Sunitinib toxicity management – a practical approach

Sandeep Sehdev, MD, FRCPC

Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Cite as: *Can Urol Assoc J* 2016;10(11-12Suppl7):S248-51.
http://dx.doi.org/10.5489/cuaj.4296

Abstract

This article summarizes the adverse events (AEs) of sunitinib that are commonly encountered in a community oncology practice, and provides practical recommendations for their management based on the available literature and on the author's own experience.

Introduction

Sunitinib, a multitargeted tyrosine-kinase inhibitor (MTKI), is a standard of care in the first-line treatment of metastatic renal cell carcinoma (mRCC) in Canada. Sunitinib inhibits the vascular endothelial growth factor receptor (VEGFR) and other tyrosine kinases, including the platelet-derived growth factor (PDGF) and c-kit receptor at nanomolar concentrations. Sunitinib is generally well-tolerated; however, it is associated with some distinct adverse events (AEs) that can impact quality of life (QOL) and adherence to therapy, both of which require monitoring and treatment. In clinical practice, the most common AEs of sunitinib treatment tend to be fatigue/asthenia, hand-foot syndrome, hypertension, hypothyroidism, and diarrhea.

The approach to management of the toxicities of sunitinib in a community practice may differ somewhat from that in a clinical trial. Clinical trials are concerned largely with Grade 3/4 toxicities, the frequency of which in the sunitinib clinical trials has been relatively low.[1] However, for many patients in the real-world practice setting, even chronic Grade 2 fatigue can severely impact QOL and activities of daily living. Common terminology criteria for adverse events [CTCAE] grades for select AEs of sunitinib are provided in Table 1. It should also be noted that clinical trials tend to combine Grade 1 and 2 toxicities, while in reality, Grade 2 toxicities are very different from Grade 1 toxicities when managed over the long term. Elderly patients in particular may not tolerate even chronic Grade 2 side effects very well. This becomes an issue, as some dose-optimization protocols aim for at least Grade 1 side effects as a goal.

From the community perspective, it can be challenging to convince patients to adhere to therapy, as patients may not fully understand the adverse consequences of their cancer progressing without treatment. This article reviews the common AEs encountered in a community practice, with practical recommendations for management based on evidence, as well as experience from the author.

Fatigue

The incidence and impact of fatigue among patients with mRCC who are undergoing treatment with sunitinib are generally greater than is suggested by the results of the sunitinib registration trials and phase 3 trials. In the pivotal phase 3 trial,[1] the control, interferon-alfa, was associated with a greater incidence of Grade 3/4 fatigue than sunitinib, while the overall incidence of fatigue was equivalent. Although fatigue has been underrepresented in clinical trials, in clinical practice, asthenia and fatigue tend to have a much greater impact. This may be the result of selection bias in clinical trials, with a tendency to include patients with a better performance status, younger age, and fewer comorbidities. In reality, fatigue is among the most challenging AEs to deal with in the community setting, largely because of its subjective nature and since real-world community patients may not be as motivated or as tolerant of side effects as patients enrolled in a clinical trial.

Management of fatigue often involves a schedule change (for example, changing the schedule of sunitinib from four weeks on/two weeks off to two weeks on/one week off) or, if absolutely necessary, a dose reduction. However, a dose response has not been established for fatigue and, anecdotally, dose reductions do not seem to have a tremendous impact on reducing fatigue (unlike other side effects, such as cytopenias and liver enzyme changes). Some patients

Table 1. Common terminology criteria for adverse events (CTCAE) grading system – select adverse events associated with sunitinib[17]

Adverse event	CTCAE grade				
	1	2	3	4	5
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL	–	–
Hand-foot syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL	–	–
Hypertension	Prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg)	Stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg); medical intervention indicated; recurrent or persistent (≥24 hours); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg if previously WNL; monotherapy indicated	Stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

ADL: activities of daily living; BP: blood pressure; WNL: within normal limits.

seem to benefit from drug holidays — extending the time off therapy to allow more time for recovery to at least a Grade 1 or 2, and then resuming therapy at a lower dose.

