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Tolerability of Alternative Dosing Schedules for Sunitinib: A Systematic Review and Meta-Analysis

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Purpose: The standard schedule for sunitinib treatment is 4 weeks on and 2 weeks off (4/2) in first-line treatment for metastatic renal cell carcinoma (mRCC). Schedule modifications, including 2 weeks on and 1 week off (2/1), appear to reduce the total number of treatment-related adverse events (TRAEs) without compromising efficacy. Even though TRAEs can qualitatively differ from each other, it is not clear as to what effects a 2/1 schedule has on individual TRAEs.

Materials and Methods: This meta-analysis included one randomized controlled trial (RCT) and four non-randomized controlled studies (non-RCTs) that compared the two schedules in parallel. The primary objective was to estimate risk of individual adverse events (AEs) with a sunitinib 2/1 schedule versus a 4/2 schedule. Seven representative AEs were evaluated as standard data for the RCT and as weighted pooling data of the non-RCTs. Random effects modelling with Review Manager v5.3 was used to pool study-level data using the inverse-variance of each study as the weight.

Results: The five selected studies included a total of 484 patients with mRCC. Risk ratios for fatigue for a 2/1 schedule were significantly lower than those for a 4/2 schedule {0.69 [95% confidence intervals (CI), 0.51, 0.95] in the RCT and 0.77 (95% CI, 0.63, 0.94) in the non-RCTs}. Other TRAEs, except diarrhea and anorexia, also tended to decrease in both sets. Efficacy outcomes were comparable between 2/1 and standard schedules.

Conclusion: This meta-analysis suggests that a 2/1 schedule of sunitinib lowers the risk of fatigue and the occurrence other AEs without compromising efficacy.

Key Words: Sunitinib, drug administration schedule, meta-analysis, renal cell carcinoma

INTRODUCTION

Since obtaining regulatory approval in 2006, sunitinib has remained the first-line treatment for metastatic renal cell carcinoma (mRCC)[1] in countries where it is not available to use immune checkpoint inhibitors. The sunitinib molecule is an ATP mimic and inhibits a variety of tyrosine kinase receptors by competition at the ATP binding site. Its main therapeutic mechanism of action is anti-angiogenesis via targeting of vascular epithelial growth factor receptors (VEGFR) in renal cell carcinoma.

In addition to clinical trial data, a meta-analysis has shown that exposure to a higher dose of sunitinib is associated with higher response rates, longer times to progression, and better overall survival.[2] A long treatment duration at an optimized dose is crucial to achieving maximal clinical efficacy.[2,3] However, in the administration of sunitinib, managing treatment-related adverse events (TRAEs) is a critical challenge. In pivotal mRCC phase 3 trials, more than 50% of patients required either dose reduction and/or dose interruption due to TRAEs,[4] which included various non-hematologic adverse events (AEs) [fatigue, nausea, diarrhea, stomatitis, and hand-foot syndrome (HFS)] and hematologic AEs (thrombocytopenia and neutropenia). Even though these AEs can be manageable, TRAEs affect the tolerability of treatment and quality of life for the patients during treat-

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ment. Paradoxically, the presence of TRAEs is associated with improved efficacy outcomes and is considered as a predictive marker of treatment. Therefore, it is important that patients be able to tolerate sunitinib administration at proper exposure levels while remediating TRAEs.

In early phase clinical trials, various schedules of sunitinib treatment were studied, including a 3-week cycle with 2 weeks on treatment and 1 week of rest (2/1 schedule), a 4-week cycle with 2 weeks on and 2 weeks off (2/2 schedule), a 6-week cycle with 4 weeks on and 2 weeks off (4/2 schedule), and continuous daily dosing.[5-7] Among these, the 4/2 schedule was selected as the standard regimen with the most efficacious outcome. Subsequent research supported this schedule for use in treating mRCC and gastrointestinal stromal tumors without any further regulatory concerns in terms of the relationship between dose schedule and TRAEs.[8]

Despite the fact that sunitinib has been approved by regulatory authorities around the world since 2006, many clinical studies have been conducted to identify a proper regimen with a reduce dose and schedule modification to improve tolerability. Among them, an alternative schedule of 2 weeks on 1 week off was been found to reduce the total number of TRAEs without compromising efficacy.[9-12]

However, it not clear as to what types of TRAEs might be influenced by a 2/1 schedule. This meta-analysis was conducted to delineate any differences that might exist in the frequency of TRAEs between the standard (4/2) and alternative (2/1) schedules and to understand if any decrease in TRAEs comes at a detriment to clinical efficacy.

