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Optimisation of sunitinib therapy in metastatic renal cell carcinoma: adverse-event management

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ABSTRACT

Reliance on cytokine therapy for the treatment of metastatic renal cell carcinoma (mRCC) has been all but eliminated by the introduction of novel targeted agents. Several of these agents, including the receptor tyrosine kinase inhibitor sunitinib, have demonstrated efficacy in the treatment of mRCC. Sunitinib treatment is generally well tolerated, and is associated with a low incidence of grade 3 or 4 adverse events. However, a distinct pattern of novel adverse events associated with sunitinib treatment has been identified. These events require monitoring and management to help reduce their frequency, severity, clinical significance and nature. This article summarises the most important adverse events observed during sunitinib treatment and suggests measures to manage the event, while also helping patients to sustain an optimal treatment schedule and gain maximum clinical benefit from sunitinib.

1. Introduction

A key factor in management of metastatic renal cell carcinoma (mRCC) is controlling the progression of existing metastases and minimising the risk of further metastasis through adequate and appropriate long-term maintenance therapy. Patient perception of positive treatment outcome is important in achieving long-term care. This is greatly facilitated by an efficacious and well-tolerated treatment programme that includes appropriate management of adverse events (AEs) and patient expectations of treatment.

Over the last few years the widespread use of targeted therapies has led to greater understanding and experience of how to maximise the benefits of treatment while minimising the impact of AEs. This review provides an overview of the tolerability of sunitinib in patients with mRCC and discusses practical strategies for optimising treatment, including AE management, patient education and adapting the dosing schedule or duration of treatment. The recommendations provided represent the author's opinion, as few AE management strategies have been validated in this setting.

2. Tolerability of sunitinib therapy in mRCC

The tolerability of sunitinib has been assessed in several randomised clinical trials as well as a large, international expanded-access trial in >4,000 patients. Similar AEs were reported in phase II evaluation of sunitinib in patients with cytokine-refractory mRCC [1,2] and a phase III study comparing first-line sunitinib with IFN-α. [3] In patients receiving first-line sunitinib, the most

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common AEs reported were diarrhoea (53%), fatigue (51%), nausea (44%), stomatitis (25%), vomiting (24%), hypertension (24%), and hand–foot syndrome (20%). [3] The proportion of patients experiencing treatment-related grade 3 or 4 fatigue was significantly higher in the IFN-α arm compared with the sunitinib arm (12% versus 7%; $p < 0.05$), while rates of grade 3 or 4 diarrhoea (5% versus 0%, for sunitinib and IFN-α, respectively), vomiting (4% versus 1%), hypertension (8% versus 1%) and hand–foot syndrome (5% versus 0%) were higher in the sunitinib arm than the IFN-α arm ($p < 0.05$ for all comparisons).

Haematological toxicity in sunitinib-treated patients included leukopenia (78%), neutropenia (72%), anaemia (71%) and thrombocytopenia (65%). [3] These abnormalities were more common in sunitinib-treated patients than those who received IFN-α. The incidence of grade 3 or 4 leukopenia (5% versus 2%, for sunitinib and IFN-α, respectively), neutropenia (12% versus 7%), and thrombocytopenia (8% versus 0%) was significantly higher in the sunitinib arm than in the IFN-α arm ($p < 0.05$ for all comparisons).

The frequency of grade 3 decline in left ventricular ejection fraction (LVEF) was similar in the sunitinib and IFN-α arms (2% versus 1%). [3] In the sunitinib group, this decline was reversible after dose adjustment or treatment discontinuation and was not associated with clinical sequelae. No grade 4 LVEF decline was observed. Overall, most sunitinib-related AEs were ameliorated by treatment interruption or dose-adjustment; 8% of sunitinib-treated patients discontinued their treatment due to AEs compared with 13% in those treated with IFN-α.

The results of an ongoing expanded-access trial in cytokine-refractory patients also provide important data on the safety and tolerability of sunitinib. Of more than 4,000 patients enrolled, data are available for 2,341 patients with cytokine-refractory or -intolerant RCC treated with sunitinib at a dose of 50 mg/day in repeated 6-week cycles consisting of 4 weeks on treatment followed by 2 weeks off treatment (the 4/2 schedule). [4] To date, the most common treatment-related grade 3 or 4 AEs observed in this study have been fatigue (7.1%), hypertension (5.4%), asthenia (5.0%), hand–foot syndrome (4.5%) and diarrhoea (3.6%) (Table 1). Grade 3–4 haematological toxicity included thrombocytopenia (6.4%), neutropenia (4.1%) and anaemia (2.6%). The AE profile was similar across all subpopulations analysed, including patients with performance status $\geqslant 2$, patients with brain metastases and older patients (>65 years). In this study, median PFS was 8.9 months (95% CI: 8.3–9.9) and ORR was 9.3%, with stable disease of $\geqslant 3$ months duration noted in 43.1% of patients.

