

Does an alternative sunitinib dosing schedule really improve survival outcomes over a conventional dosing schedule in patients with metastatic renal cell carcinoma? An updated systematic review and meta-analysis

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1. Background

Think Safety Build Value⁺

- 1. It is well known that sunitinib has a good oncological effect in patients with metastatic kidney cancer. It is still a popular drug in patients with metastatic renal cell carcinoma.
- 2. However, Treatment-related adverse events (AEs) can obfuscate the maintenance of a conventional schedule (4/2) of sunitinib in patients with metastatic renal cell carcinoma.
- 3. Therefore, several alternative schedules have been introduced, of which 2/1 schedule is the most used. However, large-scale RCT studies on 2/1 schedules compared to conventional schedules have not been conducted.
- 4. Therefore, we conducted a meta-analysis about comparison of adverse events and oncological outcomes according to sunitinib dosing schedules in patients with metastatic renal cell carcinoma.



2. Materials and Methods



1. Systematic literature searches were conducted in PubMed/Embase and Cochrane library for all studies that examined dosing schedule of sunitinib for mRCCa.

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더하다

- 2. We performed this study according to the Preferred Reported Items for Systematic Reviews and Metaanalysis guidelines.
- 3. Endpoints were progression-free (PFS), overall (OS) survival and adverse events rate.

3. Results

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*Progression-free survival (PFS)

*Overall-survival (OS)

A. Progression-free survival

B. Overall survival



(2) Adjusted HRs

(2) Adjusted HRs



Hazard Ratio Hazard Ratio Study or Subgroup log[Hazard Ratio] SE Weight IV, Random, 95% CI IV, Random, 95% CI Atkinson et al. 2014 -0.33 0.3 61.0% 0.72 [0.40, 1.29] Suo et al. 2017 -0.46 0.44 28.4% 0.63 [0.27, 1.50] Zhang et al. 2018 -0.79 0.72 10.6% 0.45 [0.11, 1.86] Total (95% CI) 100.0% 0.66 [0.42, 1.04] Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 2 (P = 0.83); l² = 0% 0.01 0.1 10 100 Test for overall effect: Z = 1.77 (P = 0.08) Favours [2/1 dosing] Favours [4/2 dosing]



