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Targeted Therapies for Metastatic Renal Cell Carcinoma: An Overview of Toxicity and Dosing Strategies

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LEARNING OBJECTIVES

After completing this course, the reader should be able to:

1. Evaluate the recommended clinical doses and the associated safety data for targeted therapies in RCC.
2. Identify clinical circumstances for which dose modifications should be considered in RCC patients treated with targeted therapies.
3. Employ prescribing guidelines for the management of drug-related toxicities.

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ABSTRACT

The targeted therapies sunitinib, sorafenib, temsirolimus, and bevacizumab (when used in combination with interferon-α2a) have dramatically improved outcomes for patients with advanced renal cell carcinoma (RCC). Clinical application of these novel agents outside the trial setting, however, may present some challenges for treating individual patients with unique needs. In some patients, dose modifications may be considered for potential drug interactions and for management of severe cases of hematologic or nonhematologic toxicities. The more common grade 3 or 4 side effects with sunitinib and sorafenib include hypertension, fatigue, hand–foot syndrome, elevated lipase, lymphopenia, and neutropenia. Congestive heart failure is a less common but serious side effect that warrants treatment discontinuation. Temsirolimus exhibits a different side-effect profile, with the more common grade 3 or 4 side effects being metabolic in nature (i.e., elevated triglycerides, elevated glucose, hypophosphatemia) as a result of its

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inhibitory effects on the mammalian target of rapamycin–regulated lipid and glucose pathways. Asthenia, rash, and dyspnea also occur in patients receiving temsirolimus. Virtually all of the side effects associated with these agents can be managed effectively in the majority of patients with medical treatment or supportive interventions. Recognition and prompt management of side effects are important to avoid unnecessary dose reductions that may result in suboptimal efficacy. ***The Oncologist*** 2008;13:1084–1096

Introduction

Whereas chemotherapy dosing is based on the maximum-tolerated dose (MTD) of a drug, dosing of targeted cancer therapies is not necessarily the MTD but, rather, is based on the inhibition of biologic targets in the tumor and surrogate tissues as well as safety assessments. Investigational dosing regimens are then fine-tuned during phase II and III testing to recommend a clinical dose that maximizes tolerability while providing optimal biologic activity and clinical efficacy [1].

This paper describes the clinical rationale for the recommended dosing and reviews the safety data at clinical doses for each of the novel targeted therapies approved for treatment of renal cell carcinoma (RCC): sunitinib, sorafenib, and temsirolimus. Because no randomized controlled clinical trials directly compare the relative safety and tolerability of these targeted agents, we compare the available published data from pivotal trials (Tables 1 and 2). Guidelines for dose modifications and for adjustment/interruption for management of toxicities are summarized for each therapy (Table 3).

Approved Targeted Therapies for RCC

Sunitinib

Sunitinib is a small molecule inhibitor of certain receptor tyrosine kinases, including vascular endothelial growth factor receptor (VEGFR) types 1 and 2 (FLT-1 and FLK-1/KDR), platelet-derived growth factor receptors (PDGFR-α, PDGFR-β), stem cell factor receptor (c-KIT), and the FLT-3 and RET kinases [2]. Clear cell RCC is characterized by frequent loss of the von Hippel-Lindau tumor suppressor gene, resulting in increased transcription of several proteins, including VEGF and PDGF [3]. Tumor angiogenesis is stimulated in part by VEGF binding to its receptor. Signaling through this receptor can be blocked in preclinical models by treatment with sunitinib. Preclinical data suggest that sunitinib has antitumor activity that might result predominantly from inhibition of tumor angiogenesis, although sunitinib also has direct antiproliferative and apoptotic effects on certain tumor types [4]. Sunitinib doses selected for phase I clinical testing were based on biologic activity in preclinical models (i.e., the dose needed to achieve the plasma concentration necessary to inhibit the VEGF receptor) rather than on MTD, which is reflected in animal models as weight loss [2].

Early sunitinib phase I studies included single-dose studies of the oral drug in healthy adults to assess toxicity and pharmacokinetic parameters, and several multidose studies in patients with acute myelogenous leukemia or a variety of advanced solid tumors [2]. Because of the prolonged half-life of sunitinib and its main metabolite and evidence of accumulation with continuous daily dosing, alternate dosing schedules were explored. Schedules evaluated in cancer patients included daily and every-other-day administration and incorporated planned rest periods (i.e., 3-week cycle of 2-week treatment, then 1-week rest period [schedule 2/1]; 4-week cycle of 2-week treatment, then 2-week rest period [schedule 2/2]; or 6-week cycle of 4-week treatment, then 2-week rest period [schedule 4/2]). Confirmed partial responses were observed at the 50-mg and 75-mg dose levels on schedules 4/2 or 2/2. Fatigue was the most common adverse event (AE) reported in phase I studies, regardless of tumor type. Based on the results of these studies, the recommended dose for phase II trials was 50 mg orally once daily using schedule 4/2 [5]. Two single-arm phase II trials of oral sunitinib on this schedule displayed high partial response rates (34%–40%) and a median time to tumor progression of 8.3 months in patients with cytokine-refractory advanced RCC. Toxicities were similar to those in phase I studies, with fatigue being the most common grade 3 AE (11%) [6, 7].

The phase III trial of oral sunitinib (50 mg, 4/2 schedule) versus interferon (IFN)-α (9 MU s.c., thrice weekly) as first-line therapy enrolled patients with good- and intermediate-risk clear cell RCC, per the Memorial Sloan-Kettering Cancer Center risk group classification (Table 1) [8]. Patients receiving sunitinib experienced a significantly longer progression-free survival (PFS) time than those receiving IFN-α (hazard ratio [HR], 0.42; $p < .001$; sunitinib median, 11 months versus IFN-α median, 5 months). However, the prespecified analysis of overall survival did not reach significance. A subsequent exploratory analysis of these data suggested that there may be a significant survival advantage, particularly after censoring the 25 patients receiving IFN-α who were crossed over to sunitinib on study

Table 1. Comparison of dose reductions/discontinuations in the phase III setting

Study	*n*	Population, MSKCC risk, % (low/intermediate/poor)	Drug/dose	≥1 Dose reduction (TEAEs), %	≥1 Dose delay (TEAEs), %	Discontinuation due to TEAEs, %
Motzer et al. [8]	375	Previously untreated (38/56/6)	Sunitinib, 50 mg, oral, once daily × 4 wks, 2 wks no treatment (4/2 schedule)	32	38	8
Escudier et al. [18]	451	Cytokine refractory (52/48/0)	Sorafenib, 400 mg, oral, twice daily	13	21	4
Hudes et al. [45]	209	Previously untreated (0/31/69)	Temsirolimus, 25-mg i.v. infusion, once weekly	23	66	7

Abbreviations: MSKCC, Memorial Sloan-Kettering Cancer Center; TEAEs, treatment-emergent adverse events.

