REVIEW

# *Treatment options for metastatic renal cell carcinoma: a review*

Uzma Athar, MD, Teresa C. Gentile, MD

Division of Hematology Oncology, Regional Oncology Center, SUNY Upstate Medical University, Syracuse, New York, USA

ATHAR U, GENTILE TC. Treatment options for metastatic renal cell carcinoma: a review. The Canadian Journal of Urology. 2008;15(2):3954-3966.

*Metastatic renal cell carcinoma (RCC) has a poor overall survival. Localized RCC remains a surgical disease. About 20%-30% patients who present with limited disease at the time of nephrectomy develop metastasis. The median time to relapse after nephrectomy is 15-18 months. The maximum numbers of relapses are within the first 3 years. In metastatic RCC, immunotherapy is effective in a relatively small percentage of patients but is very toxic. In recent years, there has been an improved understanding of the biology of RCC. This has lead to the development of various agents that target ligands at the molecular level. The hypoxia inducible factor-alfa (HIF-α)/ vascular endothelial growth factor (VEGF) pathway and mammalian target of rapamycin (mTOR) signal transduction pathway are targets for some of these novel agents. Recent randomized phase III trials have shown an improved outcome in patients with metastatic disease who received these targeted agents. This review deals with management of advanced and metastatic renal cell cancer with an emphasis on recently developed targeted therapies.*

**Key Words:** RCC, metastatic renal cell carcinoma, targeted therapy, treatment

## Epidemiology

Malignant tumors of the kidney account for 2% of all cancers in the United States each year. It is estimated that there will be 54390 new cases and 13010 deaths from renal cell (kidney and renal pelvis) cancer in the United States in 2008.[1] The median age at diagnosis is 66 years and median age at death is 70 years. The autopsy incidence is approximately 2%-5%. The incidence of renal cell cancer has increased both in the United States and in Europe.[2] It is twice as common in men compared to women.[3] In the United States, there has been an increase in incidence seen in women[4] and in blacks.[5]

Renal cell carcinoma (RCC) accounts for approximately 85% of kidney tumors followed by transitional cell carcinomas (~ 11%) and sarcomas and other soft tissue malignancies (~ 2%).

Accepted for publication January 2008

Address correspondence to Dr. Uzma Athar, Department of Medicine, Division of Hematology Oncology, Regional Oncology Center, 750 East Adams Street, Syracuse, New York 13210 USA

## Presentation/diagnosis

Few patients present with the classic triad of flank pain, palpable abdominal mass and hematuria. Incidental tumor detection from abdominal imaging for other reasons has led to a tumor size and stage migration and an excellent prognosis for 70% of patients with early disease. However, the prognosis remains guarded for 30% of patients who present with metastasis or later develop metastatic disease. In patients with stage IV RCC the 5-year overall survival is less than 10%.[6]

## Risk factors

RCC occurs in sporadic and familial forms. There is a 2-4 fold increase in the risk of RCC in patients who have a first degree relative with the disease.[7] Cigarette smoking is a well-established risk factor. In a meta analysis the relative risk of 1.5 and 1.2 for male and female smokers were reported. The risk increases in heavy smokers (relative risk of 2.0 in males and 1.6 in females). There is a decrease in the risk of RCC by 15%-30% 10 to 15 years following cessation of smoking.[8] Other risk factors include obesity, hypertension and occupational exposure to toxic compounds, such as cadmium, asbestos, and petroleum by-products.[9]

## Genetic basis of RCC

Renal cell carcinoma is no longer considered a single disease ("hypernephroma, renal cell") but instead a family of distinct tumors with unique histological and cytogenetic defects. There are four well-defined familial renal neoplasms- Von Hippel-Lindau (VHL) disease, hereditary papillary renal carcinomas (HPRC), Birt-Hogg-Dube syndrome (BHD) and hereditary leiomyomatosis and renal cell cancer (HLRCC). Approximately 4% of RCC are inherited. These inherited forms usually present at an early age and are often bilateral and multifocal.

The Von Hippel-Lindau gene is a tumor suppressor gene found in patients with VHL disease.[10] RCC occurs in these patients as a result of inactivation of the normal (wild type) VHL allele. Mutations of VHL gene are also present in 60% of patients with sporadic disease. The VHL gene encodes the VHL protein. This protein inhibits hypoxia inducible genes including proteins involved in angiogenesis (e.g., vascular endothelial growth factor [VEGF]), cell growth (e.g., transforming growth factor-alfa and beta [TGF-α TGF-β]), and glucose uptake (e.g., GLUT-1 glucose transporter).

