The Emergence of Thalidomide in Treating Advanced Renal Cell Carcinoma

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Purpose/Objectives: To review standard and investigational treatments in advanced renal cell carcinoma, with a focus on thalidomide.

Data Sources: Published articles, conference proceedings, treatment guidelines, and textbooks.

Data Synthesis: The prognosis for advanced renal cell carcinoma when treated with standard regimens is poor; therefore, new treatments are needed.

Conclusions: Treatment with thalidomide, alone and in combination with other therapies, may improve survival for patients with advanced renal cell carcinoma.

Implications for Nursing: Proactive management of adverse effects associated with thalidomide, alone and in combination, may increase patient tolerance and compliance.

Renal cell carcinoma is the tenth leading cause of cancer death among men in the United States, accounting for 3% of malignancies (Jemal et al., 2003). Of the forms of kidney cancer, renal cell carcinoma accounts for 85% of diagnosed cases (Motzer, Bander, & Nanus, 1996). The average age at diagnosis is 50–70 years, with a 2:1 male to female predominance (Bukowski & Novik, 1997). An estimated 31,900 new cases of kidney cancer are projected to be diagnosed in the United States in 2003 (Jemal et al.), and 25%–33% of these patients will present with metastatic or advanced disease. Although the overall survival is approximately 50% for renal cell carcinoma, the median survival rate for patients with metastatic disease is 7–11 months (Amato, 2000).

Renal cell carcinoma historically has been considered a single cancer expressing multiple possible histologic appearances. Currently, the disease is viewed as a group of cancers resulting from different genetic abnormalities that have distinct morphologic features, all derived from renal tubular epithelium (Pantuck, Zisman, & Belldegrun, 2001). The size of the tumors can range from a few centimeters to very large tumors that fill the peritoneal space (Early & Poquette, 2000). Clear cell carcinoma (also known as conventional or nonpapillary) is the most common type of renal tumor, accounting for approximately 70%–80% of cases. Clear cell renal cell carcinoma is believed to begin in the proximal renal tubule in a hereditary or sporadic form (Pantuck et al.).

Papillary renal cell carcinoma is the second most common histologic type of renal cell carcinoma, accounting for approximately 10% of cases (Mancilla-Jimenez, Stanley, & Blath, 1976). Like clear cell tumors, papillary renal cell carcinoma is believed to begin in the proximal renal tubular epithelium in

Key Points . . .

- Despite extensive investigation of systemic chemotherapy, hormonal therapy, and immunotherapy, the survival rate for patients with advanced renal cell carcinoma remains low.
- Immunotherapy, including treatment with interferon-a and interleukin-2, is currently the most common treatment for advanced renal cell carcinoma.
- Renal cell carcinoma is a highly vascular tumor, and angiogenesis is central to its growth. Antiangiogenic agents such as thalidomide may inhibit tumor growth.
- The most common side effects of thalidomide are somnolence, constipation, peripheral neuropathy, and rash.

Goal for CE Enrollees:

To further enhance nurses' knowledge regarding the treatment of advanced renal cell carcinoma.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Describe the current treatment options available for patients with renal cell carcinoma.
2. Describe the most common side effects of thalidomide for renal cell carcinoma.
3. Discuss the nursing management of the side effects of thalidomide.

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either a hereditary or sporadic form (Zambrano, Lubensky, Merino, Linehan, & Walther, 1999).

In addition to age and gender, race and geographic location are related to kidney cancer incidence. Occurrence among whites and blacks is about equal; however, Hispanics are diagnosed 33% more often than white Americans (Early & Poquette, 2000). Although the etiology of renal cell carcinoma is unknown, several risk factors have been identified, including obesity, smoking, hypertension, diuretic use, consumption of fried meat, asbestos exposure, petroleum exposure, and frequent analgesic use (Dhote, Pellicer-Coeuret, Thiounn, Debre, & Vidal-Trecan, 2000).

Advanced Renal Cell Carcinoma

Renal cell carcinoma is associated with a wide range of systemic symptoms, such as microscopic and gross hematuria, anemia, polycythemia, hypercalcemia, weight loss, malaise, acute varicocele, and fever (Skinner, Colvin, Vermillion, Pfister, & Leadbetter, 1971). The most common presentations are hematuria (50%–60% of patients), pain (40%), and a palpable flank or abdominal mass (30%–40%) (Early & Poquette, 2000; Motzer et al., 1996). Approximately 10%–20% of patients present with all three common manifestations (Early & Poquette). Evaluation of the cancer's extent should include a bone scan, a chest x-ray, and head, chest, abdominal, and pelvic computerized tomography scans to examine the regional nodes and lung, which are the most common sites of early metastatic disease (Newhouse, 1993; Russo, 2000; Tammela, Leinonen, & Kontturi, 1991).

At diagnosis, prognostic determinants of five-year survival are the local extent of the tumor, presence of regional node metastases, and presence of metastatic disease. Two staging systems are in use: the International Union Against Cancer tumor-node-metastasis (TNM) classification and the Robson system (Russo, 2000). The TNM system more explicitly describes the extent of local and regional disease (Fleming et al., 1998; Russo) (see Table 1). Table 2 presents Robson staging by the TNM classification (Robson, Churchill, & Anderson, 1969; Russo). Advanced renal cell carcinoma is defined as stages III and IV.

The most significant prognostic factor in renal cell carcinoma is the stage at presentation. Surgical resection is the sole effective treatment for clinically localized tumors (Russo, 2000). Of patients with clinically localized disease, 20%–30% develop metastatic disease following nephrectomy (Godley & Taylor, 2001). At the time of presentation, 30% of patients have metastatic disease with a variable five-year survival rate generally less than 2% and a median survival of less than one year (Childs et al., 2000; Figlin, 2000; Godley & Taylor).

Of patients with metastatic renal cell carcinoma, 75% have metastasis to the lung and 36% to soft tissues. Following these, 20% of patients experience metastasis to the bone, 18% to the liver, 11% to the brain, 8% to cutaneous sites, and 8% to the central nervous system (Linehan, Zbar, Bates, Zelefsky, & Yang, 2001) (see Table 3).

Treatments for Advanced Renal Cell Carcinoma

Despite extensive investigation of systemic chemotherapy, hormonal therapy, and immunotherapy, alone or in combination, the five-year survival rate for patients with metastatic renal cell carcinoma is only 5%–10% (Russo, 2000). Radical nephrectomy is the standard of care for early-stage renal cell carcinoma. Partial nephrectomy or nephron-sparing surgery may be performed when preservation of renal function is needed (Godley & Taylor, 2001). Nephrectomy plus interferon-a (IFN-a) has prolonged survival compared with IFN-a alone (Flanigan et al., 2001).

Historically, a radical nephrectomy has included a concomitant and complete retroperitoneal lymph node dissection (Russo, 2000). Today, the accepted rationale for lymphadenectomy is to (a) improve staging accuracy, (b) resect micrometastatic disease, and (c) determine whether enlarged regional nodes are inflammatory or metastatic (Russo; Studer et al., 1990). The therapeutic advantage of complete lymph node dissection at the time of nephrectomy remains unclear; however, clinical data compiled since the 1970s show that finding even one positive lymph node signifies poor prognosis (Russo). In general,

Table 1. Tumor-Node-Metastasis Classification

Category	Description
T: Primary tumor	
Tx	Primary tumor cannot be assessed.
T0	No evidence of primary tumor
T1	≤ 7.0 cm; limited to kidney
T2	> 7.0 cm; limited to kidney
T3	Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3a	Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3b	Tumor grossly extends into renal vein(s) or vena cava below diaphragm
T4	Tumor invades beyond Gerota's fascia
N: Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph nodes metastasis
N1	Metastasis in a single regional lymph node
N2	Metastasis in > 1 regional lymph node
M: Distant metastasis	
Mx	Distant metastasis cannot be assessed.
M0	No distant metastasis
M1	Distant metastasis

Note. From "Renal Cell Carcinoma: Presentation, Staging, and Surgical Treatment" by P. Russo, 2000, *Seminars in Oncology, 27*, 162. Copyright 2000 by W.B. Saunders. Reprinted with permission.

Table 2. Stage Grouping

Stage	Tumor-Node-Metastasis Class
I	T1, N0, M0
II	T2, N0, M0
III	T1, N1, M0
	T2, N1, M0
	T3, N0, N1, M0
IV	T4, N0, N1, M0
	Any T, N2, M0
	Any T, any N, M1

Note. From "Renal Cell Carcinoma: Presentation, Staging, and Surgical Treatment" by P. Russo, 2000, *Seminars in Oncology, 27*, 163. Copyright 2000 by W.B. Saunders. Adapted with permission.

Table 3. Sites of Metastasis for Renal Cell Carcinoma

Site	Patients (%)
Lung	75
Soft tissues	36
Bone	20
Liver	18
Brain	11
Cutaneous sites	8
Central nervous system	8

Note. Based on information from Linehan et al., 2001.

the presence of positive lymph nodes is associated with a five-year survival rate of less than 20% (Russo).

Surgical resection of metastases is recommended for patients with stage IV disease who present with a solitary site of metastasis at the time of diagnosis or who experience a solitary recurrence following nephrectomy (Motzer, Bahnson, et al., 2002). In one study of 59 patients with renal cancer who underwent surgical resection for a solitary metastasis, the three- and five-year survival rates were 45% and 34%, respectively (Linehan et al., 2001; Middleton, 1967).

The intrinsic resistance of advanced renal cell carcinoma to chemotherapy, although poorly understood, is a hallmark of this diagnosis (Linehan et al., 2001; Middleton, 1967). No single agent has produced consistent, overall response rates higher than 10%–15% (Godley & Taylor, 2001; Motzer, 1997; Vogelzang & Stadler, 1998; Yagoda, Petrylak, & Thompson, 1993). Combination chemotherapy has not been successful, and no regimen has yielded results that are superior to single-agent therapy (Motzer). A phase II trial evaluated weekly gemcitabine plus continuous infusion 5-fluorouracil in 41 patients with metastatic renal cell carcinoma (Rini et al., 2000). Eighty percent of the patients had multiple sites of metastasis. No complete responses were noted, and 17% of patients achieved partial responses. Progression-free survival was 28.7 weeks.

A comprehensive review of systemic chemotherapy examined 4,542 patients enrolled in 83 clinical trials published from 1983–1993 and included reports of the use of compounds from every class of anticancer agent (Yagoda, Abi-Rached, & Petrylak, 1995). A 6% response rate was recorded among the 4,093 evaluable patients, with 53 complete responses (1.3%) and 192 partial responses (4.7%). Linehan et al. (2001) concluded that systemic chemotherapy is ineffective in the treatment of advanced renal cell carcinoma; new agents and new approaches are needed.

Immunotherapy is currently the most common treatment for advanced renal cell carcinoma (Linehan et al., 2001). Cytokines interleukin-2 (IL-2) and IFN-a, alone or in combination, have yielded response rates of 10%–20% (Godley & Taylor, 2001). In a retrospective analysis of 670 patients with advanced renal cell carcinoma (Motzer et al., 2000), patients treated with cytokine therapy had a significantly longer survival rate compared with those treated with chemotherapy. The optimal dose and schedule for IL-2 and IFN-a have not been determined (Linehan et al.), and clinical trials continue to evaluate these agents in the treatment of advanced renal cell carcinoma. Table 4 summarizes the results of clinical trials of IL-2 and IFN-a as single agents and in combination.

Common side effects of IL-2 and IFN-a include flu-like symptoms, fatigue, cognitive dysfunction, myelosuppression, abnormal liver function, and anorexia (Early & Poquette, 2000). With bolus-infusion IL-2, toxicity depends on the dose used (Bukowski, 2001). High-dose IL-2 has exhibited cardiovascular, pulmonary, and central nervous system toxicity (Yang et al., 1994). Lower dose regimens are associated with less severe toxicity; however, the response frequency, duration, and median survival remain preliminary (Yang & Rosenberg, 1997).

The value of adjuvant external beam radiation for patients with renal cell carcinoma remains unclear. For patients with metastatic brain lesions, radiation can improve quality of life, local control, and overall survival (Godley & Taylor, 2001). Palliative radiotherapy also can be beneficial for patients with symptomatic, metastatic bony lesions (Linehan et al., 2001).

Although vaccine-based approaches for advanced renal cell carcinoma have been studied for a number of years, these approaches generally have been unsuccessful (Nanus, 2000). Because of advances in basic immunology since the early 1990s, identifying specific tumor antigens in kidney cancer that the immune system can recognize may be possible (Wolchok & Motzer, 2000). Several possible targets for new vaccines are being explored (see Table 5).

Investigations into new treatments for advanced renal cell carcinoma are being conducted in other areas of clinical science, including T cell immunity, bone marrow transplantation, and monoclonal antibodies (Nanus, 2000). Each of these areas may hold some promise in finding better ways to elicit tumor response, stabilize disease, and prolong survival. Identifying new agents with increased antitumor activity is a high priority (Nanus).

Thalidomide

Thalidomide is classified as an immunomodulatory agent because it affects the level of an immune response. Although its spectrum of activity is not fully characterized (Celgene Corporation, 2003), thalidomide has been shown to affect multiple targets within the immune system and microenvironment. This agent can suppress levels of angiogenic and growth factors including tumor necrosis factor-a, basic fibroblast growth factor, vascular endothelial growth factor, and IL-6.

Thalidomide first was used in Europe in the late 1950s, both as a sleeping aid and as a treatment for morning sickness during pregnancy. However, its use by pregnant women resulted in the birth of thousands of deformed babies with attenuated, flipper-like extremities (Lenz, 1966, 1968; Richardson, Hideshima, & Anderson, 2002). Research into the cause of this teratogenicity revealed thalidomide's antiangiogenic properties (D'Amato, Loughnan, Flynn, & Folkman, 1994). Thalidomide was not approved for any indication in the United States until the late 1990s, when it was found to have a role in the treatment of erythema nodosum leprosum, a serious inflammatory condition in patients with Hansen disease (i.e., leprosy).

Renal cell carcinoma is a highly vascular tumor, and angiogenesis is central to its growth. Angiogenesis in carcinomas frequently is associated with metastasis and a potentially poorer prognosis (Folkman, 1995). Antiangiogenic

Table 4. Trials of Cytokines in Advanced Renal Cell Carcinoma

Agent and Trial	Regimen and Dose	N	Median Age (years)	Response Rate (%)	Median Survival (months)	Complete Response		Partial Response		Comments
						n	%	n	%	
IL-2 (Fyfe et al., 1995)	High-dose bolux infusion 600,000 IU/kg or 720,000 IU/kg	255	52	14	11	12	5	24	9	Substantial toxicity was found in 50% of patients requiring vasopressors. Responses occurred in all sites of disease.
IL-2 (Law et al., 1995)	Inpatient high-dose bolus infusion	537	NR	19	NR	33	6	70	13	This literature survey examined 39 published studies.
	Inpatient moderate-dose bolus or continuous IV	650	NR	15	NR	29	4	76	11	
	Outpatient low-dose SC or IV	104	NR	20	NR	4	4	13	13	
IL-2 (Yang & Rosenberg, 1997)	High-dose bolus infusion (720,000 IU/kg)	115	NR	19	NR	9	8	13	11	Patients had no previous IL-2 therapy. Median follow-up at 52 months showed no significant difference in overall survival between the two arms.
	Low-dose IV (72,000 IU/kg)	112	NR	10	NR	5	4	6	5	
IL-2 and IFN-a (Vogelzang et al., 1993)	Wide variations in dose and route of administration	607	NR	19	NR	NR	NR	NR	NR	This literature survey of 23 studies revealed similar results to IL-2 alone. Variations in dose, schedule, and patient criteria did not clearly identify an optimal dose and schedule for combining these agents.
IFN-a (Wirth, 1993)	Various doses and routes of administration (IM, SC, IV)	1,042	NR	12	NR	22	2	111	10	A positive correlation was found between the dose and response. Increasing the IFN dose led to more frequent and more pronounced side effects.
IFN-a (Medical Research Council Renal Cancer Collaborators, 1999)	5–10 MU per injection	167	NR	16	8.5	2	2	14	2	Fifty-eight percent of patients had nephrectomy, and 83% had multiple sites of metastases.
IFN-a and vinblastine (Kriegmair et al., 1995)	8 MU SC per day of IFN-a and 0.1 mg/kg/day vinblastine via IV	41	62.4 ($\bar{X}$)	20.5	16	4	10	5	12	Fifty-seven percent of patients had lung metastases, 35% bone metastases, and 25% lymph node metastases.
IFN-a and vinblastine (Pyrhonen et al., 1999)	3–18 MU IFN-a per SC injection and 0.1 mg/kg/day vinblastine via IV	79	60	16.5	17	7	9	6	8	Ninety percent of the patients had prior nephrectomy, 67% had lung metastases, and 43% had lymph node metastases.
IFN-a	3–9 MU SC per day	145	60	6	15	1	1	8	5	Fifty-one percent had prior nephrectomy, and 65% had two or more sites of metastases.
IFN-a plus 13-cis-retinoic acid (Motzer et al., 1999)	3–9 MU IFN-a SC per day and 1 mg/kg/day cis-retinoic acid PO	139	60	11	15	5	4	10	7	

IFN-a—interferon-a; IL-2—interleukin-2; IM—intramuscular; MU—million units; NR—not reported; PO—orally; SC—subcutaneous

Table 5. Possible Targets for New Kidney Cancer Vaccines

Vaccine Target	Rationale
Prostate-specific membrane antigen	Expression on the tumor vasculature of numerous solid tumors, including renal cell carcinomas
MAGE-3	T cell target in melanoma; expressed in a large percentage of kidney tumor samples and cell lines
HER-2/neu	Growth factor receptor overexpressed in renal cell carcinomas
von Hippel-Lindau gene	Unique mutations in kidney cancer

Note. From "Management of Renal Cell Carcinoma" by J.D. Wolchok and R.J. Motzer, 2000, *Oncology (Huntington)*, *14*(1), 32. Copyright 2000 by *Oncology*. Adapted with permission.

agents, such as thalidomide, may prove valuable as a new approach for inhibiting cancer growth (Stebbing et al., 2001). The antiangiogenic activity of thalidomide has been shown to eradicate experimental tumors in mice (Ching et al., 1995).

Thalidomide as a Single Agent

A British phase II study evaluating high-dose thalidomide (i.e., 600 mg a day) demonstrated that the agent has antitumor activity in previously treated patients with advanced renal cell carcinoma (Stebbing et al., 2001). Although results varied among patients, 2 of 22 evaluable patients (9%) achieved a partial response and seven patients (32%) achieved disease stabilization for more than six months. Table 6 summarizes the results of phase II clinical trials of single-agent thalidomide in patients with metastatic renal cell carcinoma. Overall, the researchers of these trials believed their results warranted further investigation of thalidomide as a single agent and in combination regimens.

Thalidomide in Combination Regimens

Combination therapy, including the use of thalidomide with other cytotoxic drugs, may have greater activity against renal cancer than using these treatments alone (Stebbing et al., 2001). Two recent phase I trials evaluated dose, side effects, and potential response for thalidomide in combination with IL-2 (see Table 7). A study conducted at the Cleveland Clinic reported moderate side effects, including dyspnea in one patient, grade two desquamation and pruritus in five patients, and grade three symptomatic neutropenia in three patients (Olencki, Dreicer, Elson, Wood, & Bukowski, 2002). Amato, Breheny, and Tracy (2002) reported that thalidomide generally was tolerated well.

The highest documented response rates in kidney cancer occurred in one study that evaluated a combination of IFN-a, 5-fluorouracil, and IL-2; however, considerable side effects were reported (Lopez-Hanninen, Kirchner, & Atpodien, 1996). The activity of thalidomide may provide a rationale for combining this agent with biochemotherapy to reduce side effects and increase the efficacy of treatment (Eisen et al., 2000). Single-agent thalidomide, as well as biotherapy, has demonstrated activity in renal cancer. Therefore, combining several active agents may increase efficacy. Because combinations of biotherapy agents have resulted in considerable toxicity, adding thalidomide and altering the biotherapy combination may reduce toxicity.

Palliative Effects of Thalidomide

Thalidomide appears to have some palliative effects, including enhanced or maintained appetite, improved sleeping, and reduced sweating, on the symptoms of renal cell carcinoma. Patients receiving diabetic treatment have reported marked improvements in their glucose tolerance while receiving thalidomide, sometimes allowing a reduction in their diabetic medication. In patients receiving concomitant IFN-a, thalidomide has helped to reduce anorexia and other IFN-a–related side effects (Eisen, 2000).

Issues Related to Use

The U.S. Food and Drug Administration has imposed unprecedented restrictions on the distribution of thalidomide because of its potential for causing birth defects (Richardson et al., 2002; Zeldis, Williams, Thomas, & Elsayed, 1999). In addition, the System for Thalidomide Education and Prescribing Safety (STEPS® [Celgene Corporation, Warren, NJ]) program was designed to maximize the safety of thalidomide use (Celgene Corporation, 2003). The STEPS program, a patient registration and tracking system, requires that only registered doctors prescribe thalidomide, only registered pharmacies dispense the drug, and only properly counseled and registered patients receive the drug. Anyone taking thalidomide, regardless of age, sex, or health status, must register with STEPS (Celgene Corporation).

Patient education is particularly important with thalidomide use. Women must be counseled to take frequent pregnancy tests and use two forms of birth control for four weeks before, during, and four weeks after thalidomide treatment when having heterosexual intercourse. Men taking thalidomide must use condoms, even if they have had vasectomies. In addition, patients taking thalidomide must not breastfeed or donate blood or sperm (Celgene Corporation, 2003).

Administration

Thalidomide is an oral agent that is supplied in 50 mg, 100 mg, and 200 mg capsules (Celgene Corporation, 2003). Optimal dose and duration of thalidomide treatment in renal cell carcinoma is not yet established. Because of the somnolence associated with higher doses, a dose of 200 mg a day usually is prescribed at the outset of treatment, with a target dose of 400 mg a day (Stebbing et al., 2001). Patient tolerance to thalidomide may be improved by slow dose titration and proactive management of side effects.

Baseline Assessment and Monitoring

Before starting thalidomide, as well as during the course of treatment, patients may undergo several tests to assist in monitoring the response to the drug and its toxicities. These tests include a complete blood count, serum chemistry, liver function tests, a sensory nerve action potential test, electrocardiogram, and serum pregnancy test for women of childbearing potential (Stebbing et al., 2001).

Side Effects

The most common side effects of thalidomide therapy include drowsiness and somnolence, constipation, peripheral neuropathy, and rash (Celgene Corporation, 2003; Eisen et al., 2000; Motzer, Berg, et al., 2002; Stebbing et al., 2001). Other side effects include edema, ataxia, bradycardia, deep vein thrombosis, and neutropenia (Celgene Corporation; Motzer,

Table 6. Results of Phase II Thalidomide Trials

Study	Thalidomide Dose (mg)	N	Median Age (years)	Partial Response		Stable Disease		Minor Response		Selected Patient Characteristics
				n	%	n	%	n	%	
Eisen et al., 2000	100	18	NR	3	17	13	72	NR	NR	Aggressive, advanced disease progressed after treatment with IFN-a, 5-fluorouracil, and IL-2.
Minor & Elias, 2000	400–1,200	12	NR	1	8	3	25	1	8	Advanced, metastatic disease was found. Previous high-dose IL-2 had been used by responders.
Escudier et al., 2001	400–1,200	33	61	2	6	11	33	1	3	Heavy pretreatment was reported with nephrectomy, immunotherapy, radiotherapy, and/or chemotherapy.
Li et al., 2001	200–1,200	29	53	2	7	9	31	NR	NR	Disease progressed after treatment with IL-2.
Novik et al., 2001	100–1,000	27	59	–	–	7	26	NR	NR	Prior therapy with high-dose, moderate, or SC IL-2; IFN-a; or IL-2 or IFN-a was reported.
Srinivas, 2001	200–800	10	61	–	–	3	30	1	10	Prior nephrectomy and/or immunotherapy was reported. Lung metastasis was found in 80% of patients.
Stebbing et al., 2001	600	22	51	2	9	7	32	NR	NR	All but one patient was treated previously with surgery or systemic therapy. All patients had progressive disease.
Motzer, Berg, et al., 2002	200–800	25	58	–	–	16	64	NR	NR	Prior nephrectomy, cytokine therapy, and monoclonal antibody therapy were reported. Some patients had previously untreated renal cancer.

IFN-a—interferon-a; IL-2—interleukin-2; NR—not reported; SC—subcutaneous

Berg, et al.). To help prevent lethargy, thalidomide should be taken midevening, at least two hours after eating, or at bedtime; the dose may be increased gradually until the optimum dose is achieved (Eisen, 2000). Drowsiness can carry over into the following day; therefore, patients should be instructed to avoid activities such as driving a car or operating equipment. Other lethargy-inducing drugs (e.g., antihistamines) and alcohol are not recommended during treatment. Conducting quality-of-life assessments with patients can help to identify patients' experiences with and reactions to lethargy. For some patients, chronic drowsiness can lead to feelings of depression. Patients experiencing unacceptable drowsiness may have their dosage reduced (Stebbing et al.).

Constipation, although common, is rarely severe and can be alleviated by fluid intake and aggressive laxative therapy (Eisen, 2000). Adding fiber to the diet can help to minimize

Table 7. Phase I Thalidomide Trials in Combination With Low-Dose Subcutaneous Interleukin-2

Study	Thalidomide Dose (mg)	N	Median Age (years)	Complete Response		Partial Response		Stable Disease		Selected Patient Characteristics
				n	%	n	%	n	%	
Amato et al., 2002[a]	200–600 and low-dose IL-2 7 mIU/m^2	10	56	1	10	5	50	2	20	All patients had prior nephrectomy. Patients completed 12 weeks of therapy.
Olencki et al., 2002[b]	100–400 and varying low-dose IL-2	19	62	NR	NR	1	5	NR	NR	Prior nephrectomy (95% of patients) or systemic treatment (63% of patients) with immunotherapy, radiotherapy, or chemotherapy was reported.

[a] Phase II portion of study is continuing.

[b] Study is continuing.

IL-2—interleukin-2; NR—not reported

the risk of constipation. Fruit smoothies, which can support hydration needs, bowel function, and daily vitamin and nutrient requirements, also can help to reduce constipation. If constipation becomes severe, physicians may lower the thalidomide dose (Stebbing et al., 2001).

Peripheral neuropathy during thalidomide treatment often presents as a tingling sensation in the hands and feet; however, in rare cases, peripheral neuropathy can be severe and painful. Baseline and follow-up sensory nerve action potential tests may be conducted before and during treatment to identify the existence of subclinical neuropathy (Eisen, 2000; Eisen et al., 2000). Amitriptyline or gabapentin may be ordered because they have been reported anecdotally to reduce neuropathy.

Up to 21% of patients may develop an itchy skin rash (Celgene Corporation, 2003). This rash can be pruritic and erythematous, can occur during thalidomide therapy (Eisen et al., 2000), and usually is alleviated by prescribing a nonsedating antihistamine (Eisen, 2000). Topical corticosteroids also may provide relief. Severe and potentially fatal dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis syndrome, occur more rarely and require cessation of treatment and immediate attention (Celgene Corporation). For patients experiencing symptoms of desquamation, baths and lotions such as colloidal oatmeal may provide adequate relief.

Discussion

Although more data are needed to fully evaluate the potential of thalidomide in the treatment of advanced renal cell carcinoma, the therapy shows activity in producing disease stabilization and, secondarily, partial response when administered as a single agent. As the results of clinical trials are aggregated and analyzed, more will be understood about the action of thalidomide as a single agent and in combination with other therapies, including side effects and palliative effects on the symptoms of advanced renal cell carcinoma.

Additional research is needed to understand the potential effectiveness of thalidomide in achieving a response when used in combination with the cytokine therapies IL-2 and IFN-a. Early indications show potential in disease stabilization and partial response. Issues of dose, schedule, and management of toxicities must be resolved in future studies evaluating thalidomide, IL-2, and IFN-a.

Nurses play an important role for patients receiving thalidomide for advanced renal cell carcinoma with respect to providing patient education about the drug and helping patients to manage side effects. Nursing interventions may contribute to patients staying on thalidomide for the determined course of treatment.

Education

Before starting on therapy, patients need to understand their role in the registration requirements for thalidomide treatment, including providing informed consent and participating in comprehensive counseling on the benefits and risks of thalidomide (e.g., contraceptive counseling). Following this, education on the dose, schedule, and common side effects of thalidomide, including IL-2 and IFN-a if patients receive combination therapy, must be presented so that patients can monitor their functional status while on the drug. Patients should understand the signs and symptoms of the more serious side effects, including progressive neuropathy, deep vein thrombosis, and dermatologic reactions.

Other important information about the treatment that nurses must emphasize to patients includes avoiding driving or operating equipment when experiencing drowsiness, drinking adequate fluids to support hydration needs and bowel function, eating a nutritious diet, and exercising and maintaining activities of daily living as much as possible.

Monitoring

Ongoing clinical monitoring is critical to early intervention and to increasing patients' tolerance to thalidomide for the duration of the therapy schedule.

Routine monitoring includes assessing patients' alertness, energy level, and gait; chemistry profiles for magnesium or other vitamin and mineral deficiencies; signs of peripheral neuropathy, rash, desquamation, and deep vein thrombosis; laboratory values for indications of neutropenia and eosinophilia, particularly in patients receiving thalidomide in combination with IL-2; and injection sites for reactions to IFN-a and IL-2.

Summary

Renal cell carcinoma is associated with high rates of morbidity and mortality. No current standard treatment option exists for metastatic renal cell carcinoma. Despite extensive investigation of systemic chemotherapy, hormonal therapy, and immunotherapy, alone or in combination, the five-year survival rate for patients who have undergone treatment for metastatic renal cells carcinoma remains only 5%–10% (Russo, 2000).

Thalidomide has been shown to suppress levels of several cytokines, several angiogenic and growth factors, and IL-6. Because of the role these factors play in renal cell carcinoma, thalidomide should be investigated as a treatment option. Researchers have concluded that current study results warrant further investigation of thalidomide as a single agent and in combination regimens for the treatment of metastatic renal cell carcinoma (Eisen et al., 2000; Escudier et al., 2001; Li et al., 2001; Novik, Kutcher, Larkin, & Wiernik, 2001; Stebbing et al., 2001).

Because of the unique toxicities of this therapy, the role of nurses in educating and monitoring patients receiving thalidomide is of great importance. Skillful nursing may maximize patient compliance for the duration of treatment with thalidomide while limiting the incidence of side effects.

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References

Amato, R. (2000). Chemotherapy for renal cell carcinoma. *Seminars in Oncology, 27,* 177–186.

Amato, R.J., Breheny, S., & Tracy, E. (2002). Phase I/II study of thalidomide + interleukin II (IL-2) for patients with metastatic renal cell carcinoma [Abstract 759]. *Proceedings of the American Society of Clinical Oncology, 21,* 190a.

Bukowski, R.M. (2001). Cytokine therapy for metastatic renal cell carcinoma. *Seminars in Urologic Oncology, 19,* 148–154.

Bukowski, R.M., & Novik, A.C. (1997). Renal-cell carcinoma. *New England Journal of Medicine, 335,* 865–875.

Celgene Corporation. (2003). Thalomid® [Package insert]. Warren, NJ: Author.

Childs, R., Chernoff, A., Contentin, N., Bahceci, E., Schrump, D., Leitman, S., et al. (2000). Regression of metastatic renal cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. *New England Journal of Medicine, 343,* 750–758.

Ching, L.M., Xu, Z.F., Gummer, B.H., Palmer, B.D., Joseph, W.R., & Baguley, B.C. (1995). Effect of thalidomide on tumour necrosis factor production and anti-tumour activity induced by 5,6-dimethylxantheone-4-acetic acid. *British Journal of Cancer, 72,* 339–343.

D'Amato, R.J., Loughnan, M.S., Flynn, E., & Folkman, J. (1994). Thalidomide is an inhibitor of angiogenesis. *Proceedings of the National Academy of Sciences of the United States of America, 91,* 4082–4085.

Dhote, R., Pellicer-Coeuret, M., Thiounn, N., Debre, B., & Vidal-Trecan, G. (2000). Risk factors for adult renal cell carcinoma: A systematic review and implications for prevention. *British Journal of Urology International, 86*(1), 20–27.

Early, L.M., & Poquette, R.M. (2000). Bladder and kidney cancer. In C.H. Yarbro, M. Goodman, M.H. Frogge, & S.L. Groenwald (Eds.), *Cancer nursing: Principles and practice* (5th ed., pp. 973–993). Boston: Jones and Bartlett.

Eisen, T., Boshoff, C., Mak, I., Sapunar, F., Vaughan, M.M., Pyle, L., et al. (2000). Continuous low dose thalidomide: A phase II study in advanced melanoma, renal cell, ovarian, and breast cancer. *British Journal of Cancer, 82,* 812–817.

Eisen, T.G. (2000). Thalidomide in solid tumors: The London experience. *Oncology (Huntington), 14*(12 Suppl. 13), 17–20.

Escudier, B., Lassau, N., Couanet, D., Angevin, E., Leborgne, S., Garofano, A., et al. (2001). Phase II trial of thalidomide in renal-cell carcinoma [Abstract 718]. *Proceedings of the American Society of Clinical Oncology, 20,* 180a.

Figlin, R.A. (2000). Renal cell carcinoma: Current status and future plans. *Cancer Journal From Scientific American, 1*(Suppl. 6), S52–S54.

Flanigan, R.C., Salmon, S.E., Blumenstein, B.A., Bearman, S.I., Roy, V., McGrath, P.C., et al. (2001). Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *New England Journal of Medicine, 345,* 1655–1659.

Fleming, I.D., Cooper, J.S., Henson, D.E., Hutter, R.V.P., Kennedy, B.J., Murphy, G.P., et al. (1998). *AJCC cancer staging manual* (5th ed., pp. 215–218). Philadelphia: Lippincott Williams and Wilkins.

Folkman, J. (1995). Clinical applications of research on angiogenesis. *New England Journal of Medicine, 333,* 1757–1763.

Fyfe, G., Fisher, R.I., Rosenberg, S.A., Sznol, M., Parkinson, D.M., & Louie, A.C. (1995). Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *Journal of Clinical Oncology, 13,* 688–696.

Godley, P.A., & Taylor, M. (2001). Renal cell carcinoma. *Current Opinion in Oncology, 13,* 199–203.

Jemal, A., Murray, T., Samuels, A., Ghafoor, A., Ward, E., & Thun, M. (2003). Cancer statistics, 2003. *CA: A Cancer Journal for Clinicians, 53,* 5–26.

Kriegmair, M., Oberneder, R., & Hofstetter, A. (1995). Interferon alpha and vinblastine versus medroxyprogesterone acetate in the treatment of metastatic renal cell carcinoma. *Urology, 45,* 758–762.

Law, T.M., Motzer, R.J., Mazumdar, M., Sell, K.W., Walther, P.J., O'Connell, M., et al. (1995). Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in the treatment of patients with advanced renal cell carcinoma. *Cancer, 76,* 824–832.

Lenz, W. (1966). Malformations caused by drugs in pregnancy. *American Journal of Diseases of Children, 2,* 99–106.

Lenz, W. (1968). The susceptible period for thalidomide malformations in man and monkey. *German Medical Monthly, 4,* 197–198.

Li, Z., Amato, R., Papandreou, C., Pagliaro, L., Kim, J., Millikan, R., et al. (2001). Phase II study of thalidomide for patients with metastatic renal cell carcinoma (MRCCD) progressing after interleukin-2 (IL-2)-based therapy (Rx) [Abstract 717]. *Proceedings of the American Society of Clinical Oncology, 20,* 180a.

Linehan, W.M., Zbar, B., Bates, S.E., Zelefsky, M.J., & Yang, J.C. (2001). Cancer of the kidney and ureter. In V.T. DeVita, S. Hellman, & S.A. Rosenberg (Eds.), *Cancer: Principles and practice of oncology* (6th ed., pp. 1362–1396). Philadelphia: Lippincott Williams and Wilkins.

Lopez-Hanninen, E., Kirchner, H., & Atpodien, J. (1996). Interleukin-2 based home therapy of metastatic renal cell carcinoma: Risks and benefits in 215 consecutive single institution patients. *Journal of Urology, 155,* 19–25.

Mancilla-Jimenez, R., Stanley, R.J., & Blath, R.A. (1976). Papillary renal cell carcinoma: A clinical, radiologic, and pathologic study of 34 cases. *Cancer, 38,* 2469–2480.

Medical Research Council Renal Cancer Collaborators. (1999). Interferon-alpha and survival in metastatic renal carcinoma: Early results of a randomised controlled trial. *Lancet, 353,* 14–17.

Middleton, R.G. (1967). Surgery for metastatic renal cell carcinoma. *Journal of Urology, 97,* 973–977.

Minor, D., & Elias, L. (2000). Thalidomide treatment of metastatic renal cell carcinoma [Abstract 1384]. *Proceedings of the American Society of Clinical Oncology, 19,* 352a.

Motzer, R.J. (1997). Chemotherapy for renal cell carcinoma. In D. Raghavan, H.I. Scher, S.A. Leibel, & P.H. Lange (Eds.), *Principles and practice of genitourinary oncology* (pp. 885–896). Philadelphia: Lippincott-Raven.

Motzer, R.J., Bahnson, R.R., Carducci, M.A., Fishman, M., Hancock, S.L., Hauke, R.J., et al. (2002). NCCN practice guidelines for kidney cancer. In *The complete library of NCCN practice guidelines* [CD-ROM]. Rockledge, PA: National Comprehensive Cancer Network.

Motzer, R.J., Bander, N.H., & Nanus, D.M. (1996). Renal-cell carcinoma. *New England Journal of Medicine, 335,* 865–875.

Motzer, R.J., Berg, W., Ginsberg, M., Russo, P., Vuky, J., Yu, R., et al. (2002). Phase II trial of thalidomide for patients with advanced renal cell carcinoma. *Journal of Clinical Oncology, 20,* 302–306.

Motzer, R.J., Mazumdar, M., Bacik, J., Russo, P., Berg, W.J., & Metz, E.M. (2000). Effect of cytokine therapy on survival for patients with advanced renal cell carcinoma. *Journal of Clinical Oncology, 18,* 1928–1935.

Motzer, R.J., Murphy, M., Mazumdar, M., Loehrer, P., Wilding, G., Schwartz, T., et al. (1999). Randomized phase III trial of interferon alfa-2a (IFN) versus IFN plus 13-cis-retinoic acid (CRA) in patients with advanced renal cell carcinoma (RCC) [Abstract 1271]. *Proceedings of the American Society of Clinical Oncology, 18,* 330a.

Nanus, D.M. (2000). New treatment approaches for metastatic renal cell carcinoma. *Current Oncology Reports, 2,* 417–422.

Newhouse, J.H. (1993). The radiologic evaluation of the patient with renal cell cancer. *Urologic Clinics of North America, 20,* 231–246.

Novik, Y., Kutcher, J.P., Larkin, M., & Wiernik, P.H. (2001). Phase II study of thalidomide (T) in advanced refractory metastatic renal cell cancer (MRCC): A single institution experience [Abstract 1057]. *Proceedings of the American Society of Clinical Oncology, 20,* 265a.

Olencki, T., Dreicer, R., Elson, P., Wood, L., & Bukowski, R.M. (2002). Phase I trial of thalidomide and interleukin-2 (IL-2) in patients (pts) with metastatic renal cell carcinoma (RCC) [Abstract 2430]. *Proceedings of the American Society of Clinical Oncology, 21,* 154b.

Pantuck, A.J., Zisman, A., & Belldegrun, A. (2001). Biology of renal cell carcinoma: Changing concepts in classification and staging. *Seminars in Urologic Oncology, 19,* 72–79.

Pyrhonen, S., Salminen, E., Ruutu, M., Lehtonen, T., Nurmi, M., Tammela, T., et al. (1999). Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. *Journal of Clinical Oncology, 17,* 2859–2867.

Richardson, P., Hideshima, T., & Anderson, K. (2002). Thalidomide: Emerging role in cancer medicine. *Annual Review of Medicine, 53,* 629–657.

Rini, B.I., Vogelzang, N.J., Dumas, M.C., Wade, J.L., Taber, D.A., & Stadler, W.M. (2000). Phase II trial of weekly intravenous gemcitabine with continuous infusion fluorouracil in patients with metastatic renal cell cancer. *Journal of Clinical Oncology, 18,* 2419–2426.

Robson, C.J., Churchill, B.M., & Anderson, W. (1969). The results of radical nephrectomy for renal cell carcinoma. *Journal of Urology, 101,* 297–301.

Russo, P. (2000). Renal cell carcinoma: Presentation, staging, and surgical treatment. *Seminars in Oncology, 27,* 160–176.

Skinner, D.G., Colvin, R.B., Vermillion, C.D., Pfister, R.C., & Leadbetter, W.F. (1971). Diagnosis and management of renal cell carcinoma: A clinical and pathologic study of 309 cases. *Cancer, 28,* 1165–1177.

Srinivas, S. (2001). A randomized trial of two dosing schedules of oral thalidomide in metastatic renal cell carcinoma [Abstract 2386]. *Proceedings of the American Society of Clinical Oncology, 20,* 159a.

Stebbing, J., Benson, C., Eisen, T., Pyle, L., Smalley, K., Bridle, H., et al. (2001). The treatment of advanced renal cell cancer with high-dose oral thalidomide. *British Journal of Cancer, 85,* 953–958.

Studer, U.E., Scherz, S., Scheidegger, J., Kraft, R., Sonntag, R., Ackermann, D., et al. (1990). Enlargement of regional lymph nodes in renal cell carcinoma is often not due to metastases. *Journal of Urology, 144,* 243–245.

Tammela, T.L., Leinonen, A.S., & Kontturi, M.J. (1991). Comparison of excretory urography, angiography, ultrasound, and computed tomography for T category staging of renal cell carcinoma. *Scandinavian Journal of Urology and Nephrology, 25,* 283–286.

Vogelzang, N.J., Lipton, A., & Figlin, R.A. (1993). Subcutaneous interleukin-2 plus interferon alfa-2a in metastatic renal cancer: An outpatient multicenter trial. *Journal of Clinical Oncology, 11,* 1809–1816.

Vogelzang, N.J., & Stadler, W.M. (1998). Kidney cancer. *Lancet, 352,* 1691–1696.

Wirth, M.P. (1993). Immunotherapy for metastatic renal cell carcinoma. *Urologic Clinics of North America, 20,* 283–295.

Wolchok, J.D., & Motzer, R.J. (2000). Management of renal cell carcinoma. *Oncology (Huntington), 14*(1), 29–36.

Yagoda, A., Abi-Rached, B., & Petrylak, D. (1995). Chemotherapy for advanced renal-cell carcinoma: 1983–1995. *Seminars in Oncology, 22,* 42–60.

Yagoda, A., Petrylak, D., & Thompson, S. (1993). Cytotoxic chemotherapy for advanced renal cell carcinoma. *Urologic Clinics of North America, 20,* 303–321.

Yang, J.C., & Rosenberg, S.A. (1997). An ongoing prospective randomized comparison of interleukin-2 regimens for the treatment of metastatic renal cell cancer. *Cancer Journal From Scientific American, 3*(Suppl. 1), S79–S84.

Yang, J.C., Topalian, S.T., Parkinson, D., Schwartzentruber, D.J., Weber, J.S., Ettinghausen, S.E., et al. (1994). Randomized comparison of high-dose and low-dose intravenous interleukin-2 for the therapy of metastatic renal cell carcinoma: An interim report. *Journal of Clinical Oncology, 12,* 1572–1576.

Zambrano, N.R., Lubensky, I.A., Merino, M.J., Linehan, W.M., & Walther, M.M. (1999). Histopathology and molecular genetics of renal tumors toward unification of a classification system. *Journal of Urology, 162,* 1246–1258.

Zeldis, J.B., Williams, B.A., Thomas, S.D., & Elsayed, M.E. (1999). S.T.E.P.S: A comprehensive program for controlling and monitoring access to thalidomide. *Clinical Therapeutics, 21,* 319–330.

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