Maximizing clinical outcomes with axitinib therapy in advanced renal cell carcinoma through proactive side-effect management

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Renal cell carcinoma (RCC) continues to exert a substantial disease burden. Increasing knowledge of the molecular signaling pathways associated with renal cancer has led to the development of targeted therapies for advanced RCC, including several antiangiogenic agents designed to inhibit development of abnormal blood vessels that sustain tumor growth. Axitinib is an investigational antiangiogenic agent that targets vascular endothelial growth factor receptors 1, 2, and 3. In phase II studies, axitinib elicited significant response rates in patients with advanced RCC refractory to cytokines or sorafenib. In a phase III study of axitinib versus sorafenib in patients with metastatic RCC, axitinib demonstrated clinically significant improvement in progression-free survival compared with sorafenib. As with other targeted agents, side effects associated with axitinib, such as hypertension, fatigue, and diarrhea, can negatively affect the patient's physical and emotional states and quality of life, thus jeopardizing adherence to and the effectiveness of the treatment plan. Clinicians should be aware of side effects that may occur during treatment and manage them proactively. Nurses should educate patients about possible side effects and their management before axitinib treatment is initiated. Management strategies include early reporting of the symptoms, regular clinic visits and laboratory tests, ongoing review of concomitant medications, and prompt treatment of side effects and follow-up to assess the effectiveness of interventions, which could include treatment interruption and/or dose reduction. These approaches would help maximize the patient adherence to therapy, quality of life, and clinical outcomes.

Approximately 60,920 individuals in the United States are expected to be diagnosed with cancer of the kidney and renal pelvis in 2011, with an estimated 13,120 dying from the disease.[1] One-third of patients will have metastatic disease at diagnosis, and between 25% and 50% of patients thought to be cured after partial or radical nephrectomy will develop metastatic disease.[2] The limited efficacy of cytokine-based therapies (interferon-alfa and interleukin-2) in metastatic renal cell carcinoma (RCC) has prompted the development of new compounds. Chemotherapy is generally of limited value and should be considered only for patients with relapsed or medically unresectable stage IV disease with non-clear-cell histology.[3] In recent years, several novel targeted therapies have been approved by the US Food and Drug Administration (FDA) for the treatment of advanced RCC. Many of these agents are designed to inhibit the abnormal development of tumor-associated blood vessels (pathological angiogenesis), a key driver of the growth and metastasis of RCC.[4] In this review, we describe these agents and discuss how the nursing professional and oncologist can help optimize their clinical use by managing side effects. We focus on the investigational agent axitinib (AG013736), a

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TABLE 1 Approved targeted therapies for RCC in the United States

Drug (brand name)	FDA approval date	Target	Indication
Sorafenib (Nexavar®)	2005	VEGFR, PDGFR, RAF, c-KIT	Advanced RCC
Sunitinib (Sutent®)	2006	VEGFR, PDGFR, c-KIT	Advanced RCC
Temsirolimus (Torisel®)	2007	mTOR	Advanced RCC
Everolimus (Afinitor®)	2009	mTOR	Advanced RCC after failure of sunitinib or sorafenib
Bevacizumab (Avastin®) in combination with interferon-alfa	2009	VEGF	Metastatic RCC with interferon-alfa
Pazopanib (Votrient®)	2009	VEGFR, PDGFR, c-KIT	Advanced RCC

Abbreviations: c-KIT, stem cell factor receptor; FDA, US Food and Drug Administration; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor

TABLE 2 Survival in pivotal clinical trials of targeted therapies for advanced renal cell carcinoma

