et al. compared the differential effects of sunitinib or AG-028262 (a selective VEGFR inhibitor) and CP-673,451 (a selective PDGFR inhibitor) on tumour endothelial cells or pericytes in pancreatic islet tumours from RIP-Tag2 transgenic mice at dose levels associated with complete inhibition of intended targets. In these studies, sunitinib treatment was associated with a 75% reduction in the density per unit area of endothelial cells and a 63% reduction in that of pericytes (Figure 3). In contrast, AG-028262 alone reduced the tumour endothelial cell density (–61%) but had no effect on the tumour pericyte population (+0.6%), while CP-673,451 alone reduced pericyte density (–50%) but had no effect on endothelial cells (–5%). The combination of AG-028262 plus CP-673,451 treatment had comparable effects to sunitinib on both endothelial cells and pericytes. These results suggest that sunitinib causes regression of endothelial cells and pericytes by inhibiting VEGFR and PDGFR, respectively, and produces more comprehensive effects on the tumour vasculature and supporting cells than agents that target either VEGFR or PDGFR alone.

Based on collective non-clinical data, the potent efficacy of sunitinib probably results from simultaneous inhibition of individual target receptors expressed both in cancer cells and in tumour neovasculature. These data support the hypothesis that simultaneous inhibition of multiple critical targets that cooperate in tumour progression by a multitargeted agent results in robust antitumour activity and may recapitulate the cumulative antitumour efficacy of multiple single-target inhibitors.

**translating preclinical findings to the clinical setting**

Preclinical findings have been useful in identifying clinical tumour types most likely to respond to sunitinib therapy. In addition, in-vivo tumour modelling studies have established pharmacokinetic/pharmacodynamic (PK/PD) parameters for sunitinib antitumour activity that have utility for designing optimal clinical dosing regimens. The results of dose-response and dose-schedule studies in preclinical models indicated that 40 mg/kg/day was a fully efficacious dose and that full efficacy was observed when a target plasma level for sunitinib plus SU12662 (its primary active metabolite) of ≥50 ng/mL was maintained for at least half of the daily dosing interval [25]. In the clinical setting, a dose-ranging pharmacokinetic trial of patients with advanced solid tumours identified 50 mg/day (administered in 6-week treatment cycles of 4 weeks on and 2 weeks off) as the recommended sunitinib dose, based on the demonstration of clinical efficacy and acceptable tolerability [44]. This trial demonstrated that a dose of 50 mg/day resulted in plasma levels exceeding the minimum target total-drug plasma levels of 50 ng/mL, with moderate interpatient variability and a long half-life for the full dosing interval. Clinical trials have also demonstrated that sunitinib inhibits its intended RTK targets in tumour cell populations at plasma concentrations of ≥50 ng/mL. In a phase I study of AML patients, sunitinib was found to inhibit FLT3 and FLT-ITD phosphorylation in a dose-dependent manner, providing evidence of anti-FLT3 activity in patients [45]. Clinical efficacy and evidence of target inhibition by sunitinib was also demonstrated in patients with GIST or RCC. As discussed earlier and also in more detail in the following articles,

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**Table 1. Effect of sunitinib on neoangiogenesis of established tumour xenografts (adapted from Potapova et al., 2006 [22])**

<table>
<thead>
<tr>
<th>Tumour model</th>
<th>Treatment day</th>
<th>MVD</th>
<th>Percent inhibition</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vehicle</td>
<td>Sunitinib</td>
<td></td>
</tr>
<tr>
<td>C6 glioma</td>
<td>12</td>
<td>24.6</td>
<td>31.8</td>
<td>76</td>
</tr>
<tr>
<td>786-O renal</td>
<td>14</td>
<td>106.2</td>
<td>25.3</td>
<td>0.027</td>
</tr>
<tr>
<td>WM-266-4 melanoma</td>
<td>29</td>
<td>43.2</td>
<td>13.7</td>
<td>68</td>
</tr>
<tr>
<td>NCI-H226 lung</td>
<td>14</td>
<td>74.2</td>
<td>8.4</td>
<td>0.012</td>
</tr>
<tr>
<td>SF763T glioma*</td>
<td>13</td>
<td>39.3</td>
<td>24.2</td>
<td>38</td>
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<td></td>
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<td>&lt;0.05</td>
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*aFrom Mendel et al., 2003 [26].
MVD, microvessel density (mean number of microvessels/100 × field).
activating mutations of KIT or PDGFRA underlie most cases of GIST, and VEGFR- and PDGFR-dependent angiogenesis is implicated in progression of RCC. Given the potent inhibition of each of these RTKs by sunitinib in preclinical studies, GIST and RCC patients were chosen for sunitinib proof-of-concept efficacy studies.

