Treatment of Advanced Renal Cell Carcinoma

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**Prognostic Factors**

**Surgical Management of Metastatic Renal Cell Carcinoma**

**Immunologic Approaches in the Management of Advanced Clear Cell Renal Cell Carcinoma**

**Molecular Basis for Targeted Approaches in Clear Cell Renal Cell Carcinoma**

**Targeted Molecular Agents in Clear Cell Renal Cell Carcinoma**

**Systemic Therapy for Non–Clear Cell Variants of Renal Cell Carcinoma**

Renal cell carcinoma (RCC) is a term that includes a variety of cancers arising in the kidney and comprises several histologically, biologically, and clinically distinct entities (Linehan et al, 2007, 2009). An estimated 58,240 new cases of cancer arising in the kidney or renal pelvis were diagnosed in 2010 in the United States (Jemal et al, 2010). Approximately one third of all newly diagnosed RCC patients present with synchronous metastatic disease and an additional 20% to 40% of patients with clinically localized disease at diagnosis will eventually develop metastases (Skinner et al, 1971; Rabinovitch et al, 1994; Bukowski, 1997). Metastatic RCC is almost always fatal, with 10-year survival rates of less than 5% (Bukowski, 1997; Motzer et al, 1999, 2000; Motzer and Russo, 2000; Négrier et al, 2002); patients with metastatic disease account for the majority of deaths (approximately 13,000 a year in the United States) related to RCC (Jemal et al, 2010).

Advances in our understanding of the genetic and molecular defects underlying the individual subtypes of RCC have led to the development of novel agents designed to reverse or modulate aberrant pathways contributing to renal oncogenesis. These “targeted” therapeutic strategies have largely supplanted other treatment modalities in the initial management of metastatic clear cell kidney cancer; however, surgery, irradiation, and cytokine therapy remain appropriate choices in the management of selected patients with advanced clear cell RCC. Although agents effective in clear cell RCC are often used in patients with other subtypes of RCC there is scant evidence from prospective studies demonstrating benefit in non–clear cell RCC variants. More recently, elucidation of aberrant oncogenic pathways in papillary, chromophobe, and other variants of RCC has paved the way for evaluation of targeted therapeutic approaches in these histologic subtypes (Linehan et al, 2009).

**PROGNOSTIC FACTORS**

Patients with metastatic RCC generally have a poor prognosis, with the majority succumbing to their disease. Ten-year survival in patients diagnosed with metastatic disease was estimated to be less than 5% in the era of cytokine therapy and is unlikely to change significantly with the advent of targeted therapy. However, several clinical features such as a long time interval between initial diagnosis and appearance of metastatic disease and presence of fewer sites of metastatic disease have been observed to be associated with better outcome. Conversely, poor performance status and the presence of lymph node and/or liver metastases are some factors associated with shorter survival. Investigators at the Memorial Sloan-Kettering Cancer Center evaluated a variety of clinical and laboratory parameters in 670 patients enrolled on various clinical trials of chemotherapy or immunotherapy in an effort to identify those pretreatment factors that were able to best predict outcome (Motzer et al, 1999). In a multivariate analysis, a poor performance status (Karnofsky score <80), an elevated serum lactate dehydrogenase (LDH) level (>1.5 times upper limit of normal), a low hemoglobin (less than the lower limit of normal), an elevated corrected calcium concentration (>10 g/dL), and lack of prior nephrectomy were independent predictors of a poor outcome (Table 50–1). Patients could be stratified into three distinct prognostic groups based on these five poor prognostic factors (Table 50–2). The overall survival (OS) times in patients with no adverse factors (favorable-risk group), one to two risk factors (intermediate-risk group), and more than three risk factors (poor-risk group) were 20 months, 10 months, and 4 months, respectively (Fig. 50–1) (Motzer et al, 1999). Subsequently, the same group
Table 50–1.

Adverse Prognostic Factors in 670 Patients Treated with Chemotherapy or Immunotherapy at the Memorial Sloan-Kettering Cancer Center

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>NO. OF ADVERSE PROGNOSTIC FACTORS</th>
<th>MEDIAN OVERALL SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>0</td>
<td>20 months</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1-2</td>
<td>10 months</td>
</tr>
<tr>
<td>Poor</td>
<td>3-5</td>
<td>4 months</td>
</tr>
</tbody>
</table>


Table 50–2.

Risk Stratification Based on Adverse Prognostic Factors in 670 Patients Treated with Chemotherapy or Immunotherapy at the Memorial Sloan-Kettering Cancer Center

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>NO. OF ADVERSE PROGNOSTIC FACTORS</th>
<th>MEDIAN OVERALL SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>0</td>
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</tr>
<tr>
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<td>10 months</td>
</tr>
<tr>
<td>Poor</td>
<td>3-5</td>
<td>4 months</td>
</tr>
</tbody>
</table>


Figure 50–1. Survival analysis stratified according to risk group in 670 patients treated with chemotherapy or immunotherapy at the Memorial Sloan-Kettering Cancer Center (n = 656; 14 patients missing one or more of the five risk factors were excluded). KPS, Karnofsky performance score; HGB, hemoglobin; LDH, lactate dehydrogenase. (From Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 1999;17:2530–40.)

SURGICAL MANAGEMENT OF METASTATIC RENAL CELL CARCINOMA

Debulking or Cytoreductive Nephrectomy in Patients with Metastatic RCC

The role of cytoreductive nephrectomy preceding systemic therapy has been extensively studied in the era of cytokine therapy. The impetus for exploring this approach in metastatic RCC was provided both by the perception that bulky tumors might inhibit key components of the immune system critical for combating cancer and by observations suggesting that removal of large primary tumors may provide clinical benefit. To support this practice early proponents of cytoreductive nephrectomy had cited (1) the rare but well-described occurrence of spontaneous regression of metastatic lesions after nephrectomy (Bloom, 1973; Middleton, 1980; Snow and Schellhammer, 1982; Marcus et al, 1993); (2) preclinical data suggesting that large primary tumors may inhibit T-cell function (Kudoh et al, 1997; Bukowski et al, 1998; Liu et al, 1998; Uzzo et al, 1999a, 1999b); and (3) the inability of systemic agents, particularly cytokines, to induce meaningful responses in primary renal tumors in most patients (Sella et al, 1993; Rackley et al, 1994; Wagner et al, 1999). However, the risk of perioperative morbidity and mortality and the inability of a significant proportion of patients undergoing nephrectomy to subsequently receive systemic therapy clearly underlined the need for unequivocal evidence of clinical benefit as well the ability to identify patients likely to benefit from this approach.

Nephrectomy as the sole therapeutic intervention in the context of metastatic disease is unlikely to alter outcome, as suggested by small retrospective analyses (DeKernion et al, 1978). However, several retrospective studies have demonstrated the feasibility of a combined modality approach in which nephrectomy is followed by cytokine therapy, with some suggesting that this approach may favorably impact response and survival. Investigators from the National Cancer Institute (NCI) reported their experience in 195 patients undergoing nephrectomy followed by high-dose interleukin-2 (II-2) therapy between the years 1985 and 1996 (Walther et al, 1997b). An overall response rate of 18% (including a complete response rate of 4%) after IL-2 therapy was observed in this study. A notable finding that emerged from this study was that although the majority of patients underwent successful resection of the primary tumor only 107/195 (55%) went on to receive IL-2 therapy. Rapid postoperative disease progression and perioperative surgical and medical morbidity were the most common factors preventing delivery of systemic therapy, suggesting that careful patient selection may play an important role in determining which patients are suitable candidates for this approach.

Identified poor performance status, high calcium level, low hemoglobin value, elevated LDH level, and short time interval from initial diagnosis to treatment as factors that could best predict a poor outcome in 463 patients receiving interferon-based therapy in the first-line setting (Motzer et al, 2002). This prognostic model was found to be predictive of survival in an independent data set derived from patients treated at the Cleveland Clinic and provides independent, external validation of the proposed model (Mekhail et al, 2005). Similar prognostic schemes have also been proposed by the Groupe Francais d’Immunotherapie and by investigators from the University of California, Los Angeles (Tsui et al, 2000). Validated prognostic models are used in clinical practice to help make appropriate management decisions as well as in the design and interpretation of clinical trials. Modifications of these prognostic schemes as well as identification of reliable molecular markers are under investigation as suitable predictors of response to and survival after therapy with newer targeted agents against vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathway components (Choueiri et al, 2007, 2008b; Motzer et al, 2008a).
role in the successful application of this combined modality approach. The impact of patient and/or disease characteristics on outcome is further highlighted by a retrospective study. In Bennett and associates’ (1995) series of 30 patients, which included several patients with unfavorable performance status (Eastern Cooperative Oncology Group [ECOG] 2) and multiple metastatic sites including patients with brain or liver metastases, only 7 (23%) were able to proceed with IL-2 after nephrectomy. Conversely, in a series that included only patients with favorable clinical/prognostic factors (e.g., good performance status, minimal comorbidity, no liver or brain metastases), the majority of patients were able to proceed to systemic therapy after nephrectomy, with high response rates (35% to 40%) and OS (median 20 to 22 months) after cytokine-based treatment (Fallick et al, 1997; Flanigan et al, 1997). Although these retrospective analyses and small single-arm prospective studies confirmed the feasibility of a tandem surgical/cytokine therapeutic approach, their major contribution was in laying the foundation for controlled, prospective studies to determine if outcomes with cytokine therapy could be improved by prior nephrectomy.

