RESEARCH ARTICLE

Utilization of Sunitinib for Renal Cell Cancer: an Egyptian University hospital experience

Ezz El Din M

Abstract

Background: Metastatic renal cell carcinoma (mRCC) status as poor prognosis improved with the introduction of tyrosine-kinase inhibitors, especially sunitinib. There is sparse data reporting from our region on use of sunitinib in metastatic RCC. Thus the present study explores sunitinib usage at our institute. Materials and Methods: An unselected population of patients with metastatic RCC receiving sunitinib was analyzed with respect to patient characteristics, response, toxicity, and outcomes. Results: Fourty-nine patients with a median age of 50.5 years (range 21-71 years) were included. Most were male (61.2%). Twenty-one (42.9%) had metastatic disease at presentation. Sunitinib was first line therapy in 45. Conventional clear cell carcinoma was the most common pathology present (39 patients; 79.59 %). The most common site of metastasis was the lung (75.5%). Most patients (30) were started at a dose of 50 mg once a day for 4 weeks and then 2 weeks rest. Clinical benefit rate was 73.5% (n= 36), and 22.5% (n= 11) demonstrated progressive disease at first imaging evaluation within the first 3-6 months. The following objective response performed for patients was 48.9% (n=24) and progression at 24.5 % (n=12). The median follow-up was 16 months (range, 4-34 months), the overall estimated median PFS was 9 months and the estimated median OS was 15 months. Conclusions: This study demonstrated sunitinib is tolerable and effective in advanced/metastatic RCC Egyptian patients and indicates we should further seek second and third lines to increase survival equivalence as reported in the worldwide literature.

Keywords: Metastatic - renal cell cancer - sunitinib - ethnic variation - tyrosine kinase inhibitors

Asian Pac J Cancer Prev, **17 (7)**, 3161-3166

Introduction

Renal-cell carcinoma (RCC) represents approximately 3.8% of all new malignancies worldwide, and is increasing in incidence by 1.6 % each year from 2002 till 2011. (Siegel et al., 2014).

The majority of RCC (70-80%) are clear-cell tumours. The prognosis for advanced/metastatic RCC (a/mRCC) is dismal and, prior to the era of targeted therapies, median survival time was in the range of 10 months (Motzer et al., 1999).

Cytokine-based therapy (interferon-alfa and/ or interleukin-2) resulted in modest clinical benefit but also significant toxicity. (Negrier et al., 1998). However with the unveiling of the molecular pathways the majority of cases (45-80%) clear-cell RCC was found to be associated with abnormalities of the von Hippel-Lindau (VHL) gene that results in dysregulation of hypoxia-inducible factor (HIF) and vascular endothelial growth factor (VEGF)/ VEGF receptor (VEGFR) pathways. The mammalian target of rapamycin (mTOR) is also activated in clear-cell RCC, and is associated with increased levels of HIF proteins and angiogenesis (Pantuck et al., 2003, Pantuck et al., 2007).

Therefore pursuing these abnormalities; namely via vascular endothelial growth factor (VEGF)-targeted agents and mammalian target of rapamycin (mTOR) inhibitors theoretically should be beneficial. Both, first and second line treatment is of proven benefit and these agents have replaced immune therapies that were previously standard of care for metastatic RCC (Motzer et al., 2009).

Sunitinib is a multitargeted tyrosine kinase inhibitor (TKI) that mainly targets VEGF. It also has 'off target' effects, involving other tyrosine kinases that may account for some of its activity and toxicity (Motzer and Bukowski, 2006). Motzers' pivotal trial of sunitinib was published in 2006; and hence establishing it as one of the standard first line therapies (Motzer et al., 2009). The specific mechanism of its activity in RCC remains unidentified, and thus far not yet feasible to identify specific cohorts of patients who benefit from therapy. Sunitinib and the other drugs are only effective in controlling the disease for a certain period before the eventual progression occurs stressing on the importance of investigating mechanisms of resistance. (Motzer and Bukowski, 2006)

Cumulative data mainly from Western and Asian countries have reported on their use of sunitinib; we would like to report our institution's experience as a

*Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt *For correspondence: maiooyaz@yahoo.com*

representative of the African continent in terms of efficacy and adverse events in this different ethnic group.

