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# Re-escalation of sunitinib dose following dose reduction for thrombocytopenia

We report the case of a patient with metastatic renal cell carcinoma who achieved long-term benefit with the tyrosine kinase inhibitor, sunitinib. After initiation, sunitinib dose was reduced due to thrombocytopenia. Dosing was re-escalated after progression, and stable disease >12 months achieved.

## Initial treatment

A 59-year-old male patient presented with haematuria in June 1999 and was subsequently diagnosed with a right renal carcinoma, with no evidence of metastatic disease. In March 2000, a right nephrectomy was performed and subsequent histology was consistent with renal cell carcinoma (adenocarcinoma). During routine follow-up in December 2001, computed tomography (CT) scan showed two mediastinal lesions, which were resected laparoscopically. Intraoperatively, these lesions were noted to be adherent to the pulmonary artery, therefore, surgery was followed by adjuvant radiotherapy for five weeks.

In May 2005, two further metastatic lesions were surgically removed: a single para-aortic lymph node and a supra-renal nodule (found not to be adrenal on pathology). Treatment with interferon-alpha (IFN- $\alpha$ ), escalating to 9 MU three times weekly, was initiated in April 2006 for multiple intra-abdominal nodules. However, after three months of treatment, disease progression was observed on CT scan, with a 50% increase in nodal disease. Therefore, IFN- $\alpha$  was discontinued and the patient was referred to our institution for consideration of treatment with sunitinib via an expanded-access programme [1].

## Treatment for metastatic disease

It was noted that the patient had a medical history of hypertension, managed with three antihypertensive agents (diltiazem, bendroflumethiazide and valsartan) and was an ex-smoker of 15 years. The patient presented with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0. Blood pressure was elevated at 169/105 mmHg. Baseline full blood count was normal and analysis of serum electrolytes revealed mild renal impairment. A CT scan prior to treatment showed retroperitoneal lymphadenopathy and a 1 cm peritoneal deposit.

The therapeutic goal for this patient with good performance status was to prolong survival by maximising efficacy. An additional aim was to maintain the patient's performance status and quality of life. It was also important to ensure that the patient's concomitant hypertension was effectively controlled during treatment.

Sunitinib was initiated in August 2006 for metastatic renal cell carcinoma (mRCC) at the recommended dose of 50 mg once



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daily (four weeks on treatment followed by two weeks off treatment; Schedule 4/2). After the first four weeks of treatment the patient experienced a number of drug-related side effects, including grade 3 hand-foot syndrome (HFS) with erythema, blistering and soreness of the hands and feet (see Figure 1). Other side effects included fatigue, flushing,

mucositis, stomatitis and diarrhoea (all grade 1). Grade 1 alopecia, areas of hair depigmentation, and a yellowish tinge to skin were also noted.

All these symptoms improved considerably during the 2-week off treatment period. HFS was treated mainly with emollient creams and the avoidance of harsh detergents and hot water, where possible. Diarrhoea, when it occurred, responded well to treatment with loperamide. Mucositis was managed with advice regarding oral

hygiene and the regular use of chlorhexidine mouthwash. The patient kept a meticulous diary throughout treatment and all noted side effects of treatment improved after the 2-week off treatment period. The patient was given advice on managing fatigue. Grade 1 alopecia, hair depigmentation, and skin discolouration do not require medical intervention. The patient was counselled ahead of treatment commencement about the possible occurrence of these changes.

After two cycles of sunitinib treatment, widespread bruising (ecchymoses) was observed on the patient's torso. Grade 3 thrombocytopenia was reported (platelet count of  $37 \times 10^9/L$ ). There was no evidence of active bleeding and so this was managed conservatively. At this time, a CT scan showed a significant treatment response (not amounting to a partial response)

Figure 1: Side effect of the treatment



Grade 3 hand-foot syndrome observed on the patient's feet following sunitinib treatment.

**Figure 2: Computed tomography (CT) scans**

Computed tomography scans of lymphadenopathy in the pre- and para-aortic areas. A: pre-treatment demonstrating pathologically enlarged left para-aortic node; B: after two cycles of treatment with sunitinib, demonstrating a reduction in size of left para-aortic node from 22 mm diameter to 16 mm with noted reduction in parenchymal density, approaching that of fluid. Appearances consistent with a response to treatment.

with respect to lymphadenopathy in the pre- and para-aortic areas (see Figure 2). The patient's dose of sunitinib was reduced to 37.5 mg once daily (Schedule 4/2). Within two weeks the patient's platelet count returned to normal ( $153 \times 10^9/L$ ). HFS also improved to grade 2 and diarrhoea, mucositis and fatigue continued, but they were manageable with standard medical intervention as described above and in the discussion.

After five cycles of sunitinib treatment, subclinical hypothyroidism (thyroid-stimulating hormone [TSH] 83.76 mU/L and free T4  $< 5.1$  pmol/L) was observed and treatment with thyroxine 100  $\mu$ g was commenced. The patient's response continued to be monitored by CT scans with alternate cycles. After four cycles of treatment stable disease was observed and after six cycles a further reduction in the retroperitoneal lymph nodes was demonstrated.

In September 2007, after 10 cycles of sunitinib treatment, CT showed a measurable increase in the retroperitoneal lymph nodes and the decision was taken to re-escalate sunitinib to 50 mg once daily (Schedule 4/2). The platelet count remained stable and within the normal reference range. HFS and diarrhoea worsened briefly but returned to baseline (grade 1 or 2) within two cycles. HFS and diarrhoea were managed as previously described.

After three months, a CT scan showed stable disease with no further increase in the size of the retroperitoneal lymphadenopathy. During the subsequent 12 months the patient experienced slow, small volume disease progression (stable by Response Evaluation Criteria in Solid Tumours [RECIST] [2]) seen on sequential CT scans. In early 2009, the patient exhibited deterioration in ECOG PS and clinical signs of disease progression and was admitted to his local hospital with a lower

respiratory chest infection. Sunitinib was therefore discontinued at this point. The patient is currently being treated symptomatically in the community, with an emphasis on palliative care. For the majority of time that the patient was receiving treatment with sunitinib he had a good quality of life and continued to work in his chosen profession whilst on treatment.

## Discussion

Sunitinib is approved internationally for the treatment of advanced or metastatic renal cell carcinoma with a recommended starting dose of 50 mg once daily on Schedule 4/2. In the case reported, thrombocytopenia associated with sunitinib treatment resulted in a temporary dose reduction to sunitinib 37.5 mg once daily (Schedule 4/2), in line with recommendations in the product labelling [3]. Following disease progression, the patient was successfully dose re-escalated to sunitinib 50 mg once daily (Schedule 4/2) which resulted in stabilisation of disease for >12 months.

Across clinical trials, sunitinib has demonstrated a consistent adverse event profile, with the majority of events grade 1–2 in severity. As such, sunitinib is associated with a distinct and predictable profile of adverse events [4]. In the pivotal phase III trial assessing first-line treatment with sunitinib in patients with mRCC, diarrhoea, fatigue and nausea were the most common adverse events observed during sunitinib treatment [5]. In general, adverse events improved during the 2-week off treatment period. Therapy management by prompt and effective treatment of adverse events may help to reduce their impact on patients. The majority of adverse events associated with sunitinib are manageable with standard medical intervention; however, for some adverse events temporary cessation of drug or dose reduction may be necessary. Within the phase III study, 38% of patients on sunitinib had a dose interruption and 32% underwent a dose reduction.

In this case report, adverse events were similar to those observed in the phase III trial. Hypertension is a recognised side effect of several targeted agents, and blood pressure monitoring is recommended for every clinic visit [3, 6–8]. Treatment with antihypertensive agents may prove necessary and these agents can generally be combined with sunitinib without interactions. Interestingly, in this case the patient was already suffering from elevated blood pressure prior to initiation of therapy and there was no worsening of this during sunitinib treatment. HFS is also well recognised, with patients describing erythema of the palms of hands and soles of feet, dry skin, desquamation, hyperkeratosis and increased skin sensitivity [9]. This particular side effect is treatable and responds best if detected early. Typical interventions to mitigate this problem include the liberal use of emollients, avoidance of irritants including hot water and bright sunlight, use of cotton socks and gloves and well-fitting footwear. Diarrhoea generally responds well to anti-diarrhoeal agents such as loperamide. Stomatitis may be treated with appropriate oral care [10]. Management of fatigue first requires exclusion of any reversible contributing factors such as anaemia and hypothyroidism. Following this, advice is given to patients regarding energy saving, accepting help from others, taking regular exercise and maintaining regular sleeping habits. Help with time planning is also offered, in particular taking advantage of the 2-week break off treatment when symptoms such as fatigue often improve.

In the phase III trial, grade 3 thrombocytopenia was observed in 8% of patients receiving sunitinib; other haematological abnormalities were also seen, including neutropenia and anaemia. Interestingly, in this case, re-escalation of the sunitinib dose from 37.5 mg once daily to 50 mg once daily did not result in reappearance of previously documented thrombocytopenia. This may be explained by the pharmacological phenomenon of tachyphylaxis where a decreasing response to a drug given over a period of time is observed (with reference to toxicity in this case). Thrombocytopenia is usually managed conservatively with either time off sunitinib or a dose reduction in the drug. Further measures such as platelet transfusion are not usually required.

When considering dose reductions, it is important to note that exposure-response models have demonstrated that there is a correlation between higher sunitinib exposure and improved progression-free survival and overall survival [11]. In this case, re-escalation of the sunitinib dose following disease progression resulted in stabilisation of disease. This demonstrates the importance of using the optimal sunitinib dose, and maintaining therapy while efficacy is observed, to achieve maximum clinical benefit.

In conclusion, this case demonstrates that a patient can achieve long-term benefit with sunitinib through appropriate therapy management by treatment of adverse events and sunitinib dose

modification where necessary. The dose of sunitinib can be re-escalated to maintain clinical benefit.

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