3. Results

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Adverse events No. studies Dosing schedule (95% CI) P-value I ² (%) P _a -value Hypothyroidism ¹ 9 2/1 309 0.84 0.79 0.04 0 0.53 Leukopenia* 8 2/1 268 0.79 0.04 60 0.01 Anemia 7 2/1 288 0.86 0.10 27 0.22 Thrombocytopenia 9 2/1 309 0.89 0.10 27 0.22 Thrombocytopenia 9 2/1 309 0.89 0.11 62 0.007 Liver dysfunction 5 2/1 161 0.88 0.31 0 0.84 Anorexia 5 2/1 169 0.77 0.41 38 0.17 Nausea 3 2/1 109 0.77 0.41 38 0.2 Vomiting 2 2/1 79 0.62 0.33 0 0 Diarrhea* 8									
Hypothyroidism* 9 2/1 309 0.84 0.04 0 0.53 Hypothyroidism* 9 2/1 209 0.04 0 0.53 Leukopenia* 8 2/1 268 0.79 0.04 0 0.53 Leukopenia* 8 4/2 205 (0.72-103) 0.04 60 0.01 Anemia 7 2/1 288 0.86 0.10 27 0.22 Thrombocytopenia 9 2/1 161 0.88 0.31 0 0.84 User dysfunction 5 2/1 161 0.88 0.31 0 0.84 Anorexia 5 2/1 161 0.88 0.31 0 0.84 Nauses 3 2/1 109 0.77 0.41 38 0.21 Vomiting 2 2/1 179 0.62 0.33 0 0 Diarrhee* 8 4/2 275 (0.39-0.9	Adverse events	No. studies	Dosing	No. of Patients	RR	P-value	l ² (%)	P _u -value	
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Thrombocytopenia 9 2/1 309 0.089 0.11 62 0.007 Liver dysfunction 5 2/1 161 0.88 0.31 0 0.84 Anorexia 5 2/1 159 0.70 0.00 38 0.17 Anorexia 5 2/1 159 0.70 0.84 38 0.17 Nausea 3 2/1 159 0.70 0.08 38 0.17 Nausea 3 2/1 109 0.77 0.41 38 0.2 Vomiting 2 2/1 79 0.62 0.33 0 0 Diarrhea* 8 2/1 309 0.62 0.33 0 0 Dysgeusia* 3 2/1 112 0.6 0.02 0.000 0.68 Hand-foot syndrome* 9 2/1 309 0.70 0.0002 16 0.30 Hypertension* 9 2/1 309			4/2	275	(0.72-1.03)				
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Hand-foot syndrome* 2/1 309 0.68 38 0.17 Hand-foot syndrome* 2 2/1 159 0.70 0.08 38 0.17 Nausea 3 2/1 109 0.77 0.41 38 0.2 Vomiting 2 2/1 79 0.62 0.33 0 0 Diarrhea* 8 2/1 309 0.62 0.010 62 0.007 Dysgeusia* 3 2/1 112 0.6 0.02 0 0.68 Hand-foot syndrome* 9 2/1 112 0.6 0.02 0 0.68 Hypertension* 9 2/1 309 0.68 <0.0001			2/1	101	0.00				
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$\begin{tabular}{ c c c c c c c } \hline Anorexia & 5 & $\frac{2/1}{4/2}$ & $326 & $(0.47-1.04)$ & 0.08 & 38 & 0.17 \\ \hline $1000 $Mausea $& $326 & $(0.47-1.04)$ & 0.08 & 38 & 0.17 \\ \hline $1000 $Mausea $& 38 & $2/1$ & $109 & 0.77 & 0.41 & 38 & 0.2 \\ \hline $1000 $Mausea $& $2/1$ & 74 & $(0.42-1.45)$ & 0.41 & 38 & 0.2 \\ \hline $1000 $& $2/1$ & 74 & $(0.24-1.62)$ & 0.33 & 0			2/1	150		0.08	38		
Nausea 3 $4/2$ 109 0.77 0.41 38 0.2 Vomiting 2 $2/1$ 79 0.62 0.33 0 0 Diarrhea* 8 $2/1$ 79 0.62 0.33 0 0 Diarrhea* 8 $2/1$ 309 0.62 0.010 62 0.007 Dysgeusia* 3 $2/1$ 112 0.6 0.02 0 0.68 Mand-foot syndrome* 9 $2/1$ 112 0.6 0.02 0 0.68 Hand-foot syndrome* 9 $2/1$ 309 0.68 <0.0001 25 0.22 Hypertension* 9 $2/1$ 309 0.70 0.0002 16 0.30 Fatigue* 9 $2/1$ 309 0.69 <0.0001 29 0.19 Ktin color change* 4 $2/1$ 309 0.70 0.0006 10 0.35	Anorexia	5	2/1 A/2	326	(0.47-1.04)			0.17	
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Vomiting2 $2/1$ 10 0.02 0.33 00Diarrhea*8 $2/1$ 309 0.62 0.010 62 0.007 Dysgeusia*3 $2/1$ 112 0.6 0.02 0 0.62 0.007 Dysgeusia*3 $2/1$ 112 0.6 0.02 0 0.68 Other adverse eventsHand-foot syndrome* 9 $2/1$ 309 0.68 <0.0001 25 0.22 Hypertension*9 $2/1$ 309 0.69 <0.0001 25 0.22 Hypertension*9 $2/1$ 309 0.69 <0.0001 25 0.22 Hypertension*9 $2/1$ 309 0.69 <0.0001 29 0.19 Stomatitis*8 $2/1$ 262 0.70 0.0006 10 0.35 Stin color change*4 $2/1$ 180 0.70 0.004 0 0.98	Vomiting	2	2/1	79	0.62	0.33	0	0	
