Second- and Third-Line Treatment

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Abstract

Sunitinib (sunitinib malate; SU11248) is a novel oral multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenic activities. Sunitinib has been identified as a potent inhibitor of VEGFR-1, VEGFR-2, fetal liver tyrosine kinase receptor 3 (FLT3), KIT (stem-cell factor [SCF] receptor), PDGFRα, and PDGFR. Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. Regorafenib blocks the activity of several protein kinases involved with angiogenesis (vascular endothelial growth factor [VEGF] receptors 1–3 and TIE2), oncogenesis (KIT, RET, RAF1, B-RAF, and B-RAF V600E), and the tumor microenvironment (platelet-derived growth factor receptor [PDGFR] and fibroblast growth factor receptors [FGFR]). Sunitinib and Regorafenib are two targeted agents with worldwide approval for second- and third-line treatment, respectively, in metastatic GIST.

Keywords

GIST · Sunitinib · Regorafenib · Imatinib resistance

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9.1 Second-Line Treatment

9.1.1 Sunitinib

9.1.1.1 Mechanism of Action

Sunitinib (sunitinib malate; SU11248) is a novel oral multitargeted tyrosine kinase inhibitor with antitumor and antiangiogenic activities. Sunitinib has been identified as a potent inhibitor of VEGFR-1, VEGFR-2, fetal liver tyrosine kinase receptor 3 (FLT3), KIT (stem-cell factor [SCF] receptor), PDGFRα, and PDGFRβ in both biochemical and cellular assays [1]. In vitro, sunitinib inhibited the growth of cell lines driven by VEGF, SCF, and PDGF and induced apoptosis of human umbilical vein endothelial cells. In vivo, sunitinib caused bone marrow depletion and effects in the pancreas in rats and monkeys, as well as adrenal toxicity in rat (micro hemorrhage) [2]. In monkeys, a slight increase in arterial blood pressure and QT interval was reported at higher doses. Sunitinib exhibited dose- and time-dependent antitumor activity in mice, potently repressing the growth of a broad variety of human tumor xenografts.

9.1.1.2 Pharmacological Parameters

Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite [*N*-desethyl metabolite (SU012662)]. SU012662 is considered equipotent to the parent compound regarding the inhibition of VEGFR, PDGFR, and KIT [2–5]. In a human mass balance study of sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4%, and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance ranged from 34 to 62 L/h with an inter-patient variability of 40%.

9.1.1.3 Clinical Trial

Preclinical

Molecular mechanisms by sunitinib that exerts its antitumor function are not clearly elucidated, partly because available preclinical data are scarce. Preclinical studies with GIST cell lines suggest that SU11248 induces growth arrest and apoptosis of GIST cells. In addition, GIST cells exposition to SU11248 inhibits c-KIT autophosphorylation and the phosphorylation of AKT and ERK, key components of PI3K-Akt-mTOR and MAPK pathways, respectively, involved in cell survival and proliferation. This fact provides a rational for combining sunitinib with other target therapies directed to the mentioned pathways [6].

Phase I/II

An open-label, single-arm, dose escalation phase I/II trial in Western population enrolled 97 patients with metastatic GIST who have progressed to imatinib or they were intolerant to it [7]. Several doses and schedules were tested in different cohorts

in order to evaluate treatment safety: schedule 2/2 (2 weeks ON sunitinib, 2 weeks OFF) at doses of 25, 50, or 75 mg/day, and schedules 4/2 and 2/1 starting at 50 mg/day. The dose of 50 mg/day was defined as maximum tolerated dose because two of four patients treated at 75 mg/day 2/2 experienced dose-limiting toxicities during the first cycle (fatigue, nausea, and vomiting). Pharmacokinetic analysis revealed that steady-state was achieved by days 7–10 and 7–21 for sunitinib and SU12662, respectively. In order to maximize sunitinib exposure, the schedule 4/2 was selected for further development. Promising sunitinib activity was observed in this trial since 54% of patients benefited from the treatment. More concisely, 7 patients presented PR with a median time of 8.3 months to achieve it and 45 patients experienced long-lasting stable disease for a minimum of 6 months. Median PFS was 7.8 months (95% condense interval [CI], 5.1–10.4 months), and median OS was 19 months (95% CI, 12.9–21.5 months). Approximately 60 participants of this trial had a baseline positron emission tomography with 18Fluorodeoxyglucose (FDG-PET) and another on day 7 of cycle 1. Even if it will be detailed later, early metabolic responses correlated with better clinical outcomes.

