Current status of sunitinib combined with radiotherapy or surgery: summary of available data and implications for patient care

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Sunitinib malate (Sutent®) is an oral multi-target receptor tyrosine kinase (RTK) inhibitor with potent anti-angiogenic and antitumour activities. It was recently approved for treatment of patients with metastatic gastrointestinal stromal tumour (GIST), resistant or intolerant to imatinib and for treatment of advanced renal cell cancer (RCC).

Several preclinical studies suggest that combining angiogenesis inhibitors with radiation may enhance the therapeutic ratio of radiation via targeting vasculature and tumour cells. Therefore, several clinical studies have been initiated to investigate the possible efficacy and tolerability of the combination of sunitinib and radiotherapy, with promising, though preliminary results. Sunitinib has also been used in association with surgery, in the neoadjuvant setting to facilitate resection of the primary tumour, as consolidative surgery to remove resting tumour after sunitinib treatment and in the emergency setting to treat complications such as bowel perforation, haemorrhage or tumour rupture.

To date, no evidence-based recommendations have been formulated regarding the combination of sunitinib with radiotherapy or surgery, e.g. only few clinical data are available on the recommended time interval between sunitinib and radiotherapy or surgery or on the management of possible complications associated with the use of combinations of the different treatment modalities. The objective of this short review is to summarise the available preclinical and clinical data on the association of sunitinib with radiotherapy or surgery, to reflect on the possible implications for patient care and, finally, to present some guidance for daily practice in treating patients with sunitinib and radiotherapy or surgery.

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Introduction

Sunitinib is an oral RTK inhibitor inhibiting vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR)

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Conflict of interest: The Department of General Medical Oncology at the University Hospitals Leuven has received research grants from Pfizer Inc. to study side-effects of tyrosine kinase inhibitors and has received honoraria for inclusion of patients in Pfizer-related trials. P. Wolter has received honoraria from Pfizer for invited lectures and active participation in scientific events.

Key words: sunitinib, toxicity, radiotherapy, surgery.

isoforms which play a role in tumour proliferation, angiogenesis and metastasis.

Sunitinib is approved for treatment of patients with metastatic malignant GIST with intolerance to or disease progression on imatinib and advanced or metastatic RCC.[1]

As an anti-angiogenic agent, sunitinib reduces the formation of new blood vessels resulting in stabilisation of tumour growth or even tumour regression. Although stabilisation of the disease or partial responses can be achieved in the majority of metastatic RCC patients under sunitinib, complete responses have been described only rarely, and the majority of patients will ultimately develop tumour progression. For this reason, the question is raised whether the combination of sunitinib with other treatment modalities such as radiotherapy or surgery could yield better results. The combination of radiation and sunitinib is used in several trials to enhance the efficacy of both therapies. Metastatic RCC is often considered as a radioresistant malignancy and radiotherapy is mostly reserved for palliative treatment of metastatic lesions in the bone, the lymph nodes or the brain in selected patients. Since, at least in preclinical models, sunitinib sensitises cancer cells to the cytotoxic effect of radiation, there is a rationale to test this in clinical studies. However, until now clear data on e.g. the doses and fractions to use or on the recommended time interval between sunitinib and radiotherapy or on the management of possible complications associated with the use of radiotherapy are lacking. The same holds true for the combination of sunitinib with surgery.

In this short review we describe the mechanism of action of sunitinib and the clinical efficacy of the drug and summarise the available preclinical and clinical data on the association of sunitinib with radiotherapy or surgery.

