

# Renal Cell Carcinoma

## Today's Targeted Therapies Improving Tomorrow's Outcomes

A continuing education newsletter offered free of charge to nurses

*This educational activity is based on a symposium offered in conjunction with the Oncology Nursing Society's 30th Annual Congress.*

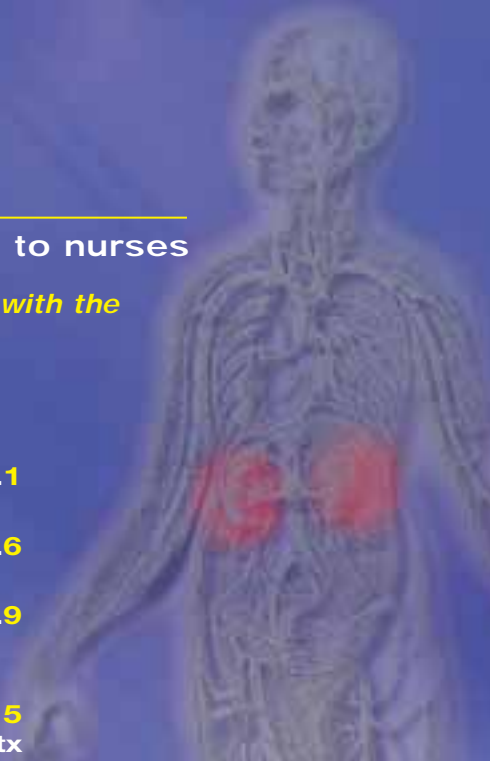
### Contents

**Renal Cell Carcinoma: Risk, Diagnosis, and Staging** .....1  
*Janice P. Dutcher, MD*

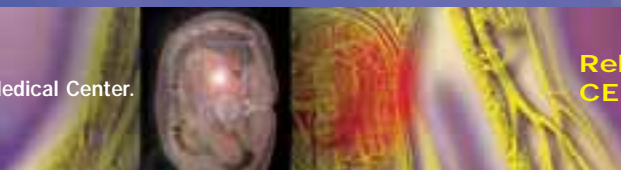
**Current and Emerging Treatments for Renal Cell Carcinoma** .....6  
*Robin I. Green, MSN, FNP-C, OCN*

**Managing Side Effects of Targeted Therapy and Ensuring Access to Treatment** .....9  
*Susan H. Moore, RN, MSN, ANP, AOCN*

**Learning Assessment and Evaluation** .....14-15  
Also available online at <http://www.meniscus.com/eval/rcc-targeted-tx>



The image of the CT scan is courtesy of Todd Blodgett, MD, University of Pittsburgh Medical Center.



Release date: September 2006  
CE available until: September 2007

## Introduction

At a symposium held in May of 2006, in conjunction with the Oncology Nursing Society 30th Annual Congress, three oncology experts—Robin I. Green, MSN, FNP-C, OCN, from Kaiser Permanente Riverside, Riverside, California; Janice P. Dutcher, MD, from the Comprehensive Cancer Center at Our Lady of Mercy Medical Center, Bronx, New York; and Susan H. Moore, RN, MSN, ANP, AOCN, from Rush University Medical Center, Chicago, Illinois—addressed an audience of oncology nurses regarding the care of patients with renal cell carcinoma (RCC). During the symposium, the speakers presented an up-to-date overview of this disease and discussed currently available and promising new treatments, providing advice on managing treatment side effects and other issues faced by patients. This newsletter summarizes the key elements of those presentations and supplements them with more current data presented at the 42nd annual meeting of the American Society of Clinical Oncology (ASCO), held June 2–6, 2006, in Atlanta, Georgia.

## Renal Cell Carcinoma: Risk, Diagnosis, and Staging

*Janice P. Dutcher, MD*

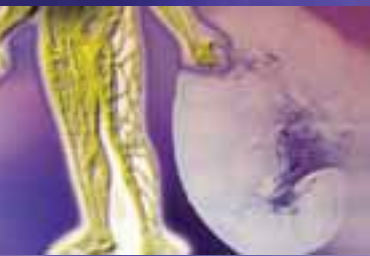
Renal cell carcinoma (RCC) is increasing in frequency in both men and women.<sup>1</sup> The age-adjusted rate for males rose from 10 per 100,000 in 1973 to 14 per 100,000 in 1995; similarly, the rate among females rose from 4 per 100,000 in 1973 to 6.5 per 100,000 in 1995. As the tenth most common malignancy, RCC represents 2.6% of adult cancers and occurs more frequently in males than females in a 1.6:1 ratio.<sup>2</sup> The usual age at diagnosis is 50 to 70 years.

### Known Risk Factors

A number of environmental risk factors for RCC have been identified.<sup>3</sup> Cigarette smoking is associated with a 20% to

*(continued on page 4)*

Janice P. Dutcher, MD, is Associate Director for Clinical Affairs and Professor of Medicine at the Comprehensive Cancer Center at Our Lady of Mercy Medical Center, a University Hospital of New York Medical College, in Bronx, New York.



# Renal Cell Carcinoma

Today's Targeted Therapies Improving Tomorrow's Outcomes

## Target Audience

The target audience for this newsletter is oncology and urology nurses who provide care to patients with renal cell carcinoma (RCC) and other nurse clinicians interested in learning more about treatments for RCC.

## Activity Rationale and Purpose

This newsletter is intended to provide nurses with an understanding of the mechanisms of action and side effects for standard and targeted therapies. Targeted therapies approved for RCC include small-molecule multikinase inhibitors (sunitinib and sorafenib). Investigational agents currently under study, some in combination with standard therapies, include anti-VEGF antibodies (bevacizumab), anti-epidermal growth factor receptor antibodies, and small-molecule inhibitors. When nurses understand this information and apply it to daily practice, they will more effectively communicate to patients the “how and why” of targeted therapies.

## Learning Objectives


After participating in this activity, nurses should be able to

- Describe renal cell carcinoma (RCC) epidemiology, clinical presentation, diagnostic evaluation, differential diagnosis, and staging
- Discuss recommended treatments for each stage of RCC, including current and emerging therapies
- Recognize major side effects and toxicities related to treatments and implement guideline-based supportive care strategies to manage these and other RCC disease-related complications
- Identify patient challenges related to RCC prescription access and cost, and provide resources for underinsured or uninsured patient assistance

When choosing among continuing education activities, clinicians should select those that are appropriate for their educational needs. Participants in educational activities have the implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional effectiveness. Clinicians should reflect on this activity and its applicability to their own patient population, and then identify and implement appropriate practice changes.

## Continuing Education

**Statement of Credit.**—Participants who successfully complete this activity (including completion and submission of the evaluation form) will be issued a statement of credit via e-mail or US mail within 4 weeks.

 This activity for 1.1 contact hours is provided by the Meniscus Educational Institute.

The Meniscus Educational Institute is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.



Provider approved by the California Board of Registered Nursing, Provider No. 13164, for 1.1 contact hours.

## Faculty Disclosures

All faculty are expected to disclose any real or apparent conflicts of interest that may have a direct bearing on the subject matter of this continuing education activity. Participants have the responsibility to assess the impact (if any) of the disclosed information on the educational value of the activity. All faculty have been offered a modest honorarium from the accredited provider for their participation in this activity.

**Janice P. Dutcher, MD**, is on the speakers bureau for Chiron Corporation. She receives grant and research support from Chiron Corporation, Bayer Pharmaceuticals Corporation, Pfizer Inc, and Genentech, Inc. Dr Dutcher is also a consultant for advisory boards for Bayer Pharmaceuticals Corporation, Genentech, Inc, and Wyeth.

**Robin I. Green, MSN, FNP-C, OCN**, is a consultant for advisory boards for Bayer and Onyx Pharmaceuticals, Inc.

**Susan H. Moore, RN, MSN, ANP, AOCN**, is on the speakers bureau for Roche Laboratories. She is also a consultant for advisory boards for Roche Laboratories.



## Product Disclosure

Reflecting standard oncology practice, which often requires the off-label or investigational use of some products, this educational activity includes information about many drugs. All faculty participating in continuing education activities are expected to disclose the approved or investigational status (related to the subject matter of this activity—renal cell carcinoma [RCC]) of all products and devices under discussion. This information, as of the time of printing, is summarized briefly in the table below. In addition, primary references and full prescribing information should be consulted for complete information. Clinicians have the professional responsibility to ensure that drugs are prescribed and used appropriately, based on their own clinical judgment and accepted standards of care.

