Therapy Management Using Modified 2-Weeks-On/1-Week-Off Dosing Schedule in Patients With Metastatic Renal Cell Carcinoma Receiving Sunitinib: A Hypothetical, Illustrative Case Scenario

KIMBERLY D. ALLMAN,[1] CNP, JOANNE C. RYAN,[2] PhD, RN, ANDREW CLAIR,[2] PhD, and SARAH YENSER-WOOD,[3] NP

From [1]Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio; [2]Pfizer Oncology, US Medical Affairs, New York, New York; [3]Duke Prostate Center, Durham, North Carolina

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Kimberly D. Allman, CNP, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195. E-mail: allmank@ccf.org

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Case Study

This patient case is fictional and does not represent events or a response from an actual patient. The authors developed this fictional case for educational purposes only.

Brady, a 54-year-old white male, was diagnosed with metastatic renal cell carcinoma (mRCC). Two and a half years prior, he had undergone a complete left nephrectomy for clear-cell RCC, with clean margins and negative lymph nodes. Post nephrectomy, he was routinely surveyed (every 3–6 months) by radiologic imaging. After 15 months of monitoring, a CT scan revealed small nodules in the left lung. Repeated scans were ordered to be taken in 6 weeks to assess growth kinetics, wherein an increase in the size of a number of nodules was detected. Of particular concern was the location of one of the larger nodules very close to a bronchus. Consequently, a needle biopsy was performed, which recovered malignant cells consistent with mRCC. It was then decided to begin systemic treatment for mRCC. Prior to starting treatment, Brady's Eastern Cooperative Oncology Group performance status (ECOG PS) was 0, and he had a Karnofsky score of 90, as he had only slightly diminished stamina that was considered disease related. Accordingly, he was classified as favorable risk by both Memorial Sloan Kettering Cancer Center and International Metastatic Renal Cell Carcinoma Database Consortium criteria (Table 1).

Brady is married and lives with his wife. He drinks alcohol occasionally but does not have a history of smoking. For the past 22 years, he has been employed full time as a factory assembly line worker, performing skilled, light assembly. In this capacity, Brady works with his hands and must remain on his feet approximately 30% of the working day. As Brady is eligible for early retirement in 11 months, he intends to continue working full time during treatment, if possible. Brady's medical history includes nonvalvular atrial fibrillation, which is treated with apixaban; hypertension that is adequately controlled (blood pressure 137/79 mm Hg) with lisinopril at 20 mg/day; coronary artery disease; and hyperlipidemia that is treated with atorvastatin at 20 mg/day. He is also taking daily low-dose aspirin (81 mg).

An estimated 73,820 patients in the United States will be diagnosed with renal cell carcinoma (RCC) in 2019 (National Cancer Institute, 2019), and up to 40% of RCC patients will eventually experience progression to metastatic disease (Ferlay et al., 2015; Znaor Lortet-Tieulent, Laversanne, Jemal, & Bray, 2015). Over the past decade, the prognosis for patients with metastatic RCC (mRCC) has improved with the development of molecularly targeted drugs (Escudier et al., 2007; Motzer et al., 2007, 2013). However, these therapies are associated with an array of adverse events (AEs) that can present challenges for patients to tolerate

Table 1. Criteria for Risk Prognostication Models

MSKCC Criteria for Metastatic Renal Cell Carcinoma Risk Model	
Risk factor	
Time from diagnosis to first systemic treatment < 12 months	
Karnofsky performance status > 80%	
Hemoglobin < lower limit of normal (normal for men: 13.5–17.5 g/dL; normal for women: 12.0–15.5 g/dL)	
Serum calcium > 10 mg/dL	
Serum lactate dehydrogenase concentration 1.5 × upper limit of normal	
Risk group	
Favorable	0 risk factors
Intermediate	1–2 risk factors
Poor	3–4 risk factors
IMDC Criteria for Metastatic Renal Cell Carcinoma Risk Model	
Risk factor	
Time from diagnosis to first systemic treatment < 12 months	
Karnofsky performance status > 80%	
Hemoglobin < lower limit of normal (normal for men: 13.5–17.5 g/dL; normal for women: 12.0–15.5 g/dL)	
Platelet count > upper limit of normal (normal: 150,000–400,000/μL)	
Neutrophil count > upper limit of normal (normal: 2.0–7.0 × 10^9/L)	
Serum calcium > 10 mg/dL	
Risk group	
Favorable	0 risk factors
Intermediate	1–2 risk factors
Poor	3–4 risk factors

Note. MSKCC = Memorial Sloan Kettering Cancer Center; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium. Information from Heng et al. (2009); Motzer et al. (1999).

treatment. Advanced practice providers (APPs) are a vital component in AE management, identifying emerging AEs, and implementing interventions aimed at balancing efficacy and tolerability for patients in their care.