The most compelling evidence in support of cytoreductive nephrectomy is provided by two randomized phase III studies conducted by the Southwest Oncology Group (SWOG) and the European Organization for Research and Treatment of Cancer (EORTC). The larger of the two studies, SWOG trial 8949, randomized 241 patients with metastatic RCC to receive interferon-α-2b either as initial therapy or after cytoreductive nephrectomy (Flanigan et al, 2001). Salient eligibility criteria included a histologic diagnosis of kidney cancer (all histologic subtypes were allowed); good performance status (ECOG 0 or 1); presence of a resectable primary renal tumor; no prior chemotherapy, irradiation, or immunotherapy; and adequate organ function. Although there were no significant differences in the response rates to interferon observed in the two study arms, OS was improved in the surgery plus interferon arm (median 11.1 vs. 8.1 months for interferon alone, \( P = .05 \) (Fig. 50–2)). These data were similar to those from a smaller EORTC trial (a total of 85 patients randomized to interferon alone or interferon after nephrectomy) that used a similar design and reported a survival advantage favoring the surgery plus interferon arm (median OS 17 vs. 7 months, \( P = .03 \) (Mickisch et al, 2001). A combined analysis of both trials revealed data that were consistent with those reported in the individual trials (Flanigan et al, 2004). These data support the use of cytoreductive nephrectomy in carefully selected patients with metastatic RCC who are likely candidates for subsequent cytokine therapy (data summarized in Table 50–3).

The impact of cytoreductive nephrectomy on outcome in patients receiving VEGF or mTOR pathway inhibitors remains to be determined and is the subject of ongoing trials. Similarly, although some patients with non–clear cell histologic subtypes of RCC were included in the aforementioned trials, the role of nephrectomy before systemic therapy in these patients is unclear.

### Resection of Metastases

Most patients with metastatic RCC will not achieve a cure or long-term disease remission with currently available systemic agents.

![Figure 50–2.](image_url)  
Figure 50–2. Actuarial survival among 241 patients with metastatic renal cell carcinoma randomized to either interferon-α alone or interferon-α after cytoreductive nephrectomy.


![Graph](image_url)  
**Table 50–3.**

Summary of Outcome in Randomized Studies of Interferon-α Alone or Interferon-α after Cytoreductive Nephrectomy in Patients with Metastatic Kidney Cancer

<table>
<thead>
<tr>
<th>STUDY</th>
<th>NO. OF ELIGIBLE PATIENTS</th>
<th>RESPONSE RATE AFTER IFN (%)</th>
<th>MEDIAN OVERALL SURVIVAL (MO)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total IFN</td>
<td>Nx Plus IFN</td>
<td>IFN</td>
</tr>
<tr>
<td>Flanigan et al, 2001</td>
<td>241</td>
<td>121</td>
<td>120</td>
</tr>
<tr>
<td>Mickisch et al, 2001</td>
<td>83</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td>Flanigan et al, 2004</td>
<td>331</td>
<td>163</td>
<td>161</td>
</tr>
</tbody>
</table>

IFN, interferon-α; Nx, cytoreductive nephrectomy.
However, resection of limited metastatic disease has been reported by several groups to be associated with long disease-free intervals and OS. It should be emphasized that metastasectomy has not been evaluated systematically in a prospective, randomized fashion and that the favorable outcome ascribed to resection of solitary metastatic disease may reflect patient selection bias, inherent differences in tumor biology, and natural history or other confounding factors.

Most studies detailing outcome after metastasectomy are retrospective series. In most series, isolated pulmonary metastases were the lesions most commonly amenable to resection with curative intent. The OS of patients undergoing complete resection of limited metastatic disease is quite impressive, with reported median 5-year survival rates of 35% to 50% in many series (Middleton, 1967; Skinner et al, 1971; Tolia and Whitmore, 1975; O’Dea et al, 1978; Pogrebniak et al, 1992; Kierney et al, 1994; Friedel et al, 1999; Murthy et al, 2005; Russo et al, 2007). The larger of these studies have also attempted to identify patients most likely to benefit from this approach. In a series of 278 patients with recurrent RCC treated at the Memorial Sloan-Kettering Cancer Center, 211 were reported to have undergone either complete (141 patients) or incomplete (70 patients) resection of recurrent tumor from a variety of metastatic sites (Kavolius et al, 1998). In this series, complete or “curative” resection was associated with a longer OS (44% 5-year survival vs. 14% in patients undergoing incomplete resection); multivariate analysis also identified the presence of a solitary metastatic lesion, age younger than 60 years, and a disease-free interval of more than 1 year as favorable prognostic indicators. In addition, some studies have suggested that pulmonary metastases, smaller tumor size (<4 cm in one series), and metachronous lesions are predictors of better outcome after metastasectomy (Friedel et al, 1999; Piltz et al, 2002; Murthy et al, 2005). Although not supported by convincing evidence of survival benefit from prospective studies, resection of isolated metastatic lesions is a reasonable and widely employed practice in selected RCC patients.

Palliative Surgery

Cytoreductive nephrectomy can be performed with palliative intent in patients with intractable pain, hematuria, constitutional symptoms, or a variety of paraneoplastic manifestations such as hypercalcemia, erythrocytosis, secondary thrombocytosis, or hypertension. Symptoms such as pain and laboratory abnormalities including hypercalcemia can often be effectively managed medically, whereas symptoms such as hematuria may be amenable to alternative treatment approaches (e.g., angioembolization). Furthermore, resection of the primary renal tumor does not always result in clinical benefit; for instance, in one series, only a little over half the patients (7/12) with hypercalcemia experienced clinically meaningful reductions in serum calcium levels (Walther et al, 1997a). Cytoreductive nephrectomy with palliative intent is therefore performed relatively infrequently but is appropriate in some patients.

Resection of metastases to alleviate pain or to forestall potentially life-threatening or debilitating complications is often indicated in a variety of situations. Patients who may benefit from noncurative resection of metastatic lesions include those with solitary brain metastases, metastatic lesions in weight-bearing bones or joints, or vertebral metastatic lesions with impending spinal cord or radicular compromise (Sundaresan et al, 1986; Kolclender et al, 2000; Sheehan et al, 2003). Surgical resection is often combined with radiation and/or systemic therapy in many of the aforementioned situations.
IMMUNOLOGIC APPROACHES IN THE MANAGEMENT OF ADVANCED CLEAR CELL RENAL CELL CARCINOMA

The host immune system has long been believed to play an important role in the causation and control of renal cell cancer. A report detailing spontaneous regression of metastatic lesions after radical nephrectomy provides perhaps the earliest evidence implicating the immune system in the regulation of kidney cancer. The phenomenon of spontaneous regression, thought to represent T- or B-cell-mediated antitumor immunity, has sparked great enthusiasm over the years and generated several reports describing this phenomenon (Braren et al, 1974; Silber et al, 1975; Middleton, 1980; Robson, 1982; Snow and Schellhammer, 1982; Kavoussi et al, 1986; Marcus et al, 1993; Edwards et al, 1996). Although rare (it is estimated that the true incidence of spontaneous regression is less than 1%) and often transient, the presumed immunologic mechanisms underlying this event have nonetheless played an important part in the development of immunotherapeutic approaches in kidney cancer. The presence of immune cells, notably cytotoxic T lymphocytes, in resected tumors and the identification of tumor-associated antigens that can serve as human leukocyte antigen (HLA)-restricted targets on tumor cells for T-cell–mediated cytotoxicity have also kindled interest in immune-based strategies in renal cell cancer (Finke et al, 1994; Boon et al, 1997; Ada, 1999; Rosenberg, 1999). Early clinical studies explored the efficacy of agents believed to act as nonspecific stimulators of the host immune system components, such as cytokines, with or without adoptive cellular therapy. More recently, investigators have evaluated a variety of novel approaches including allogeneic immunotherapy, vaccines, and modulators of T-cell function. Most immunotherapy strategies have been directed at clear cell RCC, and the utility of these approaches in non–clear cell variants remains to be explored.

