Predictive Factors of Efficacy of Sunitinib Therapy in Gastrointestinal Stromal Tumours

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Abstract

Until the introduction of tyrosine kinase inhibitors, only limited treatment options were available for advanced/inoperable gastrointestinal stromal tumours (GISTs), the most common mesenchymal tumours of the gastrointestinal tract. Initially, it was imatinib mesylate that revolutionised patient outcomes in advanced cases, followed by sunitinib malate when the activity of imatinib turned out to be time-limited. There is substantial heterogeneity between GISTs in terms of response to targeted therapy. As was the case for imatinib, the efficacy of sunitinib depends on the primary tumour's *KIT/PDGFRA* (platelet-derived growth factor receptor-alpha) genotype and on secondary mutations emerging during treatment. Interestingly, sunitinib-related adverse effects, such as arterial hypertension, may serve as biomarkers of the antitumour efficacy of the drug. Here we discuss possible mechanisms underlying these phenomena as well as data from our recently published study – the first to investigate the clinicopathologic and genetic characteristics associated with the results of sunitinib therapy in a large group of patients treated in routine clinical practice.

Keywords

Sunitinib, genotype, gastrointestinal stromal tumour, prognosis, predictive factors, arterial hypertension

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Gastrointestinal stromal tumours (GISTs) are rare mesenchymal tumours that may develop anywhere along the gastrointestinal tract. Approximately 95 % of cases share the expression of the CD117 surface antigen, also known as KIT or stem cell factor receptor. The management of localised GISTs relies on the complete surgical excision of the tumour. Until the introduction of tyrosine kinase inhibitors (TKIs), limited treatment options were available for patients once the tumour had spread or if it was inoperable.[1]

Unprecedented improvement in the management of advanced GIST has been achieved through the relatively recent recognition of the important biological role of activating mutations in the *KIT* and *PDGFRA* (platelet-derived growth factor receptor-alpha) genes. These observations led to the introduction into therapy of imatinib mesylate, a small-molecule selective TKI targeting stem-cell factor receptor (KIT, CD117), breakpoint cluster region/C-abl oncogene 1, non-receptor tyrosine kinase (BCR/ABL) and platelet-derived growth factor receptors (PDGFRs) A and B. Imatinib revolutionised the treatment of patients with advanced CD117-positive GISTs and is currently approved as first-line treatment in metastatic and/or inoperable disease.[2–6] However, approximately 10–15 % of GIST patients are initially insensitive to imatinib, around 5 % are intolerant to it, and the spectacular response of the remaining patients is time-limited. As shown by median progression-free survival (PFS), approximately 50 % of patients treated with imatinib ultimately develop secondary resistance and experience disease progression within two years of treatment initiation.[2,3,5]

The management of GIST resistant to first-line treatment represents a clinical challenge.[5] Insights into resistance mechanisms have allowed the development of several alternative strategies for patients who experience disease progression following imatinib treatment, which are currently being tested. In the case of generalised disease progression (or intolerance to imatinib), monotherapy with an alternative multitargeted TKI – i.e., sunitinib – represents the main option. Sunitinib remains the only approved second-line drug for the treatment of advanced GIST after failure of imatinib therapy.[7]

Sunitinib

Sunitinib malate is a multitargeted agent, as it has been proven to be active against a broad spectrum of tyrosine kinases: KIT, PDGFRA/B, vascular endothelial growth factor receptors (VEGFRs) 1, 2 and 3, FMS-like tyrosine kinase 3 (FLT-3), colony stimulating factor 1 receptor (CSF1-R), RET proto-oncogene and, to a lesser extent, fibroblast growth factor receptor 1 (FGFR-1).[8–13]

Sunitinib possesses both antiangiogenic and cytostatic properties and, by competing with adenosine-5'-triphosphate (ATP) binding, prevents prevents the phosphorylation of those receptor tyrosine kinases *in vitro* and *in vivo*. Daily dosing of 50 mg of sunitinib produces target plasma concentrations above the 50 ng/ml required to inhibit KIT, PDGFR and VEGFR, and a schedule of 50 mg daily for four weeks followed by a two-week break (six-week cycle) has been established as the standard for future clinical trials and subsequently for routine