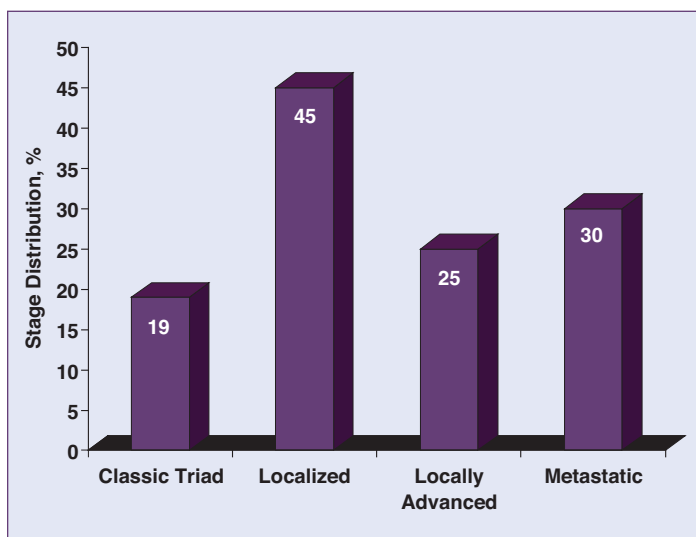
Generic Name	Brand Name	Investigational for the Treatment of Renal Cell Carcinoma	FDA Approved for the Treatment of Renal Cell Carcinoma	FDA Approved for Other Indications
Aldesleukin (IL-2)	Proleukin		✓	✓
Axitinib (AG-013736)		✓		
Bevacizumab	Avastin	✓		✓
Clindamycin	Cleocin			✓
Diltiazem	Various			✓
Erlotinib	Tarceva	✓		✓
Interferon	Roferon-A	✓		✓
Ketoconazole	Nizoral			✓
Loperamide	Imodium			✓
Prochlorperazine	Compazine			✓
Rifampin	Various			✓
Sorafenib	Nexavar		✓	
Sunitinib	Sutent		✓	
Temsirolimus (CCI-779)	NA	✓		
Thalidomide	Thalomid	✓		✓
Verapamil	Various			✓

Adapted from *Drug Facts and Comparisons*. St Louis, Mo: Facts & Comparisons; 2006. Agents may be approved for use in combination.

30% increased risk of developing RCC. Other weaker but consistent risk factors include obesity, diabetes, and hypertension. Exposure to heavy metals (eg, cadmium), gasoline, petroleum products, thorium oxide, and chronic radiation have also been implicated. People engaged in occupations such as leather tanning and shoe making that involve the use of solvents and heavy metals seem to also have a higher risk of developing RCC. According to anecdotal experience, occupations like firefighting that expose individuals to high levels of smoke may also pose an increased risk of developing RCC. Patients on chronic hemodialysis sometimes develop acquired cystic disease that may progress to RCC. Despite the identification of these numerous risk factors, many patients present with RCC without any known risk factors, indicating that much remains to be understood about the factors that trigger the development of this disease.

## Clinical Presentation

The classic triad of symptoms, a palpable mass, flank pain, and hematuria is uncommon and occurs in only about 19% of patients at presentation (Figure 1).<sup>4</sup> The presence of all 3 of these symptoms usually indicates advanced stage disease. Since almost half of patients are diagnosed with disease localized to the kidney, the presence of RCC is often asymptomatic. Some patients are diagnosed coincidentally, such as an abnormality seen on an X-ray, CT scan, or ultrasound performed for another purpose (eg, a gall bladder evaluation). Other signs at presentation include asymptomatic hematuria or one or more paraneoplastic symptoms that are associated with a poorer prognosis, such as fever, weight loss, anemia, and night sweats. Localized kidney tumors range in size from a few centimeters to up to 15 cm. A quarter of patients with RCC have locally advanced



**Figure 1.**—Distribution of stage or initial clinical presentation at diagnosis. (From Lineham et al.<sup>4</sup>)

disease at diagnosis such as lymph node involvement or extension outside of the kidney, into the fatty tissue or even the muscle surrounding the kidney. One third of patients have metastatic disease at presentation.

Anemia, hypercalcemia, hematuria, bone pain, spinal cord compression, and brain metastases are clinical signs and symptoms of kidney cancer that require interventional palliative care, and anemia is the most common blood disorder. Hypercalcemia is frequent, humoral, and usually caused by a hormonal problem rather than bone metastasis. Polycythemia is very rare. Hematuria in the more severe cases can be significant enough to cause blood clots and obstruction. Bone pain, often quite debilitating, tends to occur in the flat bones, ie, pelvis, scapula, or in the spine (axial skeleton). Spinal cord compression and brain metastases are not infrequent. Brain metastases may be amenable to surgery, radiotherapy, or radiosurgery.

## Staging and Prognosis

Table 1 shows the American Joint Committee on Cancer Tumor, Node, Metastases (AJCC TNM) staging for RCC. While T1 and T2 basically denote tumor size differences, T3 defines a tumor that has extended into the perinephric tissue, the renal vein, or the vena cava. As most clinicians who treat these patients are well aware, kidney cancers often grow into the renal vein and vena cava to form a tumor clot that is not often associated with embolization. T4 designates tumors that have invaded neighboring structures such as muscle and bowel lying outside of Gerota's fascia. Unlike TNM staging of other tumors, the N1 description in RCC refers to an exclusively homolateral lymph node, and everything else involving lymph nodes is designated N2. Staging is prognostic, with earlier stages usually having very good prognosis. Survival prediction for RCC has been based on TNM stage, histological grade, and Eastern Cooperative Oncology Group (ECOG) performance status (PS). Thus, in patients with recurrent or metastatic disease, favorable prognostic factors for survival include ECOG PS of 0 or 1; a disease-free survival interval of greater than 1 year; no weight loss; no prior chemotherapy; and a single metastatic site.<sup>6</sup>

**Table 1.**—Staging by TNM and Survival (AJCC)<sup>4,5</sup>

Stage	TNM Grouping	5-Year Survival, %
I	T1, N0	80–100
II	T2, N0	80
III	T3, N0; or T1, T2, T3, N1	60
IV	T4, any N; any T, N2; any M1	20

M = metastasis; N1 = homolateral lymph node (LN); N2 = > 1 regional LN; T1 = < 7.0 cm (confined to kidney); T2 = > 7.0 cm (confined to kidney); T3 = extending into perinephric tissues, renal vein, vena cava; T4 = invasion of neighboring structure (eg, muscle, bowel).

Motzer and colleagues at Memorial Sloan-Kettering Cancer Center (MSKCC) identified prognostic factors based on an analysis of 670 patients with kidney cancer participating in clinical trials at their institution.<sup>7</sup> Table 2 lists unfavorable clinical and laboratory prognostic factors identified by the MSKCC group. Multivariate analysis examining the interaction of clinical and laboratory risk factors revealed that poor PS, elevated lactic acid dehydrogenase (LDH), anemia, hypercalcemia, and not having had a nephrectomy were associated with an unfavorable RCC prognosis. Further, patients with no risk factors had a median survival of 20 months and a 2-year survival of 45%; those with 1 or 2 risk factors had a median survival of 10 months and a 2-year survival of 17%; and those with 3 or more risk factors had a median survival of 4 months and a 2-year survival of 3%. These authors also found that treatment type and date also affected survival (Table 3). Patients who were treated with cytokine therapy, consisting of interferon (IFN) or interleukin 2 (IL-2), fared better compared with patients treated with chemotherapy. Also, patients treated in the 1990s had prolonged median survival compared with patients treated in the 1970s and 1980s. Before 1980, CT scans were only possible for the head; therefore, some of the observed survival effect might be due to earlier diagnosis and upstaging. Improved survival observed in the past 3 decades was influenced by better imaging and staging methods, more selection criteria for cytokines IL-2- and IFN-based therapy, less chemotherapy being used in later years, better supportive therapy, and perhaps the impact of cytokine therapy.

## Histological Classification and Genetics

Like most cancer, the development of RCC is caused by cells gaining a number of genetic mutations that silence or activate key genes to cause unregulated cell growth and spread. Much is being learned about the genetics of sporadic RCC from studies of hereditary RCC and other related syndromes. The most common RCC histologic subtype is clear cell (also called conventional), followed in order of incidence by papillary and chromophobe (Table 4).<sup>2</sup> Carcinoma of the collecting duct, which is located at the end of the renal tubule, is thought to be more closely related to bladder or urothelial cancer.