Interferons

The interferons are a group of proteins with diverse biologic functions, including immunomodulatory properties. Interferon-α was one of the earliest cytokines to be evaluated for activity in RCC. Initial trials with interferon utilized leukocyte-derived interferon. The subsequent availability of recombinant interferon-α in the early to mid 1980s allowed investigators to evaluate higher doses of this cytokine in a series of phase 2 trials. Initial trials demonstrated overall response rates of 16% to 26% in patients treated with interferon-α, and several subsequent trials have confirmed the activity of this agent, with response rates generally in the 10% to 15% range (deKernion et al, 1983; Quesada et al 1983, 1985, 1989; Umeda and Niijima, 1986; Muss et al, 1987; Rosenberg et al, 1987; Figlin et al, 1988; Minessian et al, 1993; Motzer et al, 2002). The limited long-term survival data available suggest that durable complete responses with this agent are relatively rare (<2%). A variety of dosing schedules and routes have been evaluated to determine the optimal interferon regimen; no single mode of administration or dosing schedule has so far demonstrated superiority over others (Kirkwood et al, 1985; Umeda and Niijima, 1986; Muss et al, 1987; Minessian et al, 1993). Similarly, the addition of chemotherapy or other cytokines to interferon-α has failed to improve the outcomes seen with single-agent therapy (Rosenberg et al, 1989b; Sella et al, 1992; Ravaud et al, 1994, 1998; Ellerhorst et al, 1997; Tourani et al, 1998, 2003; Dorval et al, 1999; Négrier et al, 2000a, 2000b).

Several prospective, randomized trials evaluating the efficacy of interferon-α have demonstrated a modest but statistically significant improvement in outcome after treatment with this agent. A randomized phase III study that assigned 335 patients to receive either interferon-α or medroxyprogesterone demonstrated a higher response rate (14% vs. 2%) and OS (median 8.5 vs. 6 months, hazard ratio 0.72, P = .017) favoring the interferon arm of the study (Medical Research Council Renal Cancer Collaborators, 1999). A second study randomized 160 patients with metastatic RCC to receive vinblastine alone or in combination with interferon-α; a higher response rate (16% vs. 2.5%) and improved OS (median 16 vs. 9 months, P = .0049) with the addition of interferon was observed in this study (Table 50–4) (Pyrhonen et al, 1999). Two additional randomized studies suggested that vinblastine is unlikely to have contributed significantly to the activity of this combination by showing that survival was not improved with the addition of vinblastine to interferon-α (Neidhart et al, 1991; Fossa et al, 1992). Lastly, a meta-analysis of randomized trials of interferon against a variety of agents suggested that interferon-based therapy conferred a survival advantage (Coppin et al, 2005). Despite its relatively modest activity, based on the just described data and relative ease of administration compared with IL-2, interferon was commonly the agent of choice in the initial treatment of metastatic RCC until the advent of VEGF pathway antagonists.

Interleukin-2

Clinical trials in the early 1980s initially identified IL-2 as an active agent in RCC, with some IL-2–based regimens leading to objective response rates in excess of 30% (Rosenberg et al, 1989a, 1993). In a subsequent report detailing 255 patients treated on a series of

Table 50–4. Summary of Results from Selected Randomized Trials of Interferon-α in Metastatic Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>STUDY</th>
<th>AGENT(S)</th>
<th>PHASE</th>
<th>NO. OF PATIENTS TOTAL (RANDOMIZED)</th>
<th>OVERALL RESPONSE RATE (%)</th>
<th>OVERALL SURVIVAL Median (mo)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Research Council, 1999</td>
<td>IFN vs. MPA</td>
<td>3</td>
<td>335 (167 vs. 168)</td>
<td>13 vs. 7</td>
<td>8.5 vs. 6.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Pyrhonen et al, 1999</td>
<td>IFN + vinblastine vs. vinblastine</td>
<td>3</td>
<td>160 (79 vs. 81)</td>
<td>16 vs. 2.5</td>
<td>15.8 vs. 8.8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Neidhart et al, 1991</td>
<td>IFN vs. IFN + vinblastine</td>
<td>3</td>
<td>165 (82 vs. 83)</td>
<td>13 vs. 13</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>Fossa et al, 1992</td>
<td>IFN vs. IFN + vinblastine</td>
<td>3</td>
<td>178 (87 vs. 91)</td>
<td>11 vs. 24</td>
<td>12 vs. 12</td>
<td>NS</td>
</tr>
</tbody>
</table>

IFN, interferon; MPA, medroxyprogesterone acetate; NA, not available; NS, not significant.
phase 2 trials at the NCI, a more modest overall response rate of 15% (37/255 patients) was noted (Fyfe et al, 1996). **Several trials conducted by the NCI and the Cytokine Working Group as well as meta-analyses of published data have consistently demonstrated response rates in the range of 15% to 20%** (Lotze et al, 1986; Rosenberg et al, 1987, 1989a, 1993; Fisher et al, 1988; Dutcher et al, 1997a). More importantly, **7% to 9% of patients receiving high-dose IL-2 are reported to have achieved complete regression of all metastatic tumor, with the majority of complete responders (>60%) demonstrating no evidence of disease recurrence on long-term follow-up** (Fisher et al, 1997, 2000; Rosenberg et al, 1998). There have also been reports of long-term disease-free remission in partial responders whose limited disease burden after IL-2 therapy rendered them amenable to resection of localized metastases. **High-dose IL-2 was approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic kidney cancer in 1992, based largely on its ability to induce durable complete responses in some patients.**

The initial studies with IL-2 were conducted using an intravenous bolus regimen with doses of 600,000 or 720,000 IU/kg administered every 8 hours as tolerated to a maximum of 15 doses. A major limitation of this dosing regimen is the considerable toxicity that has limited its widespread use. Vascular leak syndrome, and the resulting hypotension, third-space fluid retention, respiratory compromise, and multiorgan damage are some of the more problematic concomitants of IL-2 therapy and led to an unacceptably high treatment-related mortality rate (2% to 5%) in early studies with this agent (Rosenberg et al, 1987; Kammula et al, 1998). Subsequently, careful patient selection, intensive monitoring schemes, and early interventions with IV fluids, vasopressors, and antibiotics have served to significantly reduce mortality associated with IL-2 (Kammula et al, 1998). However, the significant morbidity and expense associated with delivering bolus high-dose IL-2 have led several investigators to explore alternative regimens aimed at reducing toxicity without compromising efficacy. Numerous single-arm phase 2 studies have evaluated a variety of alternative regimens, including daily subcutaneous administration and continuous intravenous infusion (Escudier et al, 1994a, 1994b, 1995; Atkins et al, 2001; Négrier et al, 2000b, 2005, 2008). Many of these studies have reported overall response rates of 10% to 30%, suggesting comparable efficacy to high-dose bolus administration based on data from historical controls. However, two randomized studies have demonstrated that, although well tolerated, lower-dose regimens are associated with lower overall response rates, as well with fewer durable, complete responses (Table 50–5) (Yang et al, 2003b; McDermott et al, 2005).

**Attempts to enhance the efficacy of IL-2 therapy have led investigators to explore combination therapy with other cytokines, cytotoxic chemotherapy, and adoptive cellular immunotherapy. Early experience with combination cytokine therapy was promising, with one study reporting a 31% overall response rate in patients treated with high-dose bolus IL-2 and interferon (Rosenberg et al, 1989b). However, subsequent studies have indicated that this combination is more toxic and no more effective than IL-2 alone (Ravaud et al, 1994; Bukowski et al, 1997; Dutcher et al, 1997b; Tourani et al, 1998, 2003).** A multicenter, randomized phase III study compared the efficacy of intermediate-dose IL-2 administered by continuous intravenous infusion with interferon-α or the combination in 425 patients with metastatic clear cell RCC (Négrier et al, 1998). **Although the combination of IL-2 and interferon resulted in a higher response rate (18.6%) and 1-year event-free survival (EFS) 20% compared with IL-2 (overall response rate 6.5%, 1-year EFS 15%) or interferon (overall response rate 7.5%, 1-year EFS 12%) alone, there was no significant difference in survival between the groups** (Fig. 50–3). Combination therapy also resulted in higher toxicity than either agent given alone. Regimens combining IL-2 and cytotoxic chemotherapy (particularly 5-fluorouracil [5-FU]) have been the subject of numerous studies. Unfortunately, reports of high response rates in initial studies (49% in a study using IL-2, interferon, and 5-FU) could not be reproduced in later studies (Atzpodien et al, 1993; Ellerhorst et al, 1997; Dutcher et al, 2000; Négrier et al, 2000a). Similarly, despite the promise of preclinical and early clinical studies, the addition of ex-vivo expanded tumor-infiltrating lymphocytes or lymphokine-activated killer cells to high-dose IL-2 has not reliably demonstrated improved clinical benefit and these approaches have been largely abandoned (Rosenberg et al, 1993; Law et al, 1995; Figlin et al, 1999).

