Original Article

2/1 dose schedule of sunitinib is superior than the 4/2 regimen for the first-line therapy of clear cell metastatic renal cell carcinoma – An Indian experience

Jiten Jaipuria, Ankita Jain[1], Shashikant Gupta[1], Nripesh Sadasukhi[1], Priyatham Kasaraneni[1], Amitabh Singh[1], Kush Gupta[2], Girish Sharma, Vineet Talwar[3], Sudhir Kumar Rawal[1]

Amity Centre for Cancer Epidemiology and Cancer Research, Amity Institute of Biotechnology, Amity University, Noida, Uttar Pradesh, [1]Uro-Oncology Division, Rajiv Gandhi Cancer Institute and Research Centre, Rohini, Sector – 5, New Delhi, [2]Catalyst Clinical Services Pvt. Ltd., New Delhi, [3]Medical Oncology Division, Rajiv Gandhi Cancer Institute and Research Centre, Rohini, Sector – 5, New Delhi, India

Correspondence to: Sudhir Kumar Rawal, E-mail: sudhirrawal85@gmail.com

Abstract

Background: Sunitinib remains the first-line treatment for favorable risk metastatic clear cell renal cell cancer (mccRCC). It was conventionally given in the 4/2 schedule; however, toxicity necessitated trying the 2/1 regimen. Regional variations in treatment response and toxicity are known, and there is no data from the Indian subcontinent about the outcomes of the alternative dosing schedule.

Methods: Clinical records of all consecutive adult patients who received sunitinib as first-line therapy for histologically proven mccRCC following cytoreductive nephrectomy from 2010–2018 were reviewed. The primary objective was to determine the progression-free survival (PFS), and the secondary objectives were to evaluate the response rate (objective response rate and clinical benefit rate), toxicity, and overall survival. A list of variables having a biologically plausible association with outcome was drawn and multivariate inverse probability treatment weights (IPTW) analysis was done to determine the absolute effect size of dosing schedules on PFS in terms of "average treatment effect on the treated" and "potential outcome mean."

Results: We found 2/1 schedule to be independently associated with higher PFS on IPTW analysis such that if every patient in the subpopulation received sunitinib by the 2/1 schedule, the average time to progression was estimated to be higher by 6.1 months than the 4/2 schedule. We also found 2/1 group to have a lower incidence than the 4/2 group for nearly all ≥ grade 3 adverse effects. Other secondary outcomes were comparable between both treatment groups.

Conclusion: Sunitinib should be given via the 2/1 schedule in Indian patients.

Keywords:
Progression-free survival, renal cell cancer, sunitinib/administration and dosage, sunitinib/adverse effects, sunitinib/therapeutic use

Introduction

According to "Globocan," kidney cancer ranked 14th in terms of incidence, for both sexes, among all age groups in 2020.[1] It claimed more than 175,000 lives

Access this article online	
Website: www.indianjcancer.com	Quick Response Code:
DOI: 10.4103/ijc.IJC_1284_20	

How to cite this article: Jaipuria J, Jain A, Gupta S, Sadasukhi N, Kasaraneni P, Singh A, *et al.* 2/1 dose schedule of sunitinib is superior than the 4/2 regimen for the first-line therapy of clear cell metastatic renal cell carcinoma – An Indian experience. Indian J Cancer 0;0:0.
Submitted: 29-Nov-2020 **Revised:** 16-May-2021
Accepted: 30-Jun-2021 **Published:** 09-Jan-2024

worldwide in the same year, with both incidence and mortality being roughly twice in males as compared with females. A recent study found that Indian patients to have "younger age, higher male to female ratio, a lower proportion of asymptomatic patients, higher proportion of advanced stage at diagnosis, and lower stagewise survival."[2]

Clear cell is the most common subtype of metastatic renal cell cancer (mccRCC). In 2006, sunitinib (a tyrosine kinase inhibitor [TKI]) gained approval for treating mccRCC and till now remains as one of the first line "preferred regimens" for treatment of favorable risk category patients as per the National Comprehensive Cancer Network (NCCN) guidelines.[3] For intermediate and poor-risk mccRCC, NCCN suggests it as "other recommended regimens," in case one does not choose ipilimumab + nivolumab or axitinib + pembrolizumab or cabozantinib.

Conventionally, we give sunitinib as 4 weeks on, 2 weeks off (4/2) schedule. However, treatment-related toxicity necessitated investigators to try 2 weeks on, 1 week off (2/1) regimen. Evidence exists for 2/1 schedule to have lower adverse effects and superior survival.[4] There is evidence among Indian patients of sunitinib having oncological response rates well matched to other international studies (for the 4/2 schedule); however, to the best of our knowledge, there exists no data about the comparative efficacy of alternative dosing regimens.[5] Study of regional differences in drug responses are critical as a recent meta-analysis confirmed ethnic variations in toxicity of sunitinib, with Asian patients experiencing higher adverse effects in comparison with Caucasian patients.[6]

In this study, we compared 4/2 and 2/1 dosing schedules of sunitinib for the first-line treatment of mccRCC. The primary objective of this study was to determine the progression-free survival (PFS) and the secondary objectives were to evaluate the response rate (objective response rate [ORR] and clinical benefit rate [CBR]), toxicity, and overall survival (OS).