Materials and Methods

All patients who received sunitinib for metastatic RCC between January, 2012 and July, 2015 were included in the present study at Ain Shams University Clinical Oncology Depatment. The patients were given sunitinib as their first therapy or at relapse after initial treatment. Patients who had received any prior therapy, consisting of other TKIs or cytokine therapy were eligible. The patients were analyzed with respect to the demographic profile, sites of metastases, starting dose of sunitinib, response, toxicity profile, progression free survival (PFS), and overall survival (OS). Ethical approval was obtained and an informed consent prior to their inclusion in the study was required.

Patients were started on sunitinib at a dose of 50 mg once a day for 4 weeks and then a gap of 2 weeks with dose modification depending on the toxicity. Response to treatment was based on clinical progression and on radiology; RECIST 1.1 (Response Evaluation Criteria in Solid Tumors) criteria. Response was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), based on radiologist's and oncologist's evaluation. Clinical progression and cancer-related deaths were considered as progression. Response evaluation was done after 2-4 cycles of sunitinib. Progression-free survival (PFS) was calculated as the time between start of therapy and the date of progression or death from any cause. Overall survival (OS) was calculated as the time between start of therapy and the date of death due to any cause. Toxicity profile was calculated according to the common terminology criteria for adverse effects (CTCAE) version 3.0.

Data were analyzed using Statistical Program for Social Science (SPSS) version 18.0. Survival was calculated using Kaplan-Meier method. Descriptive statistics were used to describe baseline characteristics, treatment patterns and adverse events. Relationships between outcomes, demographic factors and treatment patterns were assessed using Kaplan-Meier analyses, and log-rank comparisons. A P-value <0.05 was considered significant and a P-value <0.001 as highly significant.

Results

There were 51 patients planned for therapy. Two patients did not follow-up after initial visit and therefore were excluded from analysis.

Patient baseline characteristics are shown in Table (1). Baseline thrombocytosis was found in 1 patient whilst none had neutrophilia.

Most of the patients were male (61.2%) with a median age of 50.5 years (range 21-71 years).

Twenty-eight patients had localized disease at presentation and underwent surgery upfront. One patient was inoperable and hence was started on sunitinib and was then deemed fit for nephrectomy.

These non-metastatic presenting patients had a relapse after a median period of 16 months (range 5 -54 months).

Twenty-one patients (42.86% of the patients) had metastatic disease at presentation. Twelve of these patients underwent cytoreductive nephrectomy before starting sunitinib. Among the total patient set, 45 patients received sunitinib as first line therapy, 2 as second line (after interferon - alpha) and 2 as third line (one case had received gemcitabine and interferon, whilst the second case had previous sorafenib and bevacizumab).

Conventional clear cell carcinoma was the most

Table 1. Patient Baseline Characteristics

Parameters	No.	%
Gender		
Male	30	61.2
Female	19	38.8
Age (years)		
≤50 years	25	51.2
>50 years	24	48.8
Performance status(ECOG)		
0	23	46.9
1	15	30.6
2	11	22.5
Smoker	23	46.94
Family history	4	8.2
Prior thyroid finding	7	14.3
Baseline anemia	10	20.4
Baseline hypercalcemia	2	4.1
Baseline LDH (High)	10	20.4
MSKCC		
Favorable	14	28.6
Intermediate	28	57.1
Poor	7	14.3
Time from diagnosis to ttt		
≤1y	32	65.3
>1y	17	34.7
Grade		
I	9	18.4
II	21	42.9
III	15	30.6
IV	4	8.1
Lympho-vascular invasion		
Present	3	6.1
Absent	37	75.5
NA	9	18.4
Histological subtype		
Clear cell	39	79.6
Sarcomatoid	6	12.2
Papillary	3	6.1
Oncocytic	1	2.1
Comorbidity	25	51
Hepatitis markers positive	4	8.2
Nephrectomy	40	81.6
Metastatic from start	21	42.9
Number of metastases		
≤1	17	34.7
>1	32	65.3
Site of metastasis		
Lung	37	75.5
Liver	8	16.3
Local	20	40.8
Lymph nodes	18	36.7
Brain	8	16.3
Bone	14	28.6