MATERIALS AND METHODS

We followed the standards of the Cochrane Handbook for Systematic Reviews of Intervention, and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[13] during the preparation of this systematic review and meta-analysis. We included original studies that compared the safety and efficacy of sunitinib dosing and schedules. Studies (from inception up to April 2015) were retrieved from Medline, Cochrane library, BIOSIS, Derwent Drug File, Embase, and Web of Science databases using the keywords query 'Sunitinib,' 'Alternative dosing schedule,' '4-week on 2-week off,' '2-week on 1-week off,' and 'mRCC.' Eligible studies included prospective interventional clinical research, prospective observational cohort study, retrospective studies, observational cohort studies; patients with mRCC; studies comparing alternative schedules, primarily the 2/1 schedule, initially or during treatment with the 4/2 schedule, and studies with available data on incidence of AEs. Case reports, single-group studies, review articles, and studies on patients with diseases other than mRCC and for combination therapies were excluded. Studies with sequential comparison between 2/1 and 4/2 schedules were also excluded as those required patient-level data for statistical application (Fig. 1).

Within each study, AEs were evaluated in relationship to sunitinib dosing schedule (2/1 schedule vs. 4/2 schedule). The analyzed AEs included representative non-hematologic AEs (fatigue, HFS, mucositis/stomatitis, diarrhea, and anorexia) and hematologic AEs (neutropenia and thrombocytopenia). The standard data of randomized controlled trials (RCT) were compared with the pooling results of non-randomized controlled studies (non-RCTs), considering the dependence of data strength on study design.

A random-effects model was used to calculate pooled relative risk (RR), 95% confidence interval (CI), and *p* values. Two-sided *p* values less than 0.05 were considered statistically significant. Chi-squared (χ^2) test was used to evaluate statistical heterogeneity. The I^2 statistic was also calculated to evaluate the extent of variability attributable to statistical heterogeneity between studies. Review Manager was used to pool study-level data using the inverse-variance of each study as the weight (Review Manager, Version 5.3.: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Danmark).

RESULTS

Search results and summary of the included studies

The database search results and screening steps are presented in Fig. 1. Five studies with data on 484 patients were included for meta-analysis: one RCT[12] and four retrospective, non-RCTs.[14-17] Efficacy outcomes in 2/1 groups were non-inferior to 4/2 groups in all studies except that by Bracarda, et al.,[15] in which prognosis was poorer for patients in the 2/1 schedule arm. The baseline characteristics of the included studies are summarized in Table 1.

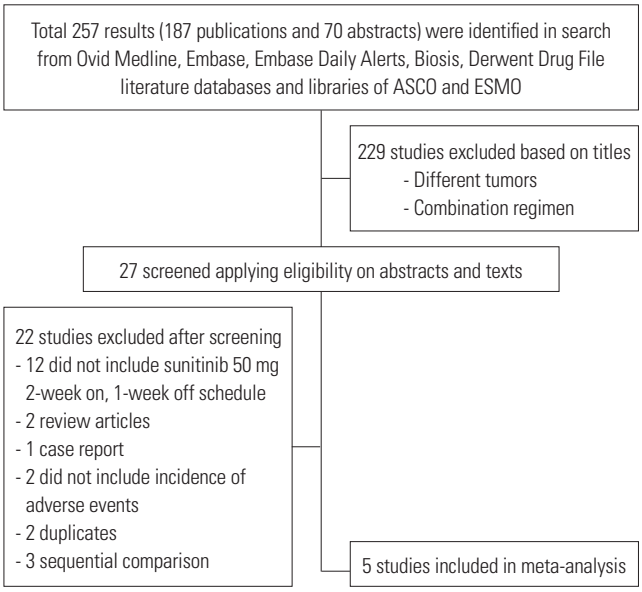

Fig. 1. Study selection process.

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Meta-analysis of treatment-related adverse events

The RR for fatigue was significantly lower for the alternative 2/1 schedule versus the standard 4/2 schedule in both RCT and weighted non-RCT meta-analysis data [0.69 (95% CI, 0.51, 0.95) in RCT and 0.77 (95% CI, 0.63, 0.94) in non-RCTs] (Fig. 2). The RRs for HFS and mucositis/stomatitis showed decreased tendency for the 2/1 schedule in the RCT [0.91 (95% CI, 0.68, 1.22), 0.83 (95% CI, 0.65, 1.05) respectively] and was significantly lower for the 2/1 schedule in the non-RCTs [0.62 (95% CI, 0.50, 0.78), 0.62 (95% CI, 0.41, 0.94) respectively] (Figs. 3 and 4).