Overall, these results provide a good indication of the likely AE profile of sunitinib in clinical practice. However, a number of strategies can be adopted that may help to reduce the potential impact of AEs, in frequency, severity, clinical significance or nature. These strategies have been discussed and refined with European investigators involved in the clinical trial programme, as well as with physicians involved in RCC management, and are outlined below. These measures may help patients to sustain an optimal treatment schedule and gain maximum clinical benefit from sunitinib.

Table 1 – Sunitinib Expanded Access Study: treatment-related AEs ($n = 2,341$)

Preferred term	Incidence (%)	
	Grade 1–2	Grade 3–4
Fatigue	28.5	7.1
Hypertension	14.7	5.4
Asthenia	13.9	5.0
Hand–foot Syndrome	12.9	4.5
Diarrhoea	35.8	3.6
Mucosal inflammation	24.5	2.5
Anorexia	20.0	2.2
Stomatitis	23.4	2.1
Vomiting	20.6	2.1
Nausea	31.7	1.9
Dysgeusia	24.6	0.5
Rash	12.5	0.5
Epistaxis	11.3	0.5
Headache	10.4	0.4
Congestive cardiac failure	0.0	0.3
Cardiac failure	0.0	0.2
Constipation	11.8	0.2
Dyspepsia	15.4	0.2
Hypothyroidism	2.7	0.1

3 patients had grade 1 bleeding and cerebral metastases

3. Treatment optimisation and AE management

The first steps in optimising clinical outcomes should be taken before treatment commences. These involve initial actions that can help to minimise the risk of AEs during treatment.

Clinicians should complete a thorough assessment of the benefit/risk ratio for the treatment, taking into account the risk profile of the patient. Table 2 lists potential questions that can be asked when taking the patient's medical history. In addition, complete blood counts should be performed at the beginning of each treatment cycle and thyroid function should be monitored in patients with symptoms suggestive of hypothyroidism. [5]

Co-morbidities should be stabilised and risk factors addressed where possible, specifically unstable hypertension or arterial tension at a spontaneous value $\geqslant$140/80 mmHg and a history of cardiovascular events.

Table 2 – Questions to include when taking patient history	
Do you suffer from/have a history of:	Hypertension
	Cardiac problems or congestive heart failure
	Vascular pathology including transient cerebral vascular attack
	Seizures
	Kidney problems
	Liver problems
	Depression
	Hypothyroidism
	Anemia
	Calluses or corns on hands or feet?
Are you taking other medications (including over-the-counter medicines and dietary supplements?)	

Table 3 – Dose modification guidelines		
Strategy	Reason for modification	Outcome
Dose delay	Functional mucositis (grade 3) Diarrhoea (grade 3/4) Rash, hand–foot syndrome (grade 3) Severe hypertension Haematological toxicity (grade 3)	Resolution of adverse event and completion of scheduled treatment
Dose reduction*	To prevent recurrence of severe AEs (fatigue, functional mucositis, diarrhoea, rash, hand–foot syndrome) Coadministration with strong CYP3A4 inhibitor	Decrease incidence and severity of anticipated adverse events
Treatment discontinuation	Severe hand–foot syndrome that does not resolve with dose delay/reduction Serious AEs (pancreatitis, congestive heart failure)	Switch to alternate anticancer agent

*Dose increase or reduction of 12.5 mg increments is recommended based on individual safety and tolerability.
AE = adverse event.

Use of concomitant drugs that may specifically increase the plasma level of sunitinib by competition at the liver level on CYP3A4 should be avoided and alternatives with no or minimal enzyme inhibition should be chosen. CYP3A4 inducers can decrease the plasma level of sunitinib, and concomitant medication with minimal or no enzyme induction is recommended.

The patient should have a thorough understanding of their disease and its treatment. Patient education should include details of any tests and procedures that may be required and, where appropriate, information given should include preparatory, perioperative and recovery instructions. Counselling may also form a useful part of the educational programme. Once treatment is started, the patient should receive intensive support for the first two treatment cycles to minimise early onset of AEs that may require treatment discontinuation and jeopardise treatment efficacy.

