Tyrosine kinase inhibition in renal cell carcinoma and gastrointestinal stromal tumours: case reports

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Introduction

Sunitinib malate (SUTENT®, Pfizer Inc.) is an oral, multitargeted receptor tyrosine kinase (RTK) inhibitor with proven antitumour and antiangiogenic activity. Sunitinib is the reference standard of care for the first-line treatment of metastatic renal cell carcinoma (mRCC) and advanced imatinib-refractory gastrointestinal stromal tumour (GIST). Greater exposure to sunitinib is associated with improved efficacy. Therefore, minimising the impact of adverse events (AEs) on patient quality of life is important to enable patients to achieve optimal exposure to sunitinib and maximum clinical benefit.

Background: Sunitinib malate is approved multinationally for the treatment of metastatic renal cell carcinoma (mRCC) and advanced imatinib-refractory gastrointestinal stromal tumour (GIST). Greater exposure to sunitinib is associated with improved efficacy. Therefore, minimising the impact of adverse events (AEs) on patient quality of life is important to enable patients to achieve optimal exposure to sunitinib and maximum clinical benefit.

Design: This report describes four patient cases in which sunitinib was utilised for the management of advanced malignancies: two cases describe mRCC patients who received first-line sunitinib and two cases describe the use of targeted therapies, including sunitinib, in patients with advanced GIST.

Results: In all four cases, effective AE management enabled patients to receive long-term therapy with sunitinib and achieve sustained clinical benefit. The two mRCC cases show prolonged responses and manageable AEs with sunitinib. The two GIST cases demonstrate that patients with imatinib-refractory GIST with KIT exon 9 mutations, including elderly patients, can achieve sustained responses to sunitinib.

Conclusions: These case studies support the long-term efficacy and safety of sunitinib in the management of mRCC and imatinib-refractory GIST and demonstrate how AE management can be used to optimise patient responses.

Key words: gastrointestinal stromal tumour, metastatic renal cell carcinoma, sunitinib malate, tyrosine kinase inhibitor

Case reports: patients with mRCC

These cases illustrate therapeutic strategies with first-line sunitinib in two mRCC patients, showing how prognostic risk stratification using Memorial Sloan-Kettering Cancer Center (MSKCC) criteria can be applied in routine clinical practice. The MSKCC model is used to stratify patients into prognostic risk groups based on the number of risk factors that they exhibit, with favourable-risk patients exhibiting no risk factors, intermediate-risk patients exhibiting one or two risk factors...
and poor-risk patients exhibiting three or more risk factors [11]. Risk factors for reduced survival comprise: low haemoglobin (<13 g/dl for males, <11.5 g/dl for females); high corrected calcium (>10 mg/dl); high lactate dehydrogenase (LDH; > 1.5 times the upper limit of normal); poor performance status (baseline Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 or 2); and an interval of <1 year from diagnosis to treatment [11].

Among the four targeted agents available in Europe, sunitinib is currently recommended in the European Association of Urology (EAU) guidelines as the first-line standard of care for patients with mRCC who are considered to be at favourable or intermediate prognostic risk [1], while for poor-prognosis patients, temsirolimus (Torisel®, Wyeth Pharmaceuticals) is recommended [1], and sunitinib may also be considered [1]. Other targeted agents licensed for mRCC include combination therapy with bevacizumab (Avastin®, F. Hoffmann-La Roche), plus interferon-alfa (IFN-α) and sorafenib (Nexavar®, Bayer Healthcare).

The cases described here demonstrate the use of sunitinib in patients with mRCC following the occurrence of metastases. In both patients, AEs were managed so that patients could continue to receive maximum exposure to sunitinib treatment.

case report 1
A 52-year-old woman who had been experiencing mild lower back pain presented with a renal mass on the left kidney of 10.0 cm in size without regional lymph node involvement and with no distant metastases. A left radical nephrectomy was performed successfully and histological examination revealed clear-cell RCC (stage T2N0M0).

The patient remained asymptomatic with unremarkable follow-up for 7 years, after which she experienced mid-abdominal pain, dyspepsia, anorexia and mild fatigue. At 7 years post-nephrectomy, metastatic disease was diagnosed by computed tomography (CT), with three liver lesions, measuring 1.0–1.4 cm, and one pancreatic lesion of 3.5 cm in size. Fine-needle aspiration biopsy of one of the liver lesions was consistent with clear-cell RCC.