Sunitinib (Sutent; Pfizer Inc, 2006) is a globally approved, multitargeted, tyrosine kinase inhibitor that has been a standard of care as first-line treatment for mRCC for over a decade (Choueiri et al., 2017; Gore et al., 2009; Motzer et al., 2006; Rini et al., 2008; Uemura et al., 2010). A well-established toxicity profile for sunitinib was developed from extensive clinical experience. Specifically, grade ≥ 3 treatment-related AEs were reported to be common in phase III sunitinib trials (Table 2), wherein approximately 20% of patients discontinued sunitinib due to serious AEs (Motzer et al., 2007, 2009). The current U.S. Food & Drug Administration (FDA) label for the treatment of mRCC with sunitinib recommends the administration of sunitinib at 50 mg once daily for 4 consecutive weeks followed by a 2-week break (schedule 4/2), in a 6-week cycle (Pfizer Inc, 2006).

To minimize toxicity and avoid negatively impacting sunitinib efficacy, clinicians have identified alternative dosing schedules as options over immediate dose reductions. The majority of these published alternative approaches include 2 consecutive weeks on therapy followed by a 1-week break (schedule 2/1), while still administering the 50-mg once-daily dose. Schedule 2/1 maintains the total dosage equivalent of 4 weeks on treatment and 2 weeks off treatment over a 6-week cycle, ensuring patients receive the same optimized cumulative exposure during the cycle. Schedule 2/1 is designed to help some patients better tolerate AEs such as hypertension, fatigue, and hand-foot syndrome (HFS) that frequently appear after the first 2 weeks in the treatment cycle and can worsen without intervention (Motzer et al., 2007, 2009).

Table 2. Treatment-Related Adverse Events (> 10% All Grades) in Sunitinib-Treated Patients

	mRCC Trial (n = 375)	
	All grades, %	**Grade 3/4, %**
Diarrhea	66	10
Fatigue	62	15
Nausea	58	6
Mucositis/stomatitis	47	3
Vomiting	39	5
Hypertension	34	13
Dyspepsia	34	2
HFS	29	8
Rash	29	2
Asthenia	26	11
Headache	23	1
Constipation	23	1
Hair color change	20	0
Dry skin	20	< 1
Hypothyroidism	16	2
Epistaxis	12	1
Pain in extremity	11	1

Note. mRCC = metastatic renal cell carcinoma; HFS = hand-foot syndrome. Information from Pfizer Inc (2006).

CASE STUDY

Patient Description and Current Issues

Brady, a 54-year-old white male, was diagnosed with metastatic (TNM stage IV: tumor size [T] = 3, lymph node [N] = 0, and metastasis [M] = 1; pT-3bN0M1) renal cell carcinoma (mRCC) 2 years after complete left nephrectomy for clear-cell RCC (with clean margins and negative lymph nodes). Brady was started on sunitinib at 50 mg/day on schedule 4/2, based on National Comprehensive Cancer Network (NCCN) Guidelines for patients who relapsed after nephrectomy and are treated in the first line. Two weeks into treatment, during the first cycle of sunitinib therapy, Brady began to experience mild AEs, including grade 1 diarrhea (increase of fewer than 4 stools per day over baseline), fatigue (relieved by rest), and a worsening of his preexisting hypertension to grade 2 (mean blood pressure [BP] increased from 137/79 mm Hg to 157/96 mm Hg; Table 3).