In addition, sunitinib activity was also demonstrated in a preclinical setting because approximately half of the patients included had pre- and post-sunitinib biopsies. After 1 week of sunitinib treatment, levels of phospho-KIT in tumor samples as well as the expression of proteins involved in cell proliferation (cyclin A and AKT) in a percentage of patients were reduced. Mentioned early changes related to lower cell proliferation could correlate with better clinical outcomes, but it is a hypothesis to be further demonstrated.

Another phase I/II nonrandomized, open-label, and dose-escalating study aimed to evaluate the safety and preliminary efficacy of sunitinib in Asiatic population [8]. About 12 patients were enrolled in part I and doses of 25, 50, and 75 mg/day of sunitinib on schedule 4/2 were tested; 50 mg/day on schedule 4/2 until progression disease and/or unacceptable toxicity was designed as recommended phase II dose and after that several dose-limiting toxicities were observed in the cohort of 75 mg/day on schedule 4/2. A total of 36 patients were included in part II of the study and received the previously defined dose. According to response evaluation criteria in solid tumors (RECIST), 11% of patients experiment a PR and the disease control rate was ~61%. Median TTP was 28.3 weeks. Regarding safety, all patients included experienced at least one adverse treatment-related event, but 84% of them were grade 1/2 and generally manageable and reversible (Table 9.1).

Table 9.1 Efficacy of sunitinib and regorafenib in trials with patients treated for GIST

	Sunitinib		Regorafenib
	Phase I [8]	Phase III [9]	Phase III [10]
	$n = 97$	$n = 207$	$n = 133$
ORR	8(8%)	17(8%)	6(4.5%)
SD	36(37%)	37(18%)	95(71.4%)
TTP/PFS	7.8M	6.3M	4.8M
OS	19.8M	NR	NR

Phase III

After phase I/II trial, sunitinib efficacy was further demonstrated in a phase III trial [11]. This one was multicenter, randomized, double-blind, and placebo-controlled in patients who had presented imatinib resistance or intolerance. A total of 302 patients were randomly assigned 2:1 to receive sunitinib at doses established in phase I (*n*: 207) or placebo (*n*: 105). However, the trial was early unblinded due to the results of planned interim analysis that clearly favored sunitinib in terms of TTP. Median TTP in sunitinib arm was 27.3 weeks (95% CI 16.0–32.1) versus 6.4 weeks in placebo ones (95% CI 4.4–10.0; hazard ratio [HR] 0.33; 95% CI 0.23–0.47; $P = 0.001$). After these results, all patients treated with placebo were allowed to receive open-label sunitinib. OS data were more difficult to analyze because of the crossover. According to Kaplan–Meier method, OS did not reveal statistically significant differences between sunitinib and placebo (73.9 weeks versus 64.9 weeks; 95% CI 45.7–96.0; $P = 0.161$). Nonetheless, a posterior long-term OS analysis was performed using another statistical method that accounts for the bias introduced by the crossover from placebo to sunitinib, the rank-preserving structural failure time (RPSFT). RPSFT method identified clear differences in median OS favoring sunitinib group (73.9 weeks; 95% CI 61.3–85.7 versus 35.7 weeks; 95% CI 25.7–49.8; $P = 0.001$) [9, 12].

9.1.1.4 Safety

In a phase I/II trial with sunitinib in patients with imatinib-resistant/-intolerant GIST (*N* 97), the most commonly reported treatment-related AEs were grade 1–2 fatigue, diarrhea, skin discoloration, nausea, and hand–foot syndrome. Treatment-related grade 3–4 AEs included hypertension (17%), asymptomatic lipase increase (13%), and fatigue (10%). Eight patients (8%) discontinued treatment due to AEs.

In a phase III randomized controlled trial of sunitinib in patients (*N* 312) with imatinib-resistant/-intolerant advanced GIST, treatment-related AEs were reported in 83% (*n* 168) of patients in the sunitinib group and 59% (*n* 60) in the placebo group [9, 11]. An updated analysis of this study (*N* 361; *n* 243, sunitinib; *n* 118, placebo) reported the incidence of treatment-related AEs for the blinded, unblinded, and overall populations [13]. The profile of AE observed was similar to that of the phase I/II study. Moreover, similar incidences of AEs were observed in the blinded and unblinded populations. A slightly higher incidence of non-hematological AEs was noted with longer duration of sunitinib therapy. Treatment-related hypothyroidism (all grades) was reported in 13% of patients. Most hematological laboratory abnormalities were grade 1–2 and were similar in frequency to those occurring with shorter-term sunitinib therapy (Table 9.2).