Drug	Control	PFS (months)	OS (months)
Sorafenib[5]	Interferon-alfa	5.5 vs 2.8, $P < .01$	17.8 vs 15.2
Sunitinib[6,7]	Interferon-alfa	11.0 vs 5.0, $P < .001$	26.4 vs 21.8, $P = .051$
Temsirolimus[8]	Interferon-alfa	5.5 vs 3.1, $P < .001$	10.9 vs 7.3, $P = .008$
Everolimus[9,10]	Placebo	4.9 vs 1.9, $P < .001$	14.8 vs 14.4, $P = .162$
Bevacizumab + interferon-alfa (AVOREN)[11,12]	Interferon-alfa + placebo	10.2 vs 5.4, $P = .0001$	23.3 vs 21.3, $P = .336$ (38.6 vs 33.6, $P = .203$ in those who received VEGFR inhibitors after progression)
Bevacizumab + interferon-alfa (CALGB)[13,14]	Interferon-alfa monotherapy	8.5 vs 5.2, $P < .0001$	18.3 vs 17.4, $P = .097$
Pazopanib[15,16]	Placebo	9.2 vs 4.2, $P < .0001$	22.9 vs 20.5, $P = .224$

Abbreviations: OS, overall survival; PFS, progression-free survival; VEGFR, vascular endothelial growth factor receptor

novel, highly potent inhibitor of vascular endothelial growth factor (VEGF) receptor (VEGFR) with activity in refractory advanced RCC.

Targeted therapies for advanced RCC

Extensive efforts to understand the biology of renal cancer, the development of agents to target relevant signaling pathways, and the completion of over 20 clinical trials have resulted in the approval of six therapies for advanced RCC (Table 1). Efficacy seen with these targeted therapies has improved progression-free survival (PFS) rates and may provide the basis for changing the natural history of advanced renal cancer. Front-line clinical trials have demonstrated improvements in PFS to as long as 11.0 months and overall survival (OS) to beyond 3 years (Table 2).[5-16] Although improvement in survival has been significant, the limited complete responses observed with current therapies, the development of resistance or intolerance to first-line agents, and a need for effective therapies in the second-line setting reinforce the need for continued research to develop better therapies for advanced RCC.

Axitinib

Axitinib is an orally administered, second-generation selective inhibitor of VEGFR-1, -2, and -3 that stops VEGF-mediated endothelial cell adhesion and migration and induces endothelial apoptosis, which leads to decreased tumor blood flow, permeability, and survival.[17-19] Axitinib has a highly selective mechanism of action,[17] which may result in different clinical activity compared with other VEGFR inhibitors and provide a possible alternative for treatment-refractory patients.

Clinical studies of axitinib have been completed in patients with renal, thyroid, pancreatic, non-small cell lung, and colorectal cancers, as well as several hematologic malignancies. A phase I study evaluating the safety, clinical activity, and pharmacokinetics of axitinib tested doses of between 5 and 30 mg, administered orally twice daily in 36 patients with refractory nonhematologic malignan-

cies.[20] Partial responses to treatment were observed in 1 patient with adenoid cystic carcinoma and 2 patients with RCC. Axitinib was generally well tolerated, with dose-limiting toxicities that included hypertension, hemoptysis, and oral stomatitis. A dose of 5 mg twice daily was chosen for phase II studies. Because of the relatively short terminal half-life of axitinib (3-5 hours), twice-daily dosing is recommended to maintain effective plasma concentrations.[21] Axitinib can be administered without regard to food intake, based on pharmacokinetic studies.[22]

Several phase II studies have been conducted in patients with cytokine- or sorafenib-refractory advanced RCC, demonstrating an acceptable side-effect profile, a significant response rate, and a prolonged duration of therapy for some patients. Axitinib 5 mg twice daily was evaluated in 52 patients with cytokine-refractory metastatic RCC with clear-cell histology.[23] The agent showed efficacy in this patient population, which included 2 complete responses and 21 partial responses, resulting in an objective response rate of 44.2%. The median time to progression was 15.7 months (range, 8.4-23.4) and median duration of response was 23.0 months (range, 4.2-29.8). Several patients continued on axitinib treatment for more than 6 years with tolerable side effects.[24] Treatment options for metastatic RCC expanded with the approval of sorafenib and sunitinib, which increased the need to understand the efficacy of drugs given sequentially after patients have developed disease progression on initial or second-line treatment. Consequently, a phase II study of axitinib was completed in 62 patients with sorafenib-refractory metastatic RCC.[25] All of the patients had disease progression on sorafenib, with 74.2% having received 2 or more previous systemic treatments. Patients were treated with axitinib 5 mg twice daily and had dose titration to 7 mg or 10 mg twice daily if well tolerated or dose reductions for side effects. Dose titration to $>$ 5 mg twice daily was initiated in 53.2% of patients, and dose reductions to $<$ 5 mg twice daily occurred in 35.5% of patients. Axitinib therapy resulted in a 22.6% response rate, with 14 patients achieving a partial response, and a median duration of response of 17.5 months.[20]