**Given the considerable toxicity associated with high dose IL-2 and the relatively small proportion of patients who derive benefit from this therapy, identification of predictors of response and**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>TREATMENT ARMS</th>
<th>NO. OF PATIENTS</th>
<th>DOSE, ROUTE, AND SCHEDULE</th>
<th>RESPONSE</th>
<th>OVERALL SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ORR</td>
<td>Median (mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>Négrier et al, 1998</td>
<td>IL-2</td>
<td>138</td>
<td>18 x 10^4 IU/m^2/d x 5 days, CIV</td>
<td>6.5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>IFN</td>
<td>147</td>
<td>18 x 10^4 IU three times a week, SC</td>
<td>7.5</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>IL-2 + IFN</td>
<td>140</td>
<td>18 x 10^4 IU/m^2/d x 5 days, CIV + 6 x 10^6 IU three times a week, SC</td>
<td>18.6</td>
<td>.01</td>
</tr>
<tr>
<td>Yang et al, 2003b</td>
<td>IL-2</td>
<td>156</td>
<td>720,000 U/kg every 8 hours x 5 days, IV bolus</td>
<td>21</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>IL-2</td>
<td>150</td>
<td>72,000 U/kg every 8 hours x 5 days, IV bolus</td>
<td>13</td>
<td>.048</td>
</tr>
<tr>
<td></td>
<td>IL-2</td>
<td>94</td>
<td>250,000 U/day x 5 days, SC, week 1</td>
<td>10</td>
<td>.033</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125,000 U/day x 5 days, SC, weeks 2 to 6</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>McDermott et al, 2005</td>
<td>IL-2</td>
<td>96</td>
<td>600,000 U/kg every 8 hours x 5 days, IV bolus</td>
<td>10</td>
<td>.018</td>
</tr>
<tr>
<td></td>
<td>IL-2+ IFN</td>
<td>96</td>
<td>5 x 10^6 IU/m^2 every 8 hours x 3, then 5 x 10^6 IU/m^2/day x 5 days/week, SC + 5 x 10^6 IU three times a week, SC</td>
<td>10</td>
<td>.21</td>
</tr>
</tbody>
</table>

CIV, continuous intravenous infusion; IFN, interferon-α; IL-2, interleukin-2; IV, intravenous; NA, not available; ORR, overall response rate; SC, subcutaneous.
Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation allows the replacement of host or recipient immune and hematopoietic systems with those of a healthy, HLA-compatible donor. The therapeutic potential of hematopoietic stem cell transplantation lies largely in the ability of the transplanted donor graft to generate an allogeneic antitumor immune response known as the graft-versus-tumor effect. This approach has been used successfully with curative intent in a variety of hematologic malignancies (Thomas et al, 1977; Weiden et al, 1979, 1981). The ability of a variety of immune-based approaches to induce remissions in patients with RCC and evidence suggesting that the host immune system in these patients may be compromised and/or tolerant to tumor cells have led several investigators to evaluate allogeneic hematopoietic stem cell transplantation in kidney cancer.

The approach was initially studied by investigators at the National Heart, Lung and Blood Institute exploring the efficacy of reduced intensity hematopoietic stem cell transplantation in patients with treatment-refractory metastatic RCC. Eligible patients underwent reduced intensity conditioning with cyclophosphamide (120 mg/kg) and fludarabine (125 mg/m²) followed by infusion of a granulocyte colony-stimulating factor–mobilized peripheral blood stem cell graft from a 5/6 or 6/6 HLA-matched sibling donor. The initial experience with hematopoietic stem cell transplantation in metastatic RCC was published by Childs and colleagues (2000). Ten of the first 19 patients treated with this transplant approach had tumor shrinkage, including 3 who had a complete response and 7 who had a partial response. As more recently reported, 74 patients have undergone hematopoietic stem cell transplantation for RCC at the National Institutes of Health. Of these, 73 patients have demonstrated durable engraftment, achieving 100% donor T-cell chimerism by day 100 posttransplant. Twenty-nine of 74 (39%) patients have had a disease response, including 7 complete (9%) and 22 partial responders (30%) (Takahashi et al, 2008). Preliminary data suggest that disease response after hematopoietic stem cell transplantation is a clinically meaningful phenomenon because regression of metastatic RCC appears to be associated with a trend toward improved survival. Survival in nonresponders has been less than 6 months, in contrast to those achieving a partial response who survived a median 2.5 years posttransplant. Several durable responses have been noted, and the first patient who underwent a transplant remains in complete remission more than 10 years after the procedure. Hematopoietic stem cell transplantation is associated with a variety of adverse events typically associated with conditioning chemotherapy (e.g., pancytopenia), a variety of opportunistic infections, and graft-versus-host disease (GVHD). Eight patients in the just-mentioned series died of transplant-related causes (transplant-related mortality of 11%), most due to GVHD and its attendant infectious complications. Several other trials have since confirmed the efficacy of this approach in RCC (Table 50–6) (Rini et al, 2001, 2002; Bregni et al, 2002; Artz et al, 2005; Barkholt et al, 2006). However, a Cancer and Leukemia Group B (CALGB) intergroup trial evaluating the feasibility of performing hematopoietic stem cell transplantation for metastatic RCC in a multi-institutional setting in the United States reported no responses in 22 patients undergoing hematopoietic stem cell transplantation from an HLA-matched sibling donor after cyclophosphamide/fludarabine–based conditioning (Rini et al, 2005; Barkholt et al, 2006).
 Median OS was only 5.5 months, with most patients dying of disease progression (median time to progression of 3 months). Inclusion of a number of patients with multiple adverse prognostic factors, sparing use of donor lymphocyte infusions (only 22 of 22 patients received donor lymphocyte infusions despite disease progression in the majority), and inclusion of patients with non-clear cell histology are some of the factors that may account for the poor outcome observed in this trial. This trial clearly highlights the importance of appropriate patient selection and the need for identifying prognostic factors likely to predict for a favorable outcome. In a European multicenter study of 106 patients undergoing transplantation, chronic GVHD, good performance status (Karnofsky score = 80), administration of donor lymphocyte infusions, and fewer than three sites of metastatic disease were identified as factors favorably impacting survival (Barkholt et al., 2006). Given the high morbidity and mortality with this approach, careful patient selection is of great importance. Hematopoietic stem cell transplantation remains an experimental approach in the management of RCC; strategies for minimizing the toxicity associated with this procedure and maximizing antitumor effects are being explored and are required to render this approach more widely applicable.

Molecular Basis for Targeted Approaches in Clear Cell Renal Cell Carcinoma

The development of antagonists of the VEGF pathway in the treatment of clear cell RCC is an often-cited paradigm in the evolution of rational targeted therapeutic strategies and represents a logical progression from identification of a defective cellular pathway to rational drug design and structured clinical evaluation. The earliest clues to the central role played by VEGF in renal oncogenesis came from studies attempting to identify the genetic basis of the von Hippel-Lindau familial kidney cancer syndrome. In the early 1990s, investigators at the National Cancer Institute studying families with von-Hippel-Lindau disease used genetic linkage analysis to identify germline mutations or deletions in the VHL gene as the basis for this disease (Latif et al., 1993). Individuals carrying germline VHL mutations are at increased risk for developing tumors in multiple organs, including bilateral, multifocal clear cell kidney cancer. The VHL gene is a classic tumor suppressor gene, with inactivation of the normal VHL allele in affected tissues by a somatic “second hit” required for tumor formation.

