Time trends for drug specific adverse events in patients on sunitinib; implications for remote monitoring

Jacob Wise,[1] Raj Tiwari, MD,[1] Sophie O'Halloran, MD,[1] Lauren Fleshner, BSc,[1] Susan Nguyen, BSc,[1] Karen Hersey, RN,[1] Nazanin Fallah-Rad, MD,[2] Neil Fleshner, MD[1]

[1]Division of Urology, University Health Network, University of Toronto, Toronto, Ontario, Canada
[2]Division of Medical Oncology, University Health Network, University of Toronto, Toronto, Ontario, Canada

WISE J, TIWARI R, O'HALLORAN S, FLESHNER L, NGUYEN S, HERSEY K, FALLAH-RAD N, FLESHNER N. Time trends for drug specific adverse events in patients on sunitinib; implications for remote monitoring. *Can J Urol* 2022;29(3):11136-11141.

Introduction: *Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor used to treat metastatic renal cell carcinoma (mRCC). Patients on sunitinib do require regular in-person appointments to monitor for adverse events (AEs). Given the Covid-19 pandemic, regular in-person visits expose patients to an increased risk of infection in addition to potentially preventable travel costs. This study investigated the feasibility of implementing a remote monitoring strategy for patients being treated with sunitinib for mRCC by examining the time trends of AEs.*

Materials and methods: *In this retrospective chart review of patients with a diagnosis of mRCC, 167 patients received sunitinib during their treatment. The time between initiation of treatment and the first AE was recorded. The AEs were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5. Survival analysis was used to calculate the time-to-AE.*

Results: *Of the 167 patients identified, 145 experienced an AE (86.8%). Hypertension was the most common AE with 80% of AEs were ≤ Grade 2. Incidence of AE dropped by 91% after 3 months follow up and a further 36% after 6 months. The cumulative incidence of AEs were 87.8%, 94.6% and 98.0%, at 3, 6 and 9 months respectively. The severity of AEs observed were 39.3%, 38.6%, 20.7%, 1.4%,0% of Grade 1-5 events respectively. A trend of grade migration to less severe grades was also shown over time, with percentage of Grade ≥ 3 toxicity dropping from 22% between 0-3 months to 14% beyond 6 months follow up.*

Conclusions: *The role of remote monitoring for mRCC patients on sunitinib remains relevant now with new waves of the Covid-19 pandemic, triggered by novel variants. The majority of AEs observed were of low severity ≤ Grade 2, with a trend of reduced AE frequency and severity most prevalent beyond 3 months of follow up. This data appears to support the implementation of a remote monitoring strategy 3 months after initiation of treatment.*

Key Words: renal cell carcinoma, sunitinib, remote monitoring, Covid-19

Accepted for publication April 2022

Acknowledgements
Queen's University Arts & Science Undergraduate Research Fund, Princess Margaret Cancer Centre's McCain GU BioBank

Address correspondence to Dr. Raj Tiwari, University Health Network, 700 University Avenue, Toronto, ON M5G 1X6 Canada

Introduction

An estimated 7,500 Canadians were diagnosed with renal cell carcinoma in 2020, with the leading cause of death being due to the presence of metastatic disease.[1] Sunitinib malate is a medication that has been widely used around the world in first and second line treatment of metastatic renal cell carcinoma (mRCC) of clear cell

histology. It is an orally administered inhibitor of multiple receptor tyrosine kinases including vascular endothelial growth factor receptors, platelet derived growth factor receptors, in addition to other kinases.[2] Sunitinib has been shown in multiple phase II and III trials to prolong progression free survival (PFS) and overall survival (OS).[3-5] It is also used in the treatment of gastrointestinal stromal tumors (GIST) after failure of imatinib treatment, and locally advanced or metastatic pancreatic neuroendocrine tumors.[6,7] The recommended treatment regimen for mRCC is 50 mg taken daily for a period of 4 weeks, followed by 2 weeks break from treatment. While immune checkpoint inhibitor (ICI) therapy has become more prominent in mRCC treatment, sunitinib remains relevant due to limited access to high-cost ICI agents with prominent reimbursement related issues in clinical practice.