Analysis of prognostic risk factors by MSKCC risk stratification revealed a corrected serum calcium level of 9.6 mg/dl, haemoglobin of 11.1 g/dl, LDH of 179 U/l, an ECOG PS of 1 (Karnofsky performance status 70–80%) and a disease-free interval of >12 months.

The patient was considered to be at intermediate risk, due to her performance status and low haemoglobin levels, and was commenced on sunitinib therapy at a dose of 50 mg/day by Schedule 4/2 (6-week cycles of 4 weeks on treatment followed by 2 weeks off treatment) in a randomised phase III trial. She achieved a partial response (PR) for >3 years, and a significant reduction in the size of liver and pancreatic lesions (Figure 1).

Toxicities reported for this patient during sunitinib therapy included weight loss (<10%), grade 3 fatigue, grade 3 neutropenia and a transient 25% reduction in left ventricular ejection fraction (LVEF). These toxicities were managed by reducing the sunitinib dose level to 37.5 mg/day and then to 25 mg/day (still on Schedule 4/2), which enabled the treatment to be continued with no unexpected long-term toxicities.

The patient’s PR was maintained for 42 months of treatment, after which disease progression occurred in the liver and sunitinib therapy was stopped.

case report 2
A 58-year-old man with a history of hypertension presented with painless haematuria. A 6.5 cm lesion was identified in the centre of the left kidney with no detectable spread to the retroperitoneal lymph nodes. The patient also exhibited metastases in the bone and mediastinal lymph nodes. A nephrectomy was performed and histological examination revealed a 6.8 cm clear-cell RCC lesion with capsular invasion, Fuhrman grade 3 (stage pT3aNxM1).

Risk factor analysis by MSKCC risk stratification revealed a Karnofsky performance status of 90% (ECOG PS 0). Treatment and follow-up were postponed for 2 months post-nephrectomy due to the patient’s work commitments. On resumption of treatment, the patient’s Karnofsky performance status remained at 90% and levels of corrected serum calcium, LDH and haemoglobin were within the normal range (9.48 mg/dl, 305 U/l and 13.0 g/dl, respectively). The patient was considered to be at favourable risk and was started on treatment with sunitinib at 50 mg/day on Schedule 4/2.

After 6 months of sunitinib therapy, the patient achieved a PR to treatment, according to Response Evaluation Criteria in Solid Tumors (RECIST). However, he experienced grade 1 fatigue during the first three treatment cycles, which increased in severity during the fourth cycle, and grade 1 diarrhoea and cutaneous erythema, and his Karnofsky performance status declined to 70% (ECOG PS 1). His toxicities were managed by temporarily reducing the sunitinib dose to 37.5 mg/day (on Schedule 4/2), which resulted in the disappearance of the diarrhoea and cutaneous toxicity and improvements in fatigue. He also received treatment for hypothyroidism.

Following treatment at the reduced dose for 4 months, the sunitinib dose was re-escalated to 50 mg/day after the identification of changes in tumour morphology (reduced tumour necrosis, increased peripheral tumoral vascular ring) suggestive of tumour regrowth. The PR was maintained on the higher dose, tumour necrosis was re-established and vascularisation was reduced. The patient remained on treatment for another 13 months (Figure 2).

At 23 months after the initiation of sunitinib therapy, disease progression occurred in the patient’s metastatic lesions and three new metastases, each measuring 2 cm in size, were identified in the lungs. Sunitinib was discontinued and the patient was administered sorafenib 800 mg/day, which was associated with some tumour shrinkage in all but one metastatic site. After 6 months of sorafenib therapy, the patient died following palliative surgery to a treatment-resistant costovertebral metastasis.

case reports: patients with GIST
The following two case studies illustrate the optimal use of targeted agents for the treatment of patients with advanced GIST exhibiting KIT exon 9 mutations. The cases also demonstrate how mutational analysis can assist with the selection of individualised therapy in patients with GIST.
Most GISTs express the gene for KIT, a transmembrane RTK for stem cell factor [14], and a substantial proportion exhibit KIT gene mutations [15,16]. KIT-activating mutations most frequently involve the intracellular domain of the KIT receptor encoded by exon 11 or the extracellular domain encoded by exon 9 [17, 18].