Fatigue management generally involves conservative measures, including ensuring a consistent sleep cycle, maintaining activity levels during the day, and avoiding excessive caffeine and alcohol. Ensuring adequate fluid and nutritional intake is important. Potential alternative causes of fatigue should be ruled out, including underlying dehydration, hypothyroidism, hypercalcemia, anemia, or depression.[2]

Hand-foot syndrome

Hand-foot syndrome (HFS) is a common side effect of targeted cancer therapies, including the MTKIs sorafenib and sunitinib. It should be noted that the clinical presentation and histopathology of HFS during MTKI therapy differ somewhat from those caused by chemotherapy, such as capecitabine and liposomal doxorubicin; therefore, some authors distinguish classic from MTKI-associated HFS.[3] While doxorubicin is thought to be secreted into the eccrine glands, resulting in direct toxicity of the skin, it is thought that the HFS associated with the MTKIs may be an indirect effect of inhibition of the proangiogenic pathways VEGF and PDGF. Inhibition of these pathways may prevent vascular repair mechanisms from functioning properly, resulting in HFS in high-pressure areas such as the palms and soles, which may be susceptible to friction trauma.[4] For this reason, many of the strategies for effectively managing HFS focus on prevention. Before therapy begins, a full-body skin exam should be conducted, especially to the palms and soles; calluses or hyperkeratotic areas that might predispose to HFS may be treated. Patients with evidence of abnormal weight-bearing might be evaluated for the need for an orthotic device. Patients should be advised to avoid exposure of their hands and feet to hot water, as this is believed to exacerbate symptoms. As the risk of HFS appears to be greatest within the first two to four weeks of treatment, prevention of traumatic activities is most important during this period. Patients should avoid constrictive footwear and take care to avoid excessive friction on the skin; avoidance of vigorous exercise or activities that place undue stress on the hands and feet should be avoided, particularly during the

first month of treatment. Particular care should be taken with patients who are exposed to frequent mechanical trauma to their hands and feet (e.g., friction trauma) through their job or hobbies (e.g., landscaping, gardening, mechanical jobs, etc).[3]

Maintaining good hygiene, avoiding digging under nails, and the use of gloves when doing dirty chores are advised. Topical creams/moisturizers (e.g., Bag Balm®, Udderly Smooth®) should be applied to hands and feet daily starting on Day 1 of therapy.[5] Those with overgrown skin may benefit from treatments with keratolytics, such as urea 20–40% or salicylic acid 6%, which help loosen and shed the outer layers of skin.[3,5]

Hypertension

Hypertension is a class effect of drugs that target VEGFR and angiogenesis. Patients with Grade 1 or 2 hypertension can generally be maintained on sunitinib treatment and their hypertension managed with a calcium antagonist, such as amlodipine, or an angiotensin-converting enzyme (ACE) inhibitor, such as ramipril. Non-dihydropyridine calcium channel blockers, such as diltiazem, should be avoided in patients taking sunitinib.[6] If hypertension is not controlled with these agents, an internal medicine specialist or cardiologist may be consulted to help with management, and other possible factors, such as worsening renal function, should be excluded.

Grade 3/4 hypertension is uncommon among patients undergoing sunitinib treatment. In these cases, the patient should be treated with an antihypertensive agent and sunitinib treatment stopped until their hypertension returns to Grade 1 or 2, at which point sunitinib therapy can be resumed.

Hypothyroidism

Up to 85% of all patients with mRCC will develop hypothyroidism.[7-10] Symptoms associated with hypothyroidism include fatigue, anorexia, edema, fluid retention, and intolerance to cold. Patients undergoing treatment with sunitinib should undergo regular monitoring of their thyroid function[9] and be treated with thyroid hormone replacement therapy if overt hypothyroidism develops. Treatment discontinuation, treatment interruptions, or dose modifications are generally not necessary.