9.1.1.5 Alternative Schedules of Sunitinib

Alternative schemes of sunitinib have been investigated in order to improve the safety profile and tolerance [14]. Sunitinib 37.5 mg once daily until PD and/or unacceptable toxicity were evaluated in an open-label, multicenter, phase II trial in which patients were randomized in a ratio of 1:1 in order to receive the mentioned

Table 9.2 Grade 3 or 4 toxicity of sunitinib and regorafenib in trials with patients treated for GIST

	Sunitinib		Regorafenib
	$n = 97$	$n = 207$	$n = 133$
Fatigue	10%	7%	1.50%
Diarrhea	7%	4%	5.30%
Nausea	4%	1%	0.80%
Dermatitis	7%	5%	19.70%
Stomatitis	3%	NA	1.50%
Lipase increase	13%	NA	NA
Hypertension	17%	4%	22.70%
Neutropenia	NA	8%	NA
Anemia	NA	4%	NA
Thrombocytopenia	NA	5%	30%

dose in the morning or in the evening [13]. The results of this trial in terms of both efficacy and toxicity overlapped with the phase III patients, with a median PFS of 34 weeks (95% CI, 24–49) and a median OS of 107 weeks (95% CI, 72 to not calculable). Consequently, sunitinib 37.5 mg once daily could be considered as an alternative dosing strategy, although it has not been directly compared with standard scheme. Regarding the optimal condition in sunitinib intake, no major differences were found between morning and evening dosing. In both the cases, no drug accumulation was observed across cycles and effective drug concentration was achieved.

Sunitinib 50 mg/daily in a schedule of 2 weeks ON/1 week OFF has been investigated in metastatic renal cell carcinoma. The RESTORE trial accrued 76 patients, and they were randomized to sunitinib 4 weeks ON/2 weeks OFF schedule or to the 2 weeks ON/1-week OFF regimen [15]. The results of this trial demonstrated better toxicity profile and better compliance with the 2/1 schedule. A retrospective analysis with 249 patients concluded with similar results [16]. Even though this scheme has not been evaluated in GIST patients, it could be considered in some patients with poor tolerance to the conventional schedule [17].

9.1.1.6 Surgery After Sunitinib Treatment

Unless treatment with sunitinib in metastatic GIST patients should be considered as palliative, a potentially radical surgery could be occasionally planned in the clinical practice if the response has been good enough. Nonetheless, the scientific evidence supporting this surgical management is very scarce. Two retrospective series with a very limited number of patients (10 and 50) suggest that post-sunitinib surgery is feasible, but the patients should be selected carefully because no clear improvement in terms of survival has been suggested. In addition, in the largest series, the surgery was frequently incomplete (not clearly related with the magnitude of the previous sunitinib response) and significant complications occurred in >50% of patients [18–20].

9.1.1.7 Mutational Status

Refractory GIST is a heterogeneous disease composed of a mixture of clones; each of them harbors different mutations mainly in KIT or PDGFRA. Despite every lesion in a given patient has the primary GIST mutation (except of wild-type GIST), secondary mutations can appear under treatment pressure and confer resistance to therapies. The percentage of secondary mutations in GIST with primary mutations is estimated to range between 44% and 90%, depending on the sensitivity of the method used to determine them. In addition, the development of several secondary mutations at the same time seems to be a common event. After imatinib exposure, secondary mutations are more commonly found in GIST with primary KIT exon 11 mutations than in GIST with primary KIT exon 9 mutations and not found in GIST wild-type. Secondary mutations after imatinib treatment are usually located at exons 13 (for example, V654A mutation) and 14 (for example, T607I mutation), both encode the ATP-binding pocket, or in exon 17 (encodes kinase activation loop) [21].

The potential role of primary and secondary mutations as predictor factors of sunitinib response has been investigated. A retrospective analysis using samples from patients who are included in a phase I/II sunitinib trial concluded that patients with KIT exon 9 mutations clearly benefited more of sunitinib than those patients who harbor KIT exon 11 mutations in terms of objective response rate (37% versus 5%; $P = 0.002$), PFS (19.4 months versus 5.1 months; $P = 0.0005$), and OS (26.9 months versus 12.3 months; $P = 0.012$). These results have also been reported in a series of 137 patients in whose tumors carried KIT exon 9 mutations or were wild-type and presented clearly better 1-year PFS compared with those whose tumors carried a KIT exon 11 or PDGFRA mutations (68% and 57% versus 34% and 15%, respectively). $KIT^{AY502\text{-}3ins}$ mutations at exon 9 is the most sensitive to sunitinib [22].