Table 2. Grade ≥3 adverse events with any agent, reported in >5% of treated patients in phase III trials in renal cell carcinoma [11, 14, 20]

	Sunitinib, 50 mg, oral, daily × 4 wks, 2 wks off, % (*n* = 375)	Sorafenib, 400 mg, oral, twice daily, % (*n* = 451)	Temsirolimus, 25 mg i.v., once weekly, % (*n* = 208)
Adverse reaction	**Grade 3 or 4 (all grades)**	**Grade 3 or 4 (all grades)**	**Grade 3 or 4 (all grades)**
Any	67 (99)	38 (95)	67 (100)
Hypertension	10 (30)	4 (17)	0 (7)
Fatigue	9 (58)	6 (37)	—
Asthenia	7 (21)	—	11 (51)
Diarrhea	6 (58)	2 (43)	1 (27)
Hand–foot syndrome	5 (21)	6 (30)	0 (0)
Dyspnea	4 (15)	4 (14)	9 (28)
Laboratory abnormalities: hematology			
Lymphocytes decreased	12 (59)	13 (23)	16 (53)
Neutrophils decreased	12 (72)	5 (18)	5 (19)
Platelets decreased	8 (65)	1 (12)	1 (40)
Leukocytes decreased	5 (78)	13 (23)	1 (32)
Hemoglobin decreased	3 (71)	2 (44)	20 (94)
Laboratory abnormalities: chemistry			
Elevated lipase	16 (52)	12 (41)	—
Elevated uric acid	12 (41)	—	—
Phosphorus decreased	5 (36)	13 (45)	18 (49)
Glucose increased	3 (15)	—	16 (89)
Triglycerides increased	—	—	44 (83)

Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [30].

[9]. Frequently occurring AEs in patients treated with sunitinib were constitutional (fatigue) and gastrointestinal (diarrhea, nausea, mucositis/stomatitis, vomiting). Patients on sunitinib had higher rates of grade 3 diarrhea, vomiting, hypertension, and hand–foot syndrome, and grade 3 or 4 leukopenia, neutropenia, and thrombocytopenia than patients on IFN-α ($p < .05$ for all) (Table 2) [8]. Fatigue occurred at similar incidence in both groups (51%), but grade 3 or 4 fatigue was more common with IFN-α (11% versus 7%; $p < .05$). Sunitinib was associated with thyroid dysfunction, including hypothyroidism [10] and anemia, which may contribute to fatigue in RCC patients.

Treatment and Dose Adjustments

The recommended dose for sunitinib for patients with advanced RCC is one 50-mg oral dose daily, with or without

Table 3. Summary of prescribing guidelines for treatment and dose modifications [11, 14, 20]

	Sunitinib	Sorafenib	Temsirolimus
Recommended dose	50 mg orally, with or without food; 4 wks on treatment, 2 wks off	400 mg (2 × 200-mg tablets) taken twice daily without food (at least 1 hour before or 2 hours after eating)	25 mg i.v. infused over 30–60 minutes once per wk; premedication with diphenhydramine (30 mg) prior to each dose
Duration of treatment	Continue until patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs	Continue until patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs	Continue until patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs
Dose modifications for AEs	Management of suspected AE may require temporary interruption and/or dose reduction Dose adjustment/reduction in 12.5-mg increments recommended based on individual safety and tolerability	Management of suspected AE may require temporary interruption and/or dose reduction When reduction is required, reduce dose to 400 mg daily; if further reduction is needed, single 400-mg dose every other day	Management of suspected AE may require temporary interruption and/or dose reduction Temsirolimus should be held for ANC $<1{,}000/\mu l$, platelet count $<75{,}000/\mu l$, or NCI CTCAE grade ≥ 3 adverse reactions Once toxicities have resolved to grade ≤ 2, temsirolimus may be restarted with dose reduced by 5 mg/wk to no lower than 15 mg/wk
Temporary or permanent interruption for specified AEs	Interruption in cases of: Severe hypertension, until controlled • RPLS, temporary suspension recommended; following resolution, treatment may be resumed at physician discretion • Venous thromboembolic events, until resolved Discontinuation: Clinical manifestations of CHF; dose should be interrupted or reduced if no clinical evidence, but ejection fraction $<50\%$ and $>20\%$ below baseline · Symptoms of pancreatitis or hepatic failure	Interruption in cases of: Hypertension—severe or persistent hypertension, despite institution of antihypertensive therapy • Major surgical procedures for wound-healing complications; resumption based on clinical judgment of adequate wound healing • Skin toxicity, including hand–foot syndrome (refer to dose modification guideline in prescribing information, Table 1) *Interruption*: Grade 2—no improvement within 7 days or second or third occurrence • Grade 3—first or second occurrence • When resuming treatment, decrease sorafenib dose by 1 dose level, as indicated above *Discontinuation*: Grade 2—fourth occurrence • Grade 3—third occurrence Discontinuation: Cardiac ischemia and/or infarction—consider temporary or permanent discontinuation • Any bleeding event that requires medical intervention • Gastrointestinal perforation	Interruption in cases of: Hypersensitivity reactions—infusion may be restarted at a slower rate (up to 60 minutes) 30 minutes after treatment with H_1 and/or H_2 receptor antagonist, and at discretion of physician Caution: Major surgical procedures—no dose modification recommended, but caution should be exercised in perioperative period for abnormal wound healing Discontinuation: Interstitial lung disease—some patients may require discontinuation and/or treatment with corticosteroids and/or antibiotics; others may continue treatment without interventions; monitor new or worsening respiratory symptoms
Dose modification for drug interactions with concomitant medications[a]	Strong CYP3A4 inhibitors: Avoid coadministration • Select alternate with no or minimal inhibitory potential • If must be coadministered, *reduce* sunitinib dose to a minimum of 37.5 mg daily Strong CYP3A4 inducers: Avoid coadministration • Select alternate with no or minimal induction potential • If must be coadministered, consider *increasing* sunitinib to a maximum of 87.5 mg daily • Monitor carefully for toxicities	Strong CYP3A4 inhibitors: No clinically significant PK interactions Strong CYP3A4 inducers: Rifampin reduced AUC 37%, consider sorafenib dose increase • If increased, monitor carefully for toxicities Other: CYP2B6 and CYP2C8 substrates: Systemic exposure increases when coadministered with sorafenib; caution recommended UGT1A1 and UGT1A9 substrates: Increased AUC of irinotecan; caution recommended Docetaxel: Increased docetaxel AUC and C_{max}; caution recommended Doxorubicin: Increased doxorubicin AUC; caution recommended Fluorouracil: Increases and decreases in fluorouracil observed; caution recommended	Strong CYP3A4 inhibitors: Avoid coadministration • If must be coadministered, *reduce* temsirolimus dose to 12.5 mg/wk • If strong CYP3A4 inhibitor is discontinued, allow a 1-wk washout period before reinstituting temsirolimus dose at the level used before initiation of the strong CYP3A4 inhibitor Strong CYP3A4 inducers: Avoid coadministration • If must be coadministered, consider *increasing* temsirolimus dose from 25 mg/wk to 50 mg/wk • Monitor carefully for toxicities • If strong CYP3A4 inhibitor is discontinued, reinstitute temsirolimus dose at the level used before initiation of the strong CYP3A4 inducer Other: Sunitinib Concomitant use of temsirolimus and sunitinib not recommended; dose-limiting toxicities at lowest doses used in phase I dose-escalation study

