

Renal Cell Carcinoma: The Translation of Molecular Biology Into New Treatments, New Patient Outcomes, and Nursing Implications

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Purpose/Objectives: To provide an overview of the current knowledge and treatment options for renal cell carcinoma (RCC).

Data Sources: Published articles, published abstracts, online databases, and package inserts.

Data Synthesis: Researchers have an increased understanding of the genetic and prognostic risk factors associated with RCC. Most patients with this rare type of cancer have or will develop metastasis. Nephrectomy treats localized disease and cytokine therapy was the previous standard for metastatic disease, but newly approved targeted agents, such as sorafenib, temsirolimus, and sunitinib, as well as investigational agents such as bevacizumab, are improving patient outcomes.

Conclusions: Understanding the biologic basis of RCC has led to therapies that are transforming the goals for treatment outcomes in patients with metastatic disease and increasing time to progression with manageable side effects.

Implications for Nursing: Counseling patients and managing treatment-related side effects of therapy are critical interventions for healthcare professionals caring for patients with RCC. Evolving treatments for metastatic disease are providing better options for patients and changing disease management.

Kidney and renal pelvic cancers have increased in incidence in the United States since the 1970s (Chow, Gridley, Fraumeni, & Jarvholm, 2000; Hock, Lynch, & Balaji, 2002). A projected 54,390 new cases are expected in 2008, roughly 85% of which will be renal cell carcinoma (RCC), and 13,010 deaths are expected (Jemal et al., 2008). RCC cases account for only 3% of patients diagnosed with cancer in the United States, but RCC is resistant to conventional chemotherapy (Motzer, 2003; Motzer, Michaelson, et al., 2006) and therefore is associated with poor prognosis. Patients diagnosed with early-stage disease have a five-year survival rate of 90%. However, about 30% of patients present with metastatic disease (Donskov & von der Maase, 2006) and 20%–30% of patients are likely to develop metastases after surgery (National Cancer Institute [NCI], 2006). The most common sites for metastases are lung, bone, brain, liver, and adrenal glands (NCI); breast metastases are uncommon (McLaughlin, Thiel, Smith, Wehle, & Menke, 2006). Patients presenting with distant metastases have about a 10% five-year survival rate. Durable responses, with survival greater than 39 months (Rosenberg, Yang, White, & Steinberg, 1998), have been achieved with high-dose interleukin-2 (IL-2) therapy, but only in a small percentage of patients (Fisher, Rosenberg, & Fyfe, 2000; Motzer, Michaelson, et al.).

Key Points . . .

- ▶ Renal cell carcinoma (RCC) is one of the most treatment-resistant solid tumors. Clinical trial participation is essential for clarifying the appropriate patient groups for specific treatments and to assess the long-term efficacy of new treatments.
- ▶ RCC incidence is increasing. Many small tumors are found during imaging scans for other conditions, creating a need for nursing support, education, management of expectations, and assessment of quality of life.
- ▶ Better understanding of hereditary forms of RCC has led to new treatment options.

Better understanding of tumor biology has led to new techniques for staging patients, new treatment approaches, and more sophisticated ways to assess patient quality of life, each of which will have an effect on nursing practice, particularly on patient counseling and management of treatment-related side effects. This review will examine the epidemiology, pathogenesis, diagnosis, and staging of RCC, with a brief discussion of developments in treatment and a range of nursing interventions that are appropriate for supporting patients with RCC and their families and caregivers.

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Epidemiology

The incidence of RCC is higher among men than women (17.9 versus 9.2 per 100,000) (Jemal et al., 2008) and is slightly higher among African Americans (NCI, 2006). The increased detection of early-stage disease has not reduced detection of late-stage disease (Chow, Devesa, Warren, & Fraumeni, 1999), and the reasons for the overall increase in diagnosed cases are unknown (Hock et al., 2002). Although patients with hereditary predispositions may develop tumors earlier in life, the median age of incidence is 65. Table 1 shows stage distribution and five-year survival for RCC in the United States by extent of disease at diagnosis (NCI). Mortality rates do not show racial differences, with the exception of renal medullary carcinoma, which is exclusively seen among African American patients with sickle cell disease (Dimashkieh, Choe, & Mutema, 2003), although the gender disparity remains consistent (NCI).

Risk Factors

Nonhereditary Factors

Smoking and RCC appear to have a stronger relationship for men than women; obesity and hypertension also are independent risk factors for development of RCC in men (American Cancer Society [ACS], 2006; Chow et al., 2000). Research suggests that body mass index (BMI) has no effect on progression-free or overall survival among patients with RCC, although increased BMI appears to complicate nephrectomy (ACS; Donat et al., 2006). Patients who have spent more than five years on dialysis also are at risk for developing RCC. In such cases, disease develops from small cysts in the renal medulla or cortex (ACS; Rioux-Leclercq & Epstein, 2003).

Hereditary Syndromes and Renal Cell Carcinoma

Studies of inherited disorders with predispositions to renal tumors have identified a variety of genes associated with angiogenesis and tumor growth, enabling researchers to better understand the pathogenesis of several forms of RCC (Linehan et al., 2004). Many sporadic cases of RCC show alterations of the same genes identified in families predisposed to particular histologic subtypes of RCC.