Material and Methods

Ours is a high-volume tertiary regional cancer center based in India, and we maintain a prospective registry of all cancer patients. Clinical management (including the schedule of follow up [once every 3 months], radiological imaging, and investigations at each visit) follows to date the NCCN guidelines.[3] We performed CT chest, abdomen, and pelvis, along with Tc99m-methylene diphosphonate (MDP) bone scan (hereafter, referred to as conventional imaging) for the evaluation of metastasis initially. Since 2016, 2-deoxy-2-[fluorine-18] fluoro-D-glucose (^{18}F-FDG) PET increasingly became our preferred choice for metastatic workup. Sunitinib became our drug of choice for the management of mccRCC since approval in 2006. Initially, we gave sunitinib as 50 mg/day in 4/2 schedule (hereafter referred as 4/2 group), with dose reductions to 37.5 mg/day and 25 mg/day in case of toxicity. As clinical data accumulated for lower toxicity with the 2/1 regimen (hereafter referred as 2/1 group) in the later years, we preferred the same since 2013, with a similar protocol of dose reduction in case of intolerable side effects.[7,8] Initially, we risk-stratified mRCC patients based on the prognostic model described by Motzer *et al*.[9] However, the International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC) prognostic model became our preferred choice since 2013, and we revisited medical records of older patients to reflect the new classification for analysis.[10] Cytoreductive nephrectomy (CRN) was almost universally performed initially for many years. However, offering it upfront for those with poor risk mccRCC increasingly fell out of favor from 2016 in the light of guideline recommendations (drawing from increasing retrospective evidence demonstrating no survival advantage), and also our own personal experience.[11]

With institutional ethical committee clearance (Res/SCM/26/2019/29), we retrospectively analyzed the clinical records of all consecutive adult patients who received sunitinib as first-line therapy for histologically proven mccRCC following CRN from November 2010 to April 2018. Inclusion criteria required a bi-dimensionally measurable and histologically confirmed metastatic disease on computed tomography (CT) imaging [whether done alone or as a companion to positron emitted tomography (PET) scan]. We used RECIST 1.1, and PERCIST 1.0 criteria for response assessment in the case of conventional imaging and FDG-PET, respectively. The oncological response was uniquely classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Experienced clinicians having more than five years of experience assessed images, with specific criteria about response categories described elsewhere.[12,13] The study was conducted according to the ethical principles stated in the latest version of the Helsinki Declaration.[14]

Definitions

We defined PFS as the time from the date of initiation of sunitinib to PD, or death from any cause, whichever occurred first. The proportion of patients achieving the best response of CR or PR were

Key Message

2/1 schedule of Sunitinib is better tolerated in Indian patients than the 4/2 schedule and is associated with higher progression-free survival.

labelled to have an objective response (ORR). Patients fulfilling the best response of CR, PR, or SD were defined to have clinically benefitted (CBR). We calculated OS from the date of therapy initiation to death, or the last follow-up (for an alive patient).

Toxicity and safety assessment

Toxicity and safety assessment included patients having a minimum follow-up of 2 months post sunitinib therapy. We reviewed individual medical records for the clinical evaluation of hematologic and non-hematologic toxicity. Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0) was used for grading adverse events.[15] Since all patients experience some side effects, we focused on grade 3 and 4 toxicity which necessitated treatment plan modification. Comorbidities were recorded using the modified Charlson Comorbidity Index (CCI) score.[16]

Statistical analysis

Quantitative data are presented as median [interquartile range (IQR)]. Count data are summarized as numbers (proportion). We drew a list of variables having a biologically plausible association with outcomes including - age, comorbidities (measured by CCI score), gender, treatment category (4/2 versus 2/1 group), Fuhrman grade, and IMDC risk category (incorporating the following variables: time from diagnosis to systemic therapy, Karnofsky performance status, hemoglobin, calcium, neutrophil count, and platelet count). We examined their association with PFS by univariate and multivariable cox proportional hazard models. The selection criteria for multivariable modelling was $P < 0.2$ on univariable analysis. Since there were a low number of deaths, univariable analysis of OS was performed by Firth's penalized survival analysis to overcome the issue of non-convergence of likelihood estimate.[17]

Further, we decided to estimate the absolute effect size of dosing schedules on PFS in terms of "average treatment effect on the treated," and "potential outcome mean" using "stt effects ipw" command in Stata (StataCorp. 2017. *Stata Statistical Software: Release 14.2* College Station, TX: StataCorp LP).[18] It allows treatment effects to be estimated using inverse-probability weights (IPW) which essentially allows "modelling of treatment assignment rather than outcome." IPW modeling allows one to replicate the measures of the effect commonly reported in randomized controlled trials; a feat not possible with conventional multivariable cox proportional hazard analysis. IPW estimators use weighted averages of the observed outcome to estimate the average treatment effect. If there is censoring, the weights must control for censoring and the missing potential outcome. In this case, IPW estimators construct the weights from two models, one for the censoring time and one for treatment assignment. We verified if model-based treatment weights balance the covariates, "overlap condition" was not violated, and that maximum propensity score for each treatment level was sufficiently less than 1.