Gastro-intestinal AEs (e.g., diarrhea and anorexia) did not demonstrate consistent results across the meta-analysis (Figs. 5 and 6). The RR for neutropenia was significantly lower for the 2/1 schedule in the RCT [0.60 (95% CI, 0.37, 0.99) and showed decreased tendency in the non-RCTs [0.56 (95% CI, 0.25, 1.23)]. The RR for thrombocytopenia showed decreased tendency for the 2/1 schedule in both the RCT and non-RCTs, but the differences between the 2/1 and 4/2 schedules were not statistically different [0.91 (95% CI, 0.70, 1.19), 0.72 (95% CI, 0.50, 1.03)] (Figs. 7 and 8).

Table 1. Baseline Characteristics of the Included Studies

	Lee, et al.[12]		Neri, et al.[17]		Kondo, et al.[16]		Bracarda, et al.[15]		Pan, et al.[14]	
Study design	Randomized				Non-randomized					
Study type	Prospective		Prospective				Retrospective			
Treatment line	1st line		1st & 2nd line*		1st line		1st line		1st line	
Intervention	50 mg 2/1 vs. 4/2		50 mg 2/1 vs. 4/2		50/37.5/25 mg 2/1 vs. 4/2		50 mg 2/1 if poor, 4/2		50 mg 2/1 vs. 4/2	
Participants	2/1	4/2	2/1	4/2	2/1	4/2	2/1	4/2	2/1	4/2
	36	38	21	10	26	22	41	208	31	50
Median age (y) (range)	57 (41–79)	60 (32–76)	68 (50–85)		65 (31–79)	63 (31–78)	62 (25–82)	61 (32–82)	66 (45–80)	62 (41–76)
Female (%)	21	11	39		23	32	37	28	41	44
Favorable risk group (%)	18	19	52		27	0	24	42	19	20
Efficacy										
ORR (%)	47	33	43 (42)		32	50	NR		14	15.7
mPFS or mTTP (m)	15.1	10.1	13 (16.4)		18.4	9.1	9.6	38.6†	11.2	9.4
mOS (m)	30.5	28.3	20 (18.1)		NR		23.2	NR	NR	
mTD (m)	7.6	6.0	NR		9.7	9.2	7.8	4.3‡	NR	

y, year; ORR, objective response rate; mPFS, median progression free survival; m, month(s); mTTP, median time-to-progression; mOS, median overall survival; mTD, median treatment duration, considered median time-to-failure is substitutable for mTD; NR, not reported.
*10% of patients were treated with cytokine as the first treatment, †Included the both periods of initial 4/2 and switching 2/1 schedule, ‡Duration on 4/2 schedule only; ( ) at Neri et al. means the overall outcomes regardless of schedules.