The VHL gene resides on the short arm of chromosome 3 and encodes the VHL protein, which can be synthesized as two alternatively spliced variants (Latif et al., 1993; Gnarra et al., 1996; Illiopoulos et al., 1998; Linehan, 2003). One of the better-understood functions of the VHL protein is its association with elongins B and C and CUL2 to form a protein complex that serves to tag certain cellular proteins for delivery to and degradation by the ubiquitin system (Duan et al., 1995; Pause et al., 1997; Stebbins et al., 1999; Linehan, 2003; Kaelin, 2004). Proteins targeted for ubiquitin-mediated degradation include the α subunits of a group of transcriptionally active proteins known as hypoxia-inducible factors (HIFs) (Illiopoulos et al., 1996; Pause et al., 1997; Maxwell et al., 1999; Cockman et al., 2000; Ohh et al., 2000; Ivan et al., 2001; Jaakkola et al., 2001). In cells with intact VHL function, HIF levels are primarily controlled by ambient oxygen tension. In normoxic conditions, hydroxylation of key proline residues on HIF promotes its association with the VHL/elongin/CUL complex and subsequent degradation; conversely, hypoxia impedes prolyl hydroxylation of HIF and its subsequent degradation, leading to intracellular accumulation of HIF α subunits. Mutations in VHL interfere with its binding to either HIF or elongin/CUL 2 and promote HIF accumulation even under normoxia. HIF accumulation, in turn, leads to the upregulation of a variety of proangiogenic and growth factors, including VEGF, platelet-derived growth factor (PDGF), transforming growth factor-α, Glut-1, and erythropoietin, which are believed to play critical roles in the development and progression of clear cell RCC (Fig. 50–4) (Duan et al., 1995; Illopolous et al., 1996; Kaelin, 2004; Linehan et al., 2007). Although originally identified as a germline defect in von Hippel-Lindau families, evidence of somatic VHL inactivation by mutation or promoter hypermethylation has been observed in a high proportion of sporadic clear cell tumors (91% in a recent series) (Herman et al., 1994; Gnarra et al., 1996; Zhuang et al., 1996a, 1996b; Nickerson et al., 2008). The recognition of VHL loss as a central event in renal oncogenesis has paved the way for the development of novel agents targeting components of this pathway in the management of metastatic clear cell RCC.

Table 50–6. Summary of Results from Selected Trials of Allogeneic Hematopoietic Stem Cell Transplantation in Metastatic Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>CONDITIONING AGENTS</th>
<th>GVHD PROPHYLAXIS</th>
<th>AGVHD (II-IV)</th>
<th>CGVHD</th>
<th>TRM</th>
<th>RESPONSE (PR OR CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childs et al, 2000; Takahashi et al, 2008</td>
<td>Cy + Flu</td>
<td>CSP (First 25 patients)</td>
<td>55%</td>
<td>21%</td>
<td>11%</td>
<td>39%</td>
</tr>
<tr>
<td>Arzt et al, 2005; Rini et al, 2001, 2002</td>
<td>Cy + Flu</td>
<td>CSP + MMF (subsequent patients)</td>
<td>22%</td>
<td>39%</td>
<td>14%</td>
<td>22%</td>
</tr>
<tr>
<td>Bregni et al, 2002</td>
<td>Cy + Flu + Thiopeta</td>
<td>Tacro + MMF</td>
<td>86%</td>
<td>71%</td>
<td>0%</td>
<td>57%</td>
</tr>
<tr>
<td>Barkholt et al, 2006</td>
<td>Multiple fludarabine-based regimens</td>
<td>CSP + MTX</td>
<td>40%</td>
<td>33%</td>
<td>16%</td>
<td>32%</td>
</tr>
<tr>
<td>Rini et al, 2006</td>
<td>Flu + Cy</td>
<td>Tacro + MTX</td>
<td>32%</td>
<td>23%</td>
<td>9%</td>
<td>0%</td>
</tr>
</tbody>
</table>

aGVHD, acute graft-versus-host disease; ATG, antithymocyte globulin; cGVHD, chronic graft-versus-host disease; CR, complete response; CSP, cyclosporine; Cy, cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; PR, partial response; Tacro, tacrolimus; TRM, treatment-related mortality.
TARGETED MOLECULAR AGENTS IN CLEAR CELL RENAL CELL CARCINOMA

Antagonists of the Vascular Endothelial Growth Factor Pathway

Bevacizumab

Bevacizumab, a humanized monoclonal antibody against VEGF-A, was the first VEGF pathway antagonist used in clinical trials to test the hypothesis that modulation of aberrantly expressed components of the VHL pathway would be associated with clinical activity in clear cell RCC. In a three-arm phase 2 study, patients with metastatic clear cell RCC whose disease had progressed after prior cytokine therapy were randomized to receive either one of two dose levels of bevacizumab (10 mg/kg or 3 mg/kg administered every 2 weeks intravenously) or placebo (Table 50–7) (Yang et al, 2003a). An interim efficacy analysis performed after 116 patients (of a planned 240 patients) were enrolled in the study demonstrated a significantly longer progression-free survival (PFS) in patients assigned to 10 mg/kg bevacizumab compared with those receiving placebo (4.8 vs 2.5 months, P < .001) (Fig. 50–5). There was no corresponding improvement in OS, although the crossover design used in this trial (patients progressing on placebo were allowed to cross over to the bevacizumab arm) may have influenced this outcome. The overall response rate in patients receiving bevacizumab was modest (objective response rate of 10%, all in patients assigned to the 10 mg/kg dose). The agent was well tolerated, with bleeding, hypertension, fatigue, and proteinuria being some of the more common adverse events reported. Single-agent bevacizumab has not been compared with either cytokines (often used in first-line treatment before the advent of VEGF pathway antagonists) or other VEGF pathway antagonists such as sunitinib in prospective trials.

Several strategies for improving the efficacy of bevacizumab have been explored, including combination with cytokines (interferon-α) and other targeted agents (e.g., erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase activity). A single-arm phase 2 study of bevacizumab plus erlotinib showed promising activity with an overall response rate of 25% (higher than would be expected with bevacizumab alone based on historical data) and median PFS of 11 months (Hainsworth et al, 2005). However, a subsequent randomized phase 2 study failed to demonstrate the superiority of this combination (median PFS 9.9 months) over bevacizumab alone (median PFS 8.5 months, P = .58) (Bukowski et al, 2007). Two large randomized phase 3 studies have compared the combination of bevacizumab and interferon-α to interferon-α alone (Table 50–8). In a Cancer and Leukemia Group B study (CALGB 90206) of 752 patients with previously untreated metastatic clear cell RCC randomized to one of two treatment arms, a higher response rate (25.5% vs. 13.1%, P < .0001) and PFS (8.5 months vs. 5.2 months, P < .0001) were observed in

![VHL pathway diagram]

Figure 50–4. Targeting the VHL pathway in clear cell renal cell carcinoma. Loss of VHL activity leads to accumulation of HIF and several proangiogenic and growth factors that can serve as targets for anticancer drugs. HIF can also be upregulated by mTOR, which promotes HIF translation. (Adapted from Linehan WM, Bratslavsky G, Pinto PA, et al. Molecular diagnosis and therapy of kidney cancer. Annu Rev Med 2010;61:329–43.)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>AGENT(S)</th>
<th>PHASE</th>
<th>STUDY POPULATION</th>
<th>NO. OF PATIENTS</th>
<th>OVERALL RESPONSE RATE (RECIST)*</th>
<th>MEDIAN PFS (MO)*</th>
<th>MEDIAN OS (MO)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al, 2003a</td>
<td>Bev (10 mg/kg) vs. Bev (3 mg/kg) vs. placebo</td>
<td>Randomized, 3-arm phase 2</td>
<td>Cytokine-refractory clear cell</td>
<td>116</td>
<td>10% vs. 0% vs. 0%</td>
<td>4.8 vs. 3.0 vs. 2.5</td>
<td></td>
</tr>
<tr>
<td>Escudier et al, 2007b</td>
<td>Bev + IFN-α vs. IFN-α</td>
<td>Randomized phase 2</td>
<td>Previously untreated clear cell</td>
<td>649</td>
<td>31% vs. 13%</td>
<td>10.2 vs. 5.4</td>
<td>NR vs. 19.8</td>
</tr>
<tr>
<td>Rini et al, 2008a</td>
<td>Bev + IFN-α vs. IFN-α</td>
<td>Randomized phase 3</td>
<td>Previously untreated clear cell</td>
<td>732</td>
<td>26% vs. 13%</td>
<td>8.5 vs. 5.2</td>
<td>NA</td>
</tr>
<tr>
<td>Bukowski et al, 2007</td>
<td>Bev + Erlotinib vs Bev</td>
<td>Randomized phase 2</td>
<td>Previously untreated clear cell</td>
<td>104</td>
<td>14% vs. 13%</td>
<td>9.9 vs. 8.5</td>
<td>20 vs. NR</td>
</tr>
</tbody>
</table>

*Statistically significant differences indicated in bold.