Table 1: Most Common Adverse Events during Sunitinib Therapy in Patients with Gastrointestinal Stromal Tumours (n=137)

Adverse Event	Any Grade		Grade 3/4	
	Number	%	Number	%
Any treatment-related adverse event	127	92.7	43	31.4
Fatigue	89	65	12	8.7
Diarrhoea	37	28	4	2.9
Hand–foot syndrome	55	40	3	2.2
Decreased appetite/dysgeusia	25	18.2	0	0
Mucositis	35	25.5	2	1.5
Hypertension	59	43	4	2.9
Neutropenia	49	36	7	5.1
Anaemia	51	37	8	5.8
Skin/hair discoloration	41	30	0	0
Dyspepsia	43	31.4	0	0
Thrombocytopenia	18	13.1	3	2.2
Hypothyroidism	42	31	2	1.5

Source: Rutkowski et al., 2012.[17]

practice. An alternative daily dose of 37.5 mg of sunitinib on a continuous schedule is also used in clinical practice, following a Phase II trial that demonstrated an acceptable safety and tolerability profile for this dosing strategy.[13]

Two Phase II, one Phase III and one 'treatment-use' trial have investigated the activity of sunitinib in GIST patients after failure of prior imatinib treatment. All these trials have shown a significant activity of sunitinib in this patient population.[13–16] In a randomised, placebo-controlled Phase III trial:[15]

- objective clinical benefit was achieved in 65 % of patients (7 % of partial responses and 58 % of stable disease, compared with 0 % and 48 %, respectively, in the placebo group);
- median time to progression was significantly longer with sunitinib than with placebo in the primary endpoint analysis (27.3 versus 6.4 weeks; hazard ratio [HR] 0.33; p<0.0001);
- PFS was four times as long with sunitinib than with placebo (24.1 versus 6.0 weeks; HR 0.33; p<0.0001);
- the most common treatment-related adverse events (AEs) were fatigue, diarrhoea, skin discoloration and nausea; they were usually grade 1/2 and easily managed; serious treatment-related AEs were reported in 40 (20 %) and five (5 %) patients in the sunitinib and placebo groups, respectively; and
- dose reductions were needed in 23 (11 %) patients receiving sunitinib on a six-week cycle schedule, but not in any patients receiving placebo.

A study performed in our institution constitutes one of the largest series of GIST cases after imatinib failure (137 patients) analysed for the outcome of sunitinib treatment in routine practice, outside randomised, controlled clinical trials.[17] Our aim was to evaluate factors predicting outcome and toxicity of sunitinib second-line therapy in inoperable/metastatic GIST after failure of imatinib therapy. We confirmed that many advanced GIST patients benefit from sunitinib therapy – mainly due to stabilisation of disease according to RECIST (response evaluation criteria in solid tumors), but not Choi criteria[18] – with overall survival (OS) exceeding 1.5 years. The median PFS of longer than seven months is almost equal to the results obtained in the Korean single-centre study.[19]

Adverse Events Related to Sunitinib Treatment

Sunitinib therapy is associated with several AEs, which are generally mild-to-moderate. As a dose–response relationship has been observed,[20] only otherwise intolerable side effects should be managed by dose modulation (including continuous administration of a lower dose).[7,19,21,22] Most of the side effects increase in intensity as the cycle progresses, but then begin to resolve during the two-week break, providing the rationale for the six-week cycle administration schedule described above.

The most common AEs related to sunitinib treatment are fatigue, diarrhoea, skin discoloration, nausea, mucositis, arterial hypertension, hand-foot syndrome, myelosupression, impairment of left ventricular ejection fraction and hypothyroidism.[15,16]