MedCalc v15.8 (MedCalc Software bvba, Ostend, Belgium) was used to analyze descriptive statistics. We compared count data using Chi-square or Fisher's exact test (if columns had ≤ 5 patients) as appropriate. Hazard ratios were reported with a 95% confidence interval (CI). R program v3.6.1 [R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria] was used for Firth's penalized survival analysis, and graphing IPW adjusted PFS and OS curves using the packages "coxphf" and "IPW survival," respectively. Alpha <0.05 was set as significant before-hand.

Results

Eighty patients comprised the study cohort; 47 (59%) patients comprised the 2/1 group. Table 1 describes the clinical and demographic characteristics of the study cohort stratified by treatment groups. Both treatment groups had patients with similar age, gender, comorbidity profile, and Fuhrman grades of tumor. However, 2/1 group had significantly higher patients with IMDC intermediate-risk disease (83%), while the proportion of IMDC poor-risk category was higher in the 4/2 group (21% versus 6%). Also, 4/2 group had patients with more frequent liver and lymph nodal metastasis than the 2/1 group, which had a higher proportion of patients with lung metastasis. Median follow-up duration was significantly more in the 2/1 group (21.5 versus 5.6 months, *P* value 0.0001).

Primary objective

Univariable and multivariable cox proportional hazards analyses of the PFS and OS are detailed

Table 1: Clinical and demographic details of the study population (*n*=80) stratified by treatment groups

Clinical Parameters	Sunitinib 4/2 schedule *n*=33	Sunitinib 2/1 schedule *n*=47	*P*
Age, years, median (IQR)	55 (45–60)	54 (45–62)	0.81
Gender, male, *n* (%)	29 (88%)	39 (83%)	0.77
CCI score, median (IQR)	2 (1–3)	2 (1–3)	0.97
IMDC risk category, *n* (%)			
Favorable risk	8 (24%)	5 (11%)	
Intermediate risk	18 (55%)	39 (83%)	*0.02*
Poor risk	7 (21%)	3 (6%)	
Fuhrman grade, *n* (%)			
2	11 (33%)	17 (36%)	
3	10 (30%)	17 (36%)	*0.70*
4	12 (37%)	13 (28%)	
Common metastatic sites at presentation, *n* (%)			
Lung	11 (33%)	25 (53%)	
Bone	11 (33%)	10 (21%)	*0.046*
Liver	12 (37%)	7 (15%)	
Lymph nodes	10 (31%)	4 (9%)	
Omentum	2 (6%)	1 (2%)	
Follow up, months, median (IQR)	5.6 (3.3-22.3)	21.5 (9.5-34.2)	*0.0001*

IQR: Inter-quartile range; CCI: Charlson Comorbidity Index; IMDC: International Metastatic Renal-Cell Carcinoma Database Consortium. *P* values rounded off to two significant decimals Significant results marked italicized

Table 2: Cox proportional hazard analyses of risk factors associated with progression free and overall survival

Variable	Univariable analysis Progression free survival Hazard ratio (standard error), *P*	Multivariable analysis[a] Progression free survival Hazard ratio (standard error), *P*	Univariable analysis Overall survival Hazard ratio (standard error), *P*[b]
Age	1 (0.01), 0.66	not included	1 (0.04), 0.19
Female gender[c]	1.9 (0.36), 0.086	***2.1 (0.37), 0.043***	3.5 (0.82), 0.14
Sunitinib 2/1 dose schedule[d]	***0.38 (0.28), 0.0007***	***0.29 (0.32), 0.0001***	0.41 (0.77), 0.23
Fuhrman grade[e]			
3	1.7 (0.33), 0.11	***2.1 (0.34), 0.03***	1.1 (0.92), 0.92
4	1.7 (0.35), 0.15	1.9 (0.36), 0.078	1.3 (0.92), 0.74
CCI score[g]	1 (0.11), 0.66	not included	1.4 (0.31), 0.28
IMDC risk category[f]			
Intermediate risk	1 (0.39), 0.88	1.9 (0.47), 0.15	0.36 (0.87), 0.22
Poor risk	***3.7 (0.50), 0.008***	***7.2 (0.55), 0.0003***	1.2 (1.1), 0.84