Diarrhea* 8 2/1 309 0.62 0.010 62 0.007 Dysgeusia* 3 2/1 112 0.6 0.02 0 62 0.007 Dysgeusia* 3 2/1 112 0.6 0.02 0 0.68 Hand-foot syndrome* 9 2/1 309 0.68 <0.0001 25 0.22 Hand-foot syndrome* 9 2/1 309 0.68 <0.0001 25 0.22 Hypertension* 9 2/1 309 0.69 <0.0001 25 0.22 Hypertension* 9 2/1 309 0.69 <0.0001 29 0.19 Stomatitis* 8 2/1 203 (0.57-0.86) 0.0006 10 0.35 Skin color change* 4 2/1 180 0.70 0.004 0 0.98			4/2	244	(0 24-1 62)				
Diarrhea* 8 4/2 513 (0.44-0.89) 0.010 62 0.007 Dysgeusia* 3 2/1 112 0.6 0.02 0 0.68 Hand-foot syndrome* 9 2/1 309 0.68 <0.0001 25 0.22 Hand-foot syndrome* 9 2/1 309 0.68 <0.0001 25 0.22 Hypertension* 9 2/1 309 0.69 <0.0001 25 0.22 Hypertension* 9 2/1 309 0.69 <0.0001 29 0.19 Fatigue* 9 2/1 309 0.69 <0.0001 29 0.19 Stomatitis* 8 2/1 262 0.70 0.0006 10 0.35 Skin color change* 4 2/1 180 0.70 0.004 0 0.98	Diarrhea*	8	2/1	309	0.62	0.010	62	0.007	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $			4/2	513	(0 44-0 89)				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Dysgeusia*	3	2/1	112	0.6	0.02	0	0.68	
Other adverse events Hand-foot syndrome* 9 2/1 309 0.68 <0.0001 25 0.22 Hypertension* 9 2/1 309 0.70 0.0002 16 0.30 Fatigue* 9 2/1 309 0.69 <0.0001 29 0.19 Stomatitis* 8 2/1 262 0.70 0.0006 10 0.35 Skin color change* 4 2/1 180 0.70 0.004 0 0.98			4/2	275	(0.39-0.92)				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Other adverse events								
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$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Hypertension*	9	2/1	309	0.70	0.0002	16	0.30	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $			4/2	513	(0.58-0.84)				
Fatigues94/2513 $(0.60-0.81)$ <0.0001 29 0.19 Stomatitis*82/1262 0.70 0.0006 10 0.35 Skin color change*42/1180 0.70 0.004 0 0.98	Fatigue*	9	2/1	309	0.69	<0.00001	29	0.19	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $			4/2	513	(0.60-0.81)				
Stomatics $4/2$ 451 $(0.57 \cdot 0.86)$ 0.000 10 0.35 Skin color change* 4 $2/1$ 180 0.70 0.004 0 0.98	Stomatitis*	8	2/1	262	0.70	0.0006	10	0.35	
Skin color change* 2/1 180 0.70 0.004 0 0.98			4/2	451	(0.57-0.86)				
4/2 203 (0.55-0.89) 0.004 0 0.36	Skin color change*	4	2/1	180	0.70	0.004	0	0.98	
			4/2	203	(0.55-0.89)		0	0.98	

Adverse events * Statistically significant val



4. Conclusions

- 1. Our meta-analysis suggests that alternative 2/1 sunitinib dosing schedule may have better PFS than conventional 4/2 sunitinib schedule. However, its level of evidence was very low, the interpretation of this result should be cautious.
- 2. Moreover, the 2/1 schedule was beneficial for reducing the incidence of AEs. Accordingly, the 2/1 sunitinib dosing schedule holds promise as an alternative means of reducing AEs, maintaining patient QOL and prolonging treatment.
- 3. We also believe that prospective large-scale studies of a 2/1 alternative schedule that demonstrate these advantages are needed.





Thank you for your attention