(continued)

Table 3. (Continued)

	Sunitinib	Sorafenib	Temsirolimus
Dose modification recommended for special populations (based on subset and PK analyses)			
Age	No dose adjustment required	No dose adjustment required	No dose adjustment required
Gender	No dose adjustment required	No dose adjustment required	No dose adjustment required
Body weight	No dose adjustment required	No dose adjustment required	No dose adjustment required
Race	No dose adjustment required	AUC 30% lower in Asians than in whites	Not specified
ECOG score	No dose adjustment required	Not specified	Not specified
Renal impairment	Data on dosing are lacking for severe impairment; PK unaltered if calculated CrCl in range of 42–347 ml/minute	No dose adjustment required for mild (CrCl >50–80 ml/minute), moderate (CrCl 30–50 ml/minute), or severe impairment (CrCl <30 ml/minute) not undergoing dialysis	Data on dosing are lacking for severe impairment; no clinical studies conducted in patients with decreased renal function or in patients undergoing dialysis
Hepatic impairment	Data on dosing are lacking for severe (Child-Pugh C) impairment; no dose adjustment required in patients with mild or moderate impairment (Child-Pugh A and B)	Data on dosing are lacking for severe (Child-Pugh C) impairment; patients with mild (Child-Pugh A) and moderate (Child-Pugh B) impairment have 23%–65% lower sorafenib AUC than subjects with normal hepatic function	No data on dosing in this population

[a]Strong CYP3A4 inhibitors include ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole. Grapefruit may also increase levels of sunitinib and temsirolimus. Strong CYP3A4 inducers include dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital, and St. John's wort.

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; AUC, area under the concentration–time curve; CHF, congestive heart failure; C_{max}, maximum concentration; CrCl, creatinine clearance; CYP, cytochrome P450; ECOG, Eastern Cooperative Oncology Group; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PK, pharmacokinetics; RPLS, reversible posterior leukoencephalopathy syndrome.

food, on schedule 4/2 (Table 3) [11]. Most side effects are reversible and should not result in discontinuation of sunitinib. If necessary, toxicities may be managed through dose adjustments or interruptions. A standard dose modification in 12.5-mg steps is recommended based on individual safety and tolerability: dose level 1, 50 mg for 4 weeks, 2 weeks off; dose level 2, 37.5 mg for 4 weeks, 2 weeks off; dose level 3, 25 mg for 4 weeks, 2 weeks off. Tumors tend to regrow during the 2-week break period or if plasma concentrations are too low for complete receptor inhibition. Discontinuation of sunitinib is indicated in the presence of clinical evidence of congestive heart failure and in patients with symptoms of pancreatitis or hepatic failure [11].

Pharmacokinetic analyses indicate no clinically relevant effects of age, body weight, creatinine clearance, race, gender, or Eastern Cooperative Oncology Group performance status score on pharmacokinetic profiles, suggesting that dose adjustment is not required based on these factors. However, studies excluded patients with serum creatinine levels >2.0× the upper limit of normal (ULN), so caution should be used in patients with severely impaired renal function. Additionally, no dose adjustment is required when administering sunitinib to patients with Child-Pugh Class A or B hepatic impairment, but sunitinib has not been studied in patients with severe (Child-Pugh Class C) hepatic impairment. Studies in cancer patients excluded patients with alanine aminotransferase or aspartate aminotransferase levels >2.5× the ULN or, if as a result of liver metastases, >5.0× the ULN [11].

Sunitinib is metabolized primarily by cytochrome P450 (CYP)3A4 to produce its primary active metabolite, which is further metabolized by CYP3A4 [12]. Therefore, strong CYP3A4 inhibitors may increase sunitinib plasma concentrations so that the selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended. A dose reduction of sunitinib to a minimum of 37.5 mg daily should be considered if a strong CYP3A4 inhibitor must be used (Table 3). Additionally, CYP3A4 inducers may decrease sunitinib plasma concentrations and should be avoided. A sunitinib dose increase to a maximum of 87.5 mg daily should be considered if coadministration with a CYP3A4 inducer is necessary; however, patients should be monitored carefully for toxicities. In human liver microsomes and hepatocytes, studies indicated that sunitinib does not induce or inhibit the major CYP enzymes [11].