In the phase III Axitinib (AG013736) as Second-Line Therapy for Metastatic Renal Cell Cancer: AXIS trial of axitinib and sorafenib in 723 patients with treatment-refractory metastatic clear-cell RCC, the median PFS was 6.7 months for patients in the axitinib arm, compared with 4.7 months for patients in the sorafenib arm ($P <$ .0001, independent review). The overall response rate by Response Evaluation Criteria in Solid Tumors (RECIST, independent reviewer assessment) was 19.4% for axitinib, compared with 9.4% for sorafenib, stable disease was 49.9% for axitinib and 54.4% for sorafenib, progressive disease was 21.6% for axitinib and 21.0% for sorafenib, and indeterminate response was noted in 6.1% for axitinib and 11.6% for sorafenib. PFS analysis by prior regimen showed that the greatest difference between the arms was in the cytokine-refractory subgroup (n = 251), where axitinib PFS was 12.1 months, compared with 6.5 months for sorafenib ($P <$ .0001).

The most common treatment-related side effects in the phase II studies included diarrhea, hypertension, fatigue, and hand–foot syndrome (Table 3). Other side effects included bleeding (epistaxis and hematuria), thromboembolic events, congestive heart failure, and proteinuria, all of which emphasizing the importance of early assessment and intervention to minimize the potential negative impact of side effects on efficacy and quality of life.[23,25]

The phase III toxicity profile is similar to that of the phase II studies (Table 3), and common treatment-emergent adverse events by type are presented in Table 4. In the phase III AXIS trial,[26] treatment-emergent adverse events that were more common (defined as $\geq$ 10% difference between the arms) with axitinib than with sorafenib included hypertension (40% vs 29%, respectively), nausea (32% vs 22%), dysphonia (31% vs 14%), and hypothyroidism (19% vs 8%); those more common with sorafenib than with axitinib included palmar-plantar erythrodysesthesia (51% vs 27%), alopecia (32% vs 4%), and rash (32% vs 13%). Hematologic toxicities were generally mild in phase II and III studies (Table 5).

Issues to consider before initiating treatment

The toxicity profile of axitinib is consistent with that of other VEGF inhibitors. Since the pattern of side effects with axitinib is variable, the probability of predicting which toxicities will occur or be most troublesome in an individual patient is very low. Detailed baseline assessment of preexisting comorbid conditions, disease-related symptoms, type and duration of previous treatment, type and severity of previously experienced side effects and their level of management by the patient, and concomitant medications will provide the nurse and oncologist with valuable insight into which axitinib-related side effects might require more intensive monitoring and management. This information will assist the clinician in determining the appropriate timing of appointments, especially during the first few cycles of treatment. Patients with significant disease-related symptoms or complex comorbid conditions will benefit from more frequent telephone and clinic assessments. Involvement of the patient's spouse and family members will facilitate appropriate monitoring and management of side effects, and early communication with the oncology team at the onset of side-effect symptoms will minimize their severity and pos-

TABLE 3 Common (>15%) axitinib adverse events in patients with metastatic renal cell carcinoma

	Phase II studies				Phase III study[b]			
	Cytokine-refractory[23]		Sorafenib-refractory[25]		TKI-refractory[51]			
	Axitinib (n = 52)		Axitinib (n = 62)		Axitinib (n = 359)		Sorafenib (n = 355)	
	Grade of adverse events, % patients							
Adverse event[a]	**All**	**3/4**	**All**	**3/4**	**All**	**3/4**	**All**	**3/4**
Diarrhea	60	10	61	15	55	11	53	7
Hypertension	58	14	45	16	40	16	29	11
Decreased appetite	NR	NR	NR	NR	34	5	29	4
Nausea	44	0	44	7	32	3	22	1
Dysphonia	NR	NR	37	0	31	0	14	0
Fatigue	52	8	77	16	29	11	32	5
PPE/HFS	8	NR	36	16	27	5	51	16
Decreased weight	27	0	31	5	25	2	21	1
Anorexia	35	2	48	0	NR	NR	NR	NR
Vomiting	21	0	32	5	24	3	17	1
Asthenia	NR	NR	NR	NR	21	5	14	3
Constipation	14	0	26	0	20	1	20	1
Hypothyroidism	NR	NR	18	0	19	<1	8	0
Cough	NR	NR	29	0	15	1	17	1
Mucosal inflammation	NR	NR	34	2	15	1	12	1
Arthralgia	14	2	27	3	15	1	11	1
Stomatitis	17	2	18	5	15	1	12	<1

Abbreviations: HFS, hand–foot syndrome; NR, not reported; PPE, palmar-plantar erythrodysesthesia; TKI, tyrosine kinase inhibitor
[a] The phase II studies reported treatment-related adverse events; the phase III study reported treatment-emergent adverse events; [b] This was a comparative effectiveness trial of axitinib versus sorafenib

TABLE 4 Axitinib most common (all grades ≥15%) treatment-emergent, all-causality adverse events by type in phase III study[51] of patients with metastatic renal cell carcinoma

General type of side effect	Specific side effect
Gastrointestinal	**Diarrhea, decreased appetite, nausea, mucosal inflammation, vomiting, weight decrease, stomatitis, constipation**
Cardiac	**Hypertension**
Constitutional	**Fatigue, asthenia**
Pulmonary	**Dysphonia, cough**
Dermatologic	**Palmar-plantar erythrodysesthesia**
Pain	**Arthralgias**
Endocrine	**Hypothyroidism**

Side effects in bold are those that occurred in >30% of patients

sible emergencies. Assessment of adherence to previous medications, the patient's attitude to the disease and motivation toward treatment, the level of support from family and friends, and other factors important for the patient's quality of life will provide the oncology practitioner with valuable information for initial and ongoing patient education.

Concomitant medications

A detailed review of the patient's current prescription and over-the-counter medications, vitamins, supplements, and similar products will allow the clinician to review and discuss the potential for food– and drug–drug interactions with the patient, while informing the oncology team about any changes in the medications or the initiation of new medications or products. For example, drug–drug interactions may occur with axitinib and cytochrome P-450 (CYP) inhibitors and inducers through the metabolism of axitinib by CYP3A enzymes in the liver (with minor contributions from CYP2C19).[21,27] Thus, coadministration of axitinib with CYP inhibitors or inducers

TABLE 5 Laboratory abnormalities reported for axitinib in patients with renal cell carcinoma

	Phase II studies				Phase III study[b]			
	Cytokine-refractory[23]		Sorafenib-refractory[25]		TKI-refractory[51]			
	Axitinib (n = 52)		Axitinib (n = 62)		Axitinib (n = 359)		Sorafenib (n = 355)	
	Grade of abnormality, % patients							
Abnormality[a]	All	3/4	All	3/4	All	3/4	All	3/4
Anemia	62	8	64[d]	0[d]	35	<1	52	4
Lymphopenia	0[c]	0[c]	66[d]	16[d]	33	3	36	4
Thrombocytopenia	28[c]	0[c]	20[d]	0[d]	15	<1	14	0
Leukopenia	14[c]	0[c]	14[d]	0[b]	NR	NR	36	4
Neutropenia	16[c]	0[c]	11[d]	0[d]	6	1	8	1
Proteinuria	8	0	5[e]	0[e]	NR	NR	NR	NR
Erythrocytosis	4	0	5[e]	0[e]	NR	NR	NR	NR
Elevated creatinine	4	0[e]	8[e]	2[e]	55	0	41	<1