Hypothyroidism was not originally highlighted among AEs in clinical trials of sunitinib and the basis of its development is not completely understood. Outside clinical trials, its occurrence has been reported in up to 46 % of GIST patients (30 % in our study).[17,23,24] More frequently observed in renal cell carcinoma (RCC) than in GIST patients, it may be influenced by previous cytokine treatment. *In vitro* studies suggest inhibition of thyroid peroxidase activity,[25] degeneration of thyroid follicular cells[26] and reduction in vascularity[27] as possible explanations. One study reported a more than doubled median duration of sunitinib treatment in patients developing hypothyroidism, compared with patients not developing thyroid function abnormality (48 versus 21 weeks), but it made no further comments on the issue.[24] Studies performed in a group of RCC patients did not support any hypothyroidism-driven sunitinib therapy advantage.[28]

The sunitinib toxicity profile observed in our study is similar to that observed in clinical trials (see *Table 1*), with the already mentioned exception of hypothyroidism. However, up to one-third of the cases in our study were classified as experiencing severe toxicity (and two deaths due to tumour haemorrhage were classified as related to sunitinib therapy). Our experience with patients with unresectable or metastatic GIST treated with TKIs suggests a higher incidence of emergency operations for gastrointestinal bleeding, bowel obstruction or abscess occurring during second-line therapy with sunitinib, compared with first-line therapy with imatinib.[29,30] This increased incidence of surgical complications with sunitinib could be associated with the presence of more advanced and drug-resistant disease, or it could be the direct result of the mechanism of action of sunitinib – i.e., the combination of cytotoxic and antiangiogenic activity – leading to dramatic tumour response.

Mutational Status of *KIT/PDGFRA* Genes in Gastrointestinal Stromal Tumours

Several studies have confirmed that activating mutations of *KIT*/*PDGFRA* genes, which can be detected in around 85 % of primary GISTs, influence dosage and general efficacy of TKI treatment.[31–33] Non-random mutation distribution has been observed, relating to functional domains of the tyrosine kinase (TK) receptor. Mutations have been detected in exon 9 (extracellular/dimerisation domain), exon 11 (juxtamembrane domain), exons 13/14 (which encode the drug/ATP binding pocket

of the receptor [TK 1 domain]) and exons 17/18 (which encode the kinase activation loop [TK 2] of KIT).

Primary mutations are found predominantly in exon 11 of *KIT* (66 % of patients), a location that correlates with the greatest clinical benefit during imatinib treatment (best response rate, best median PFS and best median OS). Ten to 13 % of cases harbour a duplication of codons 502-503 in exon 9 of *KIT*, and those patients may benefit from an increase of the standard imatinib of 400 mg/day dose to 800 mg/day. Much less frequent are primary mutations affecting two kinase domains of KIT located in exons 13/14 and 17/18 (about 1170 % each)[34] and, due to their rarity, they can not always be reliably linked to imatinib therapy results. A slightly different distribution of mutations is observed in *PDGFRA*. They typically occur in TK 2, encoded by exon 18 (6 % of all patients), with p.D842V as the prevalent mutation followed by mutations in the 'juxtamembrane' exons 12 (1 %) and 14 (<1 %).[31] Definite conclusions regarding response to imatinib are difficult to reach but, in the limited cases published, mutations in exon 12 and 14 were noted to be sensitive, while early resistance was seen with the p.D842V *PDGFRA* mutation. Primary wild-type GISTs (i.e., those 12–15 % that lack detectable *KIT* or *PDGFRA* mutations) are characterised by less objective responsiveness to imatinib therapy.

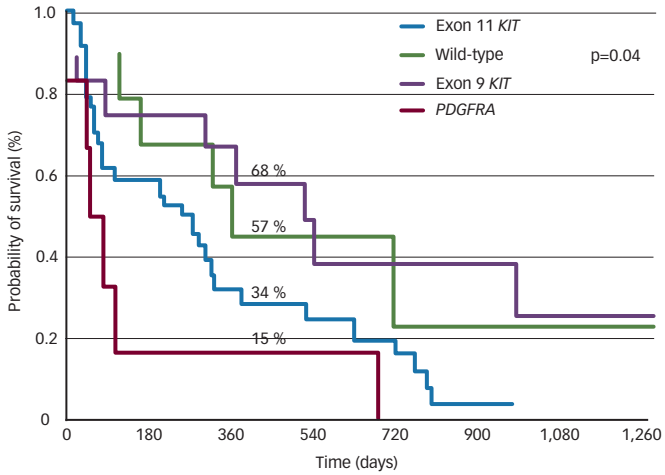
Although response rates are approximately 30–35 % higher in GIST with tumours carrying *KIT* exon 11 versus exon 9 mutation,[32] resistance due to secondary mutations and the eventual need for second-line therapy develop more frequently in tumours with primary *KIT* exon 11 mutations compared with exon 9 mutations group (73 versus 19 %).[35]