Clear cell carcinoma has been associated with the von Hippel-Lindau (VHL) genetic syndrome, which is linked to loss of a tumor suppressor gene in the 3p gene locus. Approximately 90% of sporadic clear cell RCC is characterized by VHL loss of heterozygosity (LOH).<sup>8</sup> Up to 45% of patients with VHL syndrome develop kidney cancer, usually typified by earlier onset and bilateral disease.<sup>9</sup>

The incidence of non-clear cell histology ranges from 20% to 30%, but is less than 10% among patients with advanced disease, according to one retrospective analysis of patients enrolled in clinical trials.<sup>10</sup> Kidney tumors of non-clear cell histologies are less likely to become metastatic, but if this occurs there is poor response to immunotherapy. Hopefully, these patients will respond to the newer therapies for RCC (discussed in the accompanying article by Ms Green).

**Table 2.—Unfavorable Prognostic Factors for Survival (MSKCC)**

Clinical	Laboratory	Combined Analysis
Karnofsky PS < 80%	Albumin < 4.0 g/dL	Karnofsky PS < 80%
No nephrectomy	Alkaline phosphatase > 1.5 × normal	LDH > 1.5 × normal
Disease-free interval < 1–2 years	Low hemoglobin (< 13 male, < 11.5 female)	Anemia
Prior chemotherapy or radiation therapy	Lactic acid dehydrogenase (LDH) > 1.5 × normal	Hypercalcemia
Liver metastases > 1 metastatic site	Corrected calcium > 10 mg/dL	No nephrectomy

PS = performance status.  
Data from Motzer et al.<sup>7</sup>

**Table 3.—RCC Prognostic Factors, Time, and Treatment (MSKCC)**

	No. of Patients	No. (%) of Patients Alive	Median Survival, mo (95% CI)
<b>Agent</b>			
IFN- $\alpha$ or IL-2	396	48 (12)	12.9 (11.5–14.6)
Chemotherapy	274	9 (3)	6.3 (5.1–7.6)
<b>Year of treatment</b>			
1975–1980	66	1 (2)	4.2 (3.3–5.7)
1981–1990	370	20 (5)	9.4 (8.1–10.7)
1991–1996	234	36 (15)	13.2 (11.3–15.2)

From Motzer et al,<sup>7</sup> with permission.

**Table 4.—Sporadic RCCs: Histology and Genetic Mutations**

Carcinoma Histology	Incidence, %	Mutations, Prevalence Among All RCC
Conventional or clear cell	75	VHL, 60%
Papillary	12	MET, 13% TFE3, < 1%
Chromophobe	4	
Oncocytoma	4	
Collecting duct (Bellini duct)	< 1	
Unclassified	3–5	

MET = mesenchymal-epithelial transition; TFE3 = Transcription Factor Enhancer 3; VHL = von Hippel-Lindau.  
Data from Cohen and McGovern.<sup>2</sup>

### Toward Identifying Responders to Therapy

In a retrospective pathology review of samples from RCC patients treated with IL-2–based therapy, Upton and colleagues reported a 20% overall response rate (ORR) among 148 patients with clear cell histology and a 41% ORR among 39 patients with a clear cell histology and favorable features.<sup>11</sup> The favorable features included alveolar features, no papillary features, and granular features < 50%. Among the 17 patients with other histologies, the ORR was 6%. It is hoped that ongoing studies will identify patients for whom cytokine therapy (eg, high-dose IL-2) is appropriate, since durable remissions are achievable with cytokines in selected patients with favorable prognostic features. Patients with poor prognostic features should be offered new treatments, if appropriate within the setting of a clinical trial.

### The Present and Future of RCC Prognosis

Gross measures of tumor size and stage are strong predictors of survival. These measures are further refined by histologic grade and subtype, which have a prognostic impact and may influence treatment choices. In addition, clinical features of host-disease interaction are prognostic for survival. Further improvements in our ability to accurately determine patient prognosis and select the most appropriate treatment depend on future refinements in the molecular characterization of this disease.

## Current and Emerging Treatments for Renal Cell Carcinoma

*Robin I. Greene, MSN, FNP-C, OCN*

Until late in 2005, the mainstay of therapy for RCC consisted of cytokine therapy with interleukin 2 (IL-2) and interferon (IFN). As shown in Table 5, several new drugs have

**Table 5.—Treatment Options for RCC**

FDA Approved (any indication)	Investigational
High-dose aldesleukin (IL-2)*	Axitinib (AG-013736)
Interferon	Temsirolimus (CCI-779)
Combination interferon-IL-2	
Sorafenib*	
Sunitinib*	
Bevacizumab	
Thalidomide	

\*Agents with an FDA-approved indication for RCC.

been added to this list and more agents are under investigation. IFN, sorafenib, sunitinib, IL-2, and bevacizumab are the agents most commonly used for first-line therapy in RCC. The introduction of these new agents offers great promise for the treatment of patients with this disease.

### Traditional Therapies

#### High-Dose IL-2

For 14 years, high-dose IL-2 was the only agent that had an FDA-approved indication for the treatment of metastatic RCC. High-dose IL-2 treatment is associated with a 15% ORR in stage IV disease and a 7% complete response (CR) rate.<sup>12</sup> This agent increases survival in patients with bone or liver metastases, and in those who have undergone a nephrectomy.

Unfortunately, high-dose IL-2 treatment is associated with very serious and difficult-to-manage toxicities and is usually administered at specialized institutions. In the United States there are fewer than 80 institutions that offer this type of treatment. When the agent was first introduced, there was a 4% mortality rate which has now been lowered to 1%. One of the most significant IL-2 toxicities is capillary leak syndrome which is associated with serious cardiovascular (eg, severe hypotension), central nervous system (eg, possible semicoma), and pulmonary effects. Consequently, patients need to meet certain criteria (eg, cardiac stress test, pulmonary function test, good PS, low creatinine, no anemia) to qualify for this challenging treatment. In addition, patients receiving high-dose IL-2 treatment should be treated by a team of nurses and physicians with specialized knowledge (eg, steroids negate effects of IL-2) and in an appropriate setting such as an ICU or a medical-surgical unit with low nurse-patient (ie, 1:1 or 1:2) ratio. Treating physicians also must be trained in IL-2 treatment and its side effects.

#### Interferon

Despite the lack of an FDA-approved indication for RCC until recently, IFN has been considered the standard of care

Robin I. Green, MSN, FNP-C, OCN, is a Clinical Coordinator of the Advanced Bio-Chemotherapy Program at Kaiser Permanente Riverside in Riverside, California.

for patients with this disease for 20 years and has been used as the comparator control arm in clinical trials. About 30% of patients with RCC receive IFN therapy which improves median survival and is usually given in combination with IL-2 and/or chemotherapy. The optimal single-agent dose has not been defined, but IFN monotherapy has an ORR of 10% to 15%, including some CRs. In a meta-analysis of 4 trials comparing IFN (n = 320) with control (n = 324), patients in the IFN treatment group had a higher response rate (RR) (IFN 12.5% vs control 1.5%) and improved 1-year survival (IFN 53% vs control 4.3%).<sup>13</sup>

## New Therapies

### Sorafenib

Sorafenib is an oral small-molecule tyrosine kinase inhibitor (TKI) of cRAF, vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)- $\beta$ , Flt-3, and Kit.<sup>14</sup> Given that some of these kinases are involved in angiogenesis, it is not surprising that sorafenib inhibits angiogenesis in experimental models. Sorafenib has demonstrated the ability to inhibit the growth of human RCC, melanoma, colon, breast, ovarian, and non-small cell lung cancer xenografts experimentally implanted in mice.<sup>15</sup>