The vast majority of RCCs is clear cell carcinomas, with about 60% related to errors in the *von Hippel-Lindau (VHL)* gene (Cohen & McGovern, 2005). VHL syndrome causes patients to develop hemangioblastomas in the central nervous system and retinal tissue and increases the risk for clear cell carcinoma.

The second most common type, papillary RCC, arises from the distal convoluted tubule and occurs disproportion-

ately (5:1) among men (Cohen & McGovern, 2005). Type 1 papillary RCC is associated with hereditary papillary RCC syndrome, accompanied by *c-Met* gene alteration on chromosome seven. This alteration induces cell proliferation and migration and is associated with an increased risk of bilateral, multifocal renal tumors (Atkins, Avigan, et al., 2004; Cohen & McGovern; Curti, 2004). Type 2 papillary RCC is an aggressive cancer associated with leiomyomatosis RCC syndrome. It is caused by a damaged *FH* gene, the product of which normally functions as part of the Krebs cycle. Characteristics include small rash-like red bumps sporadically appearing on the skin.

Birt-Hogg-Dube (BHD) syndrome causes damage to the *BHD* gene, which leads to pulmonary cysts, spontaneous pneumothorax, and fibrofolliculomas on the face and neck. Patients with this syndrome are at higher risk for developing bilateral, multifocal tumors of the chromophobe RCC type that develops from cells within collecting duct cells of the renal cortex. Chromophobe-type RCC also is associated with monosomy 1, 2, 6, and 10, and can occur in patients without *BHD* mutations (Han, Pantuck, & Belldegrun, 2003). These tumors tend to overexpress c-Kit, which might be a treatment target for chromophobe RCC.

Hereditary tuberous sclerosis complex syndrome (TSC), also called Bourneville disease, damages two tumor-suppressor genes: *TSC1* on chromosome 9 (hamartin) and *TSC2* on chromosome 16 (tuberin). Pediatric patients with TSC may present with epileptic seizures, mental retardation, and, throughout life, are at high risk for developing tumors (called tubers) that form in the eyes, heart, brain, kidneys, skin, and lungs and calcify over time. Kidney tumors in these patients may be renal angiomyolipomas (not always malignant, but they may disrupt or destroy kidney function) or RCC. Individuals with mild cases of the syndrome may be asymptomatic, yet they may pass TSC in a more severe form to their children. Some adults are diagnosed at the same time as their children (National Institutes of Health, 2006).

Medullary carcinoma of the kidney is found almost exclusively among patients with sickle cell disease. The gene for β -globulin is at the end of chromosome 11p and medullary carcinoma is associated with monosomy 11, which may explain why this rare and aggressive cancer is restricted to that population (Dimashkieh et al., 2003).

Pathogenesis

RCC can occur sporadically or as a result of the hereditary predispositions previously described. Hereditary RCCs tend to occur earlier in life than sporadic cancers and are more likely to develop multifocal tumors (Cohen & McGovern, 2005). The cause of genetic dysfunctions in patients with sporadic disease that eventually lead to tumorigenesis is unclear, although many clear cell RCC cases exhibit genetic changes similar to those in patients with VHL syndrome. These similarities have allowed researchers to focus their attention on specific cellular pathways that enable a better understanding of the disease biology and lead to new, targeted treatments.

RCC now is identified as a diverse group of malignancies. Distinguishing histologic subtypes give insight into tumor pathogenesis and may provide more specific treatment. RCC subtypes were once divided into clear cell carcinomas and

Table 1. Stage Distribution and Five-Year Survival of Renal Cell Carcinoma

Extent of Cancer	Distribution (%)	Five-Year Survival (%)
Distant metastases	21	10
Localized	54	90
Regional lymph nodes or beyond primary site	20	62

Note. Based on information from National Cancer Institute, 2006.

granular cell renal carcinoma (Storkel et al., 1997), but distinctions now are based primarily on genetic features: clear cell carcinoma (altered or silenced *VHL* gene), papillary renal carcinoma (type 1: activation of the *c-Met* oncogene and trisomy 7; type 2: mutations of the fumarate hydratase enzyme that normally would suppress tumors), chromophobe renal carcinoma, and oncocytoma (loss of *BHD* gene and overexpression of *c-Kit*) (Linehan et al., 2004). An extensive review showed the distribution of subtypes to be 88% clear cell carcinoma, 10% papillary, and 3% chromophobe, although this analysis did not use the exact genetic distinctions previously listed (Patard et al., 2005).