Bev, bevacizumab; IFN-α, interferon-α; NA, not available; NR, not reached; OS, overall survival; PFS, progression-free survival.
patients assigned to bevacizumab plus interferon-α compared with those receiving interferon-α alone (Rini et al., 2008a). A multicenter European trial (AVOREN) with a similar design also reported similar results with PFS (10.2 vs. 5.4 months, \( P = .0001 \)) and objective response rate (31% vs. 13%) favoring the combination arm (Escudier et al., 2007b). Updated survival data from both trials were recently reported, demonstrating no improvement in overall survival associated with the addition of bevacizumab to interferon (Escudier et al., 2010; Rini et al., 2010). While neither study permitted crossover of patients assigned to interferon-α at progression, a significant number of patients (>60%) subsequently received anticancer therapy off protocol, potentially confounding overall survival analysis. Both trials reported a higher incidence of some grade 3 adverse events such as hypertension, fatigue, anorexia, and asthenia in patients receiving combination therapy. Both the CALGB and Avoren trials were large, well-designed, and well-conducted multicenter studies that suggest that the addition of bevacizumab to interferon may be associated with clinical benefit (i.e., improvement in PFS). However, these trials did not include an arm with bevacizumab alone (owing to insufficient evidence of single-agent activity at the time these trials were designed to justify a bevacizumab-only arm), making it difficult to determine if inclusion of interferon in this regimen, with its attendant toxicities, adds meaningful clinical benefit. Interestingly, the median PFS observed in the combination arm of the CALGB trial (8.5 months) is similar to that observed with bevacizumab alone in a phase 2 trial of previously untreated patients with clear cell RCC (Bukowski et al., 2007). Lastly, bevacizumab (either alone or in combination with interferon) has not been compared prospectively with VEGF receptor (VEGFR) antagonists such as sunitinib, arguably the current standard of care for most newly diagnosed patients with metastatic clear cell RCC. Bevacizumab is not widely used as a single agent in the initial therapy for metastatic clear cell RCC but may have a role in patients who have failed standard therapy with first-line VEGFR antagonists, either alone or in combination with other agents, particularly interferon. Ongoing and future trials may help determine the best use of this agent in the overall management of patients with clear cell RCC.

**Sorafenib**

Sorafenib is an oral receptor kinase inhibitor with activity against VEGFR2, PDGF receptor-β, and raf-1. A phase 2 trial using a randomized discontinuation design provided initial evidence that sorafenib is active in RCC (see Table 50–8) (Ratain et al., 2006). Two hundred and two patients were enrolled on this trial, and all of them received 400 mg of sorafenib twice daily for the first 12 weeks. Sixty-five patients who demonstrated stable disease at the end of this period (defined in this trial as within ±25% of baseline) were then randomized to either continued treatment with sorafenib or to placebo. Patients randomized to sorafenib had a superior PFS (24 weeks) versus 50–6) (Escudier et al., 2007b).

![Figure 50–5](image-url)

**Figure 50–5.** Kaplan-Meier analysis of 39 patients assigned to high-dose bevacizumab (10 mg/kg, A) and of 37 patients assigned to low-dose bevacizumab (3 mg/kg, B) compared with 40 patients assigned to receive placebo. (From Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 2003a;349:427–34.)

### Table 50–8.

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>AGENT(S)</th>
<th>PHASE</th>
<th>STUDY POPULATION</th>
<th>NO. OF PATIENTS</th>
<th>OVERALL RESPONSE RATE (RECIST)*</th>
<th>MEDIAN PFS (MO)*</th>
<th>MEDIAN OS (MO)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratain et al, 2006</td>
<td>Sorafenib vs. placebo</td>
<td>Phase 2 randomized discontinuation</td>
<td>Treatment-refractory, all histologic subtypes</td>
<td>202</td>
<td>6 vs. 1.5</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Escudier et al, 2007a, 2009a</td>
<td>Sorafenib vs. placebo</td>
<td>Randomized phase 3</td>
<td>Cytokine-refractory clear cell</td>
<td>903</td>
<td>10% vs. 2%</td>
<td>5.5 vs. 2.8</td>
<td>17.8 vs. 15.2</td>
</tr>
<tr>
<td>Escudier et al, 2009b</td>
<td>IFN-α vs.</td>
<td>Randomized phase 2</td>
<td>Previously untreated clear cell</td>
<td>189</td>
<td>5% vs. 9%</td>
<td>5.7 vs. 5.6</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Statistically significant differences indicated in bold.

IFN-α, interferon-α; NA, not available; NR: not reached; OS: overall survival; PFS: progression-free survival.
CHAPTER 50  Treatment of Advanced Renal Cell Carcinoma

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Overall response rate to sorafenib in this trial was relatively low, with 10% of patients experiencing a partial response; however, more than 70% of patients receiving sorafenib had some degree of tumor regression. The side effect profile of sorafenib is comparable to that of other agents in this class and includes hypertension, fatigue, rash, hand-foot syndrome, and diarrhea. The efficacy of sorafenib in the first-line setting was investigated in a randomized phase 2 study that assigned 189 previously untreated patients with metastatic clear cell RCC to receive either sorafenib or interferon-α (Escudier et al, 2009b). Although patients receiving sorafenib had a higher likelihood of achieving tumor regression (68% vs. 39%), PFS in the two groups was nearly identical (median 5.7 months for sorafenib vs. 5.6 months for interferon, P = NS) (Table 50–9). Although sorafenib is FDA-approved for the treatment of advanced kidney cancer, its precise role in the management of these patients remains to be determined in view of the plethora of VEGFR antagonists currently available or under investigation. Dose-intensive regimens of sorafenib (up to 800 mg twice daily) are being explored in an attempt to enhance.

the efficacy of this agent, but to date there is no convincing evidence that higher doses offer additional clinical benefit. **Currently, sorafenib is infrequently used in the first-line setting.** Anecdotal evidence and small case series suggest that patients whose disease has progressed on other VEGFR inhibitors may respond favorably to sorafenib, and the agent is commonly used in patients whose disease has progressed on sunitinib or similar agents.

**Sunitinib**

Sunitinib is currently the most widely used oral VEGFR kinase inhibitor in the initial treatment of metastatic clear cell RCC. It is a potent inhibitor of VEGFR2, PDGFR-β, c-KIT, and fms-like tyrosine kinase-3. As with sorafenib, simultaneous targeting of VEGF and PDGF pathways by this agent is likely to act synergistically in inhibiting tumor angiogenesis, by directly disrupting VEGF-mediated vascular endothelial development and proliferation and by interfering with vascular pericyte function, which is dependent on the integrity of PDGF signaling. Initial evaluation of sunitinib was undertaken with two single-arm open-label phase 2 trials in patients with metastatic RCC, most of whom had previously received cytokine therapy (Motzer et al, 2006a, 2006b). Sunitinib was administered orally at a dose of 50 mg/day during the first 4 weeks of a 6-week cycle on both trials (see Table 50–9). Remarkably high overall response rates (30% to 40%) with a median PFS of more than 8.5 months were observed in these trials, leading to the approval of this agent for treatment of advanced RCC by the FDA. A landmark phase 3 randomized trial comparing sunitinib with interferon-α as first-line therapy in patients with metastatic clear cell RCC further demonstrated the activity of sunitinib in this patient population (Motzer et al, 2007). In this study, 750 patients were randomized to receive either sunitinib or interferon-α. An interim analysis based on independent, third-party radiologic assessment demonstrated a significantly superior PFS (median 11 months vs. 5 months, *P* = .001) and overall response rate (31% vs. 6%, *P* = .001) favoring the sunitinib arm (Fig. 50–8). Gastrointestinal events, particularly diarrhea, dermatologic manifestations such as rash and hand-foot syndrome, constitutional symptoms such as fatigue and asthenia, and hypertension were the most commonly adverse events associated with sunitinib, whereas bone marrow suppression, decline in left ventricular ejection fraction, and hypothyroidism were other notable side effects. Sunitinib also performed better than interferon in a quality of life assessment conducted as part of the study. Mature survival data from this study were recently reported and demonstrated superior OS in the sunitinib study arm based on an intent-to-treat analysis (median OS 26.4 vs. 21.8 months, *P* = .051) (Motzer et al, 2009). Based on these data,