Diarrhea

Diarrhea is a common side effect of sunitinib treatment, but is generally mild and rarely limits therapy. However, even Grade 2 diarrhea may limit a patient's QOL and their ability to leave the home and enjoy their hobbies. Recognizing the importance of QOL, prompt intervention with loperamide for Grade 2 symptoms is warranted. In severe cases, a dose adjustment or schedule change may be necessary. If symptoms are interfering with the patient's QOL, sunitinib treatment may be stopped until symptoms reduce to Grade 1, and sunitinib restarted at the same dose. For Grade 3 diarrhea, sunitinib treatment would be stopped until Grade 1, and then restarted with a dose reduction.

A number of other gastrointestinal AEs occur with varying frequency with sunitinib treatment, including taste changes, dry mouth, nausea, vomiting, and indigestion.[2] Dose adjustments are rarely necessary for these AEs. Nausea may be prevented or relieved with common antiemetics; however, care should be taken with antidopaminergic agents, such as domperidone, or 5HT3 antagonists, such as granisetron, ondansetron, and dolasetron, which may be associated with prolonged QT/QTc interval or torsade de pointes.[11]

Individualized treatment to manage side effects

Maximizing drug exposure with sunitinib is important, as an increased steady-state area under the curve is associated with longer progression-free survival and overall survival, and a higher response rate.[12] Therefore, dose adjustment should not be undertaken without careful consideration. In many cases, individualizing the duration of sunitinib therapy through schedule modifications (e.g., from a four-week-on/two-week-off schedule to a two-week-on/one-week-off schedule) may effectively minimize toxicities and avoid the need for dose adjustments. Bjarnason explores this concept in further detail in this supplement (pages S252-5). In the event that dose adjustments are necessary, the drug monograph for sunitinib outlines a standard dose modification in 12.5 mg steps, based on individual safety and tolerability.[6]

The importance of a multidisciplinary approach to the management of side effects associated with sunitinib

The toxicities of sunitinib often lead to dose reductions, interruptions, and discontinuations.[13-16] Patients who are undergoing treatment with sunitinib should be counselled about the AEs related to their treatment and instructed on how to identify them. They should be encouraged to report any side effects to their healthcare team as soon as possible. By understanding the unique impact of toxicities on a patient's QOL — including their acceptance of AEs and threshold for tolerance — appropriate interventions can be undertaken to improve their time on treatment and, therefore, their success on therapy. It is important to include team members in management. Community resources can vary tremendously, including the amount of time that the physician can devote to AE management, the availability of specialty programs to manage oral drugs, pharmacy programs, and nursing callback programs. Selective, appropriate use of patient support

programs through the pharmaceutical company or hospital should be encouraged as an extra point of contact. The importance of early effective management cannot be underestimated, as by the time the patient returns for followup, if they have been suffering with AEs for a long period of time, they may already have given up on treatment.

The management of AEs has had to evolve with the shift from intravenous chemotherapies to oral cancer agents for the treatment of mRCC. Care teams should be aware of the available resources that are the best fit for their centre — whether it is a patient support program provided by a pharmaceutical company or a local call-back program — and establish processes to provide patients with the best support, ensuring the best opportunity for success.

Conclusion

As patients with mRCC live longer and do better for longer periods of time on treatment, even Grade 2 toxicities become more of an issue, impacting QOL and motivation to continue treatment. Future studies might consider separating Grade 1 and 2 toxicities in their reporting, which would be helpful to the community physician. Healthcare providers are encouraged to apply a multidisciplinary approach to the management of AEs associated with mRCC treatment using available resources, including patient support programs and existing infrastructure within hospitals and pharmacies. Over the past decade, we have become adept in managing sunitinib toxicities, but in rare cases, some AEs may preclude its use. For example, patients with uncontrolled hypertension or significant liver issues, such as hepatitis or cirrhosis, may be candidates for an alternate treatment. However, early, effective management of the potential AEs using a multidisciplinary approach is usually sufficient to ensure that patients complete their appropriate course of sunitinib therapy. Further, optimal management of toxicities will remain important in the future, as sunitinib remains a backbone of ongoing investigational trials incorporating immunotherapies and, in some patients, dose-optimization strategies may be recommended, targeting at least Grade 1 toxicity.