Abbreviations: NR, not reported; TKI, tyrosine kinase inhibitor
[a] The phase II studies reported treatment-related adverse events; the phase III study reported treatment-emergent adverse events; [b] This was a comparative effectiveness trial of axitinib versus sorafenib; [c] Evaluable patients for each hematologic event were as follows: anemia, n = 50; thrombocytopenia, n = 50; leukopenia, n = 50; and neutropenia, n = 51; [d] Data for eight patients were not evaluable as laboratory values were outside the National Cancer Institute Common Toxicity Criteria grading scale (thrombocytopenia, n = 2; leukopenia, n = 1; and neutropenia, n = 5). Therefore, total numbers of patients evaluated for each hematologic event were as follows: anemia, n = 56; lymphopenia, n = 55; thrombocytopenia, n = 56; leukopenia, n = 56; and neutropenia, n = 55; [e] Pfizer Inc. data on file

may alter systemic exposure to axitinib and affect its safety and/or pharmacokinetic profile. Blood levels of axitinib are known to be elevated during concurrent administration of the antifungal agent ketoconazole (CYP inhibitor)[27] and decreased by the antibiotic rifampin (rifampicin, CYP inducer);[21] consequently, axitinib dosage may need adjustment in patients receiving such medications. Individual drugs are evaluated for possible drug–drug interactions, and databases are revised as new interactions are identified. Clinicians' ongoing review of a drug's package insert and interactions with pharmacy staff regarding potential interactions are critical.

Axitinib-related hypertension

Hypertension has been observed with many of the VEGFR inhibitors and is considered a "class effect" of these therapies. Hypertension was the primary dose-limiting toxicity observed in the phase I study of axitinib and appears to be dose-dependent. No consistent shifts in renin, angiotensin II, and aldosterone were seen, suggesting that hypertension with axitinib therapy is not mediated through alterations of the renin–angiotensin–aldosterone pathway.[20] Hypertension is considered by some to be a mechanism-dependent toxicity, reflecting effective inhibition of the VEGF signaling pathway.[28-30] The inhibition of blood vessel growth and permeability seen with anti-VEGF therapies is accompanied by hemodynamic effects that impact peripheral vascular resistance, although the precise mechanism remains unclear.[31] Therefore, increase in blood pressure during treatment with antiangiogenic agents may serve as a biomarker for effective drug dosing to ensure inhibition of the VEGF pathway.[28] Hypertension as a predictor of response to treatment is supported by clinical data from studies of sunitinib[32] and axitinib.[33] However, this association yet to be demonstrated conclusively; an ongoing prospective, randomized phase II clinical trial of axitinib is investigating this hypothesis. A prospective phase II study[30] specifically looking at axitinib-induced increases in blood pressure on days 4 and 15 of treatment found that onset occurred early, by day 4, and remained consistent 2 weeks after initiation of axitinib therapy, thus supporting early monitoring and management of blood pressure. The observed blood pressure responses appeared to be independent of axitinib plasma concentrations.