CCI: Charlson's Comorbidity Index, IMDC: International Metastatic Renal-Cell Carcinoma Database Consortium Odds ratios rounded off to two decimals in case <1, otherwise rounded off to one decimal, *P* values rounded off to two significant decimals Significant results marked bold and italicized [a]All variables with *P*<0.2 included in multivariable analysis [b]Modeled using Firth's penalized maximum likelihood cox proportional hazard model to overcome the problem of non-convergence of likelihood function [c]With the male gender as reference [d]Odds ratio for sunitinib 2/1 dose schedule, with 4/2 dose schedule as reference [e]With Fuhrman grade 2 as reference [f]With IMDC favorable risk category as reference Multivariable analysis of overall survival was not done as no variable was found significant in the univariable analysis

in Table 2. We found female gender, increasing Fuhrman grade, and higher IMDC risk category to be independently associated with significantly lower PFS in the multivariable analysis. After adjusting for confounders, 2/1 schedule emerged independently associated with higher PFS (HR 0.29, 95% CI 0.16–0.55, $P = 0.0001$). For IPW modeling of PFS, both, the model of assignment to treatment, and the time-to-censoring model depended on the IMDC risk category, Fuhrman grade, and gender. If all patients received sunitinib by the 4/2 schedule in the subpopulation, the estimated average time to progression was 15.9 months (potential outcome mean). If every patient in the subpopulation received sunitinib by the 2/1 schedule, the average time to progression was estimated to be higher by 6.1 months (average treatment effect on the treated). Figure 1 depicts the IPW adjusted PFS curves (while balancing for IMDC risk category, Fuhrman grade, and gender) comparing both dose schedules, and the difference was significant (log-rank statistic – 3.35, $P < 0.0006$).

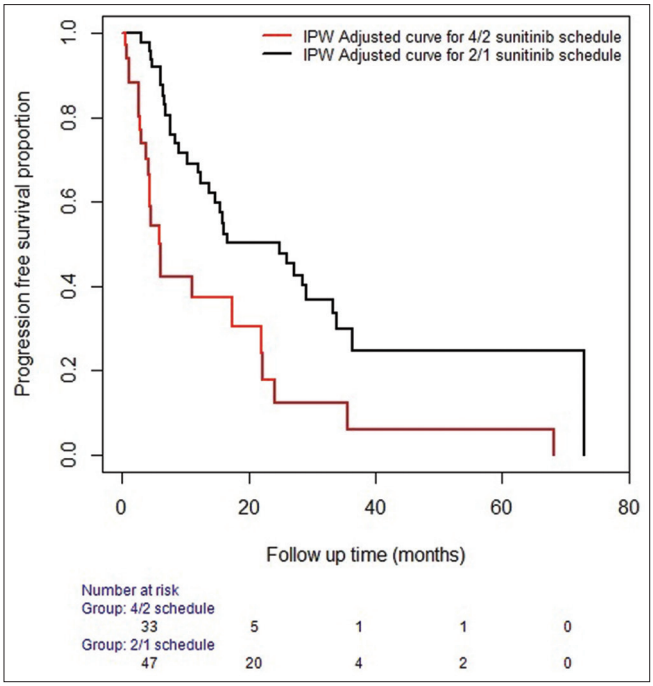

Figure 1: Inverse probability treatment weight adjusted progression free survival curves (while balancing for IMDC risk category, Fuhrman grade, and gender) comparing 4/2 and 2/1 dose schedules of sunitinib

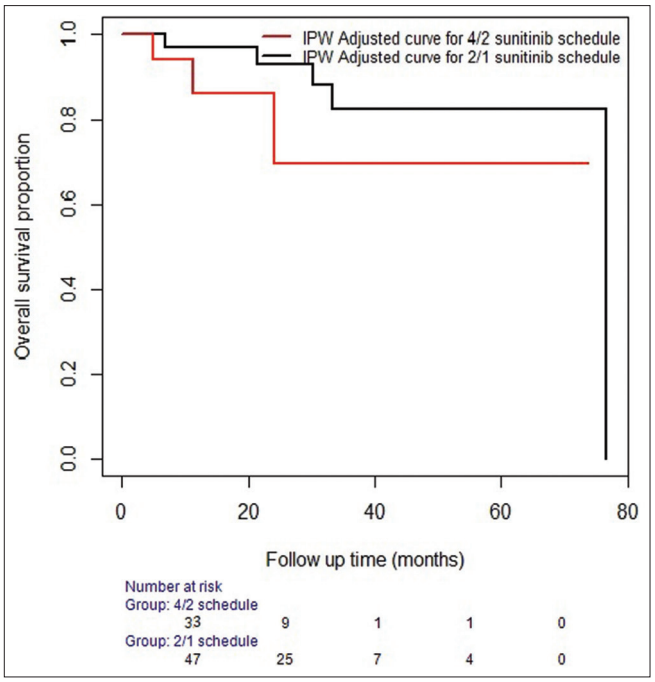

Figure 2: Inverse probability treatment weight adjusted overall survival curves (while balancing for IMDC risk category, Fuhrman grade, and gender) comparing 4/2 and 2/1 dose schedules of sunitinib