Medical Management of Selected Toxicities

Hypertension. Patients receiving sunitinib should be monitored for hypertension and, if needed, treated with standard antihypertensive therapy, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta-blockers, and diuretics [12]. Nondihydropyridine calcium channel blockers, such as verapamil and diltiazem, should be avoided because of their known inhibition of CYP3A4. Other antihypertensive drugs may also potentially interact with CYP enzymes and

could interact with sunitinib. Patients with preexisting hypertension may, therefore, require adjustment of antihypertensive medications during sunitinib therapy. The objective of treatment is to normalize blood pressure (resting rate, <140/90 mmHg). In cases of severe hypertension (>200 mmHg systolic or >110 mmHg diastolic) [13], sunitinib should be temporarily suspended until the hypertension is adequately controlled. With appropriate medical management of hypertension, sunitinib dose reductions are rarely necessary.

Reversible Posterior Leukoencephalopathy Syndrome. Temporary suspension of sunitinib is recommended in rare cases (<1%) of patients with seizures and radiologic evidence of reversible posterior leukoencephalopathy syndrome (RPLS). Signs and symptoms consistent with RPLS, such as hypertension, headache, decreased alertness, altered mental functioning, and visual loss, including cortical blindness, should be controlled with medical management. Following resolution, sunitinib may be resumed [14].

Cardiac Toxicity. Emerging safety data indicate that cardiotoxicity may be associated with sunitinib at a higher rate than that seen in clinical trials. At one institution, 12.5% of patients receiving sunitinib for either RCC or gastrointestinal stromal tumor developed symptomatic grade 3 or 4 heart failure 22–435 days after the initiation of treatment [15]. Left ventricular dysfunction is the main cardiac side effect of sunitinib and might be partly a result of cardiomyocyte toxicity exacerbated by hypertension [16]. Therefore, blood pressure and the left ventricular ejection fraction should be closely monitored in those patients receiving sunitinib who have a history of coronary artery disease or cardiac risk factors [16]. For patients without cardiac risk factors, a baseline evaluation of the ejection fraction should be considered.

Sunitinib prolongs the QT interval in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias, including torsades de pointes (<1% of sunitinib-exposed patients). Caution should, therefore, be used in patients with a history of QT prolongation and in those taking antiarrhythmics, or patients with preexisting cardiac disease, bradycardia, or electrolyte disturbances (Mg^{2+}, K^{+}) [11].

Hypothyroidism. Hypothyroidism has been reported in patients as early as 1–2 weeks after the initiation of sunitinib treatment, and the incidence increases progressively with duration of therapy [10]. In patients with RCC treated with sunitinib, 85% had abnormal results on one or more thyroid function tests, including elevation of thyroid-stimulating hormone (TSH) levels, decreased T3 levels, and, less commonly, decreased T4 or free-thyroxine index levels [10]. An abnormal serum TSH concentration and mild symptoms consistent with hypothyroidism, such as fatigue, anorexia, edema, fluid retention, or cold intolerance, may precede the onset of overt hypothyroidism, which may rapidly progress from mild to profound [13].

Regular surveillance of thyroid function is warranted in patients receiving sunitinib. TSH measurements should be taken at baseline and every 2–3 months during treatment; any abnormal TSH value or symptoms suggestive of hypothyroidism should prompt a more thorough evaluation. Patients with subclinical hypothyroidism should also be considered for treatment; typical doses of levothyroxine should normalize TSH levels and resolve symptoms. Patients with cancer, including those with RCC, who are treated with sorafenib have a significant risk of developing hypertension (relative risk, 6.1; 95% confidence interval [CI], 2.4–15.3; $p < .001$, compared with control treatments) [17]. Therefore, appropriate monitoring and treatment are strongly recommended to prevent cardiovascular complications. Hypertension associated with sorafenib has been easily managed with antihypertensive therapy (agents acting on the renin–angiotensin system, beta-blocking agents, and calcium channel blockers) and rarely has led to treatment discontinuation (<1%) [18, 19]. Prescribing guidelines suggest that patients be monitored weekly for hypertension during the first 6 weeks of treatment and regularly thereafter [20]. In cases of severe or persistent hypertension, temporary or permanent discontinuation of sorafenib should be considered, despite initiation of antihypertensive therapy. Thyroid hormone replacement benefits about 50% of patients who develop overt hypothyroidism [10].

Skin Toxicity. Skin changes associated with sunitinib include hand–foot syndrome, changes in hair color, skin rash, dry skin, skin discoloration, acral erythema, and subungual splinter hemorrhages. Skin toxicity typically occurs after 3–4 weeks of treatment. Hand–foot syndrome presents as painful symmetric erythematous and edematous areas on the palms and soles, often accompanied by paresthesia, tingling, or numbness, and desquamation can occur in severe cases. Palliative intervention includes moisturizers, foot and hand care products (e.g., gel pad inserts, cotton gloves, and clobetasol propionate cream), and medication for pain management [13]. Generalized skin rashes (erythema, maculopapular or seborrheic dermatitis) are mainly grades 1 or 2, tend to decrease over time, and rarely require dose reduc-

tion. Moisturizing skin lotions or creams may be helpful if the skin is very dry.

Sorafenib

Sorafenib targets Raf serine/threonine kinase and, like sunitinib, inhibits proangiogenic VEGFR and PDGFR tyrosine kinases, and tumorigenic FLT-3, c-KIT, and RET tyrosine kinases [21]. In preclinical tumor models, sorafenib acted on the tumor and tumor vasculature to inhibit tumor cell growth or disrupt tumor vasculature. Sorafenib has been shown to induce apoptosis in various human tumor cell lines, including RCC [22].

A pooled analysis of four phase I trials confirmed that oral sorafenib was safe and was associated with clinically meaningful disease stabilization in patients with advanced cancers [23]. Continuous administration of oral sorafenib at a dose of 400 mg twice daily was found to be the MTD and was recommended for further investigation [24].