Clear cell or conventional RCC arises from epithelial dysplasia within the proximal tubules. A high percentage of sporadic clear cell RCC cases show mutations (Han et al., 2003) or methylations of the *VHL* gene (Linehan et al., 2004), either of which can eliminate gene function. Absence of both copies of the *VHL* gene, because of genetic predisposition or other error, disrupts the availability of the product of the *VHL* gene (pVHL) that regulates hypoxia-inducible factor (HIF). In the presence of oxygen, pVHL binds to HIF and attaches a polyubiquitin chain to HIF that marks the molecule for destruction in the proteasome. In ordinary hypoxic conditions, HIF- α binds with HIF- β to activate transcription of multiple genes, coding for HIFs such as vascular endothelial growth factor (VEGF), platelet-derived growth factor- β (PDGF- β), transforming growth factor- α , and erythropoietin. When pVHL is damaged or unavailable, the microenvironment reacts as if it is in a constant state of hypoxia: HIF accumulates, leading to overproduction of the growth factors, eventually causing inappropriate angiogenesis, tumor development, and erythrocytosis (Atkins, Avigan, et al., 2004; George & Kaelin, 2003; Rini & Small, 2005). Because multiple protein interactions and transcription factors are involved, overexpression of HIF- α is necessary but not sufficient for tumor development (Cohen & McGovern, 2005). Histologic specimens of clear cell RCC exhibit finely branched vasculature around groups of cells with clear cytoplasm (Storkel et al., 1997). Replacing the protein of pVHL has been shown to inhibit RCC cell growth in vitro (Cohen & McGovern). The significant clinical implication is that supplementing defective or missing pVHL with functional protein reduces the development of VEGF and angiogenesis and, therefore, decreases the likelihood of tumor development in vivo.

Presentation and Diagnosis

Before the use of imaging technology, the classic triad of symptoms for patients with RCC was hematuria, flank mass, and flank pain (Cohen & McGovern, 2005). Renal tumors were confirmed on further investigation by characteristic tumor blood vessel patterns on renal angiograms (Rioux-Leclercq & Epstein, 2003). Improvements in and increased use of scanning devices have led to the detection of much smaller kidney tumors, usually during scans for other issues. Now, if a patient presents with flank pain or a flank mass related to cancer, the tumor may have grown large enough to displace other organs, potentially indicating advanced disease (Rosenblum, 1987) (see Figure 1). RCC screening is only performed for patients who previously have been identified as having one of the known genetic lineages associated with specific subtypes.

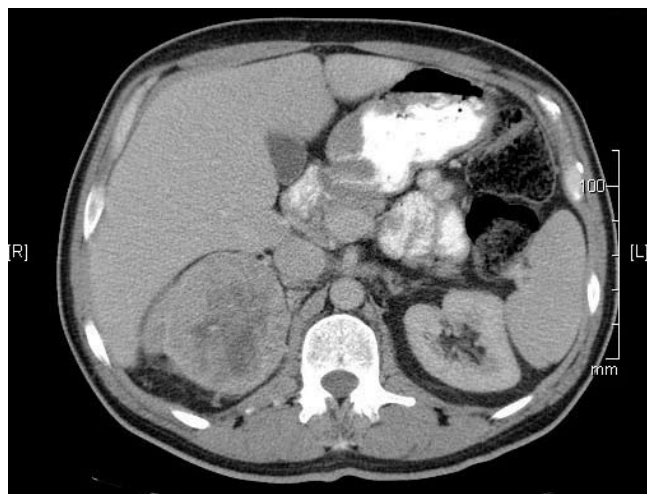


Figure 1. Computed Tomography Scan of Localized Renal Cell Carcinoma From a 55-Year-Old Patient

One of the distinctive features of RCC is the wide range of paraneoplastic syndromes with which it is associated, including hypercalcemia (Fahn et al., 1991), erythrocytosis, and hypertension, any of which may be treated symptomatically without leading to a prompt, correct RCC diagnosis (Rosenblum). Even in the absence of metastasis to the liver, 20% of patients may present with hepatic dysfunction that may resolve after removal of the primary tumor (Rosenblum). Researchers have speculated that paraneoplastic syndromes are more common in RCC because most subtypes of RCC are caused by dysregulated growth factors. Decreased albumin, elevated alkaline phosphatase, and liver function abnormalities (collectively referred to as Stauffer syndrome), and anemia and thrombocytosis observed in patients with RCC may be related to elevated serum levels of IL-6, although serum IL-6 was not linked with survival or response to treatment with IL-2 (Walther et al., 1998). Some paraneoplastic syndromes resolve after the removal of the primary tumor (Rosenblum).

Staging

From an epidemiologic perspective, classifying cancers by the extent to which they have moved beyond the primary site at time of diagnosis is useful (Bui et al., 2001), but many researchers have created staging classifications for predicting length of survival or for identifying features predictive of response to cytokine therapy. Frequently used prognosis-oriented criteria are the tumor, node, metastasis (TNM) staging system (Greene et al., 2002), Fuhrman grade (both used at diagnosis), and the Memorial Sloan-Kettering Cancer Center (MSKCC) score, a prognostic algorithm for patients with metastatic disease. The University of California, Los Angeles, Integrated Staging System (UISS) is another clinical outcome algorithm that stratifies patients into three risk groups: low, intermediate, and high based on TNM, Eastern Cooperative Oncology Group performance status, and Fuhrman grade at diagnosis (Patard et al., 2004).

The standard TNM categories used by the National Comprehensive Cancer Network ([NCCN], 2008) are displayed in Figure 2. Figure 3 provides an overview of staging, along

with five-year survival data (Cohen & McGovern, 2005) to illustrate how well the staging system reflects probable outcomes. However, researchers continue to propose refinements (e.g., to consider tumors from 5.1–7 cm as stage II rather than stage I) and to better differentiate among patient groups on the basis of probable length of survival (Elmore, Kadesky, Koeneman, & Sagalowsky, 2003).