Secondary objectives

The median OS was not reached. The univariable analysis revealed better OS for the 2/1 group; however, statistical significance was not reached (HR 0.41, 95% CI 0.1–1.8, P = 0.23, Table 2). Figure 2 shows IPW adjusted OS curves (while balancing for IMDC risk category, Fuhrman grade, and gender) for both dose schedules, and the difference was statistically insignificant (log-rank statistic – 1.38, P = 0.17). Table 3 reports the treatment response in the overall population stratified by IMDC risk criteria. The ORR and CBR in the total population were 35% and 64%, respectively; both declined with increasing IMDC risk category. However, there were no significant differences in the ORR or CBR between both dosing schedules, whether overall, or in each IMDC risk category. Table 4 compares individual CTCAE grade 4 and 5 adverse effects (AE) between both treatment groups. Overall, the 2/1 group had a lower incidence than the 4/2 group for nearly all complications. Anemia and hyponatremia were numerically the most frequent AEs, and patients in the 2/1 group experienced lower grade 4 toxicity for both than those in the 4/2 group. No patient experienced grade 5 toxicity.

Discussion

To the best of our knowledge, this is the first study to analyze alternative dosing schedules of sunitinib in the Indian population. We found 2/1 schedule to be independently associated with higher PFS on multivariable analysis. We also found 2/1 group to have a lower incidence than the 4/2 group for nearly all ≥ grade 3 AEs with grade 4 anemia and hyponatremia being significantly lower in particular.

With the recent advent of immunotherapy there is a trend away from TKIs, however, sunitinib still remains the favored treatment option in favorable risk mRCC with 42 month follow up from Checkmate 214 trial showing comparable survival between sunitinib and nivolumab + ipilimumab arms.[19] Analysis of the real world outcomes with the use of sunitinib from the STAR-TOR registry further reveals that patients with intermediate risk mRCC having only one risk factor have outcomes similar to those with favorable risk category.[20] Unsurprisingly, multiple trials are underway studying sunitinib in combination with immunotherapy agents and thus, sunitinib can be reasonably expected to remain a prime arsenal in the armamentarium of oncologists in the foreseeable future.

Toxicity of the 4/2 schedule was the primal reason for oncologists to explore the 2/1 schedule and recently two meta-analyses compared outcomes between alternative dosing schedules of sunitinib.[21,22] Majority of the studies included in both meta-analyses were retrospective design with only one randomized controlled trial. Abogunrin *et al*.[21] compared relative effects of 4/2, 2/1

Table 3: Treatment response overall, and stratified as per IMDC risk criteria

Response*	Overall *n*=80	4/2 schedule *n*=33	2/1 schedule *n*=47	IMDC favorable risk			IMDC intermediate risk			IMDC Poor risk		
				Overall *n*=13	4/2 schedule *n*=8	2/1 schedule *n*=5	Overall *n*=57	4/2 schedule *n*=18	2/1 schedule *n*=39	Overall *n*=10	4/2 schedule *n*=7	2/1 schedule *n*=3
Complete response, *n*	1	0	1	0	0	0	1	0	1	0	0	0
Partial response, *n*	27	10	17	6	4	2	19	5	14	2	1	1
Stable disease, *n*	23	9	14	1	1	0	20	6	14	2	2	0
Progressive disease, *n*	22	10	12	2	1	1	14	5	9	6	4	2
Objective response rate, *n* (%)#	28 (35%)	10 (30%)	18 (38%) *P*=0.62	6 (46%)	4 (50%)	2 (40%) *P*=1	20 (35%)	5 (28%)	15 (39%) *P*=0.56	2 (20%)	1 (14%)	1 (33%) *P*=0.53
Clinical benefit rate, *n* (%)#	51 (64%)	19 (58%)	32 (68%) *P*=0.47	7 (54%)	5 (63%)	2 (40%) *P*=0.59	40 (70%)	11 (61%)	29 (74%) *P*=0.48	4 (10%)	3 (43%)	1 (33%) *P*=1

IMDC - International Metastatic Renal-Cell Carcinoma Database Consortium. *Response was undocumented in 7 patients for various reasons (four were given sunitinib in 4/2 schedule, and three followed 2/1 regimen); the sum of numbers in individual response category columns reflects this fact. #*p* value reflects a comparison of sunitinib 4/2 versus 2/1 schedule. The denominator included patients with undocumented response for calculating objective response rate and clinical benefit rate, to help avoid inflating estimates and reflect an intent-to-treat analysis. The estimated mean progression free survival was 31.2 months, 18.8 months, and 7.6 months for patients with IMDC favourable, intermediate, and poor risk disease, respectively