Current guidelines issued by the European Society for Medical Oncology (ESMO) recommend imatinib 400 mg/day for the first-line treatment of patients with KIT-positive unresectable and/or metastatic GIST [6]. However, whilst patients with the most prevalent KIT exon 11 mutations usually respond to standard-dose imatinib [19, 20], GISTs with KIT exon 9 mutations are often resistant to imatinib at this dose [19–21]. Sunitinib has demonstrated clinical activity in patients with KIT exon 9 mutations as well as in patients with the more prevalent KIT exon 11 mutations and in those with the wild-type GIST genotype [22]. These findings indicate the potential benefit of sunitinib in certain patient subgroups, including those with KIT exon 9 mutations.

The two case studies described here demonstrate dose adjustment and AE management strategies that may be utilised to achieve long-term treatment with targeted agents in patients with GIST. In both cases, the patients presented with KIT-positive tumours with exon 9 mutations.

**case report 3**

A 70-year-old woman presented with an abdominal mass originating from the small bowel. The tumour, measuring 15 cm in diameter, was resected and examination revealed GIST histopathology. Mutational analysis showed that the tumour was KIT-positive with an exon 9 mutation. There were no detectable resistant secondary mutations. There were 50 mitoses per 50 high power fields (HPFs).
One-year follow-up showed disease progression and ileus due to peritoneal sarcomatosis. Two months later, a liver metastasis was identified and GIST histopathology was confirmed.

The patient’s physical examination was unremarkable. Her blood pressure was 140/69 mmHg, and laboratory tests revealed discrete anaemia and slight disturbances in liver function tests.

Treatment with oral imatinib 400 mg/day was initiated and a PR was observed after 2 months. This was confirmed by a CT scan after another 2 months. Disease progression occurred 10 months after therapy initiation and the imatinib dose was increased to 800 mg/day. A PR was observed 3 months after the imatinib dose escalation and was confirmed a month later by a CT scan. Imatinib therapy was stopped 17 months after the second PR due to disease progression.

Second-line treatment was started with sunitinib at 50 mg/day on Schedule 4/2. After 7 months of treatment with sunitinib, the dose was reduced to 37.5 mg/day, also on Schedule 4/2, due to grade 3 hand–foot syndrome; symptoms improved significantly following dose reduction. A PR was observed after 10 months of maintained treatment with sunitinib 37.5 mg/day and was confirmed after 1 year of treatment.

Grade 3 hand–foot syndrome recurred 11 months later and the sunitinib dose was reduced further to 25 mg/day. The PR was maintained at this dose and treatment with sunitinib is ongoing, 46 months after second-line treatment was initiated (Figure 3).

case report 4

A 55-year-old man presented with a small bowel tumour. The tumour, measuring 9.5 cm in diameter, was resected and examination revealed GIST histopathology. Mutational analysis showed that the tumour was KIT-positive with an exon 9 mutation. There were no detectable resistant secondary mutations and the tumour had 20 mitoses per 50 HPFs.

An abdominal relapse occurred 14 months later and was resected. Four months after this resection, another abdominal relapse occurred that was unresectable. The patient received initial treatment with imatinib 400 mg/day. This dose was

Figure 2. Maintenance of a partial response to treatment, re-establishment of tumour necrosis and reduction of the peripheral tumoral vascular ring in a patient with metastatic renal cell carcinoma following sunitinib dose re-escalation to 50 mg/day by Schedule 4/2. Scans show tumour status before (A) and after (B) sunitinib dose re-escalation.

Figure 3. Regression of liver metastases during treatment with sunitinib (50 mg/day reduced to 37.5 mg/day and then 25 mg/day by Schedule 4/2) in a patient with imatinib-resistant gastrointestinal stromal tumour.
reduced to 200 mg/day after 1 month due to hyperbilirubinaemia.

Disease progression occurred 6 months after the initiation of imatinib treatment and the dose was increased cautiously, first to 600 mg/day and then, after another 2 months of treatment, to 800 mg/day. The patient’s disease progressed again 6 months after the final dose increase and treatment with imatinib was stopped.

Second-line treatment with sunitinib was initiated at 50 mg/day on Schedule 4/2. A PR was achieved after 15 months of treatment and was maintained for another 10 months before disease progression occurred, when sunitinib treatment was stopped (Figure 4).

Third-line treatment with nilotinib, a targeted agent currently in development, at 400 mg twice daily, was initiated after the discontinuation of sunitinib and, after 3 months, disease progression slowed. The patient showed good tolerance to nilotinib therapy, which is ongoing.

conclusions

The case studies described here show how the clinical benefits of sunitinib therapy in patients with mRCC and advanced GIST can be optimised through AE management, to achieve maximal clinical benefit.