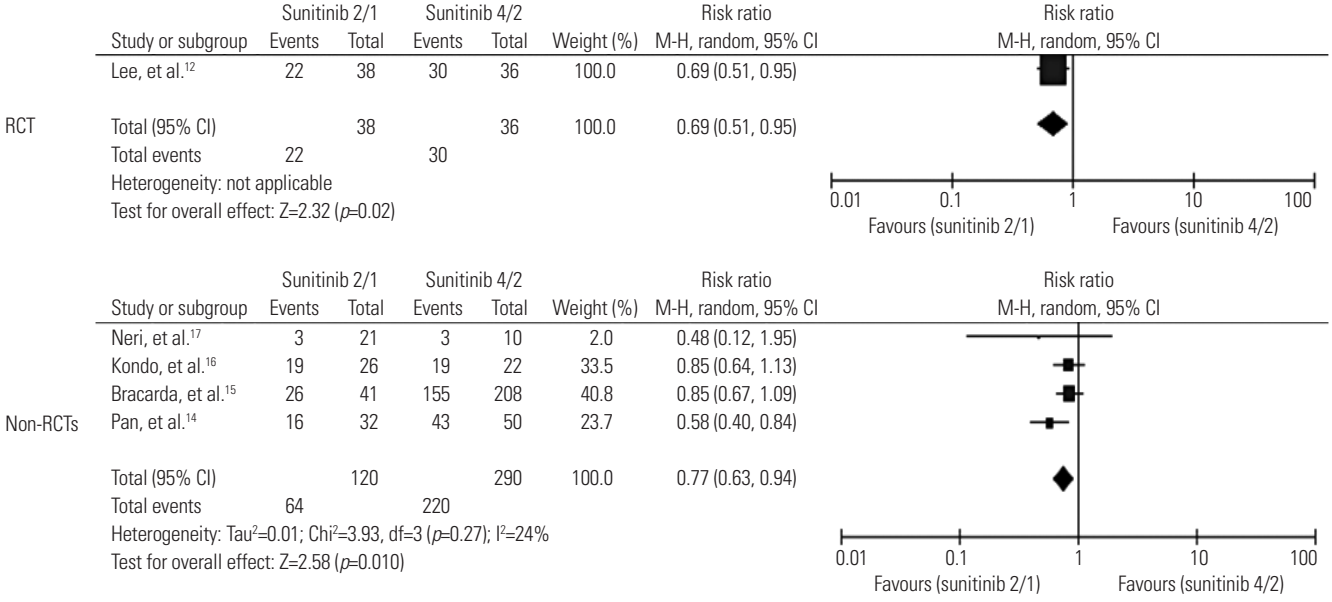

Fig. 2. Meta-analysis of fatigue with an alternative sunitinib schedule. RCT, randomized controlled trial; non-RCTs, non-randomized controlled studies, CI, confidence interval.

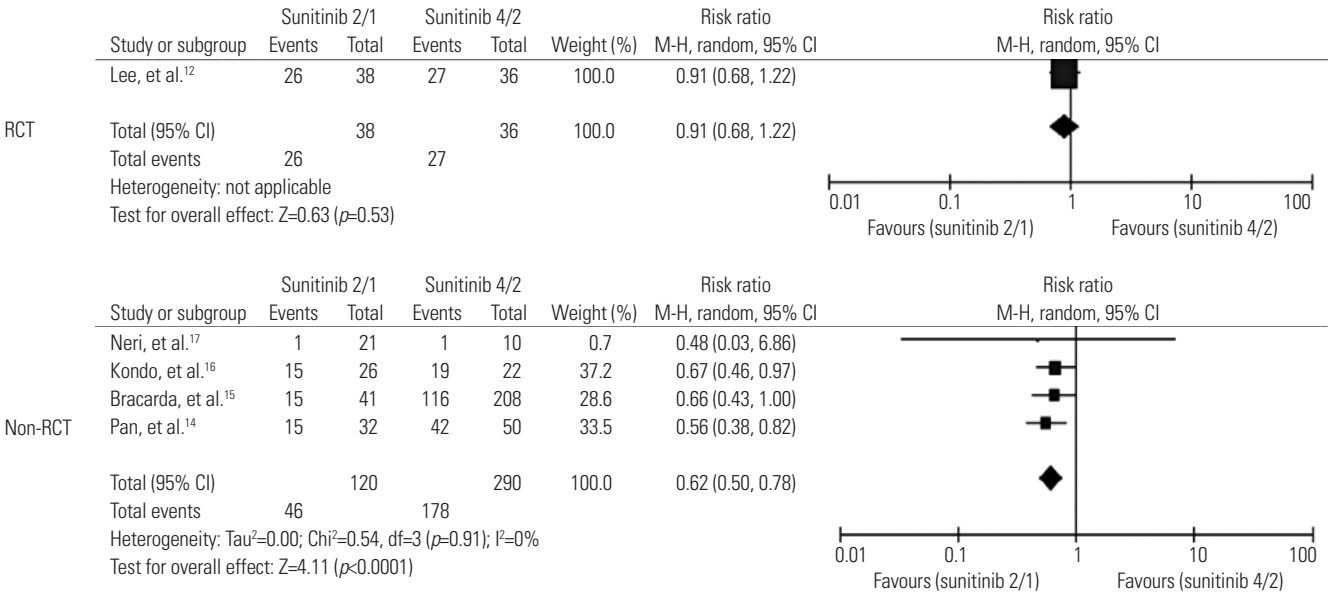

Fig. 3. Meta-analysis of hand-foot syndrome with an alternative sunitinib schedule. RCT, randomized controlled trial; non-RCTs, non-randomized controlled studies, CI, confidence interval.