Treatment

Brady was encouraged to increase his intake of fluids (juices and sports drinks) to replace the volume loss caused by his diarrhea, avoid alcohol, and make dietary changes, i.e., to include small, more frequent meals, and reduce dairy and high-

Table 3. Criteria for Adverse Event Grades for Hypertension and Hand-Foot Syndrome According to CTCAE Version 5.0

AE grade	Criteria
Hypertension	
1	Systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg
2	Systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg if previously within normal limits; recurrent or persistent (≥ 24 hr); symptomatic increase by > 20 mm Hg (diastolic) or to > 140/90 mm Hg
3	Systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg
4	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
5	Death
Hand-foot syndrome	
1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain
2	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental activities of daily living
3	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self-care and activities of daily living
4	Not applicable
5	Not applicable

Note. AE = adverse event; BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events. Information from U.S. Department of Health & Human Services (2017).

fat foods in his diet. Potential etiologies for Brady's fatigue were explored and no overt abnormalities in his bloodwork were identified as contributory. Brady was encouraged to maintain his normal physical activity level and nutritional intake, and advised on how to improve his sleep hygiene. Brady's hypertension was managed by increasing the daily dose of lisinopril from 20 to 40 mg, and he was advised to monitor his sodium intake. He was also instructed on the proper technique for monitoring his own BP prior to taking his scheduled sunitinib dose, advised to keep a daily log to bring to each clinic visit, and to report persistent BP elevations (BP elevated above systolic 139 or diastolic 89 mm Hg).

Intervention

During the third week of the second cycle of treatment, Brady began to experience grade 2 HFS (Table 3), with painful calluses on both his hands and feet (Figures 1 and 2) that ultimately affected his ability to work full time as a factory assembly line worker, where he worked with his hands and was on his feet for approximately 30% of the day. He had a worsening of diarrhea (increase of 4–6 stools per day over baseline) and fatigue (not relieved by rest, limiting instrumental activities of daily living) to grade 2. Brady's hypertension also worsened again to grade 2 (BP 156/94 mm Hg) on lisinopril at 40 mg/day. He noticed mouth pain while brushing his teeth due to the emergence of grade 1 stomatitis (localized). The worsening of Brady's AEs prompted his health-care team to consider a dose reduction of sunitinib to 37.5 mg/day. However, Brady's health-care team preferred to maintain the 50-mg/day dose; therefore, additional AE management measures were employed.

To address the HFS (in addition to preventative skin care, on which he had been previously educated), Brady was instructed to apply hypoallergenic, emollient-rich lotion twice daily as needed; avoid skin exposure to extreme hot/cold water or external temperatures; and use proper barrier support, in particular insoles and gloves at work and socks or slippers at home to protect his feet from hard surfaces. For his worsening hypertension, Brady was started on amlodipine at 5 mg/day (a dihydropyridine calcium channel blocker to avoid cytochrome P450 [CYP] 3A4 issues associated with nondihydropyridine cal-

cium channel blockers), in addition to lisinopril at 40 mg/day. Brady was instructed to take over-the-counter loperamide at 2 mg as needed (up to a maximum of 16 mg per 24 hours) to treat his continuing diarrhea. Although fatigue required a modification of his work duties, Brady was able to continue working and addressed the fatigue by maintaining nutritional/fluid intake throughout the day. To address his stomatitis, Brady was advised to avoid traumatic (e.g., hard chips) and spicy foods, change to nonalcohol-containing mouthwash and nonmint toothpaste, and use oral salt/soda rinses.

Modification to Schedule 2/1

In order to manage Brady's AEs more globally and preemptively, his health-care team decided to switch his sunitinib therapy to schedule 2/1 after completion of the second cycle of schedule 4/2 treatment. The 50-mg/day dosage and the same total number of weeks taking sunitinib over the 6-week cycle of treatment were maintained by modification to schedule 2/1. The rationale to switch Brady to schedule 2/1 while maintaining the 50-mg/day dose was based on evidence from over a dozen retrospective and prospective trials that have been performed since 2009 that support the switch as an option to help manage AEs while maintaining efficacy (Table 4).

During the first week of the third cycle, Brady's mean BP improved to 138/78 mm Hg, and he was maintained on lisinopril at 40 mg and amlodipine at 5 mg per day. Brady's diarrhea was nearly resolved by week 3, with occasional loose stools that were treated with loperamide at 1 mg (half a tablet) as needed. His fatigue gradually improved to grade 1 by the end of week 6 and his stomatitis resolved during week 6. Brady continued to experience grade 2 HFS through week 3, necessitating a 3-consecutive-day absence from work. During week 4, his HFS improved to grade 1, and he was able to resume normal work activity.