**Table 50–9.**

Summary of Selected Studies of Sunitinib in Metastatic Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>STUDIES</th>
<th>AGENT(S)</th>
<th>PHASE</th>
<th>STUDY POPULATION</th>
<th>NO. OF PATIENTS</th>
<th>OVERALL RESPONSE RATE (RECIST)*</th>
<th>MEDIAN PFS (MO)*</th>
<th>MEDIAN OS (MO)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motzer et al, 2007, 2009</td>
<td>Sunitinib vs. IFN-α</td>
<td>Randomized phase 3</td>
<td>Previously untreated clear cell</td>
<td>750</td>
<td>31% vs. 6%</td>
<td>11 vs. 5</td>
<td>26.4 vs. 21.08</td>
</tr>
<tr>
<td>Motzer et al, 2006a</td>
<td>Sunitinib</td>
<td>Single-arm phase 2</td>
<td>Cytokine-refractory clear cell</td>
<td>63</td>
<td>40%</td>
<td>8.7</td>
<td>NA</td>
</tr>
<tr>
<td>Motzer et al, 2006b</td>
<td>Sunitinib</td>
<td>Single-arm phase 2</td>
<td>Cytokine-refractory clear cell</td>
<td>106</td>
<td>44%</td>
<td>8.1</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Statistically significant differences indicated in bold.
NA, not available; OS, overall survival; PFS, progression-free survival.
Axitinib is an oral small molecule tyrosine kinase inhibitor of VEGFR1, VEGFR2, and VEGFR3. In a phase 2 trial of axitinib in 52 patients with advanced kidney cancer, an overall response of 44%, including two complete responses (4%), and a median time to progression of 15.7 months were reported (Rixe et al., 2007). Most patients treated on this study displayed some degree of tumor shrinkage, and many had been pretreated with either IL-2 or interferon. Diarrhea, fatigue, and hypertension were the most commonly encountered grade 3 and 4 events and were amenable to medical management in most patients. Several other agents with selective activity against the VEGFR family are also under investigation. One agent in this class, pazopanib, was the subject of a recent randomized, double-blind, placebo-controlled phase 3 trial in patients with metastatic clear cell RCC who had received no or one prior cytokine-based therapy (Sternberg et al., 2010). In the 405 patients randomized (2:1) to receive either pazopanib or placebo, PFS (median 9.4 months vs. 4.2 months, $P$

Inhibitors of the Mammalian Target of Rapamycin

mTOR is a key intracellular protein that is a component of several signaling cascades including those mediating the effects of some growth factors. It appears to play a role in regulating translation and stability of HIF-1α, and preclinical models have suggested that growth inhibition occurring in response to mTOR inhibitors correlates with a block in HIF-1α translation (Hudson et al., 2002; Thomas et al., 2006). Two analogues of sirolimus, temsirolimus and everolimus, have been clinically evaluated with demonstrable activity in RCC. A phase 2 trial of temsirolimus evaluated three different doses (25 mg, 75 mg, and 250 mg per week administered intravenously) in 111 patients assigned randomly to one of the dose levels (Table 50–11). The overall response rate observed on this trial was modest (7%), including one patient with a complete response, and the median PFS was 15 months (Atkins et al., 2004). Responses and PFS appeared to be independent of temsirolimus dose. An exploratory subgroup analysis based on stratification of patients according to MSKCC risk groups revealed that patients in the poor-risk group had a longer median OS compared with historical controls receiving interferon-α (8.2 vs. 4.9 months). Based on this observation, a three-arm randomized phase 3 trial of 626 patients with three or more predefined poor risk features was undertaken (Hudes et al., 2007). Patients with previously untreated metastatic kidney cancer of all histologic subtypes were eligible and randomized to receive temsirolimus alone (25 mg intravenously every week), interferon-α alone (up to 18 million units subcutaneously three times a week) or temsirolimus (15 mg intravenously every week) plus interferon-α (6 million units subcutaneously three times a week). PFS was superior in both temsirolimus-containing arms compared with interferon alone (median 3.8 months vs. 1.9 months). Importantly, the trial also demonstrated a significantly higher OS in the temsirolimus arm compared with the interferon-only arm (median OS 10.9 vs. 7.3 months, P = .008), while the addition of temsirolimus did not appear to significantly alter OS compared with interferon alone (median OS 8.4 vs. 7.3 months, P = .70) (Fig. 50–9). Temsirolimus was fairly well tolerated, and most patients with previously untreated metastatic kidney cancer while avoiding the toxicity of multiple kinase inhibitors. Prospective randomized trials of selective VEGFR inhibitors are required to determine if these agents offer tangible advantages over currently FDA-approved agents.

Table 50–10.
Summary of Selected Studies of Selective VEGFR Receptor Antagonists in Metastatic Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>STUDY</th>
<th>AGENT(S)</th>
<th>PHASE</th>
<th>STUDY POPULATION</th>
<th>NO. OF PATIENTS</th>
<th>OVERALL RESPONSE RATE (RECIST)*</th>
<th>MEDIAN PFS (MO)*</th>
<th>MEDIAN OS (MO)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternberg et al, 2010</td>
<td>Pazopanib vs. placebo</td>
<td>Randomized phase 3</td>
<td>Metastatic clear cell RCC patients with 0-1 prior cytokine therapy</td>
<td>435</td>
<td>30% vs 3%</td>
<td>9.2 vs 4.2</td>
<td>NA</td>
</tr>
<tr>
<td>Bhargava et al, 2009</td>
<td>AV-951 vs. placebo</td>
<td>Phase 2 randomized discontinuation</td>
<td>Previously untreated metastatic RCC of all histologies</td>
<td>272</td>
<td>28%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rixe et al, 2007</td>
<td>Axitinib</td>
<td>Single arm phase 2</td>
<td>Previously untreated clear cell RCC</td>
<td>52</td>
<td>44%</td>
<td>15.7</td>
<td>29.9</td>
</tr>
</tbody>
</table>

*Statistically significant differences indicated in bold.
NA, not available; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

Table 50–11.
Summary of Selected Studies of mTOR Inhibitors in Metastatic Renal Cell Carcinoma (RCC)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>AGENT(S)</th>
<th>PHASE</th>
<th>STUDY POPULATION</th>
<th>NO. OF PATIENTS</th>
<th>OVERALL RESPONSE RATE (RECIST)*</th>
<th>MEDIAN PFS (MO)*</th>
<th>MEDIAN OS (MO)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudes et al, 2007</td>
<td>Tem vs. IFN-α vs. tem/IFN-α</td>
<td>Randomized phase 3</td>
<td>Poor prognosis, previously untreated, all histologic subtypes</td>
<td>626</td>
<td>8.6% vs. 4.8% vs. 8.1%</td>
<td>5.5 vs. 3.1 vs. 4.7</td>
<td>10.9 vs. 7.3 vs. 8.4</td>
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<tr>
<td>Motzer et al, 2008b</td>
<td>Everolimus vs. placebo</td>
<td>Randomized phase 3</td>
<td>Clear cell RCC refractory to VEGF-targeted therapy</td>
<td>410</td>
<td>1% vs. 0%</td>
<td>4.0 vs. 1.9</td>
<td>NR vs. 8.8</td>
</tr>
</tbody>
</table>

*Statistically significant differences indicated in bold.
INN-α, interferon-α; NR, not reached; OS, overall survival; PFS, progression-free survival; tem, temsirolimus.
Combination and Sequential Therapy with Agents Targeting the VHL Pathway

Combinations of two or more classes of agents with activity centered on different components of the VHL pathway provides an attractive strategy that might serve to increase efficacy as well as eliminating potential mechanisms of resistance. A major limitation of this approach is the overlapping toxicity profile of several drugs, necessitating significant dose reductions (Feldman et al, 2009; Patel et al, 2009). Ongoing trials will determine if the synergy engendered by combination therapy can adequately offset the effects of dose reduction.

Given the profusion of agents with single-agent activity in RCC, identifying the optimal sequencing of these agents is a question of considerable importance. A randomized study has demonstrated that everolimus can prolong PFS compared with placebo in patients who have progressed on first-line VEGFR antagonists (Motzer et al, 2008b). Smaller retrospective analyses have suggested that a proportion of patients who have progressed on one VEGF pathway inhibitor may benefit from a second agent targeting the same pathway (Rini et al, 2008b; Tamaskar et al, 2008). Carefully designed clinical trials are required to identify the most common adverse events such as mucositis, fatigue, rash, hyperglycemia, hypophosphatemia, hypercholesterolemia, and pulmonary complications were amenable to medical and/or supportive measures. Based on these data, temsirolimus was approved by the U.S. FDA for the treatment of patients with metastatic RCC, and the agent is a reasonable front-line choice in patients presenting with poor-risk features.

Everolimus is an orally bioavailable inhibitor of mTOR. It was the subject of a phase 3 trial in patients with metastatic clear cell RCC whose disease had progressed after therapy with sunitinib, sorafenib, or both (Motzer et al, 2008b). Patients were randomized to receive either everolimus, 10 mg once daily (n = 272), or placebo (n = 138) (see Table 50–11). The trial was stopped after an interim analysis demonstrated superior PFS in the everolimus arm (median 4 months) compared with the placebo arm (median 1.9 months) (Fig. 50–10). At the time of this analysis, median survival had not been reached in the everolimus group and was 8.8 months for the placebo group; OS was not significantly different in the two groups. Although the agent offers only a modest improvement in PFS in patients progressing on first-line VEGFR antagonists, it is nonetheless a reasonable therapeutic option and has been approved by the U.S. FDA for this indication.
Other Treatment Options in Patients with Clear Cell Renal Cell Carcinoma

Chemotherapy

Conventional cytotoxic chemotherapy has been largely ineffective in the management of clear cell RCC. Numerous chemotherapeutic agents including 5-FU, platinum compounds, gemcitabine, vinblastine, and bleomycin have been evaluated as single agents in this disease but have failed to demonstrate clinically meaningful activity; a wide array of combination chemotherapy regimens have fared little better (Haas et al, 1976; Hahn et al, 1977; Zaniboni et al, 1989; Mertens et al, 1993, 1994; Amato, 2000; Rini et al, 2000, 2005; Stadler et al, 2006). Comprehensive meta-analyses of chemotherapy trials in RCC indicate the overall response rate is 5.5% to 6.0% (Yagoda et al, 1995). Although the mechanisms underlying this profound chemoresistance have not been fully elucidated, overexpression of the multidrug resistance gene (MDR) has been proposed as one possible culprit (Fojo et al, 1987). However, the addition of MDR inhibitors such as toremifene, cyclosporine, and verapamil to conventional chemotherapeutic agents has failed to improve their efficacy, suggesting that other, as yet unrecognized, factors may be at play (Braybrooke et al, 2000). Cytotoxic chemotherapy has no role in the current management of most patients with clear cell RCC. One situation in which chemotherapy may bear further investigation is in patients whose tumors demonstrate a sarcomatoid component; a small case series of papillary RCC patients (both HGF and c-MET are located on chromosome 7) has been described in more than two thirds of papillary tumors and may represent an alternative mechanism contributing to activation of the c-MET pathway (Kovacs et al, 1991; Henke and Erbersdobler, 2002).

Hormonal Therapy

Hormonal therapy had been the subject of trials in RCC in the 1970s and 1980s, preceding the advent of cytokines. These studies were prompted by both the lack of effective therapies for kidney cancer and by the belief that a male preponderance (kidney cancer by the belief that a male preponderance (kidney cancer has been promoted on the basis of cases in males) implied a hormonal basis for this malignancy. Hormonal agents such as medroxyprogesterone have been noted to induce tumor regressions in a small minority of patients, but overall response rates are too low (approximately 2%) to have meaningful clinical impact in most patients (Schomberg et al, 1993; Harris, 1983; Medical Research Council Renal Cancer Collaborators, 1999; Braybrooke et al, 2000). Progestational and other hormonal agents have no role in the current management of renal cell cancer.

SYSTEMIC THERAPY FOR NON–CLEAR CELL VARIANTS OF RENAL CELL CARCINOMA

Non–clear cell subtypes of kidney cancer are relatively rare (constituting approximately 15% of all kidney cancer) and have been the subject of few prospective studies. Given the unavailability of agents of proven efficacy in papillary, chromophobe, and other rare histologic subtypes, patients with non–clear cell renal tumors often receive agents with activity in clear cell RCC. Recent advances in our understanding of some subtypes of RCC are bound to lead to a more rational approach to their management. As with clear cell RCC, hereditary forms of papillary and chromophobe RCC may hold the key to the identification of critical molecular events leading to these tumors both in familial and sporadic settings (Linehan, 2003; Linehan et al, 2009). Hereditary papillary renal cancer (HPRC) is a familial condition characterized by the predisposition of affected individuals to develop bilateral, multifocal papillary type I RCC. HPRC is characterized by the presence of activating germline mutations in the tyrosine kinase domain of the proto-oncogene c-MET, which is located on chromosome 7; this is usually accompanied by nonrandom duplication of the chromosome containing the mutated allele (Schmidt et al, 1997, 1998, 1999, 2004; Zhuang et al, 1998; Linehan, 2003; Linehan et al, 2009). c-MET is a cell surface receptor that is normally activated on binding its ligand, hepatocyte growth factor (HGF) but is rendered constitutively active in the presence of mutations in the kinase domain of this protein (Bottaro et al, 1991; Dharmawardana et al, 2004; Peruzzi and Bottaro, 2006; Giubellino et al, 2009). The HGF/c-MET pathway is involved in regulating a variety of biologic functions, including cell growth, proliferation, and motility (Fig. 50–11) (Jeffers et al, 1998; Giubellino et al, 2009). Somatic c-MET alterations have been noted in a proportion of patients with sporadic papillary RCC, with activating mutations identified in approximately 13% of papillary tumors in one series. Trisomy 7 (both HGF and c-MET are located on chromosome 7) has been described in more than two thirds of papillary tumors and may represent an alternative mechanism contributing to activation of the c-MET pathway (Kovacs et al, 1991; Henke and Erbersdobler, 2002).

VEGFR inhibitors active in clear cell RCC do not seem to be effective in papillary RCC. Sorafenib and sunitinib were shown to have minimal activity in retrospective studies of papillary RCC patients (Choueiri et al, 2008a). Prospective phase 2 trials with sunitinib have demonstrated that this agent is associated with low response rates (5% to 10%) in papillary RCC. The Southwest Oncology Group reported an 11% overall response rate with erlotinib, an oral EGFR inhibitor, in 52 patients with metastatic papillary RCC with a 6-month PFS of only 29%. More recently, the realization that c-MET activation may play an important role in some forms of papillary RCC has led to the evaluation of foretinib (formerly known as XL880 and GSK1363089), a novel tyrosine kinase inhibitor with activity against c-MET and VEGFR2 in this RCC subtype. A multicenter, open-label phase 2 trial studied two dosing regimens (an intermittent regimen in which the drug was administered orally at a dose of 240 mg/day for the first 5 days of every 14-day cycle and a continuous or daily dosing regimen at a dose of 80 mg/day) in patients with metastatic papillary RCC and those with bilateral multifocal disease (Srinivasan et al, 2009). A recent interim analysis in the first 53 patients enrolled on trial (including seven HPRC patients with germline c-MET mutations and bilateral multifocal tumors) has been reported in abstract form. Of 44 evaluable patients in both dosing regimens, 6 had a confirmed partial response (objective response rate 14%) and an additional 34 (77%) had stable disease as their best response. Striking responses were seen in some patients, including regression of renal tumors in patients with bilateral multifocal disease. The adverse event profile associated with this drug is similar to that observed with other VEGFR antagonists. Patients on this trial will be retrospectively stratified based on the presence or absence of c-MET pathway activation (germline or somatic c-MET mutation or trisomy 7 or 7q31 amplification in
tumor tissue) to help explore the correlation between c-MET activation and response to foretinib. Foretinib and other agents targeting the c-MET pathway warrant further evaluation in patients with papillary RCC.

An exploratory subgroup analysis of patients enrolled in large randomized phase 3 study evaluating the efficacy of temsirolimus versus interferon in “poor prognosis” patients suggests that mTOR inhibitors may have activity in some non–clear cell variants. Approximately 20% of the patients enrolled in this trial had non–clear cell histologies (predominantly papillary RCC). The outcome of 37 patients with non–clear cell RCC treated with temsirolimus (both OS and PFS) was found to be better than that of 36 patients receiving interferon in this subgroup analysis. Although these data suggest that temsirolimus may have activity in some non–clear cell variants, these conclusions are limited by the fact that this is a subgroup analysis (Dutcher et al, 2009).

Prospective studies evaluating the efficacy of mTOR inhibitors are required to clarify the role of these agents in different subsets of RCC.

Cytotoxic chemotherapy has been used with modest success in collecting duct carcinoma, a rare kidney cancer variant with similarities to urothelial malignancies. In a series of 23 patients with metastatic collecting duct carcinoma, a response rate of 26% (including one complete response) was reported with a regimen comprising gemcitabine and carboplatin. Median PFS (7.1 months) and OS (10.5 months) were modest (Oudard et al, 2007). In summary there is no standard approach of proven efficacy for most patients with non–clear cell RCC, although some promising approaches are being evaluated. Enrollment in suitable trials should be considered for all patients with non–clear cell RCC.

SUGGESTED READINGS


REFERENCES

The complete reference list is available online at www.expertconsult.com.
REFERENCES