Motzer et al. (1999) reviewed data from 670 patients receiving treatment for metastatic RCC from 1982–1996 in MSKCC clinical trials. Five factors correlated well with patient outcomes and are presented in Figure 4; the MSKCC score is based on how many of the factors a patient exhibits (see Table 2). Table 3 illustrates the discrimination among median survival in patient groups in each category. Using stratification according to MSKCC risk criteria allows for more uniform patient populations in clinical trials and may allow researchers to more quickly identify treatments that are appropriate for patients with poorer prognosis.

The Fuhrman grading system assigns risk by examining features of cell nuclei (Fuhrman, Lasky, & Limas, 1982). Progressive deterioration of nucleoli organization is a measure of cancer progression. Table 4 describes the categories and data from Ficarra et al. (2002) and Fuhrman et al. that demonstrate the predictive value of the system.

The staging and grading criteria sometimes are combined to create postoperative assessments that may provide the clear-

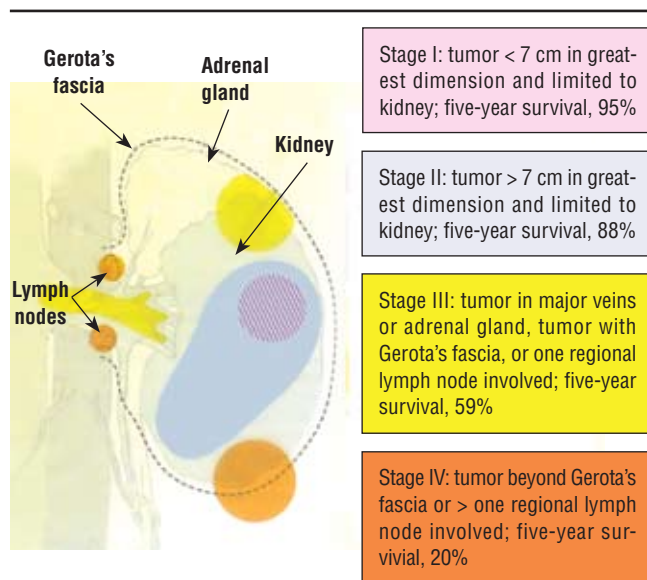


Figure 3. Staging of Primary Tumor and Five-Year Survival

Note. From "Renal-Cell Carcinoma," by H.T. Cohen and F.J. McGovern, 2005, *New England Journal of Medicine*, 353(23), p. 2478. Copyright 2005 by New England Journal of Medicine. Adapted with permission.

Primary Tumor (T)

- TX Primary tumor cannot be assessed.
- T0 No evidence of primary tumor
- T1 Tumor 7 cm or less in greatest dimension, limited to the kidney
- T1a Tumor 4 cm or less in greatest dimension, limited to the kidney
- T1b Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
- T2 Tumor more than 7 cm in greatest dimension, limited to the kidney
- T3 Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia.
- T3a Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia.
- T3b Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or vena cava below the diaphragm.
- T3c Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava.
- T4 Tumor invades beyond Gerota's fascia.

Regional Lymph Nodes (N)^a

- NX Regional lymph nodes cannot be assessed.
- N0 No regional lymph node metastasis
- N1 Metastasis in a single regional lymph node
- N2 Metastasis in more than one regional lymph node

Distant Metastasis (M)

- MX Distant metastasis cannot be assessed.
- M0 No distant metastasis
- M1 Distant metastasis

^a Laterally does not affect the N classification. If a lymph node dissection is performed, then pathologic evaluation would ordinarily include at least eight nodes.

Figure 2. Staging for Renal Cancers

Note. From *AJCC Cancer Staging Manual* (6th ed., pp. 333–334), by F.L. Greene et al. (Eds.), 2002, New York: Springer. Copyright 2002 by the American Joint Committee on Cancer. Adapted with permission.

est indications of better or poorer outcomes (Cindolo et al., 2005). The Kattan nomogram, for example, uses TNM stage, tumor size, histology, and symptoms to predict which patients are likely to have cancer recurrence within five years (Lam, Shvarts, Leppert, Figlin, & Belldgrun, 2005). The UISS is particularly useful in stratifying patients with localized disease (Patard et al., 2004).

The usefulness of histologic subtypes as prognostic indicators have been described previously. Although some studies have shown survival advantages to be associated with specific RCC subtypes, the largest study to date (N = 4,063) found no prognostic value of histology in multivariate analysis (Patard et al., 2005). However, patient records that often are collected across many years and from multiple institutions may not contain the consistent diagnostic details (e.g., pathologic description, cytogenetic information) needed to classify patients using recent RCC categories.

Patients often are overwhelmed by this kind of information and may consider the intricacies of staging to be splitting hairs, particularly when only four treatment options have been approved by the U.S. Food and Drug Administration (FDA). Nurses have an essential role in translating staging, pathology, Fuhrman grade, and risk factors into knowledge that patients can use to make decisions about treatment and life priorities.