Mechanism of action

Sunitinib (SU11248) is a small molecule RTK inhibitor inhibiting VEGFR (1, 2 ,3) and PDGFR (α, β) isoforms, stem-cell factor (SCF) receptor c-kit, FMS-like tyrosine kinase 3 (FLT3), glial cell line-derived neurotrophic factor receptor RET (Rearranged during Transfection) and colony stimulating factor 1 receptor (CSF-1R), which plays a role in tumour proliferation, angiogenesis and metastasis.[2, 3]It binds to

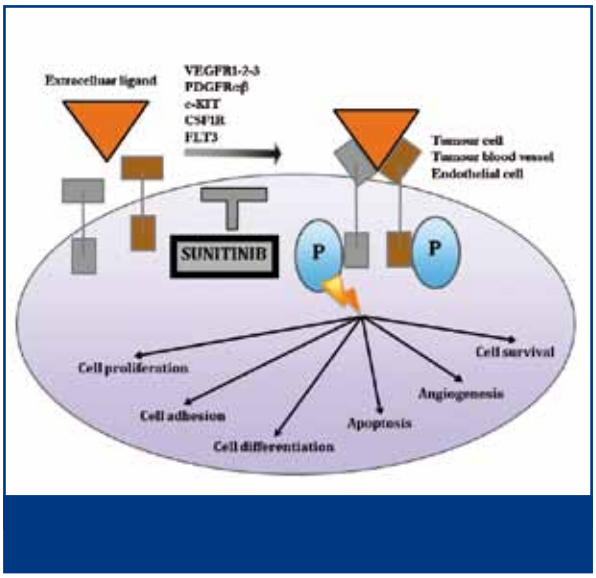

Figure 1. Mechanism of action of sunitinib.

the intracytoplasmatic domain of the RTK and acts as a direct inhibitor of the autophosphorylation step of the RTKs. This inhibition leads to blockade of the downstream signaling leading to both anticancer- and anti-angiogenic activity.[4, 5, 6] (*Figure 1*)

Angiogenesis is important for the growth of tumour cells and for their metastatic potential.[7] VEGF A and its receptor have been identified as regulators of angiogenesis.[4] Angiogenesis is a complex multistep process closely regulated by a balance between pro-angiogenic and anti-angiogenic factors under physiological circumstances .[7] Binding of VEGF to the transmenbrane receptor on endothelial cells (EC) initiates a cascade of intracellular downstream reactions mainly mediated by MAP (mitogen-actived protein kinase) kinase and PI13 (phosphatidylinositol-3-kinase)/Akt/mTOR(mammalian target of rapamycin).[4,6]

In cancer, there is an imbalance between pro-angiogenic factors such as PDGF, fibroblast growth factor (FGF) and endogenous anti-angiogenic factors such as angiostatin and endostatin, leading to an angiogenic switch.[8]This leads to the formation of new tumour blood vessels, which are abnormal in structure and function with irregular blood flow. This abnormal tumour vasculature does not permit an optimal supply of oxygen and nutrients resulting in areas of necrosis or enhancing hypoxia in growing tumours. This cellular hypoxia results in the expression of hypoxia-inducible factor-1 α (HIF-1α) with subsequent upregulation of pro-an-

Table 1. Overview of published clinical trials: Sunitinib and RT

References	Type of tumour	Number of patients	RT	Targeted therapy	RT toxicity
Kao[31]	oligometastatic cancer Phase I	21	40-50 Gy in 10 fractions	day 8 of sunitinib 37.5 mg, schedule 4/2 followed by maintenance sunitinib 50 mg on day 43	not increased (n=1) Grade 4 Mvelosuppression (n=1) Grade 3 nausea
Staehler[32]	RCC	22	40 Gy (range 25-60) in 12 fractions (range 5-30) of 3.5 Gy (range 2.5-5)	sunitinib 50 mg daily, schedule 4/2	not increased 13.6% (n=3) grade 3 or 4 nausea 4.5% (n=1) grade 4 cardiac toxicity
Wulthrick[33]	primary and metastatic CNS malignancies Phase I	23	14-60 Gy in fractions of 1.8-3.5 Gy	sunitinib 37.5 mg daily	39% grade 3 toxicities (hematologic, fatigue, DVT)
Chi[34]	HCC	23	52.5 Gy in 15 fractions	25 mg sunitinib 1 week before and during, and 2 weeks after	13% (n=3) upper GI bleeding 4.3% (n=1) pancreatitis 43.5% (n=10) ≥ grade 2 elevation of liver enzymes 65.2% (n=15) ≥ grade 2 thrombocytopenia

RT: radiotherapy; RCC: renal cell carcinoma; CNS: central nervous system; DVT: deep venous thrombosis; HCC: hepatocellular carcinoma; GI: gastrointestinal.

giogenic protein expression in the tumour cells and surrounding stromal cells leading to further vessel production.[4,9] As a VEGFR inhibitor, sunitinib reduces the formation of new blood vessels resulting in tumour growth stabilisation or regression.