Adverse events (AEs) have been thoroughly described in patients prescribed sunitinib. Sunitinib's characteristic array of AEs include diarrhea, fatigue, asthenia, altered taste, mucositis/stomatitis, anorexia, among others. Potentially serious AEs are warned against including left ventricular dysfunction, hypertension, QT prolongation, hemorrhage, thyroid dysfunction, adrenal dysfunction and hepatotoxicity.[8] Dosage modifications for drug-induced toxicities involve dose adjustments by 12.5 mg, and a transition to a 2 week on treatment, 1 week off treatment schedule.

Based on Cancer Care Ontario guidelines, patients being treated with sunitinib have clinical evaluations done before initiation of sunitinib treatment, and periodically at the beginning of each cycle. Each cycle typically lasts 6 weeks. Table 1 describes the clinical monitoring protocol in these patients. Patients are seen in-person for their first visit, and subsequently followed up using virtual appointments at the end of each 6-week cycle. During the virtual follow up period, any laboratory tests are performed at local laboratories, and results are accessible to providers over through electronic patient records.

Remote monitoring remains an important tool for patient follow up given the Covid-19 pandemic. Considering variant driven spikes in Covid-19 cases around the world, in addition to varying rates of vaccination, social distancing remains a prudent strategy for patients to minimize their risk of infection. Additionally, remote monitoring affords financial

TABLE 1. **Recommended clinical monitoring protocol for patients on sunitinib**

Monitor type	**Monitor frequency**
ECG	Baseline and each cycle if abnormal
LVEF in patients with cardiac risk factors	Baseline and each cycle if abnormal
Dental evaluation	Before starting treatment with preventative dentistry as needed
Urinalysis	Baseline
Thyroid function tests	Baseline then q3monthly, and as clinically indicated
Complete blood count	Baseline and at each cycle
Renal function tests and electrolytes (including Mg, Ca, PO_4)	Baseline and at each cycle
Liver function tests, with lipase and amylase	Baseline and at each cycle
Blood glucose patients may be needed	Baseline and at each cycle; closer monitoring in diabetic
Blood pressure and assessment for signs and symptoms of pancreatitis, thyroid dysfunction, myopathy, delayed wound healing, thromboembolism, bleeding, cardiovascular, neurologic, GI or respiratory effects, adrenal insufficiency	Baseline and each cycle

Cancer Care Ontario Formulary – Oct 2020
ECG = electrocardiogram; LVEF = left ventricular ejection fraction

TABLE 2. **Cardiac toxicity definitions and recommended actions**

Toxicity	Action	Dose
Congestive heart failure, prolonged QTc interval, AV block	Discontinue sunitinib	Not applicable
Fall in left ventricular ejection fraction < lower limit of normal or ≥ 20% from baseline, thrombotic microangiopathy, grade 3 hemorrhage	Hold sunitinib until ≤ Grade 1 CTCAE	Decrease 1 dose level (50 mg – level 3 37.5 mg – level 2 25 mg – level 1)

Cancer Care Ontario Formulary – Oct 2020
CTCAE = Common Terminology Criteria for Adverse Events

savings by minimizing transportation related costs, possibly reducing disease burden. We aimed to investigate the time trends of drug-induced AEs of sunitinib in our institution, to inform of the safety profile of future remote monitoring of mRCC patients treated with sunitinib.

Materials and methods

A retrospective single institution chart review was conducted at the Princess Margaret Cancer Centre in Canada among patients diagnosed with mRCC treated with sunitinib. Patients in this cohort were treated between 2006 to 2020. The AEs documented included: hypertension, hypokalemia, cardiac toxicity, palmar-plantar erythrodysesthesia (hand-foot syndrome), diarrhea, hypothyroidism, and abnormal liver function test. Cardiac toxicity was defined following the Cancer Care Ontario guidelines with the recommended courses of action detailed in Table 2. The duration between commencement of sunitinib to first AE was recorded. For patients who did not experience an AE, the duration from commencement of sunitinib to discontinuation of the drug or until last follow up appointment was recorded. The AEs were graded according to the Common Terminology

TABLE 3. **Time trends of adverse events comparing between 0-3, 3-6 and more than 6 months**