Treatment for Localized or Regional Renal Cell Carcinoma

Surgery

Radical nephrectomy has been the standard surgery for localized RCC, a possible curative therapy for patients without metastases. Laparoscopic nephrectomy (with or without hand assistance, which uses a second incision to allow the surgeon use of the other hand to locate and position the kidney) allows

- Absence of nephrectomy
- Elevated lactate dehydrogenase level (more than 1.5 times upper limit of normal)
- High corrected serum calcium (more than 10 mg/dl)
- Low hemoglobin (below the lower limit of normal)
- Low Karnofsky performance status (less than 80%)

Figure 4. Memorial Sloan-Kettering Cancer Center Risk Factors

Note. Based on information from Motzer et al., 1999.

for shorter recovery times but may involve longer surgical times because of their complexity. Patients with tumors smaller than 4 cm may be considered candidates for nephron-sparing surgery, also called partial nephrectomy (Ghavamian & Zincke, 2001). The option to preserve kidney function is particularly important for patients who only have one kidney and can be used even if the other kidney was removed because of RCC. Ghavamian et al. (2002) demonstrated that nephron-sparing surgery could be performed in such cases and result in good local recurrence-free and five-year survival rates. Guidelines suggest that nephron-sparing surgeries only be used for smaller tumors, but a review of data from 368 patients suggests that tumors greater than 4 cm also can be removed using nephron-sparing surgery if the tumor is localized and the surgical team believes the method is appropriate (Becker et al., 2006). Laparoscopic procedures rarely are used for partial nephrectomy because they require an expert surgical support team. Stage III tumors with renal vein or inferior vena cava involvement can be treated surgically (Parekh et al., 2005), including those growing up through a renal vein toward the heart (Swierzewski, Swierzewski, & Libertino, 1994), although laparoscopic procedures are not appropriate in these cases and participation of a cardiothoracic surgical team may be required. Treatment setting also may influence the kind of surgery recommended to patients, because surgeons with less experience with RCC may be more conservative about patient eligibility for surgery.

The likelihood of relapse after nephrectomy is 20%–30%, typically in the first three years after surgery (George & Kaelin, 2003). Surgery is not curative for stage IV disease, although it may be undertaken for palliative purposes (NCCN, 2008). Some evidence exists that cytoreductive surgery before cytokine therapy may be beneficial in a subset of patients with a low burden of metastases (Flanigan, 2004).

Ablation

In addition to surgery, cryoablation and percutaneous radiofrequency techniques (Desai & Gill, 2002) have been used to treat localized tumors in patients who might not be good candidates for surgery. Radiofrequency ablation does not appear effective for tumors larger than 5 cm or those in central areas in the kidney (Atkins, Avigan, et al., 2004). Patients receiving ablation therapy need periodic monitoring with imaging studies to ensure that remnants of the tumor do not change in size, which could indicate regrowth of cancerous cells or another complication requiring treatment.

Postsurgical Procedures

Patients usually want to know what assessments they will receive after surgery. NCCN (2008) recommended base-

line computed tomography scans four to six months after surgery, with regular updates to monitor any recurrence. Tumor recurrence and metastases development are possible, even among patients who have had successful removal of solitary tumors, particularly if that person has one of the inheritable RCC predispositions. Currently, no data support adjuvant therapy to prevent relapse, although participation in a clinical trial for adjuvant therapy might offer potential benefits (NCCN).

Treatments for Metastatic Renal Cell Carcinoma

For recurrent disease, NCCN (2008) treatment guidelines continued to recommend participation in clinical trials and the use of cytokine-based therapies; however, new targeted therapies have come into more widespread use (Atkins, Hidalgo, et al., 2004; Escudier et al., 2007; Hudes et al., 2007; Motzer et al., 2007). Table 5 lists current and potential systemic treatments for RCC, along with their mechanisms of action and side effects observed in clinical trials. As previously described in the staging section, determining which patients will respond best to therapy is difficult, but as prognostic factors are identified, future clinical trials may select their patient populations based on tumor genetics to improve likelihood of positive responses and use of the most appropriate therapies.

IL-2 is a T-cell growth factor used in multiple treatment regimens for RCC. The typical high-dose regimen, which has been the most successful to date, uses 600,000–720,000 IU/kg administered by infusion every eight hours up to a maximum of 14 doses per each admission. Objective response, as collated from seven phase II trials, was 15%, with 10%–20% of patients alive 5–10 years after treatment (Fisher et al., 2000). Toxicities are associated with immune activation and are not tolerated by all patients (thus, the lower dose regimens); but of the patients who do respond, responses are durable (high dose IL-2 21% versus 13% for low dose; median duration of response 54 months) (Curti, 2004).

Because trials with IL-2 seem to demonstrate a durable benefit for a small group of patients (Donskov & von der Maase, 2006), trials to improve outcomes with better patient selection criteria are ongoing (McDermott, 2005). Donskov and von der Maase identified high blood neutrophil counts, presence of intratumoral neutrophils, and intratumoral CD57+ natural killer cell counts as independent predictors of poor prognosis in patients receiving IL-2 therapy. Patients stratified as poor risk by Motzer (2003) or Donskov and von der Maase's criteria had a median survival of 13 months and were not good candidates for IL-2 therapy. Upton, Parker, Youmans, McDermott, and Atkins (2005)

Table 2. Memorial Sloan-Kettering Cancer Center Scoring

Score	Risk Category
0 risk factors	Favorable
1–2 risk factors	Intermediate
≥ 3 risk factors	Poor

Note. Based on information from Motzer et al., 1999.