This dose was subsequently shown in a phase II randomized discontinuation trial to be well tolerated by patients with metastatic RCC ($n = 202$) [25]. The PFS interval was longer with sorafenib than with placebo upon randomization of patients with stable disease after 12 weeks of therapy ($p = .0087$; sorafenib median, 24 weeks versus placebo median, 6 weeks) [25]. The pivotal, randomized, placebo-controlled phase III Treatment Approaches in Renal cancer Global Evaluation Trial (TARGET) ($n = 903$) further evaluated sorafenib at a dose of 400 mg twice daily versus placebo in patients with cytokine-refractory RCC (Table 1) [18]. The PFS duration was significantly longer for the sorafenib group than for the placebo group (HR, 0.44; $p < .01$). The median PFS time was twofold longer for the sorafenib group than for the placebo group (5.5 months versus 2.8 months). The final overall survival data did not demonstrate a significantly lower risk for death with sorafenib (HR, 0.88; $p = .146$), but when patients who crossed over to sorafenib were censored, the survival analysis showed a significant difference (HR, 0.78; $p = .029$) [26].

In a phase II trial of first-line treatment with sorafenib (400 mg twice daily) versus IFN-α (9 MU 3 times weekly), sorafenib exhibited activity based on the disease control rate, but the primary endpoint (PFS) was not reached [27]. Other phase II studies evaluated combined treatment with sorafenib and IFN-α, which was found to exhibit a higher response rate than either agent alone, but toxicity limited further development of this regimen [28, 29].

The TARGET study, which was placebo controlled [18], provided an ideal opportunity to discriminate between drug-related toxicities and AEs associated with the RCC disease process. Most AEs were grade 1 or 2 in severity, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI CTCAE v 3.0) [30], and occurred within the first two cycles of sorafenib treatment [31]. Common AEs in the sorafenib group, but not the placebo group, were diarrhea, rash, fatigue, hand–foot syndrome, alopecia, and nausea. Bleeding (predominantly grade 1) was also more frequent with sorafenib (15%) than with placebo (8%), but the incidence of serious hemorrhage was similar in the two groups [18].

Grade 3 or 4 AEs occurred with similar frequency in patients receiving placebo (Table 2) [18]. For example, grade 3 or 4 anemia occurred in 3% of patients receiving sorafenib and in 4% of patients receiving placebo. Febrile neutropenia or grade 4 thrombocytopenia did not occur with sorafenib. Hypertension was the most frequent sorafenib-related AE and occurred in 1% of patients receiving sorafenib and in no patients on placebo. It was generally observed during the first treatment cycle. Hypertension was also the most frequent AE that led to hospitalization or death. Ischemia or infarction also were more frequent in patients receiving sorafenib, but the absolute numbers of events were low (12 patients [3%] versus two patients [1%], respectively); most of these patients had other cardiac risk factors [18]. Dose interruptions were most frequently a result of dermatologic reactions (hand–foot syndrome or rash) and gastrointestinal AEs, including diarrhea [18].

Treatment and Dose Adjustments

The recommended sorafenib dosing regimen for treating advanced RCC is 400 mg orally twice daily, at least 1 hour before or 2 hours after a meal [20, 27, 32]. No dose adjustment is required based on age, gender, or weight. Management of suspected adverse reactions to sorafenib may require temporary interruption and/or dose reduction [20]. When reduction is necessary, the dose may be reduced to 400 mg once daily. If additional dose reduction is required, sorafenib may be reduced to a single 400-mg dose every other day (Table 3). Sorafenib should be permanently discontinued in the event of gastrointestinal perforation, which is uncommon, or any bleeding event that requires medical intervention. Temporary interruption is recommended in patients undergoing major surgical procedures. Resumption of sorafenib therapy should be based on clinical judgment of adequate wound healing. Temporary or permanent discontinuation should be considered in patients who develop cardiac ischemia and/or infarction [20].

Sorafenib is metabolized primarily in the liver by the CYP system, particularly CYP3A4, as well as glucuronidation mediated by UGT1A9 [20]. Coadministration of strong CYP3A4 inducers decreased sorafenib plasma concentrations an average of 37% (Table 3) and should be avoided. A dose increase may be considered if a concomitant strong

CYP3A4 inducer is needed, but the patient should be monitored for toxicity. A specific dose increase has not been established. Based on drug-interaction studies in healthy volunteers, sorafenib metabolism is not altered by strong CYP3A4 inhibitors, so dose adjustment should not be necessary if coadministered with these agents. Sorafenib is also a competitive inhibitor of the CYP2B6 and CYP2C8 isozymes. Therefore systemic exposure to agents that are substrates of CYP2B6 and CYP2C8 should be expected to increase when coadministered with sorafenib. The effect of sorafenib on warfarin, assessed indirectly by measuring the prothrombin time–international normalized ratio in patients treated with sorafenib versus placebo, suggested that sorafenib did not inhibit warfarin metabolism [20].

Increased systemic exposure to various other antineoplastic drugs may occur if coadministered with sorafenib; therefore, caution is recommended [20]. These compounds include docetaxel, doxorubicin, and fluorouracil or compounds that are conjugated by UGT1A1 (e.g., irinotecan) (Table 3). Sorafenib had no significant effect on the pharmacokinetics of gemcitabine, oxaliplatin, or paclitaxel/carboplatin when tested with commonly used dosing regimens [20].

Although hepatic impairment may reduce the plasma concentration of sorafenib, the optimal dose in RCC patients with hepatic impairment is not established. No dosage adjustment is necessary when administering sorafenib to patients with mild, moderate, or severe renal impairment who are not undergoing dialysis; sorafenib has not been studied in patients undergoing dialysis [20].

Medical Management of Selected Toxicities

Hypertension. Patients with cancer, including those with RCC, who are treated with sorafenib have a significant risk of developing hypertension (relative risk, 6.1; 95% CI, 2.4–15.3; $p < .001$, compared with control treatments) [17]. Therefore, blood pressure monitoring and treatment, if needed, with antihypertensive therapy (agents acting on the renin–angiotensin system, beta-blocking agents, and calcium channel blockers) are recommended to prevent cardiovascular complications [20]. Patients should be monitored weekly for hypertension during the first 6 weeks of treatment and regularly thereafter [20]. Hypertension associated with sorafenib has been easily managed with antihypertensive therapy, and rarely leads to treatment discontinuation (<1%) [18, 19].