During treatment, AE management is a critical component of patient care. Practical strategies to address the most common AEs are described below, with suggestions for appropriate patient education. Circumstances under which dose modification may be required, and the strategies to be adopted, are also detailed in Table 3.

When considering dose modifications, evidence on the exposure-response relationships of sunitinib in mRCC should be considered.[6] In an analysis of data from clinical trials in untreated and cytokine-refractory mRCC, Houk et al report a significant association between sunitinib exposure and the probability of longer time to progression and improved overall survival in patients with mRCC. This suggests that patients with increased sunitinib exposure experience a clinical benefit compared with patients with lower exposure.

3.1. *Fatigue*

Fatigue and asthenia represent a particularly common AE with sunitinib; in clinical trials fatigue has been reported by approximately 68% and 64% of patients with treatment naïve and cytokine-refractory mRCC, respectively. This AE is generally mild or moderate in severity, reaching grade 3 or 4 in only 11–12% of patients.[3,5]

Several treatable and non-treatable factors may contribute to fatigue and weakness in patients with RCC. These include pain, emotional distress, anaemia, sleep disturbance, nutrition, hypophosphatemia and hypomagnesemia, activity levels, hypothyroidism and comorbid conditions. Fatigue and asthenia may also be caused or exacerbated by underlying dehydration and care should be taken to ensure patients have adequate fluid intake. Fatigue typically occurs 2 to 3 weeks after initiating treatment and may intensify during

weeks 3 or 4. It may be a recurrent problem, although severity appears to vary from cycle to cycle. Symptoms may improve during the 2-week off-treatment period, particularly in patients with a low tumour burden. However, some patients may experience a decline during off-treatment periods due to cancer-related pain and fatigue. Patients at high risk of fatigue or asthenia include elderly, frail or obese patients and those with a large tumour burden.

AE management

Prior to treatment, patients should be counselled on what to expect from treatment, and psychological support should be provided where feasible. During the first 2 to 3 cycles of treatment it is important to provide close support to counsel and motivate the patient on how to cope with fatigue and weakness. At the end of cycle 2, a focused check-up on the level of fatigue and its potential impact on quality of life should be conducted. If quality of life is compromised because of fatigue or asthenia, the dose of sunitinib should be reduced to 37.5 mg/day on the 4/2 schedule. After cycle 3, patients should be encouraged to self-monitor levels of fatigue and weakness. Every 2 to 3 cycles, patients should also be monitored for anaemia, hypothyroidism and depression, and appropriate treatment initiated. In patients with symptoms suggestive of hypothyroidism, laboratory monitoring of thyroid function and treatment according to standard medical practice is recommended.[7] Thyroid function should also be monitored in patients with severe asthenia and those with a reduction of $\geqslant$20% in Karnofsky performance status. Patients who show an increase in thyroid stimulating hormone may benefit from thyroid supplementation, even in the absence of a change in T3 or T4 value. Patients should be monitored closely to assess the benefit of any supplementation provided.

Patient education

It is important to encourage patients to put their fatigue into context and, if necessary, to re-adjust their expectations; explaining that it may be necessary to adapt their behaviour and usual activities to conserve energy. Physicians should also encourage daytime rest. In addition, patients should be reassured that the occurrence and severity of fatigue may vary between cycles and that there may be treatment options to alleviate fatigue, depending on the underlying cause. The value of sunitinib therapy should be reinforced whilst providing encouragement and support to patients during treatment.

3.2. Hypertension

Hypertension has been reported in 24% of treatment-naïve and 17% of cytokine-refractory patients with mRCC receiving sunitinib targeted therapy.[3,5] It should be noted that increased blood pressure (BP) monitoring may lead to an increase in the observation of hypertension; daily BP measurement is associated with increased reports of patients with an increase of >2 mmHg in systolic pressure.

Although the underlying mechanism is not well defined, it has been suggested that hypertension results from a diminution of vascular surface area and an increase in peripheral vascular resistance caused by depressed angiogenesis.[8–10] The onset of hypertension has been highly variable following sunitinib treatment; symptoms may resolve during treatment and may recur in later treatment cycles.