References

1. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib vs. interferon-alfa in metastatic renal cell carcinoma. *N Engl J Med* 2007;356:115-24. https://doi.org/10.1056/NEJMoa065044
2. Kollmannsberger C, Bjarnason G, Burnett P, et al. Sunitinib in metastatic renal cell carcinoma: Recommendations for management of non-cardiovascular toxicities. *Oncologist* 2011;16:543-53. https://doi.org/10.1634/theoncologist.2010-0263
3. Lacouture ME, Wu S, Robert C, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Oncologist* 2008;13:1001-11. https://doi.org/10.1634/theoncologist.2008-0131
4. Robert C, Soria JC, Spatz A, et al. Cutaneous side effects of kinase inhibitors and blocking antibodies. *Lancet Oncol* 2005;6:491-500. https://doi.org/10.1016/S1470-2045(05)70243-6
5. BC Cancer Agency. Symptom management guidelines: Palmar-plantar erythrodysesthesia (PPE). http://www.bccancer.bc.ca/nursing-site/ Documents/ 13.%20Palmar%20Plantar%20Erythrodysesthesia.pdf. Accessed November 17, 2016.
6. Sutent® (Sunitinib capsules). Product Monograph. Kirkland, QC: Pfizer Canada Inc., December 3, 2014.
7. Rini BI, Tamaskar I, Shaheen P, et al. Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 2007;99:81-3. https://doi.org/10.1093/jnci/djk008
8. Desai J, Yassa L, Marqusee E, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumours. *Ann Intern Med* 2006;145:660-4. https://doi.org/10.7326/0003-4819-145-9-200611070-00008
9. Wolter P, Dumez H, Schoffski P. Sunitinib and hypothyroidism. *N Engl J Med* 2007;356:1580. https://doi.org/10.1056/NEJMc070327
10. Wong E, Rosen LS, Mulay M, et al. Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. *Thyroid* 2007;17:351-5. https://doi.org/10.1089/thy.2006.0308
11. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine3 receptor antagonists. *Ann Pharmacother* 2003;37:1276-86. https://doi.org/10.1345/aph.1C510
12. Houk BE, Bello CL, Poland B et al. Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: Results of a pharmacokinetic/pharmacodynamic meta-analysis. *Cancer Chemother Pharmacol* 2010; 66: 357-371. https://doi.org/10.1007/s00280-009-1170-y
13. Choueiri TK, Duh MS, Clement J, et al. Angiogenesis inhibitor therapies for metastatic renal cell carcinoma: Effectiveness, safety, and treatment patterns in clinical practice-based on medical chart review. *BJU Int* 2010;105:1247-54. https://doi.org/10.1111/j.1464-410X.2009.08972.x
14. Feinberg BA, Jolly P, Wang ST, et al. Safety and treatment patterns of antiogenesis inhibitors in patients with metastatic renal cell carcinoma: Evidence from U.S. community oncology clinics. *Med Oncol* 2012;29:786-94. https://doi.org/10.1007/s12032-011-9922-z
15. Oh WK, McDermott D, Porta C, et al. Angiogenesis inhibitor therapies for advanced renal cell carcinoma: Toxicity and treatment patterns in clinical practice from a global medical chart review. *Int J Oncol* 2014;44:5-16.
16. Ruiz JN, Belum VR, Creel P, et al. Current practices in the management of adverse events associated with targeted therapies for advanced renal cell carcinoma: A national survey of oncologists. *Clin Genitourin Cancer* 2014;12:341-7. https://doi.org/10.1016/j.clgc.2014.04.001
17. National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0, May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed October 17, 2016.