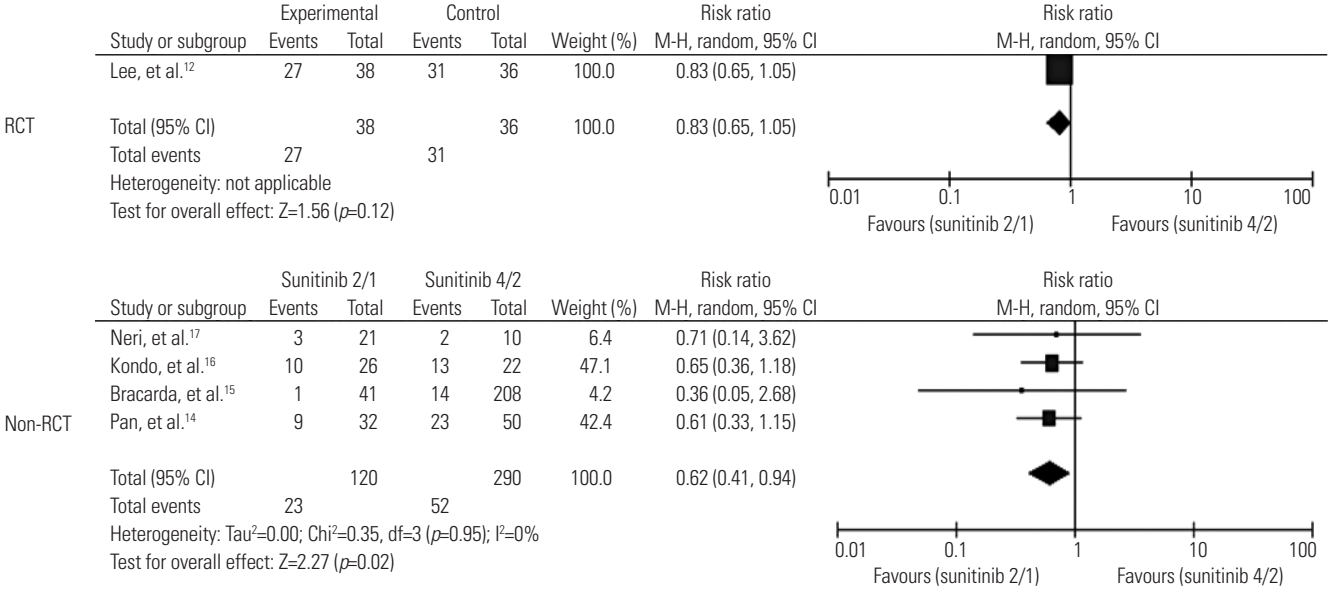

Fig. 4. Meta-analysis of mucositis/stomatitis with an alternative sunitinib schedule. RCT, randomized controlled trial; non-RCTs, non-randomized controlled studies, CI, confidence interval.

DISCUSSION

Most oral tyrosine kinase inhibitors (TKIs) have been approved for a fixed-dose prescription, although a lot of post-approval studies have revealed a need for individualized dosing schedules. In the post-marketing period of sunitinib, the 2/1 schedule was considered as an alternative treatment option rather than the standard 4/2 schedule based on clinical experiences and PK/PD evidence. Based on a PK/PD perspective, a phase 1 study of sunitinib demonstrated that blood concentrations reached a steady state within 2 consecutive weeks on treatment and that the active substances were still detectable after a 1-week break.[18] Bjarnason, et al.[11] showed that tumor blood volume was significantly lower at 2 weeks with 2/1 and 4/2 schedule using dynamic microbubble contrast-enhanced ultrasound. Most of the benefit from sunitinib therapy may be achieved after 7 to 14 days on therapy, and this is consistent with the results obtained in this study. Moreover, clinical evidence supports the benefit of optimal dose maintenance by a 2/1 schedule.[12,16,19]

In this meta-analysis, a 2/1 schedule was associated with a significantly lower incidence of fatigue, compared with the standard schedule, and demonstrated a decreased tendency for HFS, mu-