AE management

Before starting treatment, BP should be checked and where necessary hypertension controlled.[7] During the first two cycles, BP should be measured every week. Thereafter, measurements should be taken at least once a month. Twelve weeks after starting treatment, patients should be given a second full cardiovascular screen. For an individual patient, BP should be monitored using the same equipment throughout their management, since results may vary between devices.

Temporary suspension of treatment is recommended in patients with severe hypertension and in those whose hypertension is not controlled with medical therapy. Treatment may be resumed once hypertension is appropriately controlled.[7] Normal hypertension management protocols can be followed if grade 2 hypertension is identified. Treatment of severe hypertension can be adapted to reflect the discontinuous treatment cycle; during sunitinib treatment on a 4/2 schedule, the 2-week off-treatment period may relieve AEs, and dose adjustment or discontinuation of hypertension medication may be necessary during this time. Potential interactions between antihypertensive agents and sunitinib are described in Table 4.[11]

When implementing therapy to manage AEs, it is important to share all drug information between practitioners. In particular, the potential impact of CYP3A4 induction or inhibition on sunitinib metabolism when starting or stopping antihypertensive medications should be considered. Co-administration of sunitinib and potent CYP3A4 inducers or inhibitors should be avoided. If this is not possible, the dose of sunitinib should be decreased to a minimum of 37.5 mg/day, based on careful monitoring of tolerability.[7]

Patient education

Patients should be encouraged to recognise the common symptoms of hypertension, such as recurrent headache, chest pounding, and redness or flushing of the ears.

3.3. Skin toxicity

Inhibition of tyrosine-kinase receptors widely expressed in the skin structures results in a range of chronic cutaneous side effects, such as acute folliculitis, multiple

Table 4 – Potential cytochrome P450 interactions [11]

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Angiotensin-converting enzyme inhibitors				
Captopril	12.5 mg PO tid	25 mg PO tid	50 mg PO tid	CYP 2D6 substrate
Enalapril	5 mg PO QD	10–20 mg PO QD	40 mg PO QD	CYP 3A4 substrate
Ramipril	2.5 mg PO QD	5 mg PO QD	10 mg PO QD	Yes*
Lisinopril[a]	5 mg PO QD	10–20 mg PO QD	40 mg PO QD	No
Fosinopril	10 mg PO QD	20 mg PO QD	40 mg PO QD	Yes*
Perindopril	4 mg PO QD	None	8 mg PO QD	Yes[b]
Quinapril[a]	10 mg PO QD	20 mg PO QD	40 mg PO QD	No
Angiotensin II receptor blockers				
Losartan	25 mg PO QD	50 mg PO QD	100 mg PO QD	CYP 3A4 substrate
Candesartan	4 mg PO QD	8–16 mg PO QD	32 mg PO QD	CYP 2C9 substrate
Irbesartan	75 mg PO QD	150 mg PO QD	300 mg PO QD	CYP 2C9 substrate
Telmisartan[a]	40 mg PO QD	None	80 mg PO QD	Yes[b]
Valsartan[a]	80 mg PO QD	None	160 mg PO QD	Yes[b]
Dihydropyridine calcium channel blockers				
Nifedipine XL	30 mg PO QD	60 mg PO QD	90 mg PO QD	CYP 3A4 substrate + inhibitor
Amlodipine	2.5 mg PO QD	5 mg PO QD	10 mg PO QD	CYP 3A4 substrate
Felodipine	2.5 mg PO QD	5 mg PO QD	10 mg PO QD	CYP 3A4 substrate
α- and β-blockers				
Labetolol	100 mg PO BID	200 mg PO BID	400 mg PO BID	CYP 2D6 substrate + inhibitor
Selective β-blockers				
Metoprolol	25 mg PO BID	50 mg PO BID	100 mg PO BID	CYP 2D6 substrate
Atenolol[a]	25 mg PO QD	50 mg PO QD	100 mg PO QD	No
Acebutolol	100 mg PO BID	200–300 mg PO BID	400 mg PO BID	Yes*
Bisoprolol	2.5 mg PO QD	5–10 mg PO BID	20 mg PO QD	Yes*

*CYP450 unknown
[a]Suggested optimal choices to avoid or minimize potential drug interactions with sunitinib through CYP450.
[b]Not CYP450.
PO = oral administration; TID = three times daily; QD = once daily; BID = twice daily.

subungual splinter haemorrhages, and hair depigmentation and hand–foot syndrome (palmar-plantar erythrodysaesthesia). [12] During clinical trials of sunitinib for treatment-naïve mRCC, the incidence of hand–foot syndrome was 20% (all grades), and 5% and 0% for grade 3 and 4 symptoms, respectively. [3,5]

Hand–foot syndrome generally presents as dysaesthesia, tingling and erythema in affected areas, which may progress to burning pain with dryness, cracking, desquamation, ulceration and oedema. The condition can be very painful and distressing to patients, interfering with their ability to work or perform normal daily activities. [13] Visible signs of hand–foot syndrome occur more often on the palms of the hand than the soles of the feet, but pain due to the syndrome affects the hands and feet in equal measure.