Clinical efficacy

From a multicenter, randomised phase III trial in patients with previously untreated metastatic RCC median progression-free survival was doubled (11 versus 5 months)[12] in patients receiving sunitinib at the classical schedule of 50 mg/d, 4 weeks on followed by 2 weeks rest compared to those receiving interferon-α (IFN-α).[12, 13] The updated results of Motzer et al showed that the objective response rate was 47% for sunitinib compared to 12% for IFN-α[13] and that the median overall survival was greater in the sunitinib group than in the IFN-α group (26.4 versus 21.8 months).[13]

In a double-blind, placebo-controlled phase III trial of metastastic GIST after failure or intolerance to imatinib sunitinib in comparison to placebo significantly prolonged time to progression (27.3 versus 6.4 weeks)[14], by using the rank-preserving structural failure time (RPSFT) method to account for crossover, long-term overall survival benefit was also confirmed.[15]

On basis of these results, sunitinib received approval in the United States by the Food and Drug Administration (FDA) in January 2006 and in the European Union in January 2007.[1]

Sunitinib is also currently being studied with a broad range of other tumours, although results of recent clinical trials with sunitinib in breast, colorectal and lung cancer at least in monotherapy are disappointing.[16, 17, 18, 19]

Clinical use and pharmacokinetics

A dose-ranging pharmacokinetic trial of patients with advanced solid tumours identified 50 mg daily on 4/2 treatment schedule (meaning 4 weeks on treatment followed by 2 weeks without treatment) as the recommended dose of SU11248 based on the demonstration of clinical efficacy and acceptable tolerability.[20] An effective plasma concentration is reached within 30 minutes, peaks by 6 hours and remains at an effective level for 12 hours after a single dose.[5, 21]Food does not appear to affect its bioavailability. Sunitinib is metabolised hepatically by cytochrome P450 (CYP) 3 A4 to an active metabolite, SU 12662, which is further metabo-

Table 2. Overview of published clinical trials: sunitinib and surgery.

References	Type of tumour	Number of patients	Median time of withhold treatment before/after surgery	Targeted therapy	Complication rate
Bex[46]	RCC	10	48 hours/1 or 3 weeks (n=3)	sunitinib	no
Margulis[44]	RCC	44	20 days/ 11 days/ 40 days	sunitinib (n=15)/ sorafenib/ bevacizumab	39% (neoadjuvant)/ 28% adjuvant)
Hellenthal[49]	RCC	20	Not described	sunitinib	no
Amin[48]	RCC	9	6 days (range 2-28)	sunitinib/ sorafenib	no
Thomas[45]	RCC	19	7 days before or after	sunitinib (n=12)/ sorafenib/ bevacizumab + IL2	16% (1hemorraghe+ DIC; 1 anastomic bowel leak and abscess)
Raut[42]	GIST	26	5 days before/ 33 days after	sunitinib	50%
Thibault[43]	RCC	52(9)	8.5 days before/ 24.7 days after	sunitinib	18% (n=2)

RCC: renal cell carcinoma; GIST: gastrointestinal stromal tumor; DIC: disseminated intravascular coagulopathy; IL2: interleukine 2

lised by CYP 3A4 to an inactive moiety through 2 N-de-ethylation steps. The half-lives of sunitinib and SU 12662 are 40 to 60 hours and 80 to 110 hours respectively. [5,21] Steady-state concentrations of both active entities are reached after 10 to 14 days of therapy.[5,21] Fecal excretion is the major route of elimination of sunitinib.[21]