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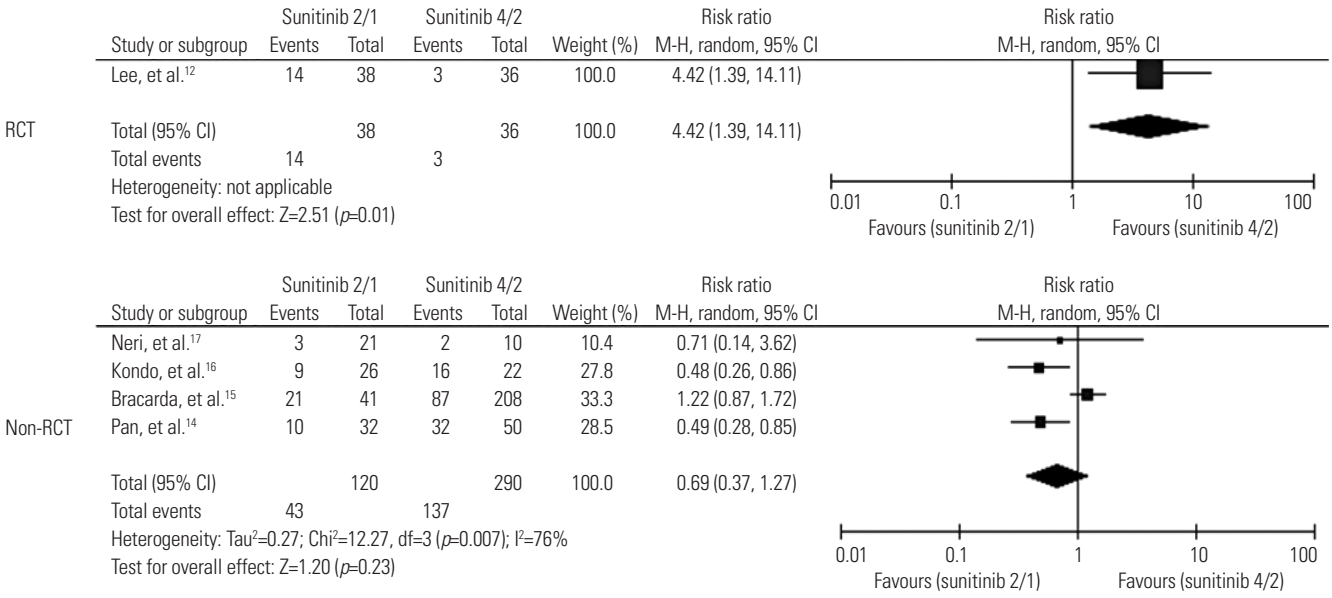

Fig. 5. Meta-analysis of diarrhea with an alternative sunitinib schedule. RCT, randomized controlled trial; non-RCTs, non-randomized con-trolled studies, CI, confidence interval.

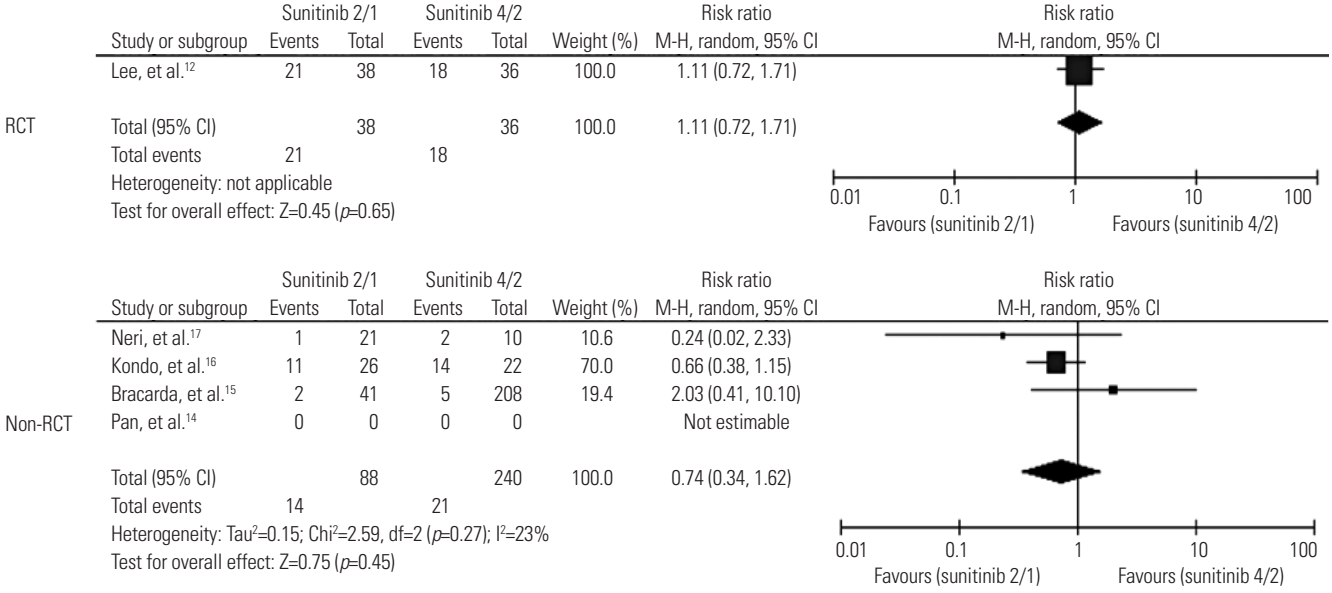

Fig. 6. Meta-analysis of anorexia with an alternative sunitinib schedule. RCT, randomized controlled trial; non-RCTs, non-randomized con-trolled studies, CI, confidence interval.

cositis/stomatitis, neutropenia, and thrombocytopenia. These results suggest that schedule modification could be a good option for physicians to remediate major TRAEs of sunitinib.