Preexisting hypertension

Control of preexisting hypertension before the initiation of axitinib therapy, through antihypertensive medication and/or lifestyle changes, may minimize the risk of developing early-onset, treatment-related hypertension. Detailed baseline cardiac assessment, pretreatment control of hypertension, and ongoing assessment and management of cardiac status are important components of treatment with antiangiogenic therapies.[34,35] A consensus report included recommendations on initial assessments, surveillance, and management of hypertension in patients receiving VEGF-pathway inhibitors (Table 6).[36]

TABLE 6 Recommendations for hypertension associated with vascular endothelial growth factor (VEGF) inhibitor therapies

1. Conduct and document a formal risk assessment for potential cardiovascular complications.
2. Recognize that preexisting hypertension should be identified and controlled before initiation of VEGF inhibitor therapy.
3. Confirm adherence to antihypertensive medication regimen.
4. Actively monitor blood pressure during treatment, with more frequent assessments during the first cycle of treatment.
5. Manage blood pressure with a goal of <140/90 mm Hg for most patients, considering a lower goal in patients with preexisting cardiovascular risk factors.
6. Maximize dose of each antihypertensive agent, adding agents based on cardiovascular risk and comorbid conditions.
7. Antihypertensive agents include ACE inhibitors, ARBs, diuretics, and beta-blockers. Each agent/class has characteristics to be considered in relation to comorbidities and drug–drug interactions.
8. Dietary and exercise recommendations appropriate for the patient's clinical condition and comorbidities. Physical therapy referral to increase activity for patients with pain or physical limitations.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker
Adapted from Maitland et al[36]

TABLE 7 Information to include in a patient information packet on axitinib

Treatment information regarding axitinib drug formulation and dosing
Information regarding possible food and drug interactions and other precautions to consider with axitinib therapy
Possible side effects, prevention, and early management strategies. This should include a discussion regarding which side effects may be prevented or less severe with prophylactic management (ie, initiation of oral and skin-care regimens prior to start of treatment)
Contact information for the nurse, oncologist, and other health-care team members, including who (and how) to contact when the office is closed. Emphasize the importance of early communication with the nurse/oncologist as side effects develop.
Specific instructions regarding home monitoring of blood pressure
Daily log to record the day, dose, and time of drug administration, along with space to document side effects and blood pressure measurements

Patient education

The oncology nurse has an important role to play in educating patients and family members about the possible side effects that may occur during axitinib treatment and how to cope with these side effects should they occur. As with other oral therapies, education at the initiation of treatment is key to raising patients' vigilance and awareness of side effects, with an emphasis on early recognition and reporting to the nurse or oncologist. Implementation of a timely, proactive approach to patient education about axitinib-related side effects might have several benefits. In addition to encouraging early identification and therefore intervention, this approach may result in greater patient satisfaction with treatment, improved adherence and persistence with treatment, and potentially improved clinical outcome as patients are able to remain on the highest tolerated dose. As part of the side effect–management strategy, the nurse should provide patients with an information packet before treatment that includes a list of potential side effects and how they may be managed. Table 7 lists the information that should be included in the packet.

The nurse's role during treatment

Oncology nurses play a key role in the management of side effects during treatment, maximizing the patient's active involvement in their treatment and providing an interface between the patient and the clinical team. Thus, it is important for nurses to understand how treatment-related side effects impact patients in their daily routine, including work, home, and social activities. The management by clinicians of side effects associated with targeted therapies for metastatic RCC has been reviewed extensively elsewhere,[37-43] and many of these same approaches could be applied for axitinib. Clinic visits and laboratory investigations should be conducted regularly, more frequently for patients with significant disease-related symptoms or multiple comorbid conditions. Side effect–management strategies are numerous and include the adjustment of current medications, addition of new medications and

TABLE 8 General management guidelines for common side effects of axitinib therapy[a]