Table 3. Memorial Sloan-Kettering Cancer Center Relation to Survival

Risk Category	Median Survival (Months)	One-Year Survival (%)	Three-Year Survival (%)
Favorable (25%)	19.9	71	31
Intermediate (53%)	10.3	42	7
Poor (22%)	3.9	12	–

Note. Based on information from Motzer et al., 1999.

also developed a model based on the presence or absence of papillary and granular features in histologic samples that can distinguish which patients are more likely to respond to IL-2 treatment. Research indicates that carbonic anhydrase IX (CA IX) is present at higher concentrations in patients likely to respond to IL-2 (Lam, Pantuck, Beldegrun, & Figlin, 2005); WX-G250, an antibody to CA IX, also is in development as a treatment for metastatic RCC (Bleumer et al., 2006). A survival prediction algorithm for patients with metastatic disease receiving nephrectomy and IL-2 immunotherapy was developed (Leibovich et al., 2003) in which regional lymph node status, constitutional symptoms, metastases location, sarcomatoid histology, and thyroid-stimulating hormone levels were associated with survival.

Interferon- α , a natural glycoprotein with immunomodulatory and antiproliferative properties, also has been used to treat RCC (Curti, 2004). About 14% of patients respond to interferon- α alone, showing some tumor regression; however, the median duration of response only is six months (Cohen & McGovern, 2005). Interferon- α as a monotherapy has been replaced as more active treatments have been established (Motzer et al., 2007).

Some patients with RCC have tumors or distant metastases that grow very slowly and cases of spontaneous remission in the absence of therapeutic intervention have been documented (Motzer, 2003). RCC also has demonstrated a wide variance in rates of disease progression depending on the presence of several newly identified prognostic factors (Motzer). This complicates the interpretation of trial results, creating the need for patients in trials to be stratified according to risk factors so that treatment groups are as similar as possible.

The newest agents for treating RCC have been designed to target molecules that influence tumorigenesis, angiogenesis, pH regulation, metastasis, and glucose control (Lam, Shvarts, et al., 2005). Particular attention has been paid to VEGF because of its association with clear cell RCC and VHL syndrome (Rini & Small, 2005). The FDA has approved two orally administered tyrosine kinase inhibitors

for the treatment of RCC. Sorafenib (Onyx Pharmaceuticals and Bayer Pharmaceuticals, 2008) interacts with multiple intracellular and cell surface kinases, including cRAF, bRAF, VEGF receptor, and PDGFR- β receptor-mediated signaling (Onyx Pharmaceuticals and Bayer Pharmaceuticals). Sorafenib significantly prolonged progression-free survival compared to placebo (5.9 versus 2.8 months, $p < 0.001$) in a study of 903 patients with advanced clear cell RCC that had progressed after one systemic treatment (Escudier et al., 2007). Disease control rates favored sorafenib (62% versus 37%), as did overall survival (19.3 versus 15.9 months, $p = 0.02$), although this difference did not meet the prespecified boundary for statistical significance. Sunitinib malate (Pfizer Inc., 2006) inhibits kinases such as VEGFR, PDGFR- α , and PDGFR- β . In an uncontrolled phase II trial of 63 patients with RCC who had progressive disease after initial cytokine therapy, 40% of treated patients achieved a partial response and 27% demonstrated stable disease (Motzer, Michaelson, et al., 2006). In a second single-arm study of 106 patients with cytokine-refractory metastatic clear cell RCC, 34% of patients achieved partial responses and median progression-free survival was 8.3 months (Motzer, Rini, et al., 2006). A phase III trial comparing sunitinib to interferon- α in 750 patients with previously untreated, metastatic RCC found that both median progression-free survival (11 versus 5 months, $p < 0.001$) and objective response rate (31% versus 6%, $p < 0.001$) favored patients receiving sunitinib (Motzer et al., 2007).

Antibodies that could block angiogenesis and associated growth factors also are being explored for the treatment of RCC (e.g., bevacizumab [antibody to VEGF] given with erlotinib [antibody to epidermal growth factor receptor]). Objective responses were achieved in 25% of patients, and 61% had stable disease (Hainsworth et al., 2005). However, a randomized, double-blind phase II study comparing the combination of bevacizumab and erlotinib with that of bevacizumab and placebo found no improvement in efficacy with the addition of erlotinib (Bukowski et al., 2006). Another part of the signaling cascades associated with RCC is the mammalian target of rapamycin (mTOR); temsirolimus (CCI-779) (Wyeth Pharmaceuticals, Inc., 2007) is meant to suppress mTOR and, therefore, regain control of cell cycle processes. Patients treated with this drug had significantly longer survival than those treated with interferon- α (10.9 versus 7.3 months, $p = 0.0069$) (Hudes et al., 2007).

These drugs add a new dimension to the care of patients with RCC; however, none is curative. At best they provide partial responses and disease stabilization, concepts that may be difficult for patients to accept at the time of initial diagnosis.