Fatigue is a subjective symptom associated with a multifactorial process, and its underlying pathophysiology remains unclear.[20,21] Hypothyroidism and anemia are suggested as the main mechanism behind VEGFR TKIs-induced fatigue; however, disease-related comorbidities, such as cachexia, depression, anxiety, sleep disorders, and physical inactivity, also contribute to this general symptom. A 2-week-on-1-week-off can be a preventative approach to minimizing fatigue and helpful for patients switching from a 4/2 schedule to 2/1 schedule.[10,15,19,22]

Other TRAEs also tended to occur with less frequency with the 2/1 schedule. When patients were treated on a 2/1 schedule, the incidences were significantly lower for HFS and mucositis/stomatitis in grade 3 and 4 TRAEs in the pooled data of non-RCTs, while the RCT only showed a tendency for lower incidence. Grades 3 and 4 TRAEs for HFS and mucositis/stomatitis critically impact the quality of life for patients and treatment discontinuation. Also, the incidences of thrombocytopenia and neutropenia showed only a reduced tendency for a 2/1 schedule, but was statistically significant when the data were

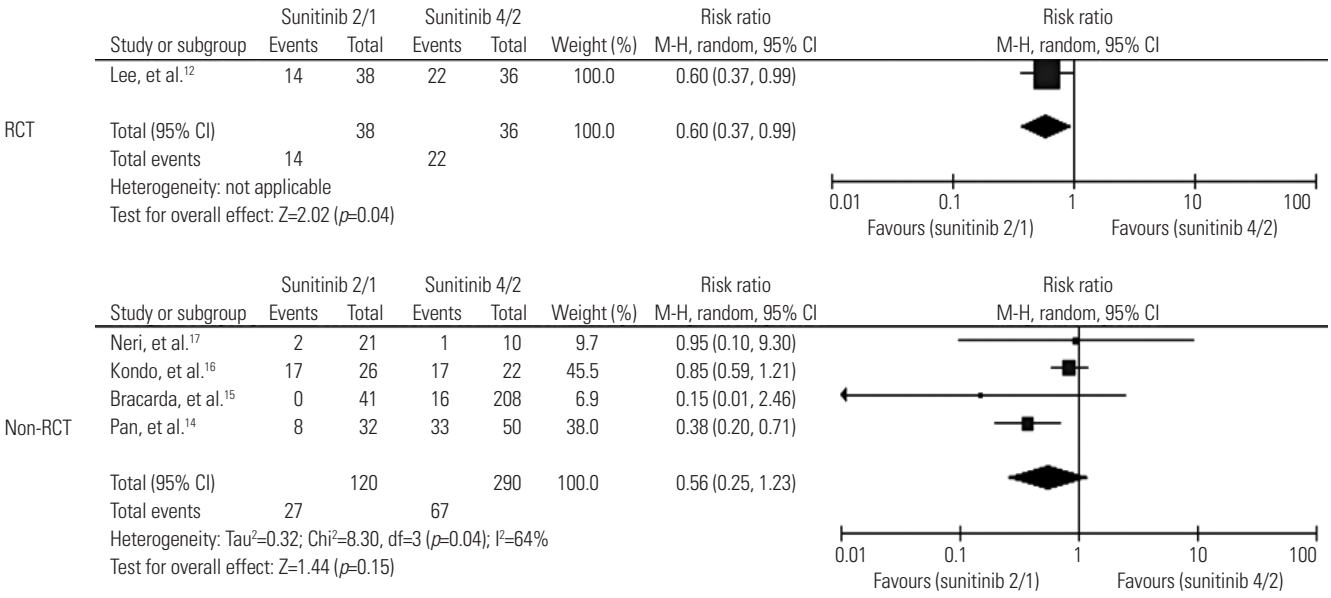

Fig. 7. Meta-analysis of neutropenia with an alternative sunitinib schedule. RCT, randomized controlled trial; non-RCTs, non-randomized con-trolled studies, CI, confidence interval.