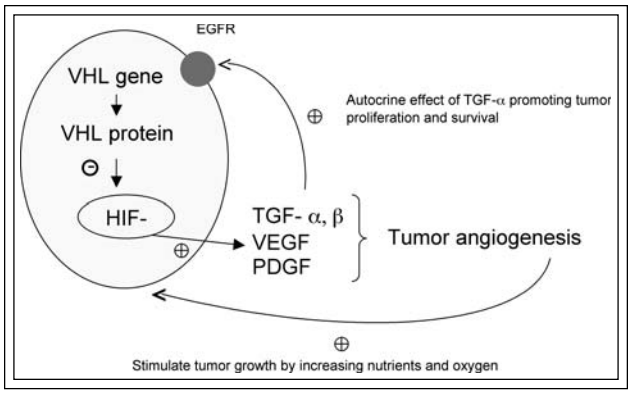


**Figure 1.** Under normoxic conditions VHL protein inhibits hypoxia inducible factor (HIF-α). Whereas under hypoxic conditions and in the presence of deleted or mutated VHL gene, inhibition of HIF-α is lost and a number of molecules are activated including transforming growth factor- alfa and beta (TGF-α and TGF-β), vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) which play a role in tumor growth and proliferation.

Under normoxic conditions, hypoxia inducible factor-alfa (HIF- α) is hydroxylated and binds to the VHL protein. This leads to ubiquitination and destruction of HIF- α by the proteasome pathway. When the VHL gene is mutated or deleted the hydroxylated HIF- α accumulates and forms a dimer with HIF-β leading to activation of hypoxia response elements including TGF-α, TGF-β, VEGF and platelet derived growth factor (PDGF-B), Figure 1. The overexpressed VEGF, PDGF-B and TGF-β act on vascular cells and promote tumor angiogenesis. The increased tumor vasculature provides additional nutrients and oxygen to the tumor cells. TGF-α causes autocrine stimulation of tumor cells through the epidermal growth factor receptor (EGFR) and causes tumor proliferation and survival. In addition to the VHL gene there are a number of other genetic changes associated with both sporadic and familial renal cell carcinomas, Table 1. In recent years there has been an increased interest in targeted therapies directed at the molecular level.

## Prognostic factors

Motzer et al[13] developed a model for prognostic stratification of patients with advanced RCC based on multivariate analysis. In their retrospective review of patients treated at the Memorial Sloan Kettering Cancer Center (MSKCC), five pretreatment features were associated with an adverse prognosis. These included a Karnofsky performance status of < 80%,

TABLE 1. **Genetic defects in histologic subtype of renal cell carcinoma.[10,11]**

| Histologic subtype | Incidence[10] | Early genetic defect | Late genetic defect |
|---|---|---|---|
| Clear cell carcinoma* | 75% | 3p loss of heterozygosity | +5q |
| Von Hippel Lindau | | VHL gene mutation | -8p, -9p, -14q |
| Hereditary RCC | | | p 53 mutation |
| Sporadic RCC | | | C-erbB1-oncogene expression |
| Papillary renal carcinoma | 12% | +7, +17 | + 12, +16, +20 |
| (PRC type1& 2)** | | -Y | -9p,-11q,-14q,-17p,-21q |
| Hereditary papillary (HPRC) | | Met gene mutation | PRCC-TFE3 gene mutation |
| Sporadic papillary RCC | | | |
| Chromophobe | 4% | -1 | -1p,-2p,-6p,-13q,-21q,-Y |
| Birt Hogg Dube | | | p 53 mutation |
| Oncocytoma | 4% | -1, -Y, 11q rearrangement | |
| Familial oncocytoma | | | |
| Collecting Duct | < 1% | -18, -Y | -1q,-6p,-8p,-11,-13q,-21q |
| Renal medullary carcinoma | | | C-erbB1 oncogene expression |

*5% of clear cell RCC undergo sarcomatoid changes and are associated with a poor prognosis
**Type 1 papillary renal carcinoma consists of papillae and tubular structures covered by small cells with pale cytoplasm, small oval nuclei with inconspicuous nucleoli, frequent glomeruloid papillae, papillary edema, foamy macrophages and psammoma bodies. Type 2 PRC consists of papillae covered by large cells with abundant eosinophilic cytoplasm and characterized by pseudostratification and large spherical nuclei with prominent nucleoli. Glomeruloid papillae, psammoma bodies, edematous papillae, and foamy macrophages are uncommon. Type 1 tumors are low-grade and have a better prognosis, while type 2 lesions are high-grade and have a poorer prognosis.[12]

serum LDH greater than 1.5 times normal, anemia, corrected serum calcium of greater than 10 and the absence of nephrectomy, Table 2. Based on these features patients were classified into favorable risk (no risk factor), intermediate risk (one or two risk factors) and poor risk (three or more risk factors) groups. The median duration of survival in the favorable, intermediate and poor risk groups were 20 months, 10 months and 4 months respectively. Similarly the 1-year, 2-year and 3-year survival was much better in the favorable risk group, Table 3. In addition, the median survival time of patients treated with immunotherapy was better than patients treated with chemotherapy (26, 12 and 6 months).

TABLE 2. **Adverse prognostic factors in multivariate analysis**

| Adverse prognostic factor | Risk ratio |
|---|---|
| Serum LDH > 1.5 times normal | 2.5 |
| Corrected serum calcium > 10 mg/dl | 1.7 |
| Anemia | 1.7 |
| Karnofsky performance status < 80% | 1.5 |
| Absence of nephrectomy | 1.4 |

Negrier et al[14] identified independent predictors of rapid disease progression i.e. within 10 weeks of initiation of therapy. These included greater than one metastatic site, disease free interval of less than 1 year, presence of liver metastasis and mediastinal nodes and type of immunotherapy used. Patients with liver metastasis, more than one primary site, and disease free interval of less than 1 year had a lower response rate and median overall survival of less than 6 months when treated with subcutaneous IL-2 and IFN-α.