Side effect	Management strategies
Diarrhea	Baseline assessment: frequency, consistency of stool, laxative or stool softener use; opioid use Monitor frequency and consistency of bowel movements: note changes from baseline Dietary modifications: avoid high-fat and gas-producing foods, milk products, cold foods/liquids Maximize fluid and electrolyte intake: use of salty soups, beverages such as Pedialyte, and Gatorade Antidiarrheal agents (loperamide, diphenoxylate/atropine, tincture of opium) Bulking agents (Benefiber® tablets) Probiotics (Activia®, Align®) Pancreatic enzymes Dose interruption or reduction, as necessary
Hypertension	Baseline assessment of blood pressure Educate patient and family members on how to measure blood pressure and to ensure proper fit of the cuff Maximize blood pressure control prior to initiation of axitinib with antihypertensive agents Verify accuracy of home blood pressure kit Review blood pressure diary sheet Dietary management: DASH Diet (Dietary Approaches to Stop Hypertension)[b] Cardiology consult for difficult-to-manage hypertension
Fatigue	Baseline assessment of activity level and comorbid conditions that may limit activities Baseline and ongoing monitoring of thyroid function lab tests (TSH, T3, T4/FTI) Pace work and social activities, if appropriate Encourage acceptance of help from others
Hypothyroidism	Baseline TSH, T3, T4/FTI testing, repeating every 10–12 weeks for new or existing hypothyroidism Initiate levothyroxine for patients with elevated TSH level and low T4 level or for patients with subclinical and symptomatic hypothyroidism Adjust levothyroxine based on lab results
Anorexia and weight loss	Baseline assessment of oral cavity Dental exam and cleaning, if not done in the previous 6 months Small, frequent meals to maximize calorie intake Provide written information and Web sites to assist in maximizing calorie intake Supplements Nutritional consult
Dermatologic side effects	Baseline assessment of skin: presence of dry skin, rash, callus formation Education regarding skin care prior to initiation of axitinib Appropriate shoes with support and cushioning to minimize friction Frequent application of topical moisturizers Podiatry consult
Dysphonia (hoarseness)	Educate patient that this may occur, is usually mild, and is reversible Maximize fluid intake, use of lozenges

Abbreviations: FTI, free thyroxine index; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone
[a] This list is not all inclusive and is based on the clinical experience of the authors. Efficacy of recommended interventions has not been measured; [b] http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf

supportive care products, and, lastly, treatment interruption and/or dose reduction if warranted.

In our experience, the side effects associated with targeted therapies can usually be managed effectively with minimal impact on patients' quality of life by the strategies outlined above (patient education, early reporting, monitoring, and treatment). The same general principles and considerations apply to the management of toxicities emerging during treatment with axitinib (Table 8).

Hypertension

Hypertension is generally manageable with early and ongoing assessment, appropriate use of antihypertensive medications, and treatment interruption for severe cases. Patients receiving VEGFR inhibitors should have their blood pressure monitored regularly, with consideration given to initiation of antihypertensive medication or adjustment of existing medication for elevated readings (≥ 150/90 mm Hg). Multiple antihypertensive drugs may often be required for optimal management of hypertension. There should be ongoing review of concomitant medications and the patient's adherence to the treatment plan.

Fatigue

Fatigue may occur during treatment with targeted agents, including axitinib. The National Cancer Comprehensive Network (NCCN) advocates four types of intervention before treatment initiation for fatigue that

is not related disease progression: patient education and counseling, general strategies for coping (self-monitoring, energy conservation, and distraction), nonpharmacologic interventions (activity enhancement, psychosocial interventions, attention-restoring therapy, nutritional consultation, sleep therapy), and pharmacotherapy (psychostimulants such as methylphenidate and modafinil for depression, treatment for anemia, or sleep medication).[44]

Severe fatigue may be linked to the development of hypothyroidism, which is not common in the studies of axitinib in patients with RCC, but has been associated with axitinib and other VEGFR inhibitors.[45] Administration of thyroid hormone–replacement therapy to prevent severe fatigue related to axitinib treatment was reported in a phase I study with Japanese patients with solid tumors.[46] Consequently, proactive management of axitinib-related severe fatigue should involve regular monitoring of thyroid-stimulating hormone (TSH) levels and the use of thyroid hormone–replacement therapy, as needed, to maintain a euthyroid state (Table 8). Thyroid hormone–replacement therapy is recommended in patients with overt hypothyroidism (defined as an elevated TSH level and a low thyroxine level) and symptoms consistent with hypothyroidism.[47,48] It has been suggested that thyroid dysfunction associated with VEGFR inhibitors may be a marker of treatment efficacy, rather than an unwanted side effect.[49,50]

Diarrhea

Diarrhea as a side effect of axitinib therapy requires early and ongoing evaluation of interventions. Aggressive management strategies for diarrhea include dietary modification, use of antidiarrheal agents, maximization of fluid intake and electrolyte balance, frequent communication with the health-care team to modify interventions as appropriate, and possible treatment interruption or dose reduction. These strategies can reduce the need for drug discontinuation and increase adherence to the treatment plan.