Clinical efficacy of sunitinib in patients with imatinib-resistant GIST was demonstrated in an open-label phase I/II trial and a placebo-controlled phase III trial [38, 46]. Because KIT mutations are implicated in the pathogenesis of the majority of GIST cases, additional studies were initiated as part of the phase I/II trial to demonstrate the inhibition of KIT by sunitinib in tumour tissue. Immunohistochemical analyses of tumour biopsies from sunitinib-treated patients in the phase I/II trial demonstrated near-complete inhibition of KIT activity 1 week after initiation of treatment (G. Demetri, personal communication). In addition, a recent study reported that GIST patients who demonstrated objective responses to sunitinib exhibited a sustained decline in plasma levels of soluble KIT (sKIT), while no trend was observed in patients without objective responses [25]. Additional analyses from the phase I/II trial also point to the importance of KIT inhibition for sunitinib GIST activity. In particular, Heinrich and coworkers showed that median progression-free survival with sunitinib was significantly longer in patients with imatinib-resistant GISTs who had primary/secondary sunitinib was significantly longer in patients with imatinib-resistant GIST including primary/secondary KIT mutations highly sensitive to sunitinib inhibition in vitro than in patients whose tumours contained less sensitive KIT mutations [38]. This observation is the strongest evidence linking the importance of KIT inhibition to clinical benefit in GIST patients treated with sunitinib.

The anti-angiogenic effects of sunitinib have also been implicated in its activity in GIST. Patients with GIST containing wild-type KIT and PDGFRA who progressed during imatinib treatment demonstrated evidence of sunitinib clinical benefit (median overall survival 30.5 months), potentially implicating other sunitinib targets or anti-angiogenic activity in these patients [47]. A pharmacodynamic analysis of PDGFR-β and VEGFR-2 inhibition and apoptosis from the phase I/II trial showed decreases in PDGFR-β and VEGFR-2 phosphorylation and increases in endothelial and tumour cell apoptosis relative to baseline in tumours from patients showing clinical benefit with sunitinib; that is, partial responses or stable disease greater than 6 months [48, 49]. In contrast, levels of PDGFR-β and VEGFR-2 phosphorylation were higher and apoptosis was unchanged in GISTs from patients without clinical benefit or with progressive disease.

Anti-angiogenic effects have also been linked with sunitinib activity in RCC. Sunitinib efficacy in patients with RCC refractory to cytokine-based therapy was demonstrated in two phase II trials [17, 50] as well as in previously untreated patients in a phase III trial [51]. In one of the phase II trials, Motzer and coworkers reported that plasma levels of VEGF-A and placentation growth factor (PIGF) significantly increased in RCC patients during sunitinib therapy and tended to return to near-baseline during off-treatment periods [17]. In addition, sunitinib treatment was associated with decreases in soluble VEGFR-2 (sVEGFR-2) and sKIT [52]. VEGF and sVEGFR-2 levels were modulated to a greater extent in patients exhibiting objective responses relative to those exhibiting progressive or stable disease [52]. Sunitinib-related increases in plasma VEGF and decreases in plasma sVEGFR-2 have also been reported in patients with metastatic breast cancer [53] and patients with neuroendocrine tumour [54]. Although the exact mechanisms of modulation of VEGF-A and sVEGFR-2 are unknown, these data provide evidence that sunitinib is inhibiting target VEGFRs in patients, since similar changes are observed clinically for other inhibitors of the VEGF pathway. Sunitinib treatment also produced decreases in plasma sKIT levels in metastatic breast cancer patients, and decreases of more than 50% at the end of cycle 2 were significantly associated with treatment-related improvements in time to progression and survival [53]. A more complete overview of the data with respect to biomarkers will be discussed in the following article.

conclusions

Sunitinib is an inhibitor of multiple class III and V RTKs, which are implicated in the pathogenesis of various cancers, including GIST and RCC. Preclinical studies demonstrated the selective inhibition of target RTKs and linked RTK inhibition with anti-angiogenic and direct antitumour effects in in-vitro cellular assays or in vivo tumour models. Subsequently, clinical trial results demonstrated the efficacy of sunitinib in patients with several different tumour types. In addition, clinical data were found to be consistent with the antitumour mechanisms of action of sunitinib demonstrated in preclinical studies. Future goals include understanding the molecular basis of drug sensitivity in selected populations, identifying clinically relevant biomarkers (discussed in more detail in the following article) and determining optimal use in combination with other anticancer therapies.

disclosures

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