NA= not available

common pathology present (39 patients; 79.59 %) while accompanying sarcomatoid component was found in 6 cases (12.2%), papillary in 3 (6.1%) and oncocytic in 1 (2.1 %).

The most common site of metastasis was the lung (75.5%), followed by local metastasis in the form of a local recurrence or an abdominal lymphadenopathy (40.8%). Other lymphatic metastases (mainly in the mediastinum) occurred in 36.7% of cases. Skeletal events were present in 28.6%. Hepatic and cerebral metastases were equally distributed at a 16.3% each.

Baseline performance status of ECOG 0 or 1 was recorded for 77.5% (38) of patients, whilst 11 patients (22. 5%) had performance status of 2.

A total of 305 cycles (range 1-20) was received with a median of 6 cycles. Most patients (30) were started at a dose of 50 mg once a day for 4 weeks and then 2 weeks rest. Six patients required dose reduction to 37.5 mg due to side effects. Of these patients, 10 had dose interruptions or delays due to logistical reasons. The remaining 19 patients received an alternate schedule consisting of 2 repetitive cycles of 2 weeks on the same dosage of sunitinib and 1 week off. Details of received treatment and response rate are documented in table 2. Two patients achieved complete remission after 2-4 cycles of sunitinib as documented in the first/ initial response. Two patients died due to progression during the first cycle. For the second/delayed response 4 patients had discontinued therapy due to toxicity and 4 did not do any imaging after initial presentation and were lost to follow-up and 3 had died as a result of disease progression.

On follow-up, there were 15 deaths while 2 more patients discontinued therapy due to toxicity. One patient discontinued therapy after 20 cycles due to unwillingness for further therapy. Objective response and clinical benefit rate was complete response /partial response/stable disease 73.5% (n= 36), whilst progressive disease occurred in 22.5% (n= 11) at first imaging evaluation within the first 3-6 months. The following objective response performed for patients during their course of treatment was 48.9% (n=24) and progression at 24.5 % (n=12).

The median follow-up was 16 months (range, 4-34 months), the overall estimated median PFS was 9 months (Figure 1). The estimated median OS was 15 months (Figure 2). Additional overall survival analysis was done for patients from the date of diagnosis of RCC (Figure 3).

The most common grade 3 and 4 adverse effects were

Table 2. Details of Treatments Received and Response to Therapy

	Frequency	Percent		
Regimen schedule				
4 weeks	30	61.2		
2 weeks	19	38. 8		
Dose modification	6	12.2		
Additional targeted therapy				
No	42	85.7		
Yes	7	14.3		
Supportive treatment				
No	29	59.2		
Yes	20	40.8		
Response	Initial evaluation		Delayed evaluation	
	Frequency (number)	Percent	Frequency (number)	Percent
CR	2	4.1	3	6.3
PR	15	30.6	4	8.2
SD	19	38.8	17	34.7
PD	11	22. 5	12	24.5

CR=complete response, PR= partial response, SD=stable disease, PD= progressive disease