0-3 months on sunitinib					
Adverse event	**Total (127)**	**CTCAE Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hypertension	63	4	34	24	1
Hand-foot syndrome	20	14	6	0	0
Diarrhea	29	21	6	2	0
Hypothyroidism	7	5	2	0	0
Liver dysfunction	5	0	3	2	0
Hyperkalemia	1	1	0	0	0
Cardiac event	2	0	1	0	1
3-6 months on sunitinib					
Adverse event	**Total (11)**	**CTCAE Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hypertension	5	0	3	2	0
Hand-foot syndrome	3	2	1	0	0
Diarrhea	3	2	1	0	0
6+ months					
Adverse event	**Total (7)**	**CTCAE Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hypertension	2	0	1	1	0
Hand-foot syndrome	4	3	1	0	0
Diarrhea	1	1	0	0	0

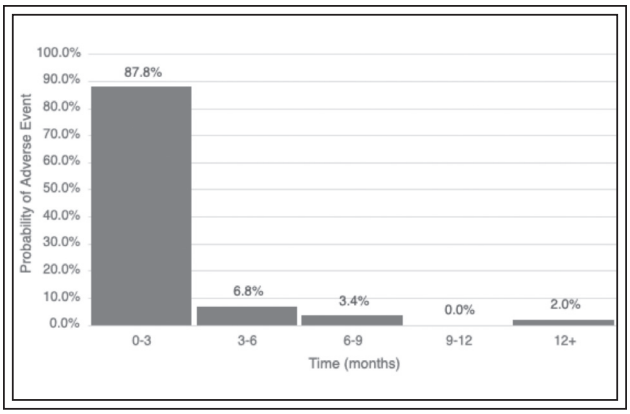

Figure 1. Time trends of adverse events in patients taking sunitinib for mRCC.

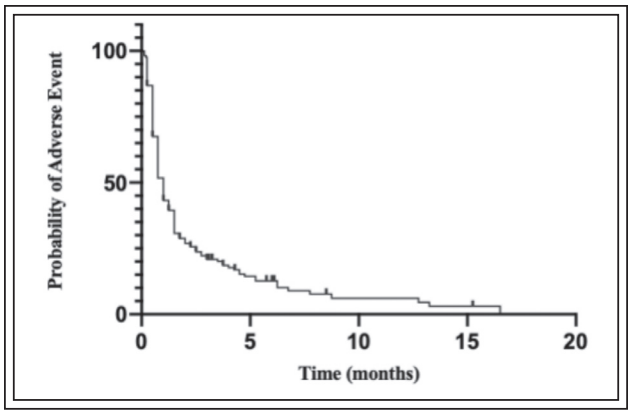

Figure 2. Kaplan-Meier curve outlining the time-to-adverse event for those treated with sunitinib for mRCC.

Criteria for Adverse Events, v5.0. If two or more AEs were identified on the same date, the most severe AE was recorded. Kaplan-Meier method was used to determine the time-to-AE. AEs were also compared across 3 monthly blocks to investigate time trends with regards to frequency and CTCAE grade severity. Analysis was calculated using GraphPad Prism, v8.

Results

In total, 167 patients were identified to have received sunitinib treatment. Of these patients, 86.8% (145 patients) experienced an AE during the course of their treatment. Hypertension was the most common AE followed by hand foot syndrome and diarrhea. 80% of AEs were ≤ Grade 2. We observed 127 AEs between 0-3 months, 11 AEs between 3-6 months and 7 AEs beyond 6 months follow up, Table 3. This decreasing trend represents a 91% drop in AE frequency after 3 months and a further 50% drop after 6 months. Cumulative incidence of AE calculated at 3, 6 and 9 months were: 87.8%, 94.6% and 98.0%, respectively, Figure 1. We calculated a time-to-event analysis to illustrate the probability of an AE decreasing with time, Figure 2.

Overall, AE severity was reported as 39.3% CTCAE Grade 1, followed by 38.6% Grade 2, 20.7% Grade 3 and 1.4% Grade 4 events. There were no Grade 5 AEs observed. The frequency of AE's amongst CTCAE grades are illustrated in Table 4. We observed a trend of AE grade migration to lower severity over time, with proportion of Grade ≥ 3 AE under 3 months being 22% and dropping to 14% beyond 6 months of follow up, Table 3.