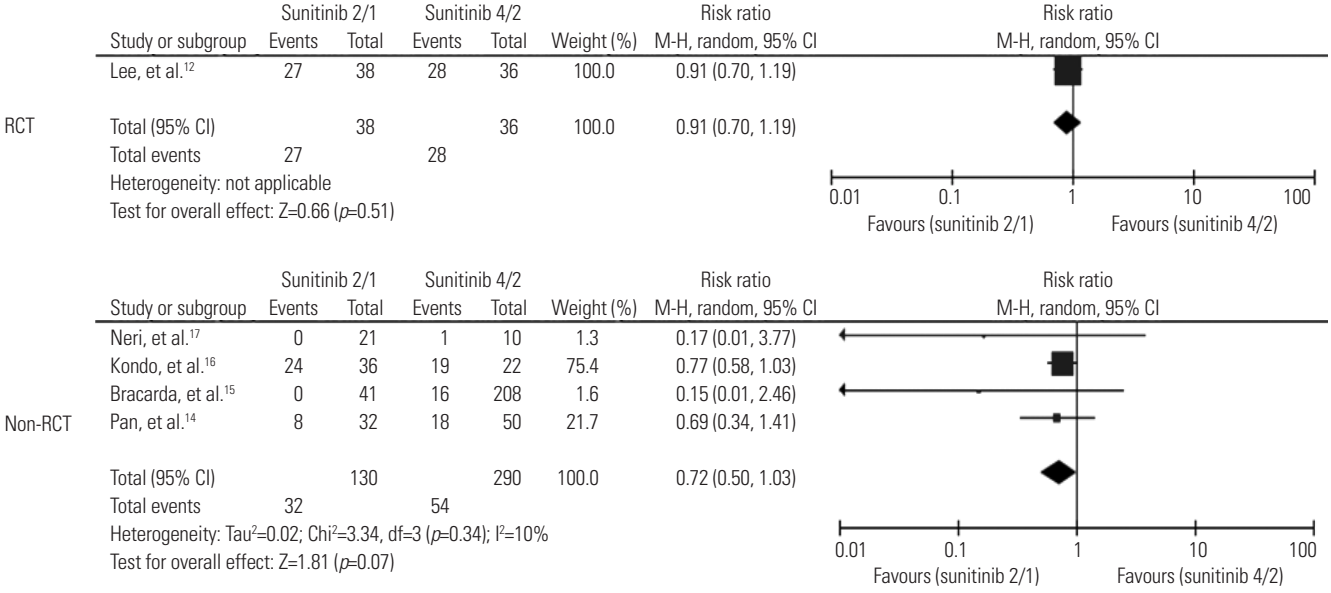

Fig. 8. Meta-analysis of thrombocytopenia with an alternative sunitinib schedule. RCT, randomized controlled trial; non-RCTs, non-randomized con-trolled studies, CI, confidence interval.

confined to Grade 3 and 4 TRAEs. Considering individual TRAEs have a distinct timing of onset,[23,24] physicians ought to be able to anticipate sunitinib-related TRAEs, and schedule modifications could improve the health-related quality of life of the patients.[19]

While no direct comparison can be made between trials, a 2/1 schedule was associated with less toxicity, and consequently fewer patients required dose reductions, which could be beneficial for patient adherence by reducing treatment-related AEs and maintaining dose intensity.

Although the meta-analysis highlighted the impact of common TRAEs on 2/1 schedule, there are several study limitations to be discussed. This meta-analysis only included a single RCT, with the remaining data pooled from non-RCTs with relatively small sample sizes. Including non-RCTs remain prone to different confounders that may influence the prognosis of the study population. For the confirmatory results, RCT data need to be added.

This study is the first meta-analysis comparing TRAEs between 2/1 and 4/2 schedules for sunitinib treatment of mRCC and suggests that a 2/1 schedule of sunitinib may decrease the risk of fatigue and help limit AEs, such as HFS, mucositis/stomatitis, neutropenia and thrombocytopenia, without compromis-

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ing efficacy. For a better safety profile, it is important to apply the best supportive care based on understanding the underlying mechanisms of toxicities.

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AUTHOR CONTRIBUTIONS

Conceptualization: Hee Jung Kang and Soohyeon Lee. Data curation: Hee Jung Kang. Formal analysis: Hee Jung Kang. Investigation: Hee Jung Kang and Soohyeon Lee. Methodology: Hee Jung Kang and Soohyeon Lee. Project administration: Hee Jung Kang. Resources: Hee Jung Kang. Software: Hee Jung Kang. Supervision: Soohyeon Lee. Validation: Soohyeon Lee. Visualization: Hee Jung Kang and Soohyeon Lee. Writing—original draft: Hee Jung Kang. Writing—review & editing: Soohyeon Lee. Approval of final manuscript: all authors.

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