Table 3. Adverse Events Reported in the Study Group

TOXICITY	Frequency	Percentage
Neutropenia		
None	22	44.9
Grade 1 & 2	24	48.9
Grade 3 & 4	3	6.3
Thrombocytopenia		
None	31	63.3
Grade 1 & 2	15	30.6
Grade 3 & 4	3	6.1
Anemia		
None	30	61.2
Grade 1 & 2	13	26.5
Grade 3 & 4	6	12.2
Constitutional/ fatigue		
None	21	42.9
Grade 1 & 2	25	51
Grade 3 & 4	3	6.1
LFT		
None	44	89.8
Grade 1 & 2	3	6.1
Grade 3 & 4	2	4.1
KFT		
None	38	77.6
Grade 1 & 2	9	18.4
Grade 3 & 4	2	4
Rash		
None	42	85.7
Grade 1 & 2	7	14.3
HFS		
None	21	42.9
Grade 1 & 2	21	42.9
Grade 3	7	14.2
Hypothyroidism		
None	30	61.2
Grade 1 & 2	14	28.6
Grade 3 & 4	5	10.2
Hypertension		
None	30	61.2
Grade 1 & 2	16	32.7
Grade 3 & 4	3	6.1
Abdominal pain		
None	33	67.4
Grade 1 & 2	16	32.6
Mucositis		
None	38	77.6
Grade 1 & 2	7	14.3
Grade 3 & 4	4	8.1
Vomiting		
None	32	65.3
Grade 1 & 2	14	28.6
Grade 3 & 4	3	6.1
Diarrhea		
None	33	67.4
Grade 1 & 2	16	32.6

LFT= liver function tests constituting liver enzymes, KFT= Kidney function tests denoting serum creatinine.

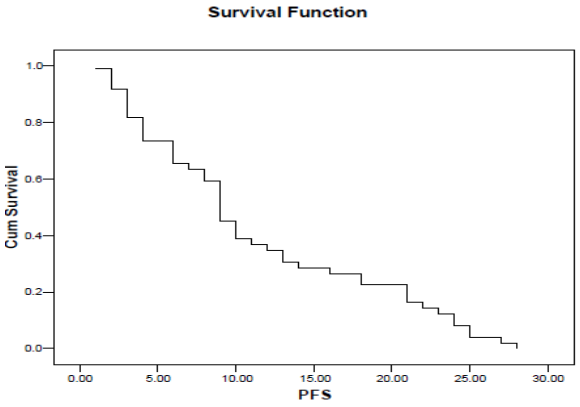

Figure 1. PFS from Study Initiation

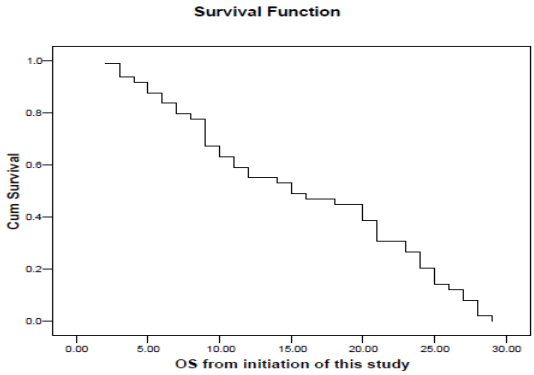

Figure 2. OS from Study Initiation

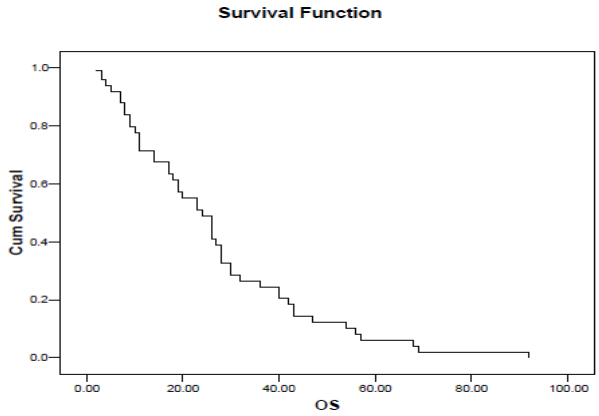

Figure 3. OS from First diagnosis with RCC

HFS (grade 3 only) occurring in 14.3% patients followed by thyroid dysfunction in 10.2%. Hematologic toxicity of grades 3 and 4 anemia, thrombocytopenia, and neutropenia occurred in 6, 3 and 3 patients, respectively.