Brady was maintained on schedule 2/1 with continued supportive care through cycle 4, during which his mean BP was 134/80 mm Hg, and his other AEs maintained their lowest grade during cycle 3. Brady has required no additional treatment adjustments and is currently receiving treatment cycle 5 on schedule 2/1. The AEs Brady experienced are summarized by treatment cycle in Figure 3.

Figure 1. Grade 2 hand-foot syndrome with finger callus. Courtesy of Cleveland Clinic Taussig Cancer Center.

Figure 2. Grade 2 hand-foot syndrome: feet. Courtesy of Cleveland Clinic Taussig Cancer Center.

Outcome

A follow-up CT scan of Brady's chest at 3 months after sunitinib treatment initiation revealed a partial response from a reduction in size of his previously detected lung nodules, with no new disease

Table 4. Summary of Key Findings From Retrospective Studies of Real-World Clinical Experience Using Dose Modification to Schedule 2/1

Study	N	Most common AEs prompting switch from schedule 4/2 to 2/1	Percentage of patients reporting AEs in switching from schedule 4/2 to 2/1
Atkinson et al.	63	Fatigue HFS Diarrhea Mucositis	AEs of any grade: 65% on 4/2 vs. < 30% on 2/1
Najjar et al.	30	Fatigue HFS Diarrhea Mucositis	AEs grade ≥ 3: 97% on 4/2 vs. 27% on 2/1 ($p < .001$)
Bracarda et al.	208	Fatigue Mucositis Diarrhea HFS	AEs grade ≥ 3: 45.7% on 4/2 vs. 8.2% on 2/1 ($p < .001$)
Miyake et al.	45	Thrombocytopenia Leukopenia Anemia Hypothyroidism	AEs grade ≥ 3: 80.0% on 4/2 vs. 48.9% on 2/1 ($p = .002$)

Note. AE = adverse event; 4/2 = 4-weeks-on/2-weeks-off dosing schedule; 2/1 = 2-weeks-on/1-week-off dosing schedule; HFS = hand-foot syndrome. Information from Atkinson et al. (2014); Bracarda et al. (2015); Miyake et al. (2015); Najjar et al. (2014).

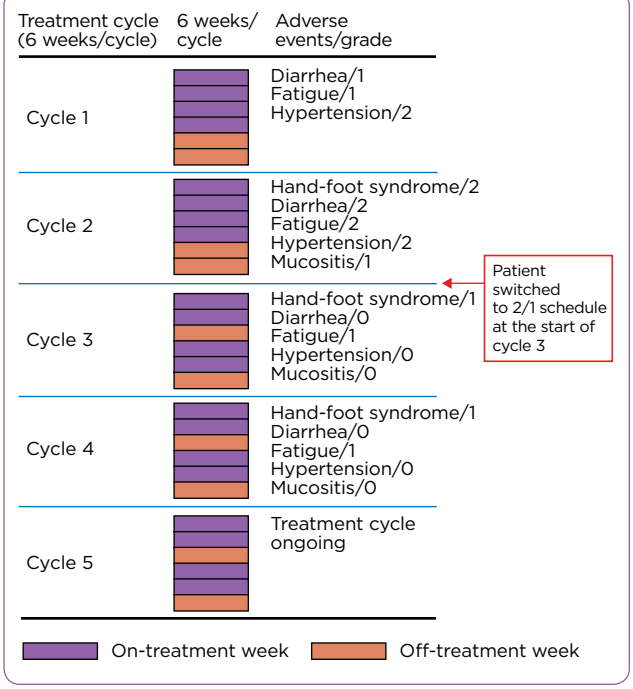

Figure 3. Adverse events and grade by treatment cycle in case study. On-treatment week = sunitinib at 50 mg per day administered; off-treatment week = no sunitinib administered. Adverse event grade was determined by the Common Terminology Criteria for Adverse Events version 5.0. Information from U.S. Department of Health & Human Services (2017).

detected on abdominal/pelvic CT. Brady's AEs were managed effectively and became tolerable within 3 months of modification to schedule 2/1. He was able to remain on treatment while maintaining a 50-mg/day dosing. Brady has been able to keep working full time during treatment.