Symptoms associated with skin toxicity have variable onset, and severity generally worsens as the cycle progresses, or in later cycles. Symptoms may recur, sometimes emerging in different areas. While most calluses or blister-like areas improve during off-treatment periods, resolution may also occur during therapy. Although there are no interventions for skin toxicity, there are several management strategies that may be employed.

AE management

The physician should perform a full foot examination during the initial screening before starting treatment. If hyperkeratosis of the palm or soles is present, a podiatrist can be consulted. Preventative and treatment recommendations for grade 1 hand–foot syndrome include advising the patient to wear thick soled shoes to ease the pressure on the feet and the use of local corticoid, vitamin A, and urea creams. If grade 2 hand–foot syndrome is identified early in the treatment cycle (week 1), treatment can be discontinued and recommencement delayed until symptoms are grade 0 or 1 in severity. Treatment should be restarted at a

reduced dose of 37.5 mg/day. Similarly, for grade 2 hand–foot syndrome identified late in the treatment cycle (week 4), treatment should be discontinued and the next cycle dose discussed with the patient. Treatment may be restarted at a dose of 50 mg/day, or a reduced dose of 37.5 mg/day. Importantly, taking sunitinib in the evening may help to reduce the severity of hand–foot syndrome, as the maximum plasma concentration is then reached during the night when patients are likely to be less active.

Patient education

Information leaflets and brochures for patients and primary care providers should be provided in anticipation of AEs. Visuals that illustrate grade 2 hand–foot syndrome should be included in such materials to facilitate early recognition of the condition. Patients receiving sunitinib should reduce pressure on affected areas, staying off their feet when possible and avoiding friction or pressure to the hands. Patients should also be advised that depigmentation of the hair or skin may also occur during sunitinib treatment,[7] as well as a yellow-green tan to the skin.

3.4. *Diarrhoea*

Gastrointestinal AEs such as diarrhoea and stomatitis are also common occurrences with cytotoxic chemotherapies. During sunitinib therapy in treatment-naïve and cytokine-refractory mRCC, diarrhoea of any grade was reported in 53.0% and 49.1% of patients, respectively. Grade 3 diarrhoea was reported in 5.0% and 3.0% of patients, respectively, with no cases of grade 4 severity.[3,5] Diarrhoea is usually mild, and improves rapidly during the off-treatment period.

AE management

Treatments for diarrhoea include bulking and antidiarrhoeal agents to improve stool consistency and reduce frequency of bowel movements. There is also some anecdotal evidence that treatment with loperamide 30 minutes prior to eating may be helpful.

Patient education

Patients often benefit from consultations with dieticians, which should take place before starting treatment. In addition, patients should be advised to decrease or discontinue use of any stool softeners and laxatives.

3.5. *Stomatitis*

In clinical trials, stomatitis was reported by 25.0% and 41.4% of patients with treatment-naïve and cytokine-resistant mRCC, respectively (1.0% and 3.6% with grade 3). No patients had grade 4 stomatitis during sunitinib treatment in these trials[3,5] Clinical experience indicates that stomatitis often occurs during the second week of treatment. If delayed until the fourth week, symptoms can be alleviated by the 2 weeks off treatment.

AE management

Stomatitis can be effectively managed by educating patients on symptoms such that their onset can be anticipated and addressed. If the patient develops ulcers, a treatment delay of 2 to 3 days can be beneficial. A bicarbonate-based mouthwash containing paracetamol with morphine or codeine sulphate may also be helpful.

Patient education

Before starting treatment, patients should switch to a paediatric toothpaste and avoid drinking spirits.