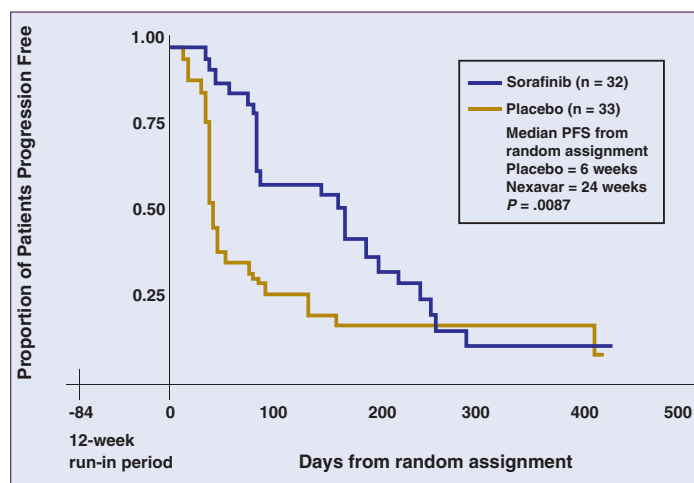
Sorafenib received FDA approval in December 2005 for the treatment of patients with advanced RCC. Approval was based on results of two studies: a randomized phase II trial and a phase III trial. In the phase II trial, 202 patients were treated for 12 weeks with open-label sorafenib 400 mg bid.<sup>16</sup> At 12 weeks of treatment, patients were evaluated for objective responses. Those with > 25% tumor shrinkage continued on sorafenib. Patients with stable disease (SD) or  $\leq$  25% tumor shrinkage were randomized in a double-blind fashion to sorafenib or placebo. Patients with progressive disease went off study. At 24 weeks, significantly more patients in the sorafenib group (16 of 32 patients, 50%) were progression free compared with the placebo group (6 of 33 patients, 18%;  $P = .0077$ ). Sorafenib treatment also improved median progression-free survival (PFS) (Figure 2). As shown in this and other trials discussed in this newsletter, achievement of durable SD is becoming an important treatment goal for patients with RCC.

In the phase III Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET), patients with unresectable or metastatic RCC who had failed 1 prior therapy within the previous 8 months were randomized to sorafenib (n = 384) or placebo (n = 385).<sup>17</sup> Patients were required to have an ECOG PS of 0 or 1 and no brain metastases. The primary end point was overall survival (OS). This trial had a planned interim analysis of median PFS, a secondary end point. The interim analysis showed that patients in the sorafenib group achieved a median 24-week PFS that compared favorably

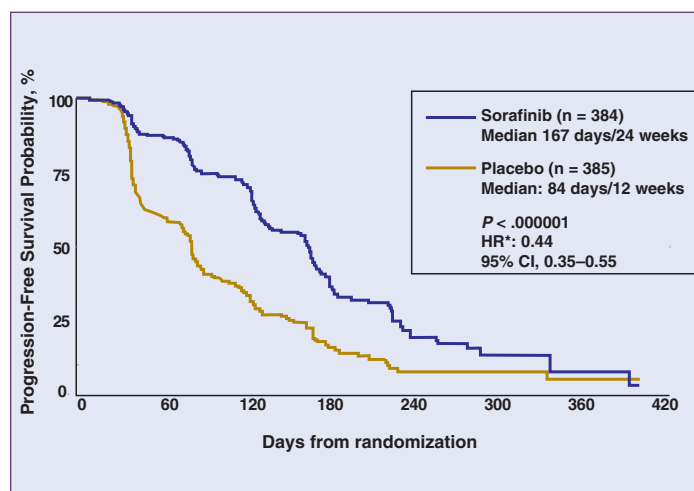
with the 12-week PFS achieved by patients in the placebo group (hazard ratio [HR], 0.44;  $P < .000001$ ) (Figure 3).<sup>17</sup> Because of this improved PFS, the study was modified in April 2005 to allow patients to cross over from placebo to sorafenib. At this year's ASCO annual meeting, this group presented an interim survival analysis, 6 months after crossover, showing a 15.9-month OS for the placebo arm and a 19.3-month OS for the sorafenib arm (HR, 0.77; 95% CI, 0.63, 0.95;  $P = .015$ ).<sup>18</sup> This favorable trend in OS did not reach the required O'Brien-Fleming value for statistical significance ( $P \leq .0005$ ) specified by the protocol at this interim point. A final analysis of OS is ongoing.

### Sunitinib

Sunitinib is also a small-molecule TKI that has a similar, but not identical, activity as sorafenib. Sunitinib inhibits the tyrosine



**Figure 2.**—Kaplan-Meier plot showing that patients randomized to sorafenib had improved investigator-assessed PFS compared with patients randomized to placebo in a phase II randomized discontinuation trial. (From Ratain et al,<sup>16</sup> with permission.)

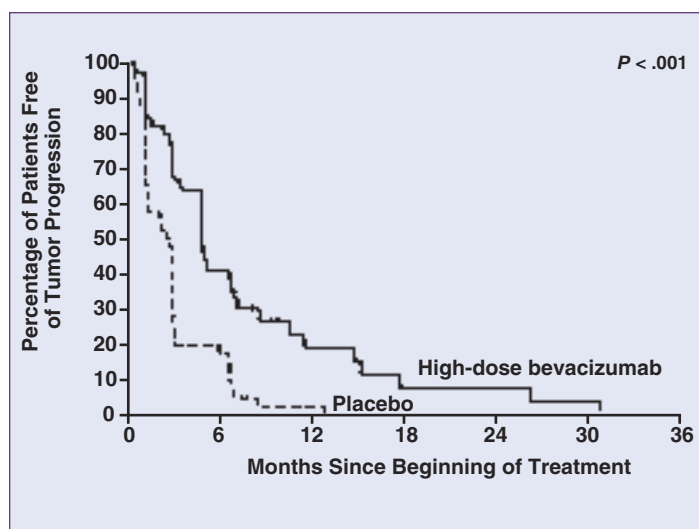


**Figure 3.**—Kaplan-Meier plot showing that patients randomized to sorafenib had improved PFS compared with patients randomized to placebo in the phase III TARGET pivotal trial. (From Escudier et al,<sup>17</sup> with permission.)

kinase activity of all 3 VEGFRs (VEGFR-1, -2, -3); PDGF- $\alpha$  and PDGF- $\beta$ , which are receptors known to be involved in angiogenesis; and Kit, RET, and Flt-3, which are receptors involved in cellular proliferation.<sup>19</sup> In preclinical studies, sunitinib inhibited growth of human glioma and colon xenografts.<sup>20</sup>

In January 2006, sunitinib received FDA approval for the treatment of gastrointestinal stromal tumor (GIST). Approval in advanced RCC was also granted based on partial response (PR) rates and duration of response from 2 nonrandomized phase II trials.<sup>19</sup> In these trials, patients received second-line sunitinib 50 mg daily for 4 weeks, followed by 2 weeks off before the beginning of the next 6-week cycle. In the smaller of these 2 trials, authors reported 25 (40%) PRs and 17 (27%) patients with SD among the 63 patients enrolled.<sup>21</sup> Overall median time to progression was 8.7 months. The larger trial, which enrolled 106 patients, resulted in 36 (34%) independently assessed PRs and a median PFS of 8.3 months (95% CI, 7.8–14.5 months).<sup>22</sup>

Results of a planned interim analysis of the phase III trial comparing sunitinib with IFN- $\alpha$  as first-line therapy for 750 patients with metastatic RCC were presented at ASCO 2006.<sup>23</sup> PFS, the primary end point, was significantly longer in the sunitinib treatment arm (11 months) compared with the IFN- $\alpha$  arm (5 months), resulting in an HR of 0.415 (Figure 4).<sup>23</sup> At the time of this interim analysis median OS had not yet been reached. According to an independent central review of best response by Response Evaluation Criteria in Solid Tumors (RECIST), there were 103 (31%) PRs among the 335 patients in the sunitinib group and 20 (6%) PRs among the 327 patients in the IFN- $\alpha$  group ( $P < .000001$ ). The 2 treatment arms had similar rates of SD (sunitinib 48%; IFN- $\alpha$ , 49%).



**Figure 4.**— Kaplan–Meier analysis of survival free of tumor progression for patients receiving high-dose bevacizumab as compared with placebo. Doses were given every 2 weeks.  $P$  values were calculated by the log-rank test. (From Yang et al,<sup>26</sup> with permission.)

## Emerging Therapies

### Bevacizumab

Bevacizumab—a humanized monoclonal anti-VEGF antibody that binds and neutralizes all biologically active forms of VEGF—inhibits angiogenesis in experimental models and the growth of human tumor xenografts in vivo, but not in vitro.<sup>24,25</sup> Bevacizumab received FDA approval in February 2005 to be administered with infusional 5-fluorouracil-based therapy for the treatment of metastatic colorectal cancer. The potential efficacy of this agent in RCC is suggested by results of 2 phase II trials. In a randomized, double-blind phase II trial of 116 patients given bevacizumab (3 mg/kg or 10 mg/kg) or placebo, there was a significant prolongation of time to disease progression in the high-dose bevacizumab group compared with the placebo group (HR, 2.55;  $P < .001$ ).<sup>26</sup> At 4 months, patients who received the high antibody dose had a 64% probability of being progression free compared with 39% for the low-dose group, and 20% for the placebo group.