DISCUSSION

Retrospective and Prospective Studies Support Modification to Schedule 2/1

Sunitinib has been a widely used treatment option for RCC since its FDA approval in January 2006 (Pfizer Inc, 2006) and has been a standard of care. The AE profile of sunitinib, although well known, can represent a challenge to APPs. In the pivotal trial of sunitinib reported by Motzer and colleagues (2007), 57% of patients treated with sunitinib experienced a grade 3 or 4 AE and 20% discontinued treatment due to AEs (Table 2). Substantial evidence from retrospective studies supporting modification to schedule 2/1 has been reported (Atkinson et al., 2014; Bracarda et al., 2015; Miyake, Harada, Miyazaki, & Fujisawa, 2015; Najjar et al., 2014; Neri et al., 2013; Table 4). These retrospective studies describe real-world clinical experience in patients who switched to schedule 2/1 and underlie the rationale for schedule modification. As reported, pa-

tients on sunitinib schedule 2/1 achieved improved AE profiles vs. schedule 4/2, with reductions in both overall and grade ≥ 3 AEs across a range of toxicities (Atkinson et al., 2014; Bracarda et al., 2015; Miyake et al., 2015; Najjar et al., 2014; Figure 4).

Prospective studies, including RESTORE, also support the use of dose modification to schedule 2/1 as an AE management option. RESTORE was a prospective, randomized, open-label clinical trial in patients with mRCC designed to investigate the im-