A total of 19 patients (38.8%) had thyroid function abnormalities, in the form of hypothyroidism, all experiencing various degrees of raised thyroid stimulating hormone, (range 8-100mIU/L). Fourteen required treatment with thyroid supplements. This hypothyroidism developed usually after the fourth - ninth cycle of treatment.

Nineteen patients developed hypertension during the treatment. All were well controlled with medications alone and did not require any dose-modification of sunitinib for hypertension.

Uncommon toxicities noted during the course of treatment included hair and skin discoloration in 3 cases, whilst scrotal ulcers and deep vein thrombosis occurred in 1 patient each. The toxicity profile is documented in Table 3.

Patients who had progression (12 patients) if feasible were given second-line treatment. Six patients received the mTOR inhibitor everolimus. Of these, 3 did not follow-up for evaluation, 2 patients progressed after 2 and 4 months of treatment and the last patient was unable to continue due to grade 3 mucositis.

Univariate analysis for factors affecting PFS were for: smoking (smoker vs non- smoker) HR 9.1, 95% CI 2.06-40.5; gender (male vs female) HR 0.204, 95% CI 0.05-0.91; histological subtype (clear cell vs others) HR 1.18, 95% CI 0.33- 4.2; grade (high vs low) HR 1.77 , 95% CI 0.98-3.18; nephrectomy HR 0.59, 95% CI 0.19- 1.87; MSKCC score (favorable and intermediate vs poor) HR 9.36 , 95% CI 3.28-26.73 and prior thyroid abnormality HR 0.47 95% CI 0.18-1.23.

Whilst for overall survival univariate analysis for these factors were: smoking (smokervs non- smoker) HR 10.36, 95% CI 2.3-46.1; gender (male vs female) HR 0.2, 95% CI 0.04-0.9; histological subtype (clear cell vs others) HR 1.04, 95% CI 0.29- 3.68; grade HR 1.86 , 95% CI 0.99-3.35; nephrectomy HR 0.57, 95% CI 0.18- 1.81; MSKCC score (favorable and intermediate vs poor) HR 13.69 , 95% CI 4.39-42.68 and prior thyroid abnormality HR 0.46 95% CI 0.17-1.23.

Prognostic indicators affecting PFS were all statistically insignificant. Baseline characteristics that were found to influence PFS significantly were being a smoker (p= 0.01) and undergoing a nephrectomy (p= 0.02). Similarly smoking was of high significance as regard to OS as well as MSKCC risk strata (p<0.001).

A noteworthy factor affecting survival was found in the category of patients achieving an objective response that fared better in terms of PFS (p= 0.04) and OS (p= 0.016). Additionally, patients that developed certain adverse events were also of superior survival. This was reflected for HFS (p=0.01 for OS and PFS), rash (p=0.05 for OS) and hypertension (p=0.014 and 0.009 for OS and PFS respectively).

Discussion

The established role of sunitinib was set in the landmark trial reported in 2007 by Motzer et al that was conducted on 750 treatment naive patients with metastatic renal-cell carcinoma. They were randomized between sunitinib and interferon and achieved an objective response rate of 31% for sunitinib and a median PFS of 11 months. Grade 3 or 4 adverse events were relatively low. Treatment-related grade 3 or 4 fatigue was 7%, grade 3 diarrhea (5%), vomiting (4%), hypertension (8%), and the hand-foot syndrome (5%).