Skin Toxicity. Prescribing guidelines for the management of sorafenib-associated skin toxicities include topical therapies, temporary interruption and/or dose modification, or permanent discontinuation in severe or persistent cases [20]. Dermatologic symptoms usually occur within 6 weeks of sorafenib therapy and management varies according to presentation [20, 31]. Skin toxicities associated with sorafenib are generally reversible and resolved using topical therapies, temporary treatment interruption, or dose modification.

Sorafenib is associated with a significant risk of developing hand–foot syndrome (relative risk, 6.6; 95% CI, 3.7–11.7; $p < .001$, compared with control treatments) [33]. Early signs are tingling and numbness, with slight redness or a mild hyperkeratosis [31]. Clinical manifestations include painful, symmetrical, red, and swollen areas on the palms and soles; the lateral sides of the fingers or the periungual zones can also be affected [34]. If hand–foot syndrome progresses to grade 3, it is recommended that treatment be interrupted for 1–2 weeks combined with symptomatic treatment until symptoms return to grade 0–1 [20]. When treatment is resumed, the sorafenib dose should be decreased by one dose level. Patients may attempt the same dose with proper supportive care if toxicity has resolved. Upon the third occurrence of grade 3 symptoms, sorafenib should be discontinued [20].

Temsirolimus

Temsirolimus is a specific inhibitor of the mammalian target of rapamycin (mTOR complex 1) and is the first-in-class mTOR inhibitor for the treatment of RCC [35, 36]. Temsirolimus binds to an intracellular protein (FKBP-12), and the protein–drug complex binds to mTOR to inhibit its kinase activity [35]. In tumor cells, treatment with temsirolimus blocks the ability of mTOR to phosphorylate p70S6 kinase and S6 ribosomal protein, which are downstream of mTOR in the phosphatidylinositol 3′ kinase–AKT signaling pathway [37]. mTOR inhibition reduces levels of hypoxia-inducible factor (HIF)-1 and HIF-2α and VEGF in various in vitro tumor models, including RCC lines [38–40]. In preclinical tumor models, temsirolimus inhibited cell proliferation, cell growth, survival pathways, and tumor angiogenesis [40, 41].

Initial clinical studies in cancer patients investigated i.v. temsirolimus administered at dosages that were corrected for body surface area (mg/m^2) and were designed to establish tolerability, safety, and pharmacokinetic parameters [42, 43]. When administered as a 30-minute infusion once weekly, temsirolimus was well tolerated over a wide range of doses (7.5–165 mg/m^2) [42]. Rash and mucositis/stomatitis were the most frequent drug-related AEs, and thrombocytopenia was the main dose-limiting toxicity [42]. Antitumor activity was observed in heavily pretreated pa-

tients, including patients with advanced RCC, who received different doses and schedules [42, 43].

Temsirolimus is not a prodrug, although its main metabolite, sirolimus, also has mTOR inhibitory activity [14]. Exposure is considered to be a composite of temsirolimus plus sirolimus levels in whole blood. Pharmacokinetic analysis of i.v. temsirolimus dosages corrected for body surface area indicated that dose normalization did not improve variability in exposures over those of a flat dose [44]. Therefore, once-weekly flat dosing was subsequently used for phase II and III studies in patients with advanced RCC.

In the phase II RCC study, advanced RCC patients who had previously received, or were not candidates for, cytokine therapy were treated with 25 mg, 75 mg, or 250 mg i.v. temsirolimus as a once-weekly 30-minute infusion [44]. Although the objective response rate (complete response plus partial response) for the total population was only 7% (95% CI, 3.2%–13.7%), 51% of patients experienced clinical benefit defined as complete response, partial response, minor response, or stable disease lasting ≥24 weeks. Promising PFS and overall survival intervals were observed, particularly for patients with poor prognostic features who typically respond poorly to cytokine therapy. There were no differences among the three dose levels studied regarding PFS or overall survival [44].

Toxicity was similar across the three dose levels studied, but dose reductions and discontinuations were more frequent at the higher doses. Overall, the most frequent grade 3 or 4 temsirolimus-related AEs ($n = 110$) were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%) [44]. Six patients had possible nonspecific pneumonitis; five received temsirolimus at a dose of 75 mg and one received temsirolimus at a dose of 25 mg, suggesting a possible dose relationship [44]. Whole blood concentrations of temsirolimus following the lowest dose studied, 25 mg, are comparable with or higher than the temsirolimus concentrations needed for antitumor activity in tumor cells and in tumor xenografts [42, 44]. Thus, the 25-mg dose, which had optimal clinical efficacy and tolerability, was selected as the monotherapy dose for the phase III trial in patients with advanced RCC and poor prognostic features [44, 45].

The randomized phase III Global Trial for Advanced Renal Cell Carcinoma (Global ARCC Trial) compared temsirolimus, IFN-α, or the combination of these agents in previously untreated patients with advanced RCC and at least three of six poor prognostic features (Table 1) [45]. Poor prognostic features were defined as: (a) a lactate dehydrogenase level >1.5× the ULN, (b) a hemoglobin level less than the lower limit of normal, (c) a corrected calcium level >10 mg/ml, (d) <1 year from diagnosis to treatment, (e) a Karnofsky performance status score of 60 or 70, or (f) multiple organ sites of metastasis [45, 46]. Patients received i.v. temsirolimus at a dose of 25 mg once weekly, IFN-α at ≤18 MU s.c. thrice weekly, or i.v. temsirolimus at 15 mg once weekly plus IFN-α at 6 MU s.c. thrice weekly [45]. The dose selected for the combination regimen had been previously determined to be the MTD in a phase I study [47].