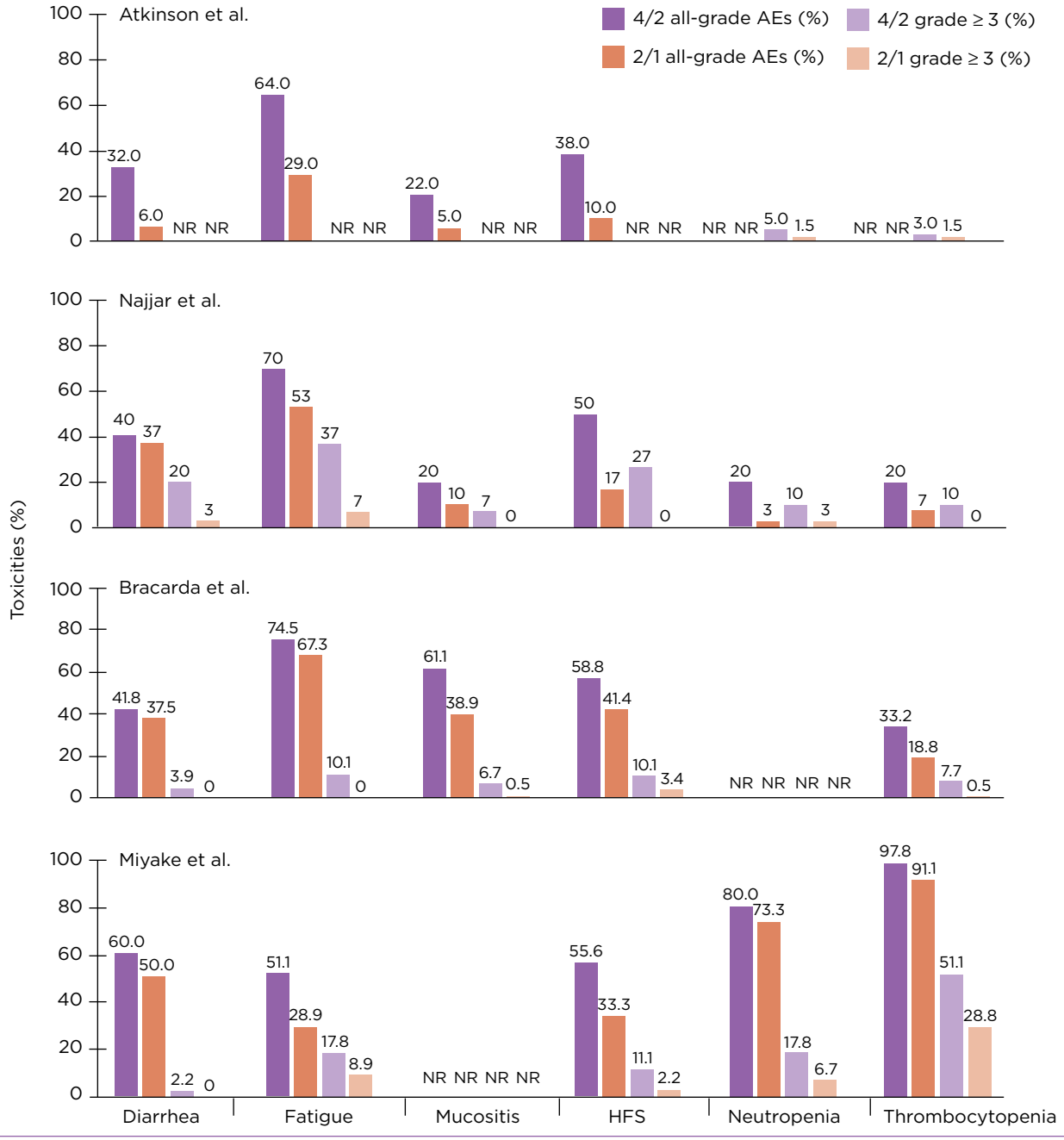

Figure 4. Most commonly reported adverse events with sunitinib prompting schedule modification across studies: adverse events reduced with schedule 2/1 vs. 4/2. Schedule 4/2 = treatment 4 weeks on and 2 weeks off; AE = adverse event; schedule 2/1 = treatment 2 weeks on and 1 week off; NR = not reported; HFS = hand-foot syndrome. Information from Atkinson et al. (2014); Bracarda et al. (2015); Miyake et al. (2015); Najjar et al. (2014).