Toxicity of sunitinib

The tolerability of sunitinib has been reported in a number of studies, including phase I, phase II, and phase III clinical trials in metastatic RCC and finally an expanded-access trial in metastatic RCC.[12,13, 20, 22] In general, adverse events have been manageable and mild-to-moderate in nature. Adverse events during treatment with sunitinib leading to treatment discontinuation appear in 8-20% of the patients, dose interruption and dose reduction were needed in about one third of the patients. [12, 22]

The most commonly reported grade 3 adverse events were hypertension (12%), fatigue (11%), diarrhoea (9%) and hand-foot syndrome (9%).[13,21] Less common reported grade 3 adverse events were nausea or vomiting (+/-5%), oral disorders such as stomatitis, dysgeusia or dyspepsia (1-2%), skin discolouration or rash (<1%).[13,21] Thyroid dysfunction under sunitinib was initially only rarely reported, but several retro- and prospective studies addressing this specific problem reported a much higher frequency of hypothyroidism and other thyroid dysfunction(36-85%).[23] The same holds true for severe cardiac toxicity which is reported in about 10% of sunitinib treated patients. [24]

Haematological and laboratory abnormalities such as liver enzymes elevation and electrolyte disturbances appear in 10% of the patients and the predominant grade 3 or 4 laboratory abnormalities were neutropenia, lymphopenia and increase in lipase (all +/-18%).[21]

Bleeding events including mostly epistaxis appear in 26% of the patients and are mostly mild of grade 1 or 2 severity.[12, 25] Je et al reported results of meta-analysis showing a twofold increased risk of bleeding in patients treated with sunitinib during more than 6 months.[26]

The risk for gastrointestinal perforation, fistula formation or peritonitis is very low except for patients with known risk factors.[25, 27] Therefore, awareness of pre-existing diseases of the patients before starting with sunitinib is of the utmost importance.

The toxicity profile of sunitinib seems to depend on the type of malignancy as well , with cardiotoxicity, hypothyroidism and bleeding events being more common in those patients with metastatic RCC than those with advanced GIST.[21]

In general, the adverse events can be easily managed by dose reduction, dose interruption or standard supportive medical therapies.[21]

Sunitinib and radiotherapy

Sunitinib is not approved for concurrent therapy with radiotherapy.[21]

Preclinical studies

The possible mechanism of action of combining sunitinib and radiotherapy is complex but some explanations can be found. Firstly, there is a synergistic or additive response to radiotherapy by improving tumour oxygenation through inhibition of the neovascularisation process and so decreasing chronic diffusion limited and acute perfusion limited tumour hypoxia.[9, 10] Anti VEGFR therapy results in transiently normalisation of the morphology and function of surviving tumour blood vessels resembling the normal vasculature. These changes reduce the intratumoural pressure and facilitate the application of other anticancer therapies to the tumour.[9] Secondly, an increased apoptosis is found in both tumour cell and stromal compartiment due to improved radiosensitivity by direct inhibiting protective cell survival signaling pathways in both endothelial and tumour cells.[9]

But on the other hand, the use of anti VEGF therapy can result in decreased microvessels density and vascular collapse and consequently, may increase tumour hypoxia and thus radioresistance. Therefore, the anti VEGF therapy needs to be combined with radiotherapy during the optimal oxygenation window of the tumour.[11] Further studies are needed to determine the most optimal time window of a combined approach with radiotherapy.

Several preclinical studies have demonstrated that sunitinib did enhance the effects of radiation in vitro with an enhancement ratio of 1.25 and in murine xenograft tumour models by selectively targeting tumour vasculature.[28,29] Schueneman et al described in murine tumour models a prolongation of tumour control with sunitinib maintenance therapy after completion of fractionated radiotherapy.[29] Yoon et al also described enhanced efficacy of radiotherapy in combination with sunitinib in a mouse model of soft tissue sarcoma (STS). They described a maximal growth inhibition of 71% in the STSs treated with sunitinib and radiotherapy. Sunitinib, or this combination with radiation decreased the microvessel density by 66% and induced significant endothelial cell apoptosis.[30]

Overview of the published clinical trials (*Table 1*)