Temsirolimus as a single agent resulted in longer overall survival (HR for death, 0.73; 95% CI, 0.58–0.92; $p = .008$) and PFS ($p < .001$) times than with IFN-α. The overall survival duration in patients receiving the combination, although longer, did not differ significantly from that in patients receiving IFN-α (HR, 0.96; 95% CI, 0.76–1.20; $p = .70$). A significantly longer PFS time was seen with the combination ($p < .01$) than with IFN-α. The median overall survival intervals in the temsirolimus, IFN-α, and combination groups were 10.9, 7.3, and 8.4 months, respectively [45]. Among phase III trials of molecularly targeted agents in patients with advanced RCC, temsirolimus is the only agent to demonstrate a statistically significant survival benefit in intent-to-treat analyses.

Fewer patients experienced serious AEs in the temsirolimus group than in the IFN-α group ($p = .02$). The most frequent grade ≥3 AEs occurring in patients treated with temsirolimus alone are listed in Table 2. Hyperglycemia, hypercholesterolemia, and hypertriglyceridemia, all grades, were more common in patients receiving temsirolimus, alone or in combination, than in patients receiving IFN-α, reflecting the inhibition of mTOR-regulated glucose and lipid metabolism. Mild-to-moderate rash, peripheral edema, and stomatitis were also more common with temsirolimus than with IFN-α. Most AEs were manageable with medical intervention, supportive measures, or dose modifications [45].

Treatment and Dose Adjustments

The recommended dose of temsirolimus for patients with advanced RCC is 25 mg infused over 30–60 minutes once weekly; the dose should not be adjusted for body surface area [14]. Patients should receive pretreatment with prophylactic i.v. diphenhydramine at a dose of 25–50 mg (or other H_1 antihistamine) approximately 30 minutes before each dose of temsirolimus. If a patient develops a hypersensitivity reaction (e.g., anaphylaxis, dyspnea, flushing, chest pain), the infusion should be stopped for at least 30–60 minutes. At the physician's discretion, the infusion may be resumed at a slower rate (up to 60 minutes), approximately 30 minutes after administration of an H_1-receptor antagonist (e.g., diphenhydramine), if not previously administered, and/or an H_2-receptor antagonist (e.g., i.v. famotidine, 20 mg or i.v. ranitidine, 50 mg) [14].

Temsirolimus treatment may be interrupted or adjusted because of AEs (Table 3). Temsirolimus should be held for an absolute neutrophil count $<1{,}000/\mu l$, platelet count $<75{,}000/\mu l$, or NCI CTCAE v 3.0 grade ≥ 3 AEs [14]. When toxicities have resolved to grade ≤ 2, temsirolimus may be restarted at a dose reduced by 5 mg/week to no lower than 15 mg weekly. In the pivotal phase III study, most patients received close to the intended exposure to single-agent temsirolimus (mean actual dose intensity, 23.1 mg/wk, or 92% of the intended 25 mg/wk) [45], indicating that this dose of temsirolimus was well tolerated, even in patients with multiple poor prognostic features.

Patient characteristics such as age, gender, and race did not affect the pharmacokinetics and disposition of temsirolimus, and dosing should not be adjusted based on these factors [14, 48]. The influence of hepatic dysfunction and/or hepatic metastases on temsirolimus disposition has not yet been fully determined, but clearance of oral sirolimus is known to be 33% lower in patients with hepatic impairment or with the concomitant use of drugs that inhibit CYP3A4 [49, 50].

Temsirolimus and sirolimus are both substrates of CYP3A4; therefore, coadministration of strong CYP3A4 inhibitors or inducers should be avoided [14]. Agents that are strong CYP3A4 inhibitors (e.g., ketoconazole) may increase exposure to the metabolite sirolimus and should be avoided. A dose reduction to 12.5 mg should be considered if a strong CYP3A4 inhibitor must be coadministered (Table 3). This dose is predicted to adjust the area under the concentration–time curve to the range observed without inhibitors. If the strong inhibitor is discontinued, a washout period of about 1 week should be allowed before the dose is adjusted back to the dose used before the strong CYP3A4 inhibitor was initiated. In contrast, strong CYP3A4 inducers (e.g., phenytoin) may decrease exposure to the metabolite sirolimus, but temsirolimus exposure is not affected [14, 51]. If an alternative to the CYP3A4 inducer cannot be administered, pharmacokinetic studies indicate that increasing the temsirolimus dose from 25 mg to 50 mg should be considered (Table 3) [14]. Upon discontinuation of the strong CYP3A4 inducer, the temsirolimus dose should be returned to 25 mg or the dose used before the strong CYP3A4 inducer was initiated. Based on in vitro drug interaction data, clinically significant effects are not anticipated when temsirolimus at a dose of 25 mg is given with agents metabolized by CYP2D6 or CYP3A4 [14].

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Hyperglycemia. Close monitoring of fasting blood sugar and hemoglobin A_{1c} and early intervention of hyperglycemia are recommended for optimal patient management [52]. Hyperglycemia may be manifested as excessive thirst or increased urination volume or frequency, and may require diet modification and initiation, or a dose increase of insulin and/or oral agents for glycemic control such as sulfonylureas [14, 52].

Hyperlipidemia. Serum cholesterol and triglyceride levels should be tested at baseline and monitored during treatment [14, 52]. Hypertriglyceridemia and hypercholesterolemia are generally manageable with diet modification and initiation of lipid-lowering agents, based on the lipid profile.

Skin Toxicity and Stomatitis. Skin rashes associated with temsirolimus are mostly low grade, maculopapular in nature, and manageable with supportive measures such as fragrance-free moisturizers and possibly topical corticosteroids [52]. Hand–foot syndrome is not associated with temsirolimus treatment [14]. Stomatitis in patients receiving temsirolimus is typically mild, and supportive management includes oral hygiene, pain control, and hydration (i.v. fluid replacement) if severe [52].

Pneumonitis/Interstitial Lung Disease. Although infrequent, surveillance for pneumonitis/interstitial lung disease is warranted because of rare fatal cases reported in phase I and II trials. In the phase III trial, four (2%) of 208 patients treated with temsirolimus developed interstitial lung disease of varying severities (one patient grade 3 or 4) during study weeks 9–41 [52]. Monitoring may include chest x-ray, computed tomography scan, or pulmonary function tests (decreased diffusing capacity of the lung to carbon monoxide measurement on pulmonary function tests) [52]. Symptoms indicative of pneumonitis include pleural effusion, hypoxia, cough, dyspnea, and malaise in the absence of a nondrug cause.