Table 4: Details of CTCAE (v5.0) grade 3 and higher toxicity stratified by sunitinib dosing schedule

CTCAE grade	Complication	Overall *n*=80	4/2 schedule *n*=33	2/1 schedule *n*=47	*P**
3	Anemia, *n* (%)	25 (31%)	11 (33%)	14 (30%)	0.93
	Hyponatremia, *n* (%)	23 (29%)	14 (42%)	9 (19%)	*0.044*
	Thrombocytopenia, *n* (%)	17 (21%)	7 (21%)	10 (21%)	0.79
	Elevated creatinine, *n* (%)	7 (9%)	4 (12%)	3 (6%)	0.44
	Neutropenia, *n* (%)	2 (3%)	1 (3%)	1 (2%)	-
	Hand foot syndrome, *n* (%)	8 (10%)	4 (12%)	4 (9%)	0.71
4	Anemia, *n* (%)	25 (31%)	16 (48%)	9 (19%)	*0.011*
	Hyponatremia, *n* (%)	22 (28%)	16 (48%)	6 (13%)	*0.0011*
	Thrombocytopenia, *n* (%)	9 (11%)	5 (15%)	4 (9%)	0.48
	Elevated creatinine, *n* (%)	9 (11%)	6 (18%)	3 (6%)	0.15
	Hand foot syndrome, *n* (%)	6 (8%)	3 (9%)	3 (6%)	0.69

*Comparing different sunitinib dosing schedules. CTCAE - Common Terminology Criteria for Adverse Events. Significant *p* values italicised. No patient experienced a grade 5 complication secondary to sunitinib

and transitional-2/1 schedules on outcomes and adverse events using Bayesian network meta-analysis. They concluded that 2/1 schedule reduced the risk of disease progression or death by 25% compared to the 4/2 schedule. Even the transitional 2/1 schedule had numerical superiority in terms of PFS over the 4/2 schedule. Patients with 2/1 schedule experienced significantly lower grade 3–4 diarrhea [HR: 0.32 (95% CrI: 0.12–0.87)], fatigue (HR: 0.34 [95% CrI: 0.15–0.75]), and hand–foot syndrome (HR: 0.37 [95% CrI: 0.18–0.75]) in comparison with the 4/2 schedule. Most recently Deng e*t al.*[22] specifically compared 4/2 and 2/1 schedules in a meta-analysis. They found 2/1 schedule to have better PFS (HR: 0.81, 95%CI: 0.66–0.99, *P* = 0.04), higher disease control rate (risk rate 1.22, 95% CI: 1.01–1.47, *P* = 0.04] and fewer dosage interruptions (risk rate 0.60, 95% CI: 0.43–0.84, *P* = 0.003). Also, the 2/1 schedule had fewer severe thrombocytopenia/platelet disorder, hand–foot syndrome, hypertension, and fatigue. Interestingly, in a sub-group analysis of treatment effects stratified by nationality, PFS was superior among East Asians using the 2/1 schedule than among other populations (HR 0.75, 95% CI: 0.58–0.98, *P* = 0.03). This finding confirms the necessity of our study to determine the treatment effects of alternative dosing schedules of sunitinib among the Indian population as race and environment may influence regional variations. Table 5 summarizes the survival outcomes of key studies (including ours) till date.[4,23-30]

Table 5: Different studies comparing alternative dosing schedules of sunitinib

References	Country	Study Duration	Treatment Groups	No. of patients (*n*)	Median age (years)	Study Design	PFS[a] (2/1 versus 4/2) (months)	OS[b] (2/1 versus 4/2) (months)
Lee *et al*.[23]	Korea	November'07–February'14	2/1 versus 4/2	38/36	57.0/60.0	RCT[c]	12.1/10.1	30.5/28.4
Miyake *et al*.[24]	Japan	January'10–January'17	2/1 versus 4/2	47/62	NA[e]	RS[d]	NA	NA
Pan *et al*.[25]	China	January'09–July'13	2/1 versus 4/2	32/50	66.0/62.0	RS	11.2/9.5	NA
Ezz El Din *et al*.[26]	Egypt	January'12–January'16	2/1 versus 4/2	26/30	49.5/49.0	RS	17/15	23/24
Suo *et al*.[27]	Canada	January'06–December'12	2/1 versus 4/2	9/59	62.3/60.8[a]	RS	NA	NA
Kondo *et al*.[28]	Japan	January'10–Decemebr'12	2/1 versus 4/2	26/22	64.6/62.7[e]	RS	18.4/9/1	NA
Zhang *et al*.[4]	China	2008–2015	2/1 versus 4/2	24/30	59.5/53.5	RS	11/12.5	28/21
Neri *et al*.[29]	Italy	January'08–May'10	2/1 versus 4/2	21/10	NA	RS	13/NA	20/NA
Bracarda *et al*.[30]	Italy	November'05–August'13	2/1 versus 4/2	41/211	61.0/59.0	RS	10.4/9.7	23.2/27.8
Our study	India	November'10–April' 18	2/1 versus 4/2	47/33	54.0/55.0	RS	22.0/15.9[h]	NR[f]