As for sunitinib, *KIT* primary mutational status appears to serve as a predictor of tumour response. It has been proven that, contrary to what is seen with imatinib, tumours initially (i.e., pre-sunitinib treatment) bearing *KIT* exon 9 mutations have a higher chance to respond to sunitinib than those with primary *KIT* exon 11 mutations (however, we have also observed some objective responses in the latter patient group).[17,36] The clinical benefit of sunitinib in wild-type (WT) cases is also clear (see *Figure 1*). We did not observe any response to sunitinib in the *PDGFRA* mutation (p.D842V predominantly) group, an observation also made when looking at preclinical data.[37]
In a Phase I/II trial of sunitinib conducted in GIST patients with imatinib-resistant tumours, the rate of partial responses was significantly higher in patients with primary *KIT* exon 9 mutations than in those with exon 11 mutations (37 % versus 5 %). Additionally, patients with *KIT* exon 9 mutations or WT *KIT* had a four times longer PFS and doubled OS compared with patients with exon 11 mutations.[36]

In vivo testing for secondary mutations, if performed, reveals them as the reason for resistance to sunitinib in at least 50 % of patients (more than 80 % if a resistant clonal nodule develops within a pre-existing tumour mass).[38,39] *In vitro*, sunitinib activity against KIT double mutants depends on the location of the secondary mutation, that always occurs in the *cis* configuration (the same allele).[40] Secondary mutations have been detected mainly in patients who were initially found to have primary *KIT* mutations and rarely in those with primary *PDGFRA* mutations.[41]

Distribution of secondary mutations is non-random and they cluster either in the first or second TK domain of KIT. These mutations are significantly more common in GISTs with primary *KIT* exon 11 mutations, since they were found in 73–86 % of imatinib-resistant patients harbouring exon 11 primary mutations and only in 19–33 % of patients with the exon 9 primary mutation.[34,35] Among all patients with secondary *KIT* mutations, the median PFS and OS with sunitinib was significantly longer for the patients harbouring *KIT* exon 13/14 mutations than exon 17/18 mutations,[36] an observation that has been confirmed by *in vitro* studies showing that sunitinib is not active against most imatinib-resistant secondary mutations involving the KIT activation loop.[37] As a substantial part of secondary mutations are located in the kinase activation loop, the phenomenon may be responsible for the more favourable outcome of patients with exon 9 mutations.[42]

Figure 1: Progression-free Survival during Sunitinib Therapy According to Primary Tumour Mutational Status



PDGFRA = platelet-derived growth factor receptor-alpha. Source: Rutkowski et al., 2011.[48]

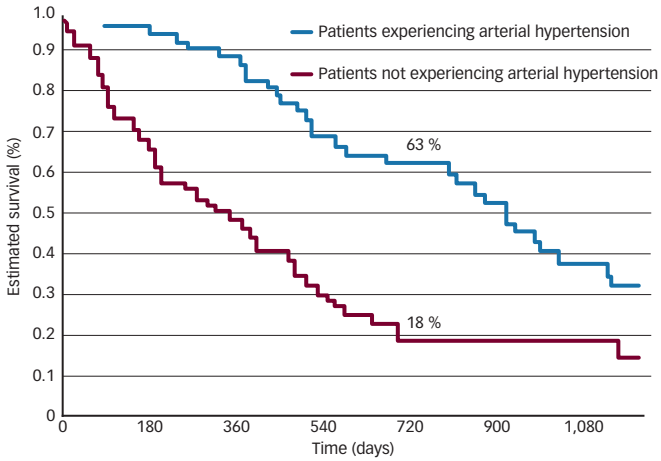
Although potentially informative, the analysis of secondary mutations is very challenging, and assessing the type of secondary mutation may have little utility in the prediction of sunitinib efficacy in routine practice, because imatinib-resistant GISTs are genetically very heterogeneous. Several teams have shown that, in most cases, the evolution of imatinib resistance is polyclonal – i.e., different lesions may have different secondary mutations and single lesions may contain more than one imatinib-resistant clone.[39,43,44] In routine practice, our therapeutic decisions are based on the primary GIST genotype.