The median number of days of treatment for this cohort was 30 days (one cycle of sunitinib). Dose interruptions occurred in 8 patients (5.5%), and dose reductions occurred in 10 patients (6.9%) due to AE's on sunitinib. There were 11 sunitinib discontinuations (7.6%) due to an occurrence of an AE.

TABLE 4. **Frequency of adverse events amongst CTCAE grades for patients taking sunitinib**

	CTCAE Grades				Total
Adverse events	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	
Hypertension	6 (4.14%)	39 (26.9%)	29 (20%)	1 (0.69%)	75
Cardiac event	0	2 (1.38%)	0	1 (0.69%)	3
Hypothyroidism	8 (5.52%)	3 (2.07%)	0	0	11
Diarrhea	24 (16.55%)	6 (4.14%)	0	0	30
Hand-foot syndrome	17 (11.72%)	5 (3.45%)	0	0	22
LFT's	0	2 (1.38%)	1 (0.69%)	0	3
Hyperkalemia	1 (0.69%)	0	0	0	1

CTCAE = Common Terminology Criteria for Adverse Events

Discussion

Sunitinib is frequently prescribed for mRCC patients, although, due to its AE profile, regular follow up appointments are necessary to monitor for side effects. The Covid-19 pande mic has necessitated a reduction in in-person medical services, and a transition to virtual care is beneficial to prevent exposure for both patients and healthcare providers. Our study is relevant because we investigated the frequency and time trends of AEs in a large population of cancer patients, making the minimization of exposure an important consideration.

We found that over 80% of AE's occurred in the first 3 months after initiation of sunitinib. Of the reported AE's, the majority of AE's occurred at Grade 1 or 2 severity, indicating that if an AE were to occur, it would potentially be of low severity. Hypertension was the most commonly reported AE amongst sunitinib users which is consistent with previous investigations.[9]

A limitation of the study includes the possibility of a subsequent AE occurring after the initial reported AE. This is currently unknown in this cohort which might impact our recommendations for remote motoring if further AE's occurred. Another limitation includes the possibility that an AE was not reported, which would lead to an underestimation of AE's amongst sunitinib patients. However, this is unlikely, given the infrastructure of the Canadian healthcare system. Additionally, it is possible that our study may present an underrepresentation of the probability of experiencing an AE for mRCC patients taking sunitinib considering that AEs that are difficult to denote in a retrospective analysis such as fatigue and mucositis were excluded from this study.

Another limitation of the study is the likelihood that in the near future, sunitinib will no longer be first line treatment for mRCC. However, until a comprehensive reimbursement schedule is widely available these data remain relevant. Excessive cost of ICI agents still remains a barrier for their use in the care of many mRCC patients. Additionally, when newer compounds replace sunitinib as first-line treatment of mRCC, sunitinib will still likely be used in second- or third-line settings.[10]

Given our findings, regular in-person follow up is appropriate for the first 3 months of sunitinib treatment. Remote monitoring after this time is a feasible option to reduce risk of infection during the Covid-19 pandemic. Furthermore, remote monitoring is likely beneficial for this patient population beyond the resolution of the Covid-19 pandemic. Virtual care eliminates the hassle, time, and cost associated with in-person appointments, making regular follow up appointments easier to attend for patients. This model of care allows for patients' family members to more easily attend their appointments and improves access to care for those living in remote and rural areas. The added convenience of virtual care for patient has been shown to improve medication adherence for patients with chronic conditions, indicating the strategy's suitability for mRCC patients.[11] Previous studies have been able to identify increases in blood pressure using an at-home blood pressure monitoring strategy that would not have been observed using traditional methods, amongst patients taking sunitinib for mRCC.[12] Therefore, it is possible that remote monitoring offers additional benefits to managing mRCC patients on sunitinib. Future research should investigate the occurrence of subsequent AEs amongst patients who had an initial AE to further validate our findings and fine-tune suggestions for remote monitoring.