Regarding secondary mutations, in vitro studies with GIST cell lines suggest that sunitinib is highly active against kinase activity of KIT containing secondary mutations at ATP-binding pocket (exons 13 and 14), in contrast to GIST cell lines harboring imatinib resistant mutations at activation loop (exon 17, for example, D820Y, D820E, and NK822K, and exon 18). These findings correlate with better PFS and OS of patients treated with sunitinib with exon 13 and 14 mutations, compared with patients with exon 17 and 18 mutations, although these results should be further validated.

The 10–15% of GIST patients defined as "wild-type" (WT, no mutations in KIT neither in PDGFRA) are of special interest, since the vast majority do not respond to imatinib. In these cases, the deficiency of succinate dehydrogenase (due to either inactivating mutations or through epigenetic mechanisms) [23] and sporadic mutations in the MAPK pathway have a major role in tumor development. Among pediatric population, GIST WT is the most frequently found, sporadically or as a part of congenital syndromes such as Carney triad or neurofibromatosis type 1. In this subset of patients, sunitinib shows promising substantial antitumor activity and acceptable tolerability. In addition, preclinical data suggest higher antitumor efficacy of sunitinib compared with imatinib [23, 24].

9.2 Third-Line Treatment

9.2.1 Regorafenib

9.2.1.1 Mechanism of Action

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. Regorafenib blocks the activity of several protein kinases involved with angiogenesis (vascular endothelial growth factor [VEGF] receptors 1–3 and TIE2), oncogenesis (KIT, RET, RAF1, B-RAF, and B-RAF V600E), and the tumor microenvironment (platelet-derived growth factor receptor [PDGFR] and fibroblast growth factor receptors [FGFR]) [25, 26].

9.2.1.2 Pharmacological Parameters

Regorafenib is metabolized by CYP3A4 and UGT1A9. The main circulating metabolites of regorafenib measured at steady-state in human plasma are M-2 (*N*-oxide) and M-5 (*N*-oxide and *N*-desmethyl), both of them having similar in vitro pharmacological activity and steady-state concentrations as regorafenib. M-2 and M-5 are highly protein bound (99.8% and 99.95%, respectively).

9.2.1.3 Clinical Trial

Phase I

Several phase I studies have been performed with regorafenib. Mross and colleagues enrolled 53 subjects (16 with colorectal cancer) in an open-label, nonrandomized, dose-escalating phase I study using oral doses of 10–220 mg daily. The dose-limiting toxicities were found to be hand–foot skin reaction, rash, abdominal pain, and asthma seen at the dose of 220 mg dose level.

Another phase I dose escalation trial enrolled 38 subjects with advanced solid tumors (colorectal 16%) and used doses of 20–140 mg. The maximum tolerated dose in this study was 100 mg orally daily every 21 days, continuously.

Strumberg and colleagues also studied 38 subjects with refractory mCRC in a phase I dose escalation study. Patients enrolled on the dose escalation portion trial received doses of 60–220 mg/day of regorafenib. Based on the positive results of the dose escalation portion of this trial, additional mCRC patients were enrolled in an extension of the trial. These patients received 160 mg orally daily for 21 out of 28 days. The most common toxicities seen were hand–foot skin reactions, fatigue, voice change, and rash. A total of 27 patients were evaluable for response; of these 74% showed some disease control with regorafenib treatment.

Awada and colleagues investigated a different schedule of administration of regorafenib in their phase I trial. Patients received treatment in a 28-day cycle with 21 days of regorafenib treatment followed by 7 days off. Patients received oral doses of 10–120 mg daily. Pharmacokinetic and pharmacodynamic parameters as well as tumor response were evaluated in 44 patients with solid tumors. PK parameters

showed a linear association with dose and PD parameters correlated with dose exposure. Partial response and stable disease were achieved in two and four patients, respectively. The dose-limiting toxicity was reported in patients receiving the 120 mg dose. Adverse events included gastrointestinal (75%), dermatologic (71%), constitutional (68%), pain (64%), and hepatic (61%).