4/2: 4 weeks-on and 2 weeks-off; 2/1: 2 weeks on and 1-week off [a]PFS: Progression free survival [b]OS: Overall survival [c]RCT: Randomized controlled trail [d]RS: Retrospective study [e]NA: Not available [f]NR: Median overall survival not reached [g]Mean[h]Multivariate inverse probability treatment weight adjusted estimate

Limitations

Our study suffers from inherent biases of a retrospective design though we tried adjusting for confounders using advanced statistical techniques and multivariate analysis. Since the number of patients in the study were relatively low, "sparse data" bias may inflate estimates of the effect size.[17] Thus, the conclusion of average time to progression to be higher by 6.1 months could still be somewhat inflated despite statistical adjustments. Though this does not invalidate the finding that patients in the 2/1 group experienced a clinically meaningful longer PFS. We did not analyze the variables of treatment interruptions, dose reduction, and discontinuation due to toxicity as they do not matter in the "intent to treat analysis" of survival and other outcomes ultimately. Lastly, there is an allocation bias such that patients got 4/2 schedule in the relatively initial time period of study and 2/1 schedule later. Thus, patients with 2/1 schedule had theoretically higher probability of getting access to newer immunotherapeutic drugs upon disease progression thus positively influencing OS. However, this does not invalidate the conclusions about PFS and toxicity. Also, second line immunotherapy (nivolumab) became available in India from October 2016, and only a small number of patients got it following disease progression during the study period.[31]

Conclusions

In comparison to the conventional 4/2 schedule, 2/1 schedule of sunitinib was found to be associated with higher a PFS and lower incidence of nearly all ≥ grade 3 adverse effects. 2/1 schedule of sunitinib should be preferred over the 4/2 regimen for the Indian patients.

Acknowledgments

No research support was sought from any commercial agency related directly or indirectly with the outcome of the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

ORCID iDs

Jiten Jaipuria: https://orcid.org/0000-0003-3223-8155
Ankita Jain: https://orcid.org/0000-0002-1325-6377
Shashikant Gupta: https://orcid.org/0000-0002-7264-0635
Nripesh Sadasukhi: https://orcid.org/0000-0002-6630-3130
Priyatham Kasaraneni: https://orcid.org/0000-0002-5747-1933
Amitabh Singh: https://orcid.org/0000-0002-8180-1891
Kush Gupta: https://orcid.org/0000-0002-5962-5879
Girish Sharma: https://orcid.org/0000-0003-2127-5700
Vineet Talwar: https://orcid.org/0000-0001-9149-6969
Sudhir Rawal: https://orcid.org/0000-0002-3331-2372

References

1. Global Cancer Observatory. Cancer today statistics for 2020. Available from: https://gco.iarc.fr/today/home. [Last accessed on 2024 Jan 3].
2. Tiwari P, Kumar L, Singh G, Seth A, Thulkar S. Renal cell cancer: Clinicopathological profile and survival outcomes. Indian J Medical