A trial of bevacizumab given in combination with erlotinib (a TKI that has indications in non-small cell lung cancer and pancreatic cancer) reported objective responses in 15 (25%) patients and SD in 36 (61%) patients of 59 evaluable patients with metastatic RCC.<sup>27</sup> The median PFS was 11 months and the 1-year PFS was 43%. This trial suggests the potential of combination therapy with novel agents that target different pathways. Future trials are needed to demonstrate if such an approach will improve patient care.

### Axitinib (AG-013736)

Axitinib is a small-molecule TKI that targets all 3 known VEGFRs, PDGFR- $\beta$ , and Kit. Similar to the other agents in this class, it inhibits angiogenesis in experimental models.<sup>28</sup> A phase II trial that enrolled 52 patients with cytokine-refractory metastatic RCC being administered axitinib 5 mg bid (under fasting conditions) resulted in PR in 24 (46%) patients and SD in 21 (40%) patients, as evaluated by RECIST.<sup>29</sup>

### Temsirolimus (CCI-779)

Temsirolimus, a water-soluble ester of sirolimus, binds with high affinity to the immunophilin FKBP forming a complex that inhibits the mammalian target of rapamycin (mTOR) kinase activity.<sup>30</sup> This intravenously administered agent exhibited immunosuppressive and antitumor activity, as well as the ability to inhibit tumor growth in preclinical studies.<sup>31</sup> In a phase II trial in patients with advanced refractory RCC, temsirolimus produced an ORR of 7% (1 CR and 7 PRs among 111 patients treated at 3 different dose levels) and minor response in 26%.<sup>32</sup> Median time to tumor progression was 5.8 months and median survival was 15.0 months. In a phase III trial, temsirolimus significantly increased the OS of first-line, poor-risk advanced RCC patients compared to interferon.<sup>33</sup>

## What Else Is on the RCC Horizon?

Table 6 lists some of the phase II and III trials in RCC that are ongoing or have recently stopped accruing patients. These trials are testing a variety of new agents against the old standbys, IFN and IL-2. RCC remains a major cause of cancer deaths and there is still an urgent need to develop additional treatment options particularly for late-stage disease. Another area that needs to be developed is new adjuvant treatment options. In this regard, ECOG has recently opened a phase III trial comparing sorafenib, sunitinib, and placebo in high-risk (stage III) patients. If the results of this trial are favorable with a viable option, they will fill a void in the treatment of patients with RCC.

**Table 6.—Summary of Ongoing and Recently Completed Phase II/III RCC Trials**

Regimen	Phase	Sponsor	Status
Sorafenib vs placebo	III	Bayer/Onyx	Completed (interim results reported)
Sorafenib vs IFN	II	Bayer/Onyx	Completed
Sunitinib vs IFN	III	Pfizer	Completed (interim results reported)
Bevacizumab + IFN vs IFN	III	Genentech	Accruing
IFN ± temsirolimus vs temsirolimus	III	Wyeth	Completed
Bevacizumab ± erlotinib	II	Genentech	Completed
Bevacizumab + high-dose IL-2		Chiron/Genentech	Accruing
Bevacizumab + low-dose IL-2	II	Genentech	Accruing
Bevacizumab + sorafenib	II	CTEP	Accruing
Neoadjuvant sorafenib	II	CTEP	Accruing
Sunitinib in bevacizumab-refractory patients	II	Pfizer	Accruing

CTEP = Cancer Therapy Evaluation Program; IFN = interferon- $\alpha$ ; IL-2 = interleukin 2.

## Managing Side Effects of Targeted Therapy and Ensuring Access to Treatment

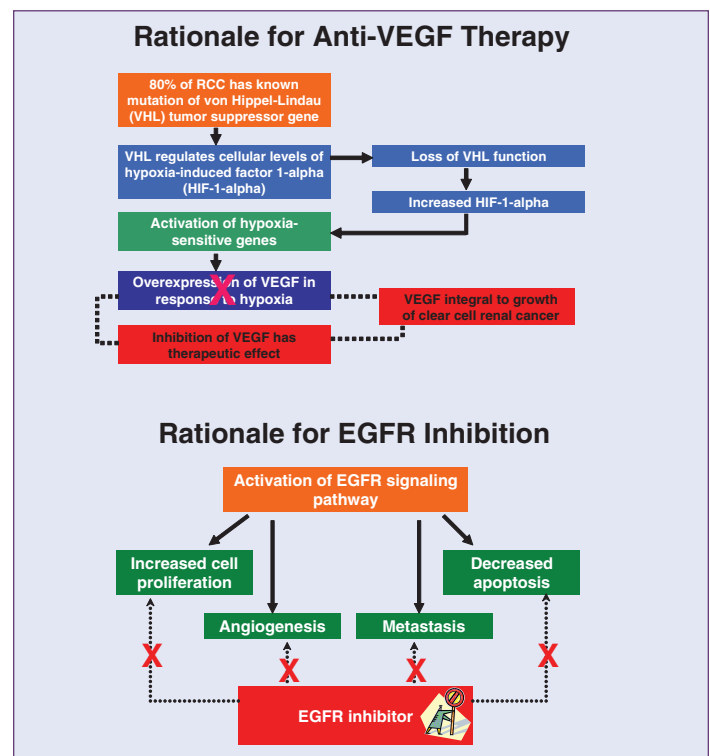
*Susan H. Moore, RN, MSN, ANP, AOCN*

Targeted therapy has only recently been introduced for management of RCC with the first multitargeted TKI having come on the market late in December 2005 and the second

in January 2006. It is notable that 2 unique agents were FDA approved in such a short time for the same disease—a disease for which few options were previously available. The addition of sorafenib and sunitinib to the treatment armamentarium for RCC presents a variety of nursing management issues associated with controlling the side effects of these oral agents.

## Rationale for Multitargeted TKI Therapies in RCC

The multitargeted TKIs sorafenib and sunitinib are thought to have antitumor effects by inhibiting tumor angiogenesis and tumor growth (Figure 5).<sup>34,35</sup> Tumor angiogenesis is necessary for the tumor to grow beyond about 2 mm in size and to metastasize. TKIs downregulate angiogenic pathways that are stimulated by VEGF by inhibiting the tyrosine kinase activity of many key receptors (VEGFR, PDGFR) that provide the necessary signals to activate the growth of new blood vessels. These TKIs also inhibit activation of the tumor growth signaling pathways (Kit, RET, Flt-3, Raf) that would normally (among several things) increase cell proliferation and decrease apoptosis (programmed cell death).



**Figure 5.—Rationale for anti-VEGF and EGFR therapy.** (Data from Richards<sup>34</sup> and Baselga.<sup>35</sup>)

At the time this symposium was presented, Susan H. Moore, RN, MSN, ANP, AOCN, was a Nurse Practitioner in Medical Oncology at Rush University Medical Center, Division of Hematology/Oncology, in Chicago, Illinois.

## Patient Education and Management

The entry of 2 novel oral agents in RCC treatment brings a host of new nursing educational interactions with patients who until now were treated with intravenously administered therapy. Chemotherapy nurses may feel that they don't have a role in the care of these patients who usually see the treating physician or advance practice nurse to get started on their new oral medication and bypass the treatment room. However, because education is crucial to patient compliance, oncology nurses can take a lead role in educating the patients and their families on the appropriate use of these oral medications, including recognition, management, and reporting of possible side effects. Nurses will also be instrumental in defining side effect experiences (eg, through photo documentation of skin effects, efficacy of specific skin care products), devising novel systems for distance monitoring, and coaching to ensure compliance.