Management guidelines are not yet established for patients who develop radiographic changes, with or without clinical respiratory symptoms indicative of interstitial lung disease, while on temsirolimus therapy. In the clinical trial experience, patients treated with temsirolimus who displayed radiologic changes but no symptoms continued temsirolimus treatment without dose reduction or interruption. Temsirolimus was temporarily interrupted in patients with radiologic changes and a few symptoms consistent with interstitial lung disease until these symptoms resolved. For patients with increasing clinical symptoms in conjunction with decreased pulmonary function, temsirolimus was discontinued and patients were treated with high-dose prednisone [52].

Bevacizumab

Bevacizumab is a humanized monoclonal antibody that inhibits VEGF. Unlike the other targeted therapies for RCC, bevacizumab dosing is adjusted for body weight. A randomized phase II study of bevacizumab monotherapy in patients with metastatic RCC showed a significantly longer time to disease progression with 10 mg/kg dosing given every 2 weeks than with placebo (HR, 2.55; $p < .001$) [53]. A lower bevacizumab dose (3 mg/kg given every 2 weeks) also exhibited a slightly longer time to disease progression, but had borderline significance compared with placebo (HR, 1.26; $p = .053$) [53].

Based on the results of a randomized phase III trial, bevacizumab in combination with IFN-α has been approved in Europe for the treatment of patients with metastatic RCC. The AVOREN trial compared bevacizumab (10 mg/kg every 2 weeks) and IFN-α (9 MU s.c. thrice weekly) with placebo and IFN-α in previously untreated patients with metastatic clear-cell RCC [54]. Compared with patients receiving IFN-α alone ($n = 322$), patients receiving bevacizumab plus IFN-α ($n = 327$) had a significantly longer PFS time (HR, 0.63; 95% CI, 0.52–0.75; $p = .0001$; bevacizumab plus IFN-α median, 10.2 months versus IFN-α median, 5.4 months), as well as a higher overall objective response (complete response plus partial response) rate (31% versus 13%; $p = .0001$) [54]. Preliminary results of a second phase III study, the Cancer and Leukemia Group B 90206 trial, support these findings of a PFS benefit of bevacizumab plus IFN-α over IFN-α alone [55]. Although overall survival was a secondary endpoint in the AVOREN trial, no survival benefit of bevacizumab plus IFN-α was detected [54].

Bevacizumab is approved in the U.S. for use in combination with 5-fluorouracil–based chemotherapy for the treatment of metastatic colorectal cancer, in combination with carboplatin and paclitaxel for the treatment of non-small cell lung cancer, and in combination with paclitaxel for the treatment of metastatic human epidermal growth factor receptor 2–negative breast cancer [56]. Thus, the safety profile of bevacizumab has been characterized when administered in combination with a range of chemotherapeutic agents. Bevacizumab has resulted in gastrointestinal perforation (sometimes fatal) and wound-healing complications. Other serious side effects in patients receiving bevacizumab with chemotherapy included nongastrointestinal fistula formation, strokes or blood clots, and hypertension [56]. There are no dose-reduction recommendations for the use of bevacizumab; if needed, bevacizumab should be either discontinued or temporarily suspended.

In the AVOREN trial, the most common grade ≥ 3 AEs were known IFN-α–associated toxicities (e.g., fatigue, asthenia, and neutropenia); bevacizumab-related toxicities included proteinuria, bleeding, and hypertension [54]. Among patients who received bevacizumab, four experienced grade 3 or 4 gastrointestinal perforations (three grade 4) and 10 experienced grade 3 or 4 thromboembolic events (four grade 4). Proteinuria, hypertension, and gastrointestinal perforation were the most common reasons for discontinuation of bevacizumab plus IFN-α [54]. A retrospective subgroup analysis suggested that patients who received dose-reduced IFN-α had a similar PFS duration as and better tolerability than those who received full-dose IFN-α [57]. Therefore, the dose of IFN-α can be reduced to manage side effects while maintaining efficacy in patients receiving bevacizumab plus IFN-α.

Everolimus

Everolimus (RAD001), a drug approved in Europe and other countries for the prevention of organ transplant rejection, is the second mTOR inhibitor to show activity in patients with RCC. Recent phase III data demonstrate that oral everolimus resulted in a longer PFS interval than with placebo (HR, 0.30; 95% CI, 0.22–0.40; $p < .0001$; median PFS time, 4.0 months versus 1.0 months) in patients with metastatic RCC who had progressed on VEGF-targeted therapies, including sunitinib, sorafenib, and bevacizumab [58]. This result further validates the importance of mTOR in the biology of advanced RCC and widens the range of patients who may benefit from mTOR-targeted therapy.

Hyperglycemia, hypercholesterolemia, hyperlipidemia, stomatitis, rash, and diarrhea were more common in the everolimus group than in the placebo group [58]. Pneumonitis was detected in 22 (8%) of 269 patients treated with everolimus, of whom eight had grade 3 severity pneumonitis. A direct comparison of toxicities associated with the two mTOR inhibitors, temsirolimus and everolimus, is complicated by a lack of head-to-head studies and the different study populations in the phase III trials. Given these caveats, the toxicities associated with everolimus appear, in general, to be similar in type and severity to those occurring in patients treated with temsirolimus [45, 52, 58]. A possible exception is the higher percentage of patients with pneumonitis reported in the everolimus trial, but the clinical relevance of this difference is not known.

Conclusion

The toxicities associated with the targeted therapies sunitinib, sorafenib, and temsirolimus for the treatment of

patients with RCC are well tolerated, given the benefits they provide. Treatment-related adverse reactions are mainly mild to moderate and are readily managed, in most cases, with medical treatment or supportive measures. Most cases of severe treatment-related adverse reactions are reversible and resolve after dose reduction or treatment interruption. Optimal treatment with these targeted agents requires proactive monitoring, early intervention, and appropriate management of side effects in order to avoid unnecessary dose reductions, interruptions, or even early treatment discontinuation.

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Targeted Therapies for Metastatic Renal Cell Carcinoma: An Overview of Toxicity and Dosing Strategies

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