This pivotal study also documented a neutropenia of grade3/4 in 12% of patients in the sunitinib group, lymphopenia in 12% and thrombocytopenia in 8%. A total of 38% of patients receiving sunitinib had a dose interruption because of adverse events, whereas 32% had a dose reduction but finally it was only 8% that terminated

therapy due to toxicity. The OS that was reported later with sunitinib was 26.4 months with an objective response rate of 47% for sunitinib. (Motzer et al., 2009).

In order to simulate real life and negate the clinical trial effect, results of sunitinib usage 4371 patients under an expanded access program were published in 2009. (Gore et al., 2009). In this study an unselected population that encompassed patients with poor performance status (ECOG PS 2 or higher), non-clear cell histology, age above 65 years and brain metastases were taken into account. The most common adverse effects were diarrhea and fatigue, with discontinuation due to adverse effects in 8% of the patients. The objective response rate (ORR) was 17%, median PFS was 10·9 months, and OS was 18·4months.

Fifty-nine Indian patients with metastatic RCC experience with sunitinib was reported. (Krishna et al., 2013). This unselected patient cohort included patients who had received prior cytokine therapy, patients with performance status 2 or 3 (15%), impaired renal function, low hemoglobin and non-clear cell pathology. Respiratory and skeletal systems were the most common site of metastases. The patients received a median number of 4 cycles, with 23 patients requiring dose modification and 12 discontinuing therapy due to toxicity. Overall, 65% ORR was reached at initial evaluation. The median PFS was 11.4 months and overall survival was 22.6 months. Hand-foot syndrome (51%), fatigue (53%), mucositis (29%) and skin rash (39%) all grades 3 or more were documented. Hypertension (22%) and thyroid abnormalities (23.7%) of all grades was noted.

A Korean study evaluated sunitinib in an unselected population (n=132) of advanced RCC patients. (Kim et al., 2011) The PFS was 8.2 months and OS rate was 23.1 months. Discontinuation as a consequence of toxicity was found in 7.6% of the patients. The most common toxicity in this study was hematologic (anemia, thrombocytopenia, and neutropenia). Yet despite this different toxicity profile their patients had comparable treatment outcomes.

A retrospective analysis performed on 44 Egyptian patients with metastatic renal cell carcinoma that received sunitinib concluded that efficacy data were comparable to published literature in terms of PFS and OS. (Edesa and Abdelmalek, 2015) Despite the dissimilar adverse events, as compared to Asian and western communities, Egyptian patients tolerated treatment well.

The median age of the patients was 53 years and at a median follow up of 19 months, 9 (21%) patients achieved partial remission, disease stability in 20 cases (45%) and progressive in 7 (16%), 4 (9%) were lost to follow up, and 4 (9%) had discontinued due to toxicity. The median overall survival was 23 months, while progression free survival was 12 months. Mucositis (15.9%), hand-foot syndrome (13.6%), and fatigue (9%) were the most common non hematologic events encountered at grade 3 or more, while the main grade 3 or 4 laboratory abnormalities were neutropenia (6.8%), then anemia in 4.5% of patients.

The novelty in the reporting in this category of Egyptian patients serves as a further confirmation of the unique toxicity profile experienced by this ethnic subset, even if reported from a different treatment facility. Considerably higher thyroid adverse events were experienced at our hospital (grades 3 & 4; 10.2% vs. 0%) that can possibly be attributed to previous comorbid related thyroid issues highlighting an area of needed further research. An alternative schedule was given to a notable portion of the patients (38.8 % received 2 week regimen) in the current study as the first report of its implementation in the region and perhaps accounting for the slight differences in adverse events and lower discontinuation.

The slightly lower PFS and OS, probably a consequence of the shorter follow up and the higher percentage of patients with cerebral metastases (16.3% vs. 7 %) a well-known factor per se for a worse outcome than patients with other sites of metastases. (Gore et al., 2011)

It was possible to stratify patients according to MSKCC criteria only and not the Heng classification due to absence or negligible patients with neutrophilia and thrombocytosis. This could be attributed to the small sample size primarily but needs to be further validated in a larger study in this community to truly be explored to draw such a bold conclusion.

Outcomes of the present study are similar to the majority of previous literature, with a slightly lower OS. This lower survival can be explained by the higher percentage of intermediate and poor risk category patients included (71.4%) as well as low performance patient inclusion (ECOG 2= 22.45%) or possibly the short follow-up. An additional factor that explains this diminished PFS and OS is lack of multiple usage of various treatment lines by our patients as a consequence to limited resources (85.7% used sunitinib only) making our survival figures similar to the first sunitinib trials.

Resemblance to this finding was also stated in the first UK-specific registry to provide information on real-world treatment patterns and outcomes of RCC patients- the RECCORD registry (Wagstaff et al., 2016). Only 15.8% of the 514 RECCORD patients received second-line therapy, over half treated with everolimus and this clearly influenced median OS (33 months for patients who received second-line treatment vs. those who only received first-line treatment 20.9 months, P = 0.008).

Additionally, a study of clinical outcomes in community-based practices published a median overall survival (OS) of 15.5 months, and progression-free survival (PFS) of 7.5 months. They concluded this inferior outcome, as compared to those from clinical trials, a consequence of shorter duration of therapy stressing the importance of sunitinib therapy optimization in this setting. (Schnadig et al., 2014)

The percentage of patients scoring hypothyroidism was higher than that reported in literature (38.78%) this maybe as a consequence to previous thyroid abnormalities listed in their past medical history (14.29%, with one patient giving a history of thyroid malignancy for which radioactive iodine was received 20 years earlier).

Seemingly the biomarker route holds immense promise for patient selection for future therapeutic intervention and prognosis. A pretreatment C- reactive protein (CRP) concentration was an independent prognostic factor (of PFS) in mCCRCC patients treated with first -line sunitinib in a Japanese study that found patients with high (>0.5

mg/dl) serum CRP levels may not benefit from this treatment. A meta-analysis performed also reported CRP concentration as significantly prognostic of metastasis and mortality in RCC patients (Kawai et al., 2015). Moreover, CRP's role as a predictive marker in RCC patients treated with sunitinib is well established (Fujita et al., 2012; Beuselinck et al., 2014; Dai et al., 2014).

Najjar and colleagues (2014) shared their clinical experience of an alternate sunitinib schedule 2 weeks of treatment/1 week off (schedule 2/1) at Cleveland Clinic and reported an improved toxicity profile and thus better adherence to treatment. Whilst Miyake et al. (2015) supported this schedule for its improvement in QoL. Almost a third of cases in this study received this alternate regimen, though not analyzed here, hopefully will be in a larger prospective trial.

The present study provides a different platform to view RCC disease in a different ethnic group in terms of efficacy and toxicity. The "global community" real life clinical practice echoes somewhat similarly in terms of first and second line therapies employed despite limited access to treatment. Hypothyroidism, as an adverse event, and its association with incidental thyroid abnormalities warrants further investigation in a larger trial to prove if it is of any meaningful association or perhaps linked to disease pathogenesis. Clearly the small limited single institutional sample would be improved if a collaborative database be set not only on a national but an international level. Lack of biomarker use as a prognostic and predictive tool is also another limitation.

To conclude this study has served to show sunitinib is tolerable and effective in advanced/ metastatic RCC Egyptian patients and implores us to further seek second and third lines to increase survival equivalence as reported by worldwide literature.

Acknowledgements

No financial grants or funding to be stated

References

Beuselinck B, Vano YA, Oudard S, et al (2014). Prognostic impact of baseline serum C-reactive protein in patients with metastatic renal cell carcinoma (RCC) treated with sunitinib. *BJU Int*, **114**, 81-9.