The mRCC patients described in cases 1 and 2 support data reported in the literature [3, 4], showing prolonged responses and manageable AEs with sunitinib treatment in mRCC patients. The intermediate-risk patient described in case 1 maintained a PR in response to sunitinib for 42 months through AE management and dose reductions to control grade 3 neutropenia and grade 3 fatigue. In case 2, sunitinib dose re-escalation enabled the re-establishment of a PR to sunitinib following dose reduction for AE management, such that the patient was able to maintain a response to sunitinib therapy for a total of 23 months.

The patient reported in case 1 experienced a transient 25% (grade 1) reduction in LVEF. Sunitinib-related cardiac toxicities have been reported infrequently in the literature, with grade 3 LVEF decline reported in 2% of mRCC patients (n = 375) who received first-line sunitinib in a phase III trial [3], and grade 3–4 cardiac disorders reported in <1% of 1,078 mRCC patients who received sunitinib for 6 months or more in an expanded-access study [23]. Sunitinib-associated LVEF decline is reversible with dose adjustment and is associated with no clinical sequelae [24].

The patient described in case 1 also experienced grade 3 neutropenia. Grade 3–4 neutropenia was reported in 12% of patients who received sunitinib both in the phase III trial [3] and in the expanded-access study [23]. Non-febrile neutropenia typically resolves during the off-treatment period but can be managed with sunitinib dose adjustment if it persists [24], as it did in this patient.

Both mRCC patients described here exhibited fatigue, which occurs commonly in patients with advanced malignancies as a result of a variety of factors, and is typically mild to moderate in severity in patients receiving sunitinib [24]. Effects on QoL can be minimised by monitoring patients regularly for anaemia and hypothyroidism and through patient education [24]. Management of fatigue is discussed in more detail in the article by Alain Ravaud in this supplement [25].

Two GIST patient cases are presented here that support the published literature, demonstrating clinically relevant antitumour activity of sunitinib in advanced imatinib-refractory GIST [5, 10]. These cases also show that GIST patients with KIT exon 9 mutations can achieve sustained PRs in response to long-term sunitinib therapy, again supporting trial findings [22]. Case 3 demonstrates not only the importance of sunitinib dose adjustment to achieve prolonged drug exposure, but also the safety and tolerability of sunitinib in elderly GIST patients. Findings from a treatment-use study in imatinib-refractory GIST have shown that sunitinib is effective and well-tolerated in patients aged ≥59 years [5], supported by the activity of sunitinib for >36 months in this 70-year-old patient.

The patient described in case 3 experienced grade 3 hand–foot syndrome, which was managed through sunitinib dose reductions. Grade 3 and 4 hand-foot syndrome were reported in 4% and 0%, respectively, of imatinib-refractory GIST patients receiving sunitinib in a phase III trial [10], and 8% and 0.2%, respectively, of imatinib-refractory GIST patients receiving sunitinib in a treatment-use trial [5]. Hand–foot syndrome can be managed through topical interventions and dose adjustment if symptoms are severe [26].

Figure 4. Regression of abdomino-pelvic metastases in response to sunitinib treatment (50 mg/day on Schedule 4/2) in a patient with gastrointestinal stromal tumour.
Both of the GIST patient cases discussed in this report highlight the importance of routine mutational testing in patients with advanced GIST in order to identify individuals, such as those with KIT exon 9 mutations, who may not respond well to imatinib 400 mg/day. A substantial proportion of advanced GIST patients exhibit mutations that cause primary resistance to imatinib or develop secondary mutations that result in the onset of resistance over time [22]. In these patients, sunitinib may offer a valuable alternative to prolong survival.

Mutational testing is strongly recommended in European clinical guidelines for its prognostic value [6], and may indicate which patients are likely to achieve better responses with sunitinib therapy. It is hoped that, over time, mutational screening may become a standard part of diagnostic evaluation for patients with advanced GIST.

The four patient case studies described in this article support the long-term efficacy and safety of sunitinib in the management of patients with mRCC and advanced imatinib-refractory GIST. The cases demonstrate how sunitinib therapy can be maintained with prompt and effective AE management, so that patients can continue to achieve sustained clinical benefit with this targeted therapy.

disclosures

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references