Histologic markers of response to IL-2 include the presence of clear cell histology with alveolar features. In the reanalysis of pathology specimens from the CWG trials[15] it was found that the response rate to IL-2 was 25% in patients with clear cell histology as compared to 4% in patients with papillary features, greater than 50%

TABLE 3. **Risk groups and survival time**

| | Favorable risk | Intermediate risk | Poor risk |
|---|---|---|---|
| 1 year survival | 71% | 42% | 12% |
| 2 year survival | 45% | 17% | 3% |
| 3 year survival | 31% | 7% | 0% |

granular features or absence of alveolar features. In recent years there has been an interest in molecular markers especially carbonic anhydrase IX (CA IX) expression as a predictor for response to IL-2. Atkins et al[16] retrospectively studied the expression of CA IX and its effect on response to IL-2 in 66 patients. A high CA IX expression was defined as greater than 85% of tumor cells staining for CA IX. Twenty-seven patients (41%) responded to IL-2 therapy. Seventy eight percent (21/27) of responding patients had high CA IX expression as compared to 51% (20/39) of nonresponders (p = 0.04). Median survival was 3 years and 1 year in the high and low CA IX expressors (p = 0.04) and greater than 5-year survival was seen only in the high CA IX expressing group only. These prognostic markers need to be validated prospectively to better identify patients who will respond to IL-2 therapy.

## Treatment of renal cell carcinoma

### *Surgical management*

Surgical resection can be curative in patients with localized RCC. The 5-year overall survival rate for patients with stage I and II RCC following nephrectomy is over 80% in most published series.[17] Surgical management of metastatic renal cell cancer may include nephrectomy and/or metastatectomy. Surgical intervention leads to palliation of symptoms as well as an improvement in prognosis. Nephrectomy may also lead to regression of metastatic disease.[18] The indications of palliative nephrectomy include relief of pain, control of hematuria, fatigue, fever and hypercalcemia. The survival benefit of nephrectomy prior to immunotherapy was established by two randomized clinical trials.

Flanigan et al[19] randomly assigned 246 patients with metastatic RCC to immunotherapy with interferon alpha alone versus nephrectomy followed by interferon alpha. Patients were stratified according to the presence of measurable metastatic disease, performance status (0 or 1) and the type of metastasis (lung versus other). The median duration of survival in the nephrectomy arm was 11.1 months as compared to 8.1 months in the immunotherapy alone arm (p = 0.05). The survival advantage was seen in all subgroups defined on the basis of the three stratification factors, Table 4.

Mikisch et al[20] randomly assigned 85 patients with metastatic disease to radical nephrectomy followed by interferon-α 2b versus interferon-α 2b alone. The median duration of survival was 17 months in the combined modality arm compared to 7 months in the immunotherapy alone arm. There was no increase in adverse effects in patients who underwent nephrectomy followed by immunotherapy.

The indications for metastatectomy include palliation of symptoms and improvement in prognosis. Kavolius et al[21] retrospectively analyzed 278 patients with recurrent RCC. One hundred and forty one patients (51%) underwent curative metastatectomy for their first recurrence, 70 patients (25%) had noncurative resection and 67 patients (24%) were treated nonsurgically. The 5-year overall survival (OS) in patients undergoing curative resection was 44% compared to 14% and 11% in the noncurative resection and nonsurgical management groups (p < 0.001). Multivariate analysis revealed the presence of a disease free interval of > 12 months (from the time of initial diagnosis to development of metastatic disease), solitary first recurrence, curative metastatectomy and male sex as independent predictors of survival. Lung was the single most common site of metastasis. The 5-year OS of patients undergoing a curative resection of lung metastasis was 54%. Resection of isolated brain metastasis had a poor outcome (5-year OS 18%). In addition, patients who had curative resection of second

TABLE 4. **Subgroup analysis of survival by stratification factors**

| Category | Median survival (months) | | P value |
|---|---|---|---|
| | IFN alone | Nephrectomy +IFN | |
| All patients | 8.1 | 11.1 | |
| Stratification factor | | | |
| Presence of measurable disease | 7.8 | 10.3 | 0.010 |
| Absence of measurable disease | 11.2 | 16.4 | |
| Performance status 0 | 11.7 | 17.4 | 0.080 |
| Performance Status 1 | 4.8 | 6.9 | |
| Lung metastasis only | 10.3 | 14.3 | 0.008 |
| Other metastasis | 6.3 | 10.2 | |

and third recurrences had a 5-year OS of 46% and 44% respectively. Hence metastatectomy has lead to an improvement in overall survival and quality of life. However careful patient selection is required for such surgical management based on performance status and the site and extent of disease.

### *Adjuvant studies*

In locally advanced disease, surgery followed by adjