Surgical resection remains the cornerstone of treatment for kidney cancer. The cytokines interleukin-2 and interferon-alfa were, at one time, the only available approved systemic therapies for metastatic disease. However, the two agents are toxic when used in high doses and associated with clinical benefit for only a small subset of patients. The approval of targeted agents sunitinib, sorafenib, temsirolimus, and everolimus has offered the possibility of improved outcomes for a greater number of patients. This article reviews surgical options for metastatic renal cell carcinoma as well as clinical trial data on treatment strategies with cytokines and targeted agents.

At a Glance
- High-dose interleukin-2 may induce durable responses in a small percentage of patients with metastatic renal cell carcinoma (RCC); however, the therapy is toxic and only suitable for a small patient population.
- Targeted agents approved for RCC include vascular endothelial growth factor and platelet-derived growth factor inhibitors, tyrosine kinase inhibitors, and mammalian target of rapamycin inhibitors.
- The nursing implications for those caring for patients with RCC have evolved with the addition of new treatment options.

Surgery is an important option for the initial treatment and palliation of symptoms from metastatic disease. Surgery remains the only curative option for nonmetastatic renal cell carcinoma (RCC). Radical nephrectomy, which includes a perifascial resection of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland, cures most patients with localized early-stage disease (Canda & Kirkali, 2006; National Comprehensive Cancer Network [NCCN], 2009). Radical nephrectomy is preferred for patients with large tumors or whose tumors extend into the inferior vena cava (Canda & Kirkali; NCCN).

Partial nephrectomy, or nephron-sparing surgery, preserves renal function. Because of advances in imaging techniques, tumors are being discovered at earlier stages. As a result, nephron-sparing surgery, which is recommended for tumors whose dimensions are 4–7 cm, is being increasingly used, producing outcomes equivalent to radical nephrectomy (Canda & Kirkali, 2006; NCCN, 2009). Patients with tumors in a peripheral location, or whose tumors are located over the upper or lower pole, are the most appropriate candidates for nephron-sparing surgery (NCCN), particularly important for patients who may already have had one kidney removed because of RCC or other reasons.

Surgical Management of Metastatic Renal Cell Carcinoma

About 25%–30% of patients with RCC present with metastases and about 20% of patients relapse even after complete resection of the primary tumor (Drucker, 2005; Schrader & Hofmann, 2008). An estimated 33%–50% of patients present with locally advanced or stage IV disease (Amato, 2005). The five-year survival rate for patients with metastatic RCC is less than 10% (Escudier, Eisen, et al., 2007). No systemic therapy used in the adjuvant setting has been proven to reduce the likelihood of relapse, which occurs most commonly in the lungs, bone, and brain (NCCN, 2009). For patients with metastatic RCC, surgical resection is used in combination with systemic therapy. Cytoreductive nephrectomy, by debulking the malignancy, can extend the survival of patients with metastatic disease. Randomized studies have shown that cytoreductive nephrectomy followed by systemic therapy can extend survival compared to systemic therapy alone (11.1 months versus 8.1 months; 17 months versus 7 months) (Flanigan et al., 2001; Mickisch, Garin, van Poppel, de Prijck, & Sylvester, 2001). Metastasectomy, or the surgical resection of metastases, also can be considered in some patients, particularly those with solitary or limited metastases (NCCN, 2009). In either of these settings, careful patient selection is necessary to identify patients who could benefit from this aggressive approach.

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important for the safe and rational integration of surgery and systemic therapies. Patients with a poor performance status, extensive burden of disease, sarcomatoid RCC, or uncontrolled brain or liver metastasis are not likely to benefit from surgery (Rini & Campbell, 2007).

Cytokine Therapy

RCC is resistant to traditional chemotherapy (Kroog & Motzer, 2008; Pantuck, Zisman, & Belldegrun, 2001). Interleukin (IL)-2 and interferon-alfa, which produce response rates of 10%–15%, were, at one point, the only therapeutic options for metastatic RCC (Motzer & Basch, 2007). The U.S. Food and Drug Administration (FDA) approved high-dose IL-2 monotherapy for the treatment of RCC in 1992 based on durable responses associated with prolonged disease-free survival in a small percentage of patients (objective response was observed in 15%, partial response in 8%, and complete response in 7%) (Chiron Corp., 2007). A study examining the long-term outcomes of IL-2 therapy in 330 patients with metastatic clear cell RCC showed that low-risk patients with a good Eastern Cooperative Oncology Group performance status, a long interval after RCC diagnosis, absence of liver metastasis, low number of disease sites, and normal neutrophil counts were most likely to benefit from IL-2 treatment. Patients with increased risks demonstrated a decrease in response, clinical benefit, and overall survival. Based on these findings, the authors concluded high-risk patients should not receive IL-2 but targeted agents instead (Klatte et al., 2008).

Trials of interferon-alfa have not shown a survival advantage or dose-response relationship. The agent produces a reduction in tumor burden in about 14% of RCC cases (Cohen & McGovern, 2005). Median duration of response is six months and rarely exceeds two years. Common toxicities associated with interferon-alfa include fatigue, anorexia, chills, fever, and liver enzyme abnormalities (Moldawer & Figlin, 2008).

A randomized, phase III trial by McDermott et al. (2005) assigned 192 patients with metastatic RCC to either high-dose IL-2 or IL-2 in combination with interferon-alfa. The response rate was 23.2% in the high-dose arm versus 9.9% in the combination arm. Ten patients in the high-dose interleukin arm achieved three-year progression-free survival versus three in the combination arm (see Figure 1). Median response durations were 14 and 7 months, respectively (p = 0.14), whereas median survival was 17.5 and 13 months, respectively (p = 0.24). The findings are consistent with the literature indicating that high-dose IL is the preferred form of cytokine therapy (McDermott et al.).

Targeted Therapies

Improvements in the understanding of the biology of RCC, specifically alterations in cellular protein interactions and relations to genetic mutations associated with RCC, have led to the development of targeted therapies. The number of FDA-approved treatments available for RCC has significantly risen with the development of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) inhibitors, tyrosine kinase inhibitors (TKIs), and mammalian target of rapamycin (mTOR) inhibitors.

Multikinase Inhibitors

Sorafenib, approved in 2005 for RCC, is an oral multitargeted TKI that interrupts tumor growth through inhibition of VEGF and PDGF receptors, which are important in tumor vasculature. Sorafenib acts intracellularly on the c-Raf and b-Raf kinase pathways, which normally help regulate cell proliferation by interrupting the processes that may lead to tumor regression (Wood & Manchen, 2007), and on c-kit, the receptor for stem cell factor. The Treatment Approaches in Renal Cancer Global Evaluation Trial evaluated sorafenib versus placebo in patients with treatment-refractory metastatic clear cell RCC. In the study, 903 treatment-refractory patients with relatively favorable prognoses were randomly assigned to either sorafenib or placebo (Onyx Pharmaceuticals, 2008). Patients in the sorafenib arm demonstrated longer progression-free survival across all subgroups (5.5 versus 2.8 months; p < 0.00001; hazard ratio [HR] 0.44; 95% confidence interval [CI]: 0.35–0.55), partial response (10% versus 2%), and stable disease (74% versus 53%). The most common adverse events experienced in the sorafenib arm included rash (40%), hand-foot skin reaction (30%), and diarrhea (43%) (Escudier, Eisen, et al., 2007).

HR is a measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, HR often is used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. An HR of one means that

![Graph showing Proportion Alive and Free From Progression](image-url)
there is no difference in survival between the two groups. An HR of greater than one or less than one means that survival was better in one of the groups (National Cancer Institute, 2009).

Sunitinib is an oral multitargeted agent that acts on the VEGF and PDGF receptors and c-kit. The FDA approved sunitinib for the treatment of metastatic kidney cancer in 2006. In a phase III trial of sunitinib versus interferon-alfa for the first-line treatment of clear cell RCC, the sunitinib arm showed a higher objective response (46% versus 12%), progression-free survival, and overall survival (Figlin et al., 2008) (see Figure 2). The most common adverse reactions with sunitinib included diarrhea (53% in the sunitinib arm versus 13% in the interferon-alfa arm), fatigue (51% in both arms), and nausea (44% versus 33%). The most common grade 3 or 4 adverse events were hypertension (8%), fatigue (7%), diarrhea (5%), and hand-foot skin reaction (5%). Patients in the sunitinib arm reported a significantly better quality of life than patients in the interferon-alfa arm (Figlin et al.; Kroog & Motzer, 2008).

The Adjuvant Sorafenib Sunitinib Unfavorable Renal Cell Carcinoma Trial (E2805) is an ongoing double-blind, phase III, placebo-controlled trial that randomly assigned patients to sunitinib 50 mg daily for four weeks during each six-week cycle for one year (Pfizer, Inc., 2008), sorafenib 400 mg twice a day for one year (Onyx Pharmaceuticals, 2008), or placebo daily for one year following complete surgical resection. The clinical benefit and tolerability of these agents as adjuvant therapies are being investigated (Eisen, 2007); because the study is still accruing patients, results will not be available for several more years.

Vascular Endothelial Growth Factor Inhibitors

Bevacizumab, approved by the FDA in 2009 to treat RCC, is a humanized monoclonal antibody that acts extracellularly and binds to the VEGF receptor, neutralizing its isoforms (see Figure 3). VEGF is an important regulator of angiogenesis. High expression levels correlate with poor prognosis, increased tumor vasculature, and vascular permeability, as well as endothelial cell survival, proliferation, and migration (Rini et al., 2008). In the phase III Avastin® for Renal Cell Cancer Trial, 649 patients with metastatic kidney cancer were randomly assigned to either bevacizumab and interferon-alfa or placebo and interferon-alfa (Escudier, Koralewski, et al., 2007). Bevacizumab doubled progression-free survival (10.2 versus 5.4 months; HR = 0.63; p < 0.0001) and objective tumor response rate (30.6% versus 12.4%; p < 0.0001). Combination therapy was generally well tolerated. The groups showed grade 3 and 4 toxicities associated with interferon-alfa therapy (e.g., fatigue, asthenia, neutropenia). Patients in the bevacizumab arm experienced thromboembolic events (3%) and gastrointestinal perforations (1%). Some patients in the bevacizumab arm discontinued treatment as a result of proteinuria (5%) and hypertension (2%).

mTOR Inhibitors

In 2007, the FDA approved temsirolimus, a targeted first-in-class mTOR inhibitor for the treatment of advanced kidney cancer. mTOR inhibitors block mTOR kinase, which causes the suppression of proteins that control the cell cycle and angiogenesis (Schrader & Hofmann, 2008). The phase III Global Advanced Renal Cell Carcinoma Trial evaluated 626 patients with poor risk features. Patients were randomly assigned to interferon, temsirolimus, or temsirolimus and interferon as first-line treatment. A statistically significant improvement was noted in overall survival in the temsirolimus arm (10.9 versus 7.3 months; p = 0.009; 95% CI: 0.58–0.92). The combination arm did not demonstrate benefit in overall survival, and the median progression-free survival was higher in the temsirolimus arm compared to the interferon-only arm (5.5 versus 3.1 months, respectively; p = 0.0001; 95% CI: 0.53–0.81). Temsirolimus also improved overall response rate (8.6 months versus 4.8; p = 0.1252). The most common adverse events in the temsirolimus arm included rash (47%), peripheral edema (27%), hyperlipidemia (27%), and hyperglycemia (27%). Additional studies are needed to delineate the role of temsirolimus in first-line therapy for metastatic disease and as second-line therapy after sunitinib (Hudes et al., 2007).

Everolimus, an oral mTOR inhibitor, was approved by the FDA in March 2009 for the treatment of patients with advanced RCC whose disease progressed following treatment with sunitinib, sorafenib, or both. This decision was made after everolimus demonstrated clinically significant improvement in progression-free survival in a phase III, international, multicenter trial (see Figure 4). Patients with metastatic RCC whose disease had progressed after treatment were randomized to receive everolimus 10 mg once daily (n = 277) or placebo (n = 139) along with best supportive care (Novartis Pharmaceuticals, 2009). In early
Clinical journals such as the Clinical Journal of Oncology Nursing are dedicated to providing up-to-date information on various aspects of oncology, including clinical trials, standards of care, and nursing considerations. A recent study in the journal, published in 2008, shed light on the role of an independent data monitoring committee in stopping a trial to allow patients on the placebo arm to cross over to the everolimus arm when it became evident that patients in the everolimus arm experienced delayed tumor growth or spread. The median progression-free survival was 4.9 months (95% CI: 4–5.5) versus 1.9 months (95% CI: 1.8 –1.9) in the placebo group (HR = 0.33; p < 0.0001). Overall survival results are not yet mature. The most common adverse events in the everolimus arm included stomatitis (44%), infections (37%), asthenia (33%), fatigue (31%), cough (30%), and diarrhea (30%). Adverse events warranting treatment discontinuation occurred in 14% of patients in the everolimus arm and in 3% of patients in the placebo arm. The most common adverse events leading to discontinuation were pneumonitis and dyspnea.

**Second-Line Treatment**

Clinical trials are the preferred second-line treatment for patients with metastatic RCC (NCCN, 2009). Everolimus, sorafenib, and sunitinib are recommended therapies for relapsed metastatic RCC. Other options include temsirolimus, interferon, high-dose IL-2, bevacizumab, low-dose IL-2 with and without interferon, and best supportive care. For all patients with metastatic RCC, supportive care is critical to improve outcomes. This care consists of surgical interventions for solitary brain metastases, spinal cord compression, and fractures of weight-bearing bones. Palliation therapy for metastatic RCC includes radiation therapy coupled with bisphosphonates, particularly for patients with painful bone metastases (NCCN).

**Nursing Considerations**

Just as treatment for RCC has evolved, so has the role of the oncology nurse. Disease education, presurgical education, postsurgical management (e.g., pain control, wound care, monitoring of renal function), and supportive care during treatment have long been established as important nursing functions (Moldawer & Figlin, 2008). The addition of novel targeted therapies to the RCC treatment landscape has magnified the role of the nurse as patient educator. Novel agents may be self-administered orally. The nurse is responsible for thoroughly educating patients on adherence to oral therapies. Uncontrolled side effects of novel therapies may lead to treatment interruption or discontinuation, which could negatively impact patient outcome (Onyx Pharmaceuticals, 2008; Pfizer, Inc., 2008). Therefore, nurses should be aware of the latest treatment options as well as their related side-effect profiles. Articles by Laura S. Wood, RN, MSN, OCN®, on pages 13–18 and Patricia A. Creel, BSN, RN, OCN®, CCRP, on pages 19–23 of this supplement provide more information on monitoring and managing side effects from these newer therapies.
Conclusion

Progress in understanding the biology and genetics of RCC has led to the development of novel targeted therapeutics that have demonstrated improved outcomes for a broader spectrum of patients. Ongoing clinical trials are evaluating the safety and efficacy of other cytokine therapies, including IL-6, IL-12, and IL-21, and targeted therapies including ticilumumab and ipilimumab, in an effort to expand the treatment armamentarium against metastatic RCC (Wang, 2007; Weber, 2007). Clinical trials for RCC can be found at www.clinicaltrials.gov.

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