Kao et al recently presented the results of a phase I study in 21 patients with oligometastases (1-5 metastatic sites of measuring ≤6 cm, different metastatic sites and of different metastatic cancers). The objective of this study was to determine the safety and maximum-tolerated dose of concurrent sunitinib and image-guided radiotherapy followed by sunitinib maintenance. The doses were escalated with incremental increases in either sunitinib or radiotherapy. Although the authors conclude that sunitinib can be safely integrated into dose-intense protocols of image-guided radiotherapy without potentiation of radiotherapy toxicity[31], the classical dose of 50 mg/d together with 50 Gy in 10 fractions could not be given, due to dose-limiting toxicities and the recommended dose of this trial was 37.5 mg/d with 50 Gy in 10 fractions.[31]

In contrast to this, Staehler et al reported promising results with sunitinib at the classical dose of 50 mg/d, 4 weeks on and 2 weeks off and concomitant radiotherapy in 22 patients with rapidly progressive metastatic RCC. They reported that the toxicity of combination was low and manageable.[32]

Wuthrick et al reported results of a what they called phase I study of 23 patients with primary and metastatic central nervous system malignancies, who were treated with radiation therapy and received 37.5 mg sunitinib daily with the option to continue sunitinib for 30 days after radiation. Although 39% of the patients had grade 3 toxicities, they concluded that the combination therapy is safe with acceptable toxicity.[33]

Chi et al retrospectively reviewed their results of 23 patients with advanced HCC who were treated with hypofractionated radiotherapy and 25 mg sunitinib daily 1 week before, during and 2 weeks after radiotherapy. They reported an objective response in 74% of patients with an acceptable safety profile.[34]

Case reports

Case reports of patients treated with sunitinib and concomitant radiotherapy were published for metastatic RCC, clear-cell sarcoma and metastatic papillary thyroid carcinoma.[35-37] These reports show synergetic effects between sunitinib and radiotherapy with good tumour response and without complications.

On the other hand, several case reports demonstrated serious side effects with the combination of sunitinib and radiotherapy. Basille et al described a

case of bronchial fistula associated with sunitinib after mediastinal radiotherapy and Kelly et al recently described a case of sunitinib-induced pseudoprogression after whole brain radiotherapy of brain metastases of RCC.[38,39]

Current trials

Currently, several clinical trials in many different tumour types are running and a list of these current trials can be found on http:// www.clinicaltrials.gov.
In the absence of evidence-based guidelines, we suggest interruption of sunitinib treatment during palliative radiotherapy, stopping a few days before and resuming treatment a few days after radiotherapy.[21]

Sunitinib and surgery

Until now, no evidence-based recommendations regarding the precise time interval between sunitinib and surgery[21] have been formulated, although 2 recent reviews addressed the problem of surgery and VEGF targeted therapy and give some guidance for patient care.[27, 41]

Overview of published clinical trials (*Table 2*)

Raut et al compared the rate of wound healing complications after surgery in patients with metastatic GIST treated with sunitinib to the rate in patients with metastatic GIST treated with imatinib. They concluded that no more common wound-healing complications were found after surgery.[21,42] Thibault et al evaluated postoperative complications in 52 patients treated with sunitinib for metastatic RCC during the perioperative period. They concluded that postoperative wound healing complications where higher in patients with sunitinib-induced skin toxicity before surgery.[43]
However, another study of Margulis et al concluded that surgical resection can be performed safely and without an increase in peri-operative morbidity or mortality after systemic therapy with sunitinib for RCC.[44]
Thomas et al retrospectively evaluated 19 patients with advanced RCC receiving targeted therapy prior to surgery. They concluded that surgical resection is feasible with low morbidity, although significant complications can occur. [45]
Bex et al reported to have safely performed cytoreductive surgery in a RCC patient who discontinued sunitinib treatment 48 hours before surgery, suggesting that in some patients a short time interval may be sufficient to perform surgery safely while minimising the risk for a rebound phenomenon with accelerated tumour growth in the rest period.[46, 47]
Amin et al described the results of 9 patients with locally advanced or metastatic RCC treated with sorafenib or sunitinib before nephrectomy. All patients tolerated the surgery well without complications after a median time off therapy of 6 days. [48]
Hellenthal et al evaluated 20 patients with metastatic RCC receiving sunitinib for 3 months before surgery. They concluded that preoperative treatment with sunitinib is safe.[49]