Dysphonia

Dysphonia has been reported in patients receiving axitinib treatment and can manifest as a hoarse or weak voice or as an excessively breathy, rough, or harsh voice; but in general, some level of phonation is possible. In a phase III trial comparing axitinib and sorafenib in RCC, dysphonia occurred in 31% of patients receiving axitinib (grades 1 or 2, no grades 3 and 4). There are no evidence-based interventions for the treatment of axitinib-induced dysphonia. It seems to be intermittent, and patients are advised to maintain adequate hydration and use lozenges to help minimize the effects of the disorder. Education about dysphonia and emotional support for the patients and their families is also recommended.

Dose modification

As mentioned previously in this article, the occurrence of severe side effects may warrant dose interruption and/or dose reduction to minimize their impact on the patient's quality of life. In the phase II/III RCC trials, axitinib was administered initially at a dosage of 5 mg twice daily with dose titration to 7 mg or 10 mg twice daily in patients who did not experience any severe treatment-related side effects for at least 2 weeks and whose blood pressure was $\leq$ 150/90 mm Hg without the use of antihypertensive medication. Conversely, axitinib dosage was reduced to 3 mg twice daily and then to 2 mg twice daily in patients who developed severe side effects and in patients with 2 readings of systolic blood pressure $>$ 150 mm Hg or diastolic blood pressure $>$ 100 mm Hg who were receiving maximal antihypertensive therapy. Axitinib dosing was interrupted in patients with severe side effects or who had two readings of systolic blood pressure $>$ 160 mm Hg or diastolic blood pressure $>$ 105 mm Hg. Dosing was resumed at one lower dose level after the side effects had reduced in severity and blood pressure was $<$ 150/100 mm Hg. Based on the pharmacokinetic profile of axitinib, particularly the short half-life, dose reduction should be made while ensuring twice-daily administration.[21]

Conclusions

The plethora of novel targeted agents recently developed to treat patients with advanced RCC now offers more therapeutic options than in the past. Although these newer agents generally elicit better responses compared with cytokine-based therapies, treatment for most patients consists of sequential therapy with chronic side effects that wax and wane, requiring ongoing management and adjustment of interventions to minimize the negative impact of chronic treatment. Side effects occurring with targeted therapies are generally different from those observed with immunotherapy and chemotherapy. Oncologists and oncology nurses must learn new strategies and interventions to minimize the potentially negative impact of these side effects and to avoid unnecessary treatment interruptions, dose reductions, and treatment discontinuation for reasons other than lack of efficacy. The side effects associated with axitinib are generally moderate and manageable. The improvement in PFS and OS reported for axitinib is worth the investment of time and effort needed to maximize clinical outcome and quality of life for patients with advanced RCC. Those caring for patients with advanced RCC should understand and

proactively manage the side effects that may occur with targeted therapies such as axitinib. During clinical assessment, the oncology team must inquire about and identify treatment-related side effects and then initiate and evaluate appropriate interventions. It is important to prevent side effects from limiting dosage or treatment since patients will obtain maximal benefits only at the recommended dose and schedule. Health-care providers have opportunities to enhance clinical outcomes and quality of life for patients with advanced RCC, and nurses have important roles in ensuring that patients achieve the maximal benefit from each targeted therapy. Emphasis on pretreatment education, early identification and assessment of side effects, and ongoing evaluation and modification of management strategies, should effectively optimize the benefits of therapy and the patient's quality of life.

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