Oncology nurses should

- Meet with patient at start of therapy
- Provide both written and verbal instructions
- Ask patient to make weekly phone contact with office, at least until side effects are managed and dosing is stable
- Ensure that the patient sees an MD or RN at the beginning of each treatment cycle
- Document oral therapies on chemotherapy flow sheets

Oncology nurses have a lead role in ensuring patient compliance with these new oral medications. The main issues in complying with these oral medications are

- Reliable reporting of side effects
- Confusion about dose modifications
- Non-, under-, and overcompliance
- Drug availability in community pharmacies
- Barriers to patient access to prescribed therapies (eg, lack of insurance coverage, transportation issues, etc)

Similar to the management of patients on intravenous chemotherapy, clinicians who deal with patients on oral chemotherapy must also develop a trusting relationship with patients and their caregivers to make them comfortable in truthfully reporting side effects, confessing confusion about dosing, and admitting to errors in compliance. Instructions should be explicit in keeping with patient special learning needs (eg, deficits in visual or hearing activity or slowed information processing) and desires (eg, does not want too much detail, uses an information broker within support network), and reinforced in writing in understandable language, including at each dose modification step.

## Dosing

Table 7 lists the recommended starting dose and dose reductions for sorafenib and sunitinib. Since sorafenib is

**Table 7.—Dosing Sorafenib and Sunitinib<sup>14,19</sup>**

Sorafenib	Sunitinib
<ul style="list-style-type: none"> <li>• 400 mg orally twice daily (two 200-mg tablets)</li> <li>• Taken without food (at least 1 hour before eating or 2 hours after eating)</li> <li>• Taken continuously</li> <li>• Dose modifications               <ul style="list-style-type: none"> <li>– First step: 400 mg orally once daily</li> <li>– Second step: 400 mg every other day</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• 50 mg orally daily for 4 weeks with 2 weeks off; cycle length = 6 weeks</li> <li>• Taken with or without food</li> <li>• Dose modifications               <ul style="list-style-type: none"> <li>– Reduce by 12.5 mg daily as needed to manage side effects</li> <li>– Increase dose to maximum 87.5 mg daily when coadministered with CYP3A4 inducer (ie, rifampin)</li> <li>– Decrease dose to minimum 37.5 mg daily when coadministered with CYP3A4 inhibitor (ie, ketoconazole)</li> <li>– Patients on sunitinib should not take St John's wort</li> </ul> </li> </ul>

taken continuously, it may be convenient to define a cycle as 28 days. Sunitinib is taken for 4 weeks with a 2-week break before the start of the next cycle. It is important to remember that all oral drugs are processed through the liver and thus there is a chance for drug interactions with other oral agents taken within the same 24-hour period. Note the dose modifications needed with sunitinib in patients taking CYP3A4 inducers or inhibitors. As a general precaution, consider asking patients not to take St John's wort while on chemotherapy because of its nonstandardized manufacturing and its propensity for drug interactions.

## Side Effects

Table 8 compares the side effects of sorafenib and sunitinib. The most common side effects are diarrhea, hand-foot reaction (HFR), skin rash, fatigue, and hypertension. Table 9 lists suggested interventions and possible medications to consider for managing some of the most common toxicities.

### Hypertension

Hypertension is the most common side effect of any anti-VEGF therapy, regardless of mode of administration (ie, intravenous or oral). The responsible mechanism is poorly understood. This is a class effect that is very familiar to those of us who have worked with bevacizumab. Hypertension associated with the multitargeted TKIs has a classic presentation that usually starts within 3 to 4 weeks of therapy, rises rather quickly (average  $\geq 20$  mm Hg increase over baseline) and usually persists, normally resolving only when the patient stops taking the drug. Consequently, it is important to establish baseline BP with weekly BP monitoring for at least the first 6 weeks of treat-

**Table 8.—Side Effects of Sunitinib and Sorafenib\***  
(Sorafenib prescribing information; Sunitinib prescribing information)<sup>14,19</sup>

Body System	Side Effect (most common in <i>italic font</i> )	Sunitinib	Sorafenib
Gastrointestinal	<i>Diarrhea</i>	✓	✓
	Nausea/vomiting	✓	✓
	Stomatitis/mucositis	✓	
Dermatologic	<i>Hand-foot reaction</i>	✓	✓
	Skin discoloration	✓	
	Hair depigmentation	✓	
	<i>Skin rash</i>	✓	✓
	Alopecia	✓	✓
Constitutional	<i>Fatigue</i>	✓	✓
	Asthenia	✓ <sup>†</sup>	✓
Cardiovascular	<i>Hypertension</i>	✓	✓
	Decreased LVEF	✓	
	Cardiac events	✓	
Neurologic	Sensory neuropathy		✓
Hematologic	Neutropenia	✓	✓
	Thrombocytopenia	✓	
	Hemorrhage	✓	✓
Miscellaneous	Drug-drug interactions	✓	✓ <sup>‡</sup>
	Take drug without food		✓
Metabolic	Elevated lipase-amylase	✓	✓
	Hypophosphatemia	✓	✓

\*See product labels for specific data on incidence of side effects.

<sup>†</sup>Only reported in GIST patients.

<sup>‡</sup>No clinical information in the product label with respect to CYP3A4 inducers.

LVEF = left ventricular ejection fraction.

ment; rises in BP should be reported and hypertension managed with selected antihypertensives. Ensure that the patient has a BP monitor at home that they know how to use and comply with the regular monitoring schedule.

To manage hypertension it is very important to avoid anti-hypertensive compounds (eg, verapamil, diltiazem) that inhibit the CYP3A4 pathway. Hypertension is best managed with angiotensin-converting enzyme (ACE) inhibitors. Angiotensin receptor blockers would be appropriate for patients who are allergic to or cannot tolerate ACE inhibitors. Patients whose hypertension is not managed by these agents should be referred to a cardiologist.

### Gastrointestinal Side Effects

Nausea is generally mild and can be usually managed by dietary changes. This is not an acute form of nausea and vomiting that chemotherapy nurses are used to managing with 5-HT<sub>3</sub> inhibitors. Once-daily prochlorperazine usually provides sufficient nausea control. Another option for patients taking sunitinib is to take the medication at bedtime. Sometimes taking sunitinib with food can minimize nausea. Sorafenib, on the other hand, must be administered 1 to 2

**Table 9.—Suggested Side Effect Management**

Side Effect	Interventions	Possible Medications
Hypertension	Avoid compounds that inhibit CYP3A4 pathway (eg, verapamil, diltiazem) Monitor BP	ACE inhibitors Angiotensin receptor blockers
Nausea	Make dietary changes Dose sunitinib at bedtime	Prochlorperazine
Diarrhea	Low-residue diet IV hydration and electrolyte supplementation if Gr 3–4 with evidence of dehydration	Loperamide
Stomatitis/mucositis	Rinse with baking soda and saline to keep oral cavity clear and free of debris	Biotene Mouthwash, Anbesol
Acneiform rash	Wash with hypoallergenic products Use skin emollients Avoid topical corticosteroids Avoid agents that will cause skin drying effects Avoid sun exposure Wear loose-fitting clothing to reduce friction	Antihistamines for itching (oral or topical) Clindamycin topical if pustules develop Clindamycin orally if skin rash becomes infected or fever present Follow prescribing information for dose modification or interruption
HFR	Photo-document, if possible Liberal use of emollients Avoid activities that cause pressure, abrasion, or irritation to hands or feet Avoid handling chemicals without gloves	
Hypothyroidism	Monitor thyroid function following discontinuation of sunitinib until stabilized or resolved	Standard thyroid hormone supplementation

hours prior to food ingestion to maximize absorption. Diarrhea is a relatively high-incidence problem with the TKIs, occurring in about 40% of patients. However, it is easy to control with standard interventions including a low-residue diet as the first choice. Over-the-counter loperamide, given according to package directions, is another option and usually patients respond by the second dose. Rarely, patients require dose adjustments to manage diarrhea.

Mouth sores can sometimes be a problem. Suggestions to manage this condition include baking soda rinses or over-the-counter Biotene Mouthwash or Anbesol (which allows better control on where to apply the medication).

### Dermatologic Side Effects

Skin rash and HFR are common following either sunitinib or sorafenib treatment. It is important to apprise patients of the risk and to assure them that these possibly distressing effects are temporary. Dose interruptions are sometimes necessary.

The skin rash has an acneiform appearance (Figure 6) (the rash is not acne and should not be treated as acne) and there is some evidence from clinical trials with other targeted therapies that its appearance and intensity may be associated with longer survival. Patients should be encouraged to maintain dosing despite the rash, given that the effects are temporary and will resolve after stopping the drug.