Arterial Hypertension and Pharmacogenetics of Sunitinib

Arterial hypertension is a frequent side effect associated with inhibition of the vascular endothelial growth factor (VEGF) pathway; it has been observed in 20–30 % of patients treated with bevacizumab (VEGF-A blocking antibody) and 15–60 % of patients treated with various VEGFR kinase inhibitors, including sunitinib.[45] Arterial hypertension usually occurs early after treatment initiation. Thus serial monitoring of blood pressure is recommended during therapy with sunitinib.

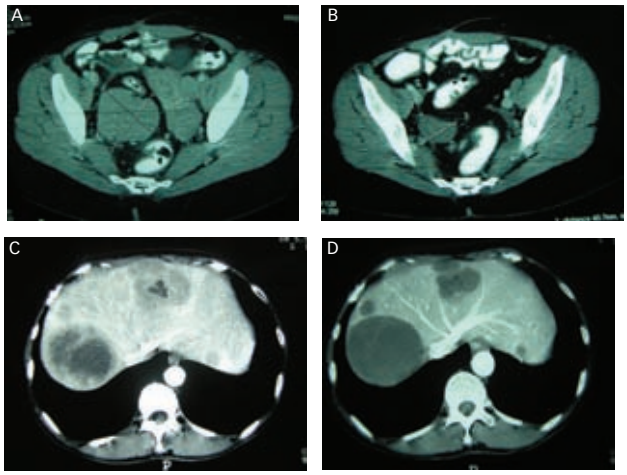
VEGFR inhibition-related toxicity of sunitinib, especially in the context of potential fatal adverse effects (FAEs), has been verified by a meta-analysis of 1,388 sunitinib-treated patients from randomised controlled trials published up until February 2011. No difference in the rate of FAEs was found between different VEGFR TKIs (all approved by

Figure 2: Overall Survival during Sunitinib Therapy According to Presence of Arterial Hypertension



Source: Rutkowski et al., 2011.[68]

Figure 3: Computed Tomography Scans Showing Responses to Sunitinib in two Imatinib-resistant Gastrointestinal Stromal Tumours Harbouring an Exon 11 KIT Mutation and Demonstrating Sunitinib-induced Arterial Hypertension



A and C = before sunitinib therapy; B and D = after sunitinib therapy.

the US Food and Drug Administration) or tumour types, but the use of VEGFR TKIs was associated with an increased risk of FAEs compared with control patients.[46]

Hypothetical mechanisms leading to arterial hypertension related to sunitinib have been proposed, including the presence of less perfused microvessels and/or a diminished number of microvessels,[47] decreasing nitric oxide production[48] and activation of the endothelin 1 pathway leading to vasoconstriction.[49]

It has been recently postulated that sunitinib-induced arterial hypertension may serve as a biomarker of antitumour efficacy. It was first reported as a predictive factor of antitumour efficacy in metastatic RCC patients – a correlation that has been extensively studied.[50–55] Treatment-induced persistent hypertension was associated with frequent tumour response, an extended time to disease progression and longer OS.[55] Clinical outcomes were not compromised by treatment with antihypertensive medication; moreover, patients who required at least three antihypertensive drugs had the longest PFS and OS.[54] The mechanism seems to be universal, as the clinical benefit seen alongside TKI-induced arterial hypertension in RCC was independent of inhibitor (sunitinib, sorafenib or bevacizumab) and line of treatment.[56] The most comprehensive study published until now regarding sunitinib-induced hypertension as a biomarker of treatment efficacy in metastatic RCC has been provided by Rini et al.[51] on the basis of a retrospective analysis of efficacy (n=544) and safety (n=4,917) in four studies that used the standard sunitinib six-week cycle schedule (four weeks of treatment followed by a two-week break). Patients who experienced sunitinib-induced arterial hypertension had better outcomes (objective response rate six times greater, OS more than four times longer) than those who did not, while the safety of treatment was not compromised (i.e., patients with sunitinib-induced arterial hypertension did not experience more AEs, apart from arterial hypertension, than other patients). In a multivariate analysis, arterial hypertension remained a statistically significant predictor of survival benefit ($p<0.001$) regardless of how it was defined and of potential confounding influences.