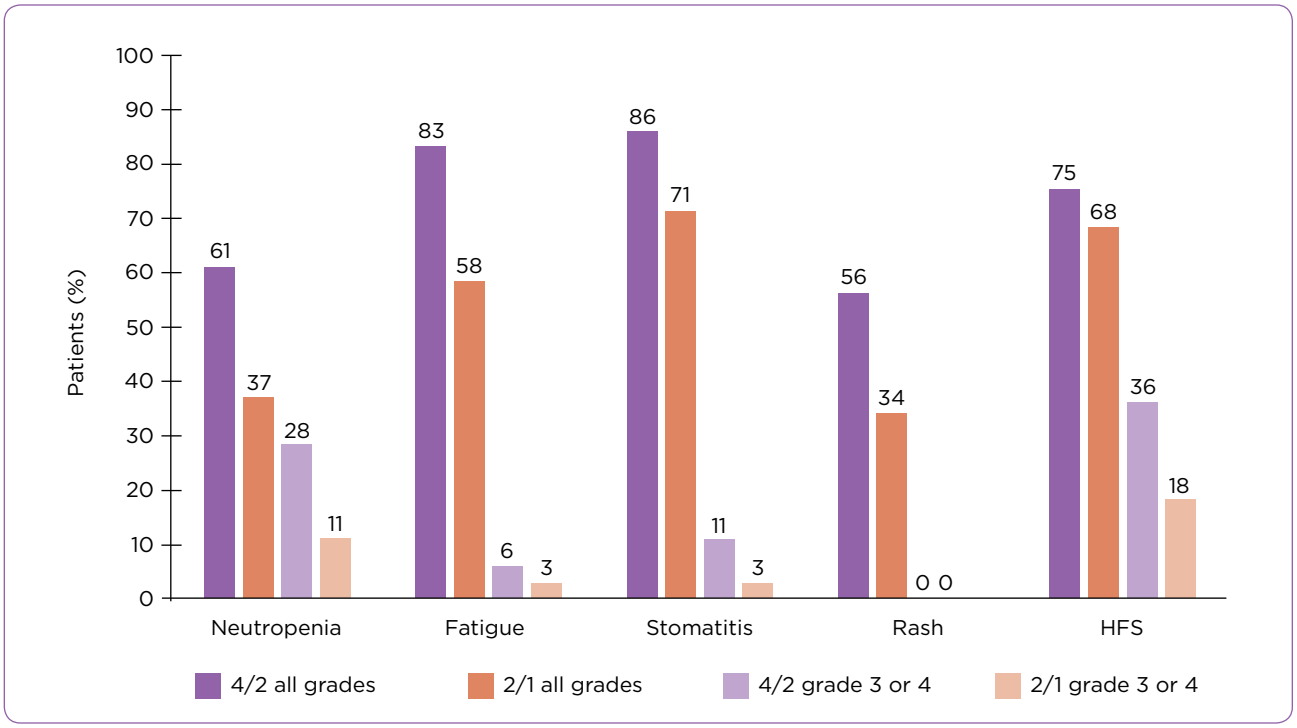

Figure 5. Most common adverse events with sunitinib, with notable differences between schedule 2/1 and schedule 4/2 in the RESTORE trial (randomized phase II trial of sunitinib 4 weeks on and 2 weeks off vs. 2 weeks on and 1 week off in metastatic clear-cell type renal cell carcinoma). Most common AEs (all grades) were defined as occurring in > 50% of patients in the schedule 4/2 arm. Information from Lee et al. (2015). Schedule 4/2 = treatment 4 weeks on and 2 weeks off; schedule 2/1 = treatment 2 weeks on and 1 week off; HFS = hand–foot syndrome.

pact of sunitinib treatment schedule 2/1 vs. schedule 4/2 (Lee et al., 2015). Patients in the schedule 2/1 treatment arm experienced a reduction in AEs vs. patients in the schedule 4/2 arm (Figure 5). Furthermore, trial results from RESTORE indicated that sunitinib schedule 2/1 dosing for the treatment of mRCC did not compromise efficacy compared with schedule 4/2 (Lee et al., 2015; Figure 6).

Another prospective trial, recently reported by Jonasch and colleagues (2018), compared the rates of specific, commonly occurring AEs in mRCC patients receiving sunitinib on schedule 2/1 vs. published rates of the same AEs in patients who received sunitinib on schedule 4/2. The trial did not reach the primary endpoint of achieving lower than grade 3 AEs for fatigue, diarrhea, and HFS in patients on schedule 2/1; however, the investigators reported similar rates (~25%) of these grade 3 AEs as has been historically reported for patients on schedule 4/2. In addition, they noted that no grade 4 AEs were reported for patients on schedule 2/1 and the discontinuation rate for patients was 10%, which compares favorably with the original pivotal trial data reported by Motzer and colleagues (2007) and the more recent COMPARZ trial data, wherein the discontinuation rates were 20% for patients on schedule 4/2 (Jonasch et al., 2018; Mangoni, Kichenadasse, Rowland, & Sorich, 2018). Jonasch and colleagues also reported efficacy results (median progression-free survival of 13.7 months; 95% confidence interval = 10.9–16.3 months) that were better than expected based on the prognostic classifications of the patient population (78% of patients were intermediate- or poor-risk according to Memorial Sloan Kettering Cancer Center criteria; Jonasch et al., 2018), suggesting that, at the least, schedule 2/1 is not associated with a reduction in efficacy (Mangoni et al., 2018).

Schedule 2/1 as Part of an Effective AE Management Strategy

Advanced practice providers play a critical role in keeping patients on treatment and in optimiz-