Case reports

Ruka et al described 4 case reports of female patients with inoperable and/or metastatic GIST resistant to imatinib responding to sunitinib therapy in 4/2 schedule. Later, they underwent surgical removal of the residual disease. Sunitinib was resumed post-surgery. None of the patients experienced any postoperative complications during the 13- 16 months of follow-up.[50]
Shuch et al reported results of 4 patients treated preoperatively with targeted therapy such as sunitinib where there was no increased surgical morbidity or perioperative complications.[51]
Interpretation of the above mentioned studies is hampered by their moderate quality. Most of the studies reported so far are retrospective, with only small and heterogeneous patient populations, sometimes even different angiogenesis inhibitors and poor standardisation of the procedures. However, several prospective clinical trials in the adjuvant and neoadjuvant setting are ongoing and will most likely answer these questions. Most of the adjuvant studies propose to wait 4 weeks after surgery, and empirically this seems to be reasonable. Awaiting the results of these studies based upon pharmacokinetic considerations, we suggest a stop of sunitinib 1 week before elective major surgery, representing 2-3 half-lives of sunitinib.[27, 52] However, the combination of several drugs with the potential toxic side effects on the gastrointestinal tract such as steroids and/or non-steroidal anti-inflammatory drugs can increase the risk of serious complications such as gastrointes-

Key messages for clinical practice

1. Sunitinib is an oral multi-target RTK inhibitor with potent anti-angiogenic and antitumour activities.

2. Sunitinib is administered as 50 mg per day for 4 weeks followed by 2 weeks rest. It is approved for treatment of patients with GIST with intolerance to or disease progression on imatinib and advanced or metastatic RCC.

3. Sunitinib is currently under investigation in clinical trials in the neo-adjuvant setting to facilitate tumour resection, in the adjuvant setting as maintenance therapy to eliminate or slow down the disease progression and in clinical trials in advanced stages in combination with radiation therapy and chemotherapy to enhance the efficacy of cancer treatment with acceptable toxicity.

4. The precise recommendations regarding the timing of surgery after neo-adjuvant therapy with sunitinib depend on the tumour type and the type of surgical resection. We suggest stopping sunitinib 7 days before major surgery and at least 3-4 days before minor surgery (see Table 2).

5. Restart of sunitinib is recommended not earlier than 4 weeks after surgery to diminish the complication rate as wound dehiscence, gastro-intestinal perforation and haemorrhage.

6. Specific guidelines for the time interval between sunitinib and radiotherapy have not been formulated. Some current studies recommend stopping 1 day before and resuming treatment 1 day after radiotherapy. Based on the pharmacokinetics of sunitinib and its metabolites of 40-110 hours, we prefer stopping sunitinib 2-4 days before radiotherapy and resuming it 2-4 days after radiotherapy, unless an emergency occurs.

tinal perforation and should be taken into account. The optimal time interval must be individualised depending on co-morbidity or health status of the patient and his wound healing process.

Conclusions

Sunitinib as a multi-target RTK inhibitor has potent anti-angiogenic and antitumour activities and is being studied as a promising treatment option for several cancer patients. Combining therapies of RTK inhibitors before or after surgery, with chemotherapy or radiotherapy are under investigation to enhance the efficacy of the different treatment modalities. However, awareness about the toxicity of sunitinib and the synergistic effects with combination therapy is needed. Until nowadays there are no evidence-based guidelines for the best suitable time interval between sunitinib and surgery or radiotherapy. We recommend stopping sunitinib at least 1 week before major surgery and to start it 4 weeks after surgery. For radiotherapy we recommend stopping it a few days before radiotherapy. Finally, we can conclude that further confirmatory prospective studies are required to assess safety and efficacy.

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