This phenomenon had not been observed in GIST patients in routine practice outside clinical trials until our recent report.[17] In our study, it proved to be an independent factor influencing both PFS and OS (see *Figures 2* and *3*).

In the clinical setting, there is a wide heterogeneity in therapeutic efficacy and degree of toxicity experienced by patients treated with TKIs, which may eventually be linked to a genetic background influencing an individual patient's susceptibility. Arterial hypertension caused by TKIs has been shown to be dependent on the potency of these inhibitors against VEGFR2.[57] In exploring individual susceptibility, genetic variations – specifically single nucleotide polymorphisms (SNPs) that reside in coding and non-coding regions within *VEGF* and *VEGFR2* – have shown potential as biomarkers of clinical response to, and/or toxicity of, VEGF pathway-targeted therapy.[58–63]

Among RCC patients, after adjustment for pre-treatment arterial hypertension and use of antihypertensive drugs, patients with less favourable *VEGF* genotypes were estimated to have a 13 to 14 times greater likelihood of being hypertensive during treatment, compared with patients with the more favourable genotypes. On the other hand, none of the *VEGFR2* SNPs analysed were associated with the prevalence of arterial hypertension.[60] That study found no association between SNPs and outcomes, and the correlation between arterial hypertension and therapy outcomes was not explored. In another, more systematic search for a genetic background indicative of a prolonged PFS and/or OS, among 11 genes studied in 136 patients, genetic variants in the *CYP3A5*, *NR1I3* and *ABCB1* genes were predictive factors of prolonged PFS. In addition, a role for an allele of *VEGFR2* in prolonged OS as a secondary outcome was found.[64]

In a subgroup of 39 patients that we analysed, a trend for a possible pharmacogenetic relationship with sunitinib tolerance emerged.[17] Due to the limited number of cases, we have not studied the correlation between SNPs of *VEGF-A*/*VEGFR* genes and outcomes of therapy, but we have found clear associations between two SNPs of the *VEGF-A* gene and sunitinib-induced hypothyroidism. As already mentioned, the molecular mechanisms of sunitinib-induced hypothyroidism are unknown, but recent studies have suggested that

VEGFR inhibition can induce vasculature regression in various organs, predominantly the thyroid – an effect that can be linked to changes in the properties of the VEGF protein resulting from gene polymorphisms and sunitinib sensitivity.[65,66]

Conclusions and Perspectives

Many advanced GIST patients benefit from sunitinib in second-line therapy, with the median OS exceeding 1.5 years. Exploring the toxicity of multi-kinase targeting agents in GIST may allow better adjusted therapy as well as detection of novel pharmacogenetic/pharmacodynamic markers. The mechanisms of appearance of side effects and their correlation with pharmacogenetic data during sunitinib therapy need to be further studied. Another issue to address is the search for predictive markers of sunitinib therapy outcome. The ideal biomarker would be easy to measure, related to an inhibited target, of low cost and reliably present either at baseline or early after initiation of therapy.[51]

Several potential biomarkers for sunitinib treatment efficacy have been recently investigated (mainly in metastatic RCC). They included functional imaging, other than the above-mentioned treatment-related AEs, circulating VEGF pathway proteins, circulating soluble KIT extracellular domain[67] and VEGF pathway SNPs. None of them have been consistently associated with patient outcomes to the same degree as treatment-induced arterial hypertension. Both arterial hypertension and primary tumour genotype in GIST fulfill most of the postulates for applicable biomarkers, with cost and feasibility of blood pressure checks currently unmatched by any other diagnostic procedure. ■

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