Table 4. Fuhrman Grading and Outcomes

Fuhrman Grade	Nuclei Features	Ficarra Data (N)	5-Year Survival (%)	10-Year Survival (%)
I	~ 10 microns, normal appearance, absent or inconspicuous nucleoli	25	94	88
II	~ 15 microns, irregular borders, small nucleoli	35	86	75
III	~ 20 microns, very irregular borders, large nucleoli	33	59	40
IV	Like grade III in size, with bizarre, multilobed nuclei and chromatin clumping (spindle cell and sarcoma-like characteristics)	7	31	31

Note. Based on information from Ficarra et al., 2002; Fuhrman et al., 1982.

Table 5. Systematic Treatment Options for Metastatic Renal Cell Carcinoma

Treatment Category and Options	Mechanism of Action	Most Common Toxicities
Approved targeted therapies		
• Sorafenib (Onyx Pharmaceuticals and Bayer Pharmaceuticals, 2008)	Inhibits cRAF, bRAF, Kit, RET, Flt-3, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β	Fatigue, hypertension, diarrhea, hand-foot skin reaction, dry skin, mucositis, skin rash, taste changes
• Sunitinib (Pfizer Inc., 2006)	PDGFR-α, PDGFR-β, VEGFR-1, VEGFR-2, VEGFR-3, Kit, Flt-3, CSF-1R, RET	Fatigue, diarrhea, nausea and vomiting, dyspnea, stomatitis, hypertension, skin color changes, hair changes, neutropenia, thrombocytopenia
• Temsirolimus (CCI-779) (Wyeth Pharmaceuticals, Inc., 2007)	Binds to the immunophilin FKBP and inhibits mTOR kinase activity, leading to downstream changes to G1 phase cell cycle arrest, effectively inhibiting cell proliferation	Maculopapular rash, mucositis, asthenia, nausea, hyperglycemia, hypophosphatemia, anemia, hypertriglyceridemia
Cytokines		
• IL-2 (high dose) (Novartis Pharmaceuticals Corporation, 2008)	Activates T cells	Hypotension, capillary leak syndrome, renal insufficiency, cardiac dysrhythmias, mental status changes, pruritus, skin sloughing, diarrhea, chills, rigors, vomiting (Some less common toxicities can be life threatening.)
• Interferon-alfa ^a	Immunomodulation, antiangiogenic, promotes cytostasis	Fatigue, anorexia, chills, fevers, liver enzyme abnormalities
• Combination IL-2/interferon	—	Fatigue, decreased appetite, fevers, chills, dry skin, nausea, vomiting
Investigational		
• Bevacizumab with or without erlotinib (Hainsworth et al., 2005)	Antibody neutralizing VEGF Inhibits EGFR tyrosine kinase	Rash diarrhea, nausea and vomiting, hypertension, bleeding, proteinuria, pruritus

^aNot approved for this indication but frequently used

CSF-1R—colony-stimulating factor receptor type 1; EGFR—epidermal growth factor receptor; FKBP—FK 506 binding protein; Flt-3—FMS-like tyrosine kinase-3; G1—growth phase 1; IL—interleukin; Kit—stem cell receptor factor; mTOR—mammalian target of rapamycin; PDGFR—platelet-derived growth factor receptor; VEGF—vascular endothelial growth factor; VEGFR—vascular endothelial growth factor receptor

Radiation Therapy

Radiation therapy for RCC currently is used only for palliation of metastatic disease (NCCN, 2008) to control bone pain, hemoptysis, obstructive pulmonary lesions, and brain lesions. Stereotactic radioablation also has been used for brain and spinal metastases. Whether other uses of radiation (e.g., chemosensitization, part of a vaccine approach) will be useful in the future is unclear.

Nursing Interventions

Building rapport with patients and their families is essential to understanding the full range of patient symptoms, needs, and expectations and their likely degree of treatment adherence. Figure 5 summarizes key nursing interventions for patients with RCC, including assessment, teaching, reinforcement, and making connections to additional resources. Because RCC is so rare, initial conversations may focus on education to help patients understand the different staging criteria and what their options are for managing local versus metastasized disease. Baseline assessments of quality of life may be established using tools such as the **Functional Assessment of Cancer Therapy–Kidney Symptom Index** (10- and 15-item scales are available), which evaluates physical and psychosocial concerns identified by patients with RCC and cancer researchers, such as fear of disease progression,

losing hope, and difficulties with family life (Cella et al., 2006). Survey results may allow nurses to more easily open conversations about staging; the difference among curative, debulking, and palliative surgery; and possible participation in clinical trials.

RCC will be a surprising diagnosis for many patients, particularly when it is detected during a scan for an unrelated condition. However, for some patients, RCC will be yet another manifestation of a genetic condition with which they and their families have been struggling for years. The psychosocial aspects of cancer predisposition have not been studied thoroughly (Giarelli, 2006) but may have a profound effect on patients' attitudes toward diagnosis and long-term compliance with therapy. Given the high rate of RCC recurrence, understanding the psychosocial aspects of lifelong self-monitoring also may be relevant to the care of patients with sporadic cancers. For many patients, the daily task of oral administration (e.g., sunitinib malate, sorafenib) reminds them of their cancer and causes them to feel that they can never put aside their diagnosis. Patients who view treatment side effects, disease recurrence, or early mortality as inevitable may need additional encouragement to regularly communicate with their treatment team about the issues.