Paediatr Oncol 2018;39:23-7.
3. Clinical practice guidelines in oncology – Kidney cancer, version 2.2020. National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/PDF/kidney.pdf. [Last accessed on 2020 Jun 23].
4. Zhang X, Sun G, Zhao J, Shu K, Zhao P, Liu J, *et al*. Improved long-term clinical outcomes and safety profile of sunitinib dosing schedule with 4/2 switched to 2/1 in patients with metastatic renal cell carcinoma. J Cancer 2018;9:3303-10.
5. Patel KB, Panchal HP, Karanwal AB, Parekh BB, Shah S, Prasad S. Sunitinib in metastatic renal cell carcinoma: Experience from single center study, efficacy and safety. Indian J Cancer 2016;53:118-22.
6. Liu X, Fiocco M, Swen JJ, Guchelaar HJ. Assessment of ethnic differences in sunitinib outcome between Caucasian and Asian patients with metastatic renal cell carcinoma: A meta-analysis. Acta Oncol 2017;56:582-9.
7. Britten CD, Kabbinavar F, Hecht JR, Bello CL, Li J, Baum C, *et al*. A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period. Cancer Chemother Pharmacol 2008;61:515-24.
8. Yoo C, Kim JE, Lee JL, Ahn JH, Lee DH, Lee JS, *et al*. The efficacy and safety of sunitinib in Korean patients with advanced renal cell carcinoma: High incidence of toxicity leads to frequent dose reduction. Jpn J Clin Oncol 2010;40:980-5.
9. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530-40.
10. Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, *et al*. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: A population-based study. Lancet Oncol 2013;14:141-8.
11. Bex A, Ljungberg B, van Poppel H, Powles T; European Association of Urology. The role of cytoreductive nephrectomy: European association of urology recommendations in 2016. Eur Urol 2016;70:901-5.
12. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al*. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
13. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. J Nucl Med 2009;50(Suppl 1):122S-50S.
14. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/. [Last accessed on2020 Jun 23].
15. Common Terminology Criteria for Adverse Events, version 5.0. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/. [Last accessed on 2020 Jun 23].
16. Schneeweiss S, Wang PS, Avorn J, Glynn RJ. Improved comorbidity adjustment for predicting mortality in Medicare populations. Health Serv Res 2003;38:1103-20.
17. Firth D. Bias reduction of maximum likelihood estimates. Biometrika 1993;1:27-38.
18. Stata manual-Survival-time inverse-probability weighting. Available from: https://www.stata.com/manuals/testteffectsipw.pdf. [Last accessed on 20202 Jun 23].
19. Motzer RJ, Escudier B, McDermott DF, Arén Frontera O, Melichar B, Powles T, *et al*. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. J Immunother Cancer 2020;8:e000891.
20. Moran M, Hubbe M, Rink M, Bergmann L, Strauss A, Bernhardt S, *et al*. Real-world outcomes in patients with metastatic renal cell carcinoma according to risk factors: Analysis of the STAR TOR registry. J Clin Oncol 2020;38. doi: 10.1200/JCO.2020.38.6_suppl. 628.
21. Abogunrin S, Ashaye AO, Cappelleri JC, Clair AG, Fahrbach K, Ramaswamy K, *et al*. Safety and effectiveness of classical and alternative sunitinib dosing schedules for metastatic renal cell carcinoma: A meta-analysis. Future Oncol 2019;15:2175-90.
22. Deng H, Li M, Wu Q, Wang L, Hong Z, Yi F, *et al*. A 2/1 Sunitinib dosing schedule provides superior antitumor effectiveness and less toxicity than a 4/2 schedule for metastatic renal cell carcinoma: A systematic review and meta-analysis. Front Oncol 2020;10:313.
23. Lee JL, Kim MK, Park I, Ahn JH, Lee DH, Ryoo HM, *et al*. RandomizEd phase II trial of Sunitinib four weeks on and two weeks off versus Two weeks on and One week off in metastatic clear-cell type REnal cell carcinoma: RESTORE trial. Ann Oncol 2015;26:2300-5.
24. Miyake H, Matsushita Y, Watanabe H, Tamura K, Suzuki T, Motoyama D, *et al*. Significance of introduction of alternative dosing schedule for sunitinib during first-line treatment of patients with metastatic renal cell carcinoma. Med Oncol 2018;35:133.
25. Pan X, Huang H, Huang Y, Liu B, Cui X, Gan S, *et al*. Sunitinib dosing schedule 2/1 improves tolerability, efficacy, and health-related quality of life in Chinese patients with metastatic renal cell carcinoma. Urol Oncol 2015;33:268.e9-15.
26. Ezz El Din M. Sunitinib 4/2 Versus 2/1 schedule for patients with metastatic renal cell carcinoma: Tertiary care hospital experience. Clin Genitourin Cancer 2017;15:e455-62.
27. Suo A, Iqbal U, Lim J, Lee C, Gesy K, Iqbal N, *et al*. Outcomes and drug costs of sunitinib regimens for metastatic renal cell carcinoma: A provincial population-based study. Clin Genitourin Cancer 2017;15:e397-404.
28. Kondo T, Takagi T, Kobayashi H, Iizuka J, Nozaki T, Hashimoto Y, *et al*. Superior tolerability of altered dosing schedule of sunitinib with 2-weeks-on and 1-week-off in patients with metastatic renal cell carcinoma--comparison to standard dosing schedule of 4-weeks-on and 2-weeks-off. Jpn J Clin Oncol 2014;44:270-7.
29. Neri B, Vannini A, Brugia M, Muto A, Rangan S, Rediti M, *et al*. Biweekly sunitinib regimen reduces toxicity and retains efficacy in metastatic renal cell carcinoma: A single-center experience with 31 patients. Int J Urol 2013;20:478-83.
30. Bracarda S, Iacovelli R, Boni L, Rizzo M, Derosa L, Rossi M, *et al*. Sunitinib administered on 2/1 schedule in patients with metastatic renal cell carcinoma: The RAINBOW analysis. Ann Oncol 2016;27:366.
31. Rauthan A, Patil P, Somashekhar SP, Zaveri S. Real world experience with nivolumab in Indian patients with metastatic renal cell carcinoma: A single centre experience. J Clin Oncol 2018;36(Suppl 15):e16546.