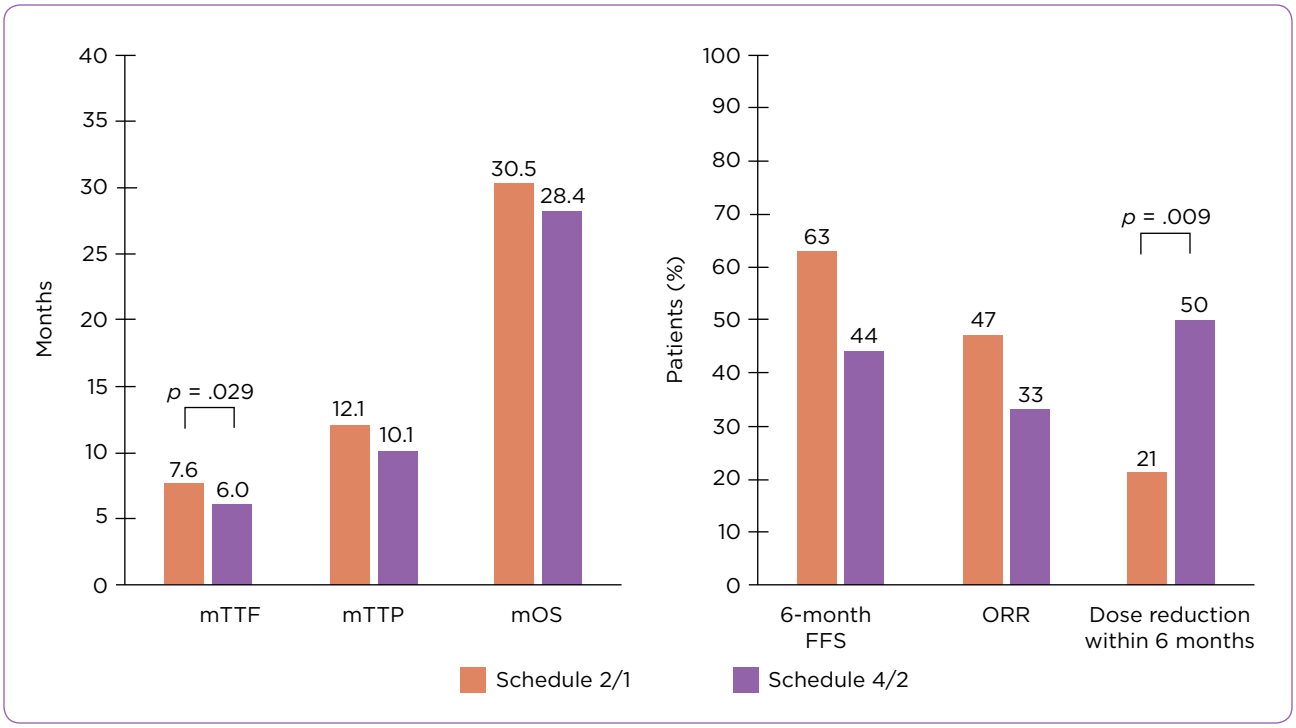

Figure 6. Schedule 2/1 maintains or improves efficacy in RESTORE trial (randomized phase II trial of sunitinib 4 weeks on and 2 weeks off vs. 2 weeks on and 1 week off in metastatic clear-cell type renal cell carcinoma. Information from Lee et al. (2015). mTTF = median time to treatment failure; mTTP = median time to progression; mOS = median overall survival; FFS = failure-free survival; ORR = objective response rate; schedule 2/1 = treatment 2 weeks on and 1 week off; schedule 4/2 = treatment 4 weeks on and 2 weeks off.

ing outcomes. It is vital to monitor and identify emerging AEs during treatment and respond with effective supportive care. To this end, a strong understanding of the AE profile of sunitinib and the NCCN Guidelines for treating mRCC is crucial. Although schedule modification can be a valuable management strategy as an alternative to dose reductions, it must be supported by aggressive proactive measures to manage AEs that emerge mid-treatment cycle, e.g., management of hypertension, diarrhea, and HFS, with standard clinical measures before schedule modification can be employed, as described in this hypothetical case study.

CONCLUSIONS

The available data from prospective and retrospective studies support modifying sunitinib treatment from schedule 4/2 to schedule 2/1 while continuing the 50-mg/day dose. Switching to this modified schedule is associated with improved tolerability and maintenance of efficacy in patients with mRCC. Modifying a patient's sunitinib dosing to schedule 2/1 gives APPs an option that maintains patients on the full 50-mg/day dose and allows patients to receive the same cumulative drug exposure over the 6-week cycles, both of which are vital considerations for helping patients potentially receive optimal therapeutic benefit.

Although schedule 2/1 may be a good alternative to dose reduction or temporary discontinuation when tolerability issues are observed with the 4/2 schedule, this hypothetical case study specifically illustrates switching, when appropriate, from a 4/2 to 2/1 schedule and does not discuss initiating sunitinib on a 2/1 schedule.

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Disclosure

Ms. Allman is a consultant for Exelixis and a speaker for Exelixis, Pfizer, and Sanofi. Ms. Wood received consulting fees from Exelixis and was a speaker for Pfizer and Exelixis. Dr. Ryan and Dr. Clair are employees of and hold stock in Pfizer.

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