3.6. *Haematological toxicity*

Both neutrophil and platelet counts can fall during sunitinib treatment. In patients with treatment-naïve mRCC, neutropenia and thrombocytopenia of all grades occurred in 72% and 65% of patients, and of grade 3 or 4 in 12% and 8% of patients, respectively.[3] For patients with cytokine-refractory mRCC, these incidences were 10.1% and 8.9% (all grades) and 5.3% and 4.2% (grade 3 or 4), respectively.[5] Onset typically occurs during the first treatment cycle, without progression in later cycles. Non-febrile neutropenia and thrombocytopenia tend to resolve during off-treatment periods, but may recur.

Anaemia has also been reported during sunitinib treatment,[3] however, in some cases, anaemia was considered to be related to the cancer rather than sunitinib therapy. A preventative approach is encouraged and patients should be monitored for myelosuppression, at least at the beginning of the treatment.

AE management

Haematological toxicity can be managed by collecting complete blood counts at least at the beginning of each treatment cycle.[7] In addition, blood counts should be monitored if a patient reports fever, chills, prolonged viral infection, or bleeding events. Patients should be assessed every 2 to 6 weeks and if a repeated low neutrophil granulocyte count is identified, treatment should be delayed for a few days and restarted when levels are restored. In patients with grade 3 neutropenia or thrombocytopenia that persists after the 2-week, off-treatment period, sunitinib treatment should be delayed or the dose reduced. Finally, where anaemia is suspected, it is necessary to eliminate hypothyroidism and implement preventative measures, such as vitamin B12 and iron supplementation.

Patient education

Patients with non-febrile neutropenia should be advised of the importance of good personal hygiene and dietary guidelines. Similarly, patients with thrombocytopenia should be warned to take precautions such as avoiding forceful coughing and straining bowel movements, in order to minimize the risk of bleeding.

3.7. Thyroid function

In registrational clinical trials, the incidence of hypothyroidism in cytokine-refractory and treatment-naïve mRCC patients was 4% and 2%, respectively.[5] Overall, 7% of patients with cytokine-refractory or treatment-naïve mRCC had either clinical or laboratory evidence of treatment-emergent hypothyroidism. However, subsequent reports of patients with RCC receiving sunitinib suggest considerably higher rates of abnormal thyroid function.[14,15] Three important issues should be considered. First, the baseline frequency of thyroid function abnormality in these populations appears to exceed that of the general population. Second, increased use of thyroid function tests during sunitinib treatment may have contributed to the increased detection of asymptomatic thyroid function abnormalities, and such abnormalities may not always have clinical consequences. Third, hypothyroidism is easily correctable with thyroid replacement hormone therapy and should not affect the use of sunitinib in mRCC.

AE management

Thyroid function test abnormalities appear to be common in patients with mRCC treated with sunitinib, and routine monitoring is warranted. Patients with symptoms suggestive of hypothyroidism should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.[5]

4. Conclusions

Major advances in understanding the molecular pathogenesis of RCC and the introduction of targeted therapies such as sunitinib, sorafenib and temsirolimus have led to substantial improvements in the treatment and outcome of this disease.[16]

Sunitinib has demonstrated a consistent toxicity profile in patients with RCC. The majority of treatment-related AEs reported to date have been grade 1 or 2 in severity and have been manageable with standard medical intervention or dose modification.[1–3] The AEs experienced by patients receiving sunitinib are comparable to those reported in patients receiving other molecularly targeted therapies (although some, such as skin/hair discolouration, appear to be unique to sunitinib).

The treatment and support of cancer patients is complex and involves essentially physical but also psychological care. Proactive assessment and management of AEs is critical. This enables patients to remain on what is determined to be the best treatment for their disease and ultimately ensures that patients obtain optimal benefit from therapy. Early AE identification and intervention may help to avoid dose interruption or reduction, thereby maximising the potential treatment benefit, and ease patient discomfort. Frequent contact with the referring oncologist, especially at the start of therapy, is important in achieving the optimal treatment course and ensuring the patient is able to manage the therapy schedule and dosage. When considered alongside the strong efficacy profile of sunitinib (reported earlier in this supplement), the recommendations made here provide a positive approach to the support of patients in managing their condition, facilitating continued therapy and maintaining the best possible quality of life in the long term.

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Conflict of interest

A. Ravaud: member of the Global, European and/or French advisory boards of Pfizer, Bayer, GSK and Wyeth. Member of RCC clinical trial steering committees for Pfizer and Novartis. Principal investigator for the S-TRAC trial sponsored by Pfizer.

S. Négrier: scientific consultant for Pfizer Europe and Pfizer France, member of scientific advisory boards for Wyeth and Sanofi Aventis.

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