Nursing assessment, care, and intervention for patients with RCC have evolved over the years into a niche that

Assess

- Patient and family readiness to learn more about disease and treatment
- Ability of patient and family to understand and adhere to treatment regimens
- Patient and family understanding of treatment side effects
- Current patient quality of life

Connect

- Use telephone follow-up and encouragement.
- Connect patients with other patients in the clinic or practice (with permission).
- Direct patients and their families to national support groups (e.g., Kidney Cancer Association, Von Hippel-Lindau Family Alliance).

Reinforce

- Use every opportunity to rehearse treatment regimens (particularly self-administered medications) with patients and their families.
- Use success stories in coaching interventions.
- Provide reminder and reinforcement tools.

Teach

- Customize education to match cultural, cognitive, and emotional needs.
- Demonstrate reminder techniques and associated materials.
- Point out the importance of tracking side effects for good cancer care; stress that side effects need to be reported when they first occur and that "over-compliance" can negatively affect treatment.

Figure 5. Nursing Discussion Points for Patients With Renal Cell Carcinoma and Their Families

encompasses innovative surgeries, intense therapies, and, now, oral agents that patients will self-administer at home. Nursing activities may involve postsurgical management (i.e., pain control, prevention of atelectasis and pneumonia, potential pneumothorax, monitoring renal function, and wound care), supportive care during cytokine treatments, and compliance education for patients who are taking self-administered oral therapies (Moldawer & Wood, 2006). Although self-administered oral therapies are less disruptive to patients' activities of daily living compared with regimens administered in a hospital or clinic, a much higher management burden exists: Some drugs may have to be taken with a meal or a certain number of hours before meals. In addition to monitoring concomitant medications, particularly conflicts with CYP3A4 metabolism (e.g., warfarin), potential drug interactions, such as with herbal remedies like St. John's wort, can occur. Although good communication among members of the treatment team should allow tracking of concomitant medications, nurses also will need to work with patients and their families to learn about any herbal and dietary supplements or alternative remedies that patients may be using (Foulad-bakhsh, Stommel, Given, & Given, 2005). As oral therapies move from investigational protocols to the patient setting, a tremendous need arises to educate nurses. Strict patient guidelines, including frequency of office visits and laboratory tests, are needed to ensure patient safety and success with oral targeted therapies.

A major concern associated with the use of oral agents is their cost to patients. Tremendous variability exists in private insurance coverage—some companies might cover through the traditional copayment whereas others might require that patients pay for the prescription in full and wait for reimbursement. Fortunately, patients who do not have insurance or have a suboptimal prescription benefit plan may qualify for one of the many patient assistance programs available through phar-

maceutical manufacturers. Although this may be a solution to some of the financial aspects associated with oral therapies, the additional stress that patients with RCC have to endure as they wait for insurance approval and delivery of the drugs is still present. For patients whose access to medications is compromised, either by a suboptimal prescription plan or poor health insurance, a social worker or case manager must be involved in their care. Patients often need information, guidance, reassurance, and an advocate to deal with the nuances of the health insurance industry and their coverage of new oral agents.

Patients with advanced RCC should be assessed for and instructed to report any respiratory distress, fatigue, hemoptysis, pain, fractures, or changes in mental acuity that might indicate brain metastases. Following patients for subtle signs that their cancer might be recurring requires advanced nursing knowledge and skills that develop over time. Although hypertension is a recognized side effect of treatment with antiangiogenic agents (Veronese et al., 2006), treatment-related symptoms must be distinguished from those that may indicate compromised renal function. Cutaneous side effects also are associated with newer agents, particularly hand-foot skin reaction, which may require supportive measures (e.g., skin lotions) and dose holding or reductions but not discontinuation of treatment if promptly brought under control.

Conclusion

Research into the genetics of inherited predisposition to RCC is beginning to yield targeted therapies for previously intractable cancers (Vogelzang, 2006). Newer agents that target the central role of angiogenesis in RCC have demonstrated improvements in time to progression and in the number of patients achieving partial response or stable disease among patients whom cytokine therapies previously failed (Escudier et al., 2007; Motzer, Michaelson, et al., 2006; Onyx Pharmaceuticals and Bayer Pharmaceuticals, 2008). Ongoing trials will determine whether these responses translate into longer survival and durable responses. Recent studies comparing newer therapies with interferon- α have demonstrated increased progression-free survival for sunitinib when given as first-line treatment and improved survival for temsirolimus in untreated patients with metastatic RCC with poor prognosis (Hudes et al., 2007; Motzer et al., 2007).

Advances in RCC research have made this an optimistic time for patients and their families. Several advances in the understanding of the disease as well as treatment options for patients with RCC have been realized since the mid-1990s. New treatments have allowed patients more freedom and opportunity to resume activities of daily living. Patients who develop RCC in the future will no longer have to endure prolonged hospitalizations for intense treatments that offer only modest clinical benefits, creating a setting in which nurses will have the responsibility of teaching patients about their disease and helping them adapt to long-term RCC management.

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