Dai J, Tang K, Xiao W, et al (2014). Prognostic significance of C-reactive protein in urological cancers: a systematic review and meta-analysis. *Asian Pac J Cancer Prev*, **15**, 3369-75.

Edesa WA, Abdelmalek RR (2015). Efficacy and toxicity of sunitinib in egyptian patients with metastatic renal cell carcinoma. *Asian Pac J Cancer Prev*, **16**, 1971-76.

Fujita T, Iwamura M, Ishii D, et al (2012). C-reactive protein as a prognostic marker for advanced renal cell carcinoma treated with sunitinib. *Int J Urol*, **19**, 908-13.

Gore ME, Szczylik C, Porta C, et al (2009). Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: An expanded-access trial. *Lancet Oncol*, **10**, 757-63.

Gore ME, Hariharan S, Porta C, et al (2011), Sunitinib in metastatic renal cell carcinoma patients with brain metastases. *Cancer*, **117**, 501-9.

Kawai Y, Osawa T, Kobayashi K, et al (2015). Factors prognostic for survival in Japanese patients treated with sunitinib as first-line therapy for metastatic clear cell renal cell cancer. *Asian Pac J Cancer Prev*, **16**, 5687-90.

Kim HS, Hong MH, Kim K, et al (2011). Sunitinib for Asian patients with advanced renal cell carcinoma: A comparable efficacy with different toxicity profiles. *Oncol*, **80**, 395-405.

Krishna VM, Noronha V, Prabhash K, et al (2013). Sunitinib in metastatic renal cell carcinoma: A single center experience. *Indian J Cancer*, **50**, 268-73.

Miyake H, Harada K, Miyazaki A, Fujisawa M (2015). Improved health-related quality of life of patients with metastatic renal cell carcinoma treated with a 2 weeks on and 1 week off schedule of sunitinib. *Med Oncol*, **32**, 78.

Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J (1999). Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol*, **17**, 2530-40.

Motzer RJ, Bukowski RM (2006). Targeted therapy for metastatic renal cell carcinoma. *J Clin Oncol*, **24**, 5601-08.

Motzer RJ, Hutson TE, Tomczak P, et al (2007). Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*, **356**, 115-24.

Motzer RJ, Hutson TE, Tomczak P, et al (2009). Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*, **27**, 3584-90.

Najjar YG, Mittal K, Elson P, et al (2014). A 2 weeks on and 1 week off schedule of sunitinib is associated with decreased toxicity in metastatic renal cell carcinoma. *Eur J Cancer*, **50**, 1084-9.

Negrier S, Escudier B, Lasset C, et al (1998). Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie. *N Engl J Med*, **338**, 1272-78.

Pantuck AJ, Zeng G, Belldegrun AS, Figlin RA (2003). Pathobiology, prognosis, and targeted therapy for renal cell carcinoma: exploiting the hypoxia-induced pathway. *Clin Cancer Res*, **9**, 4641-52.

Pantuck AJ, Seligson DB, Klatte T, et al (2007). Prognostic relevance of the mTOR pathway in renal cell carcinoma: implications for molecular patient selection for targeted therapy. *Cancer*, **109**, 2257-67.

Powles T, Chowdhury S, Jones R, et al (2011). Sunitinib and other targeted therapies for renal cell carcinoma. *Brit J Cancer*, **104**, 741-45.

Schnadig IA, Hutson TE, Chung H, et al (2014). Dosing patterns, toxicity, and outcomes in patients treated with first-line sunitinib for advanced renal cell carcinoma in community-based practices. *Clinical Genitourinary Cancer*, **12**, 413-21.

Siegel R, Ma J, Zou Z, Jemal A (2014). Cancer statistics. *CA Cancer J Clin*, **64**, 9-29.

Wagstaff J, Jones R, Hawkins R, et al (2016). Treatment patterns and clinical outcomes in patients with renal cell carcinoma in the UK: insights from the RECCORD registry. *Ann Oncol*, **27**, 159-65.