In 2010, George and colleagues undertook a phase II study of regorafenib in patients whose condition had previously failed to respond to both imatinib and sunitinib treatment for GIST [27]. In this trial of 33 patients, an impressive 75% experienced clinical benefit from the use of regorafenib (tumor response of complete or partial response, or stable disease for at least 16 weeks), with an overall PFS for the entire cohort of 10 months (95% CI 8.3–14.9 months). Both patients with wild-type GIST and KIT exon 9 and 11 mutations experienced clinical benefit at comparable rates (no PDGFRA mutations were detected among those in the trial). Those with KIT exon 11 mutations appeared to have a longer PFS compared with those with exon 9 mutations, although numbers were small. Most patients required at least one dose reduction due to toxicity (82%), with the most common adverse events being hand–foot skin reaction, hypertension, fatigue, and diarrhea. A number of these patients were subsequently able to re-escalate their dose of regorafenib. On the basis of the promising results obtained from the phase II study in GIST, the phase III GRID trial was undertaken.

Phase III

The GRID (GIST-regorafenib in progressive disease) trial, a double-blind, placebo-controlled study, enrolled 199 subjects with refractory GIST [10]. This study recruited patients with histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib (either through disease progression or from intolerance) and previous sunitinib (through disease progression only). Patients received regorafenib 160 mg by mouth or placebo daily for 3 out of 4 weeks each cycle.

The primary endpoint of the trial was progression-free survival (PFS) with overall survival (OS) as a secondary endpoint. There was a statistically significant difference between groups for progression-free survival with a median PFS of 4.8 months vs 0.9 months for the regorafenib vs placebo arms, respectively (HR 0.268, 95% CI 0.185–0.388, $P < 0.0001$). Prespecified subgroup analysis demonstrated HR mostly consistent with that of the primary analysis in favor of regorafenib. Specifically, the HR for those with exon 11 and exon 9 mutations were 0.21 (0.10–0.46) and 0.24 (0.07–0.88), respectively. Only the group that were on imatinib less than 6 months had a HR that crossed unity (HR 0.50, 95% CI 0.17–1.73).

There was no difference between groups for overall survival with a hazard ratio (HR) of 0.772 (95% confidence interval [CI]: 0.423, 1.408, p-value 0.199). Given the high level of crossover in the trial, the overall survival data should be interpreted with caution. There was no significant difference in benefit achieved between those with exon 9 or exon 11 KIT mutations in this study. Subgroup analysis showed benefit across age groups, geographic location, and line of therapy (third versus fourth line), with only those who had an imatinib duration of less than 6 months failing to show a PFS benefit [28, 29].

9.2.1.4 Safety

The most common adverse reactions reported were HFSR (56%), hypertension (48.5%), diarrhea (40%), and fatigue (38.6%). Of these toxicities less than half were grade 3 or higher. Grade 3 toxicities were seen in 19.7% of HFSR adverse events, 22.7% of hypertension adverse events, 5.3% of diarrhea adverse events, and 2.3% of fatigue adverse events. The only grade 4 toxicity was reported in patients with hypertension with only 0.8% of patients reporting this toxicity.

Severe drug induced liver injury with fatal outcome occurred in 0.3% of 1100 regorafenib-treated patients across all clinical trials. Liver biopsy results, when available, showed hepatocyte necrosis with lymphocyte infiltration. In clinical trial, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and 0.4% of patients in the placebo arm; all the patients with hepatic failure had metastatic disease in the liver.

Obtain liver function tests (ALT, AST, and bilirubin) before initiation of regorafenib and monitor at least every 2 weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the ULN or baseline [30].

Temporarily hold and then reduce or permanently discontinue regorafenib depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis [31, 32].

9.2.1.5 Mutation Status

A preplanned retrospective biomarker analysis has used the pretreatment tissue specimens from patients enrolled in the GRID trial and compared the mutations detected with those subsequently found in blood samples at the time of resistance to imatinib and sunitinib at the time of entry to GRID. The group found resistance mutations in 48% of the blood samples, but only 12% of the pretreatment tissue samples. In addition, in almost half of those samples that harbored known secondary mutations, multiple mutations were present. Regorafenib showed activity across a range of secondary KIT mutations, reinforcing its utility in this setting, but questions remain about how to differentiate those most likely to respond to treatment from those who will not. In addition, two trials are currently underway, attempting to determine biomarkers that may correlate with clinical efficacy of regorafenib when used for metastatic colorectal cancer. Any positive results from these studies would warrant investigation in the GIST population to determine if the findings were similarly useful and could lead to more judicious use of regorafenib in this group.

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