An optimal sunitinib follow up strategy for mRCC patients on sunitinib requires in-person appointments, virtual appointments, and outpatient laboratory tests. Providers should leverage in-person appointments for the diagnosis of mRCC, to ensure the provision of compassionate, person-centered care, as virtual care has been identified as troublesome for the communication of bad news.[13] However, considering that patients with mRCC typically take sunitinib for long durations, remote monitoring is optimal for the consistent follow up appointments required to screen for AEs. Remote monitoring can easily allow for the screening of sunitinib specific AEs including the electronic distribution of photographs for hand-foot syndrome, at-home blood pressure cuffs for hypertension, and verbal provider consultation for other concerns. At-home proteinuria and hematuria tests can be performed using labstick measurements, and patients can travel shorter distances to local laboratory for blood tests to screen for LFTs. The remote monitoring of cancer patients has been well described for many different cancer patient populations and treatment methods including androgen receptor antagonists,[14] chemotherapy,[15] immune checkpoint inhibitors.[16]

Conclusions

Remote monitoring of sunitinib for mRCC seems to be appropriate after 3 months of treatment with traditional monitoring. This approach could help to decrease exposure to the Covid-19 virus and dangerous new variants, in addition to providing cost savings to patients and their families. Overall, our findings indicate that remote monitoring is a desirable strategy throughout the pandemic and in the post-pandemic world. □

References

1. Kidney cancer statistics-Canadian Cancer Society. www.cancer.ca.Accessed March 30, 2021. https://www.cancer.ca:443/en/cancer-information/cancer-type/kidney/statistics/?region=ab
2. Carrato Mena A, Grande Pulido E, Guillen-Ponce C. Understanding the molecular-bases mechanism of action of the tyrosine kinase inhibitor: sunitinib. *Anticancer Drugs* 2010;21(suppl 3):S3-S11.
3. Motzer RJ, Michealson MD, Redman BG et al. Activity of SU 11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;24(1):16-24.
4. Rini BI, Hutson TE, Figlin RA et al. Sunitinib in patients with metastatic renal cell carcinoma: clinical outcome according to international metastatic renal cell carcinoma database consortium risk group. *Clin Genitourin Cancer* 2018;16(4):298-304.
5. Motzer RJ, Michealson MD, Rosenberg J et al. Sunitinib efficacy against advanced renal cell carcinoma. *J Urol* 2007;178(5): 1883-1887.
6. Raymond E, Dahan L, Raoul J-L et al. Sunitinib maleate for the treatment of pancreatic neuroendorcrine tumors. *N Engl J Med* 2011;364(6):501-503.
7. Demetri GD, van Oosterom AT, Garrett CR et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomized controlled trial. *Lancet* 2006;368(9544):1329-1338.
8. Faivre S, Delbaldo C, Vera K et al. Safety, pharmacokinetic and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor in patients with cancer. *J Clin Oncol* 2006;24(1):25-35.
9. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib. Systematic review and meta-analysis. *Acta Oncol* 2009;48(1):9-17.
10. Choueiri TK, Powles T, Burrotto M et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal cell carcinoma. *N Engl J Med* 2021;384(9):829-841.
11. Thakkar J, Rahul K, Laba T-L et al. Mobile telephone text messaging for medication adherence in chronic disease. A meta-analysis. *JAMA Intern Med* 2016;176(3):340-349.
12. Azizi M, Chedid A, Oudard S. Home blood-pressure monitoring in patients receiving Sunitinib. *N Engl J Med* 2008;358(1):95-97.
13. Wolf I, Waissengrin B, Pelles S. Breaking bad news via telemedicine: a new challenge at times of an epidemic. *Oncologist* 2020;25(6):e879-e880.
14. Fleshner L, Berlin A, Hersey K et al. Time trends of drug specific actionable adverse events among patients on androgen receptor antagonists: Implications for remote monitoring. *Can Urol Assoc J* 2022;16(3):E146-E149.
15. Maguire R, McCann L, Kotronoulas G et al. Real tie remote symptom monitoring during chemotherapy for cancer: European multicentre randomized controlled trial (eSMART). *BMJ* 2021;374:n1647.
16. Daly B, Nicholas K, Flynn J. Analysis of a remote monitoring program for symptoms among adults with cancer receiving anti-neoplastic therapy. *JAMA Netw Open* 2022;5(3):e221078.