HFR associated with sorafenib and sunitinib (Figure 7) is quite distinct from the toxicity (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) seen with capecitabine and liposomal doxorubicin. There are also differences in clinical presentation between the two TKIs. HFR occurs more frequently on the feet. The pathogenesis of this syndrome is largely not understood. Early signs include erythematous palms or soles of feet and tingling. Late signs include pain, loss of function, paresthesia, blistering, cracks in skin, and peeling of skin. The best way to minimize the effects of HFR is copious and frequent applications of skin cream (eg, at least 5 times a day and any time after hands or feet get wet). It is important to catch HFR at the earliest incipient signs of this symptom and use all possible supportive care measures. One way to protect the skin is for



**Figure 6.**—Acneiform rash associated with multi-TKI administration. (Photos courtesy of Susan Moore, Rush University Medical Center.)



**Figure 7.**—Clinical presentation of HFR associated with multi-TKI administration. (Photos courtesy of Susan Moore, Rush University Medical Center.)

patients to wear 2 pairs of socks, a thick padded pair as the inner layer and a thinner pair as the outer layer.

Sunitinib treatment is associated with 2 unique dermatologic side effects: skin discoloration and depigmentation of hair. The skin discoloration does not resemble jaundice and is characterized by an orange-yellow skin color. This coloring is caused by the yellow dye in the sunitinib tablet. The hair depigmentation effect may cause people who do not have grey hair to have salt-and-pepper hair. This effect is temporary and hair returns to its normal color when patients stop taking the drug.

### Hypothyroidism

Hypothyroidism has been reported in 4% of patients taking sunitinib in the registration trials for metastatic RCC and GIST compared with 1% of GIST patients taking placebo.<sup>19</sup> The condition is treated with standard thyroid hormone supplementation. Referral to an internist with experience in hypothyroidism or to an endocrinologist may be necessary to ensure proper dosing and monitoring. Because the thyroid stops making hormone when patients are taking thyroid hormone supplementation, thyroid medication must not be suddenly stopped when a patient goes off sunitinib. An endocrinologist should be consulted to determine the best course of thyroid medication withdrawal.

### Cost and Reimbursement Issues

One of the many roles that nurses have is to assist patients in gaining access to their prescribed oral chemotherapy medication by helping them navigate the financial and logistical issues. Like all new targeted therapies, sorafenib and sunitinib are expensive. Depending on the agent and the patient's health care plan, monthly costs could range between \$4,500 to \$6,800.

Medicare patients are covered under Medicare Part B for oral agents that have an IV equivalent. All other drugs, except those which are not approved by the FDA (ie, off-label use), are covered under Medicare part D as of January 1, 2006. Off-label use may be appealed with a letter of medical necessity. Enrollment in Medicare Part D plans had a May 15, 2006, cutoff date, with late-enrolling patients paying a 1% per month penalty in their baseline premium. Table 10 illustrates what patients pay under the Medicare Part D deductible system (Centers for Medicare and Medicaid Services). As you can see, if the medication costs more than \$5,100, the patient will pay \$3,600 plus 5% of the remaining drug cost. For newly approved drugs there may be up to a 5-month delay for Medicare Part D coverage.

For private insurers coverage depends on the patient's policy. When dealing with insurance companies that require drugs to be preauthorized, it is very important to use the ICD-9 codes.

Pharmaceutical manufacturers have a variety of resources available on the telephone and on the Internet to assist patients to gain access to their prescribed medication.

**Table 10.—Medicare Part D Deductible**

Drug Costs	What Beneficiaries Pay	What Medicare Pays	Cost for Beneficiary (Total)
First \$250 (deductible)	100%	0	\$250 (\$250)
\$250.01 to \$2,250	25%	75%	\$500 (\$750)
\$2,250.01 to \$5,100	100%	0	\$2,850 (\$3,600)
Above \$5,100	5%	95%	\$3,600 + 5% of the remaining drug cost

Data from Centers for Medicare & Medicaid Services. Available at: <http://www.cms.hhs.gov/PrescriptionDrugCovGenIn>.

## Summary

The introduction of new oral multitargeted TKI medications in RCC is an important advance for the management of this disease. These oral agents require the same level of nursing care as intravenous therapy. Oncology nurses have key roles in patient education, management of side effects in real-time, and helping patients remain compliant by making sure that they have access to the medication and understand how to take it throughout the course of their treatment. These new directions for oncology nurses offer great opportunities for growth of our role as patient advocates.

## References

- Chow W-H, Devesa SS, Warren JL, Fraumeni JF. Rising incidence of renal cell cancer in the United States. *JAMA*. 1999;281:1628-1631.
- Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med*. 2005;353:2477-2490.
- Moore LE, Wilson RT, Campleman SL. Lifestyle factors, exposures, genetic susceptibility, and renal cell cancer risk: a review. *Cancer Invest*. 2005;23:240-255.
- Linehan WM, Bates SE, Yang JC. Cancer of the kidney. In: DeVita VT, Hellman S, Rosenberg SA, eds: *Cancer: Principles and Practice of Oncology*. 7th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:1139-1168.
- Green FL, Page DL, Fleming ID, Fritz A, eds. Genitourinary sites. In: *AJCC Cancer Staging Manual*. 6th ed. New York, NY: Springer-Verlag Publisher; 2002.
- Elson PJ, Witte RS, Trump DL. Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. *Cancer Res*. 1988;48:7310-7313.
- Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol*. 1999;17:2530-2540.
- Sugimura J, Tamura G, Suzuki Y, Fujioka T. Allelic loss of chromosomes 3p, 5q and 17p in renal cell carcinomas. *Patol Int*. 1997;47:79-83.
- Walter MM, Lubensky IA, Venzon D, et al. Prevalence of microscopic lesions in grossly normal renal parenchyma from patients with von Hippel-Lindau disease, sporadic renal cell carcinoma and no renal disease: clinical implications. *J Urol*. 1995;154:2010-2014.
- Motzer RJ, Bacik J, Mariani T, et al. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. *J Clin Oncol*. 2002;20:2376-2381.
- Upton MP, Parker RA, Youman SA, et al. Histologic predictors of renal cell carcinoma (RCC) response to interleukin-2-based therapy. *Proc Am Soc Clin Oncol*. 2003;220:851. Abstract 3420. Available at: <http://www.asco.org>.
- Proleukin (aldesleukin) [prescribing information]. Chiron Corporation: Emeryville, Calif; 1992.
- Coppin C, Porzolt F, Awa A, et al. Immunotherapy for advanced renal cell cancer. *Cochrane Database Syst Rev*. 2006;3:CD001425. DOI: 10.1002/14651858.CD001425.pub. Available at: <http://www.cochrane.org>. Accessed July 24, 2006.
- Nexavar (sorafenib) [prescribing information]. Bayer Pharmaceuticals Corporation: West Haven, Conn; 2005.
- Wilhelm SM, Carter C, Tang L, et al. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the Raf/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res*. 2004;64:7099-7109.
- Ratain MJ, Eisen T, Stadler WM, et al. Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;23:2505-2512.
- Escudier B, Szczylik C, Eisen T, et al. Randomized phase III trial of Raf kinase and VEGFR inhibitor sorafenib (BAY 43-9006) in patients with advanced renal cell carcinoma. *J Clin Oncol*. 2005;24(suppl, pt 1):380s. Abstract LBA4510. Available at: <http://www.asco.org>.
- Eisen T, Bukowski RM, Staehler M, et al. Randomized phase III trial of sorafenib in advanced renal cell carcinoma (RCC): impact of crossover on survival. *J Clin Oncol*. 2006;24(suppl, pt 1):223s. Abstract 4524. Available at: <http://www.asco.org>.
- Sutent (sunitinib) [prescribing information]. Pfizer Inc: New York, NY; 2006.
- Mendel DB, Laird AD, Xin X, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clin Cancer Res*. 2003;9:327-337.
- Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2006;24:16-24.
- Motzer RJ, Rini BJ, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA*. 2006;295:2537-2538.
- Motzer RJ, Hutson TE, Tomczak P, et al. Phase III randomized trial of sunitinib malate (SU11248) versus interferon- $\alpha$  as first-line systemic therapy for patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol*. 2006;24(suppl, pt 1):2s. Abstract LBA3. Available at: <http://www.asco.org>.
- Kim KJ, Li B, Winder J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo. *Nature*. 1993;362:841-844.
- Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *J Clin Oncol*. 2001;19:843-850.
- Yang JC, Haworth L, Sherry RB, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med*. 2003;349:427-434.
- Hainsworth JD, Sosman JA, Spigel DR, et al. Treatment of metastatic renal cell carcinoma with a combination of bevacizumab and erlotinib. *J Clin Oncol*. 2005;23:7889-7896.
- Inai T, Mancuso M, Hashizume H, et al. Inhibition of vascular endothelial growth factor (VEGF) signaling in cancer causes loss of endothelial fenestrations, regression of tumor vessels, and appearance of basement membrane ghosts. *Am J Pathol*. 2004;165:35-52.
- Rini R, Rixe O, Bukowski R, et al. AG-013736, a multi-targeted tyrosine kinase receptor inhibitor, demonstrates anti-tumor activity in a phase 2 study of cytokine-refractory, metastatic renal cell carcinoma (RCC). *J Clin Oncol*. 2005;23(suppl, pt 1):380s. Abstract 4509. Available at: <http://www.asco.org>.
- Podsypanina K, Lee RT, Politis C, et al. An inhibitor of mTOR reduces neoplasia and normalizes p70/S6 kinase activity in Pten $\pm$  mice. *Proc Natl Acad Sci U S A*. 2001;98:10320-10325.
- Wu L, Birle DC, Tannock IF. Effects of the mammalian target of rapamycin inhibitor CCI-779 used alone or with chemotherapy on human prostate cancer cells and xenografts. *Cancer Res*. 2005;65:2825-2831.
- Atkins JB, Hidalgo M, Stadler WM. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol*. 2004;22:909-918.
- Hudes G, Carducci M, Tomczak P, et al. A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon- $\alpha$  (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC). *J Clin Oncol*. 2006;24(suppl, pt 1):2s. Abstract LBA4.
- Richards M. Molecular pathology of von-Hippel-Lindau disease and the VHL tumour suppressor gene. *Expert Rev Mol Med*. 2001;3:1-27.
- Baselga J. Why the epidermal growth factor receptor? The rationale for cancer therapy. *Oncologist*. 2002;7:2-8. Available at [http://www.TheOncologist.com/cgi/content/full/7/suppl\\_4/2](http://www.TheOncologist.com/cgi/content/full/7/suppl_4/2). Accessed July 24, 2006.

## Learning Assessment

- \_\_\_\_\_ is associated with a 20% to 30% increased risk of developing RCC.
  - obesity
  - hypertension
  - smoking
  - diabetes
- The classic triad of RCC symptoms consists of a palpable mass, flank pain, and \_\_\_\_\_.
  - hematuria
  - fever
  - night sweats
  - weight loss
- Which of the following agents is among those usually considered for first-line treatment of patients with RCC?
  - cetuximab
  - sorafenib
  - temsirolimus
  - axitinib
- Histology of RCC requires characterization because
  - degree of differentiation (grade) has survival impact
  - subtypes may respond differently to cytokines
  - certain subtypes may respond to chemotherapy
  - all of the above
- Which of the following agents is usually given at specialized institutions?
  - sorafenib
  - sunitinib
  - high-dose IL-2
  - IFN- $\alpha$
- Which of the following agents does not have an FDA-approved indication for RCC?
  - sunitinib
  - IFN- $\alpha$
  - sorafenib
  - high-dose IL-2
- The most common side effect of anti-VEGF therapy is
  - neutropenia
  - hand-foot reaction
  - vomiting
  - hypertension
- James is taking sunitinib. At his checkup visit at the beginning of his third cycle of therapy, he points out a rash at the bottom of his feet and describes a tingling sensation. What intervention(s) is/are most appropriate for management of this symptom?
  - dose reduction
  - frequent and generous use of skin cream
  - use of 2 sock layers to protect feet
  - b and c
- Loraine arrives at her visit at the beginning of the second cycle of sorafenib therapy upset about the skin rash that appeared on her forehead and chest. She is seriously thinking about stopping treatment. Which of the following intervention(s) would you suggest?
  - encourage patient to maintain dosing
  - use skin emollients
  - avoid topical corticosteroids
  - all of the above
- The introduction of new active oral agents in the treatment of advanced RCC
  - allows oncology nurses more time to focus on the patients taking intravenous therapy
  - requires oncology nurses to take an active role in ensuring medication compliance
  - lessens the need for oncology nurses to be involved in patient and caregiver education
  - gives oncology nurses less work to do in maintaining chemotherapy flow sheets

# Evaluation Form

## Renal Cell Carcinoma: Today's Targeted Therapies Improving Tomorrow's Outcomes

For online registration and submission, go to <http://www.meniscus.com/eval/rcc-targeted-tx>

CE Activity Number and Credit

Nursing: 6337-0614NN (1.1 contact hours)

Project: 6337

Submit this form by September 30, 2007

(Mail) Meniscus Educational Institute

18 Elizabeth Street, West Conshohocken, PA 19428

(Fax) 610-834-8856

(Internet) [www.meniscus.com/rcc-targeted-tx](http://www.meniscus.com/rcc-targeted-tx)

### Name and Address Information (PLEASE PRINT CLEARLY)

Print name, credentials \_\_\_\_\_

Nurse  Other \_\_\_\_\_

Mailing address for statement of credit \_\_\_\_\_

City/State/ZIP code \_\_\_\_\_ E-mail address\* \_\_\_\_\_

Telephone (with area code) \_\_\_\_\_ Fax (with area code) \_\_\_\_\_ Position/Title \_\_\_\_\_

\*Participants who provide an e-mail address and satisfactorily complete the activity will receive their statement of credit via e-mail.

Evaluation	Excellent	Good	Satisfactory	Poor
Accuracy and timeliness of the content	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Relevance to your daily practice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Freedom from commercial bias	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Extent to which learning objectives were met	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Overall quality of this activity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Usefulness of learning materials as future reference	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

ANSWERS				
(Refer to the learning assessment on page 14)				
1.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

What is the most important thing you learned from this activity? (check all that apply)

- Current treatment options
- Diagnostic strategies
- Quality of life issues
- Clinical trial information
- New treatment options
- Side effect management
- Other \_\_\_\_\_

What questions do you still have regarding this topic? (check all that apply)

- Clinical trial information
- Pharmacoeconomics
- None
- Side effect management
- Applicability to other populations
- Other \_\_\_\_\_

Why did you participate in this activity? (check all that apply)

- Amount of CE credit
- Convenience
- Format (live, Internet, CD-ROM, etc)
- Importance of the topic
- Quality of the faculty
- Other \_\_\_\_\_

What professional changes do you anticipate as a result of this activity? (check all that apply)

- Current treatment strategy
- Enhanced ability to educate colleagues
- Improved patient education
- Treatment options
- Diagnostic strategies
- Quality of life issues
- Offering new therapies
- Other \_\_\_\_\_

Topics for future activities \_\_\_\_\_

May we contact you via mail or e-mail to assess the usefulness of this activity?  Yes  No

Would you like to join our private mailing list and receive notifications of our newest CE activities through our monthly *Meniscus Educational Institute (MEI) CE Activities Update* e-newsletter?  Yes  No  I've already joined

How did you hear about this educational activity? (check all that apply)

- Direct mail (eg, brochure)
- E-mail announcement
- Hyperlink from another Internet site
- Journal advertisement
- MEI CE Activities Update e-newsletter
- Meniscus Limited Web site
- Sales representative
- Other \_\_\_\_\_

I hereby verify that I participated in this educational activity for \_\_\_\_\_ minutes, including the evaluation.

Signature \_\_\_\_\_ Date \_\_\_\_\_



Meniscus Educational Institute  
18 Elizabeth Street  
West Conshohocken, PA 19428-2935



Published by the Meniscus Educational Institute

**Meniscus Educational Institute**  
18 Elizabeth Street  
West Conshohocken, PA 19428-2935

**Voice:** 610-834-1810

**Fax:** 610-834-8856

**E-mail:** [email@meniscus.com](mailto:email@meniscus.com)

**Internet:** [www.meniscus.com](http://www.meniscus.com)

## Renal Cell Carcinoma

Today's Targeted Therapies  
Improving Tomorrow's Outcomes

Opinions expressed in this activity are those of the faculty and do not necessarily reflect those of the grantor or publisher. Some products and procedures discussed in this activity may be investigational in nature. The provider does not approve or endorse any particular product(s). This activity is not meant to serve as a guideline for patient management; primary references and full prescribing information should be consulted.

The Meniscus Educational Institute has a full complement of CE offerings available on our Web site.  
Please visit us at [www.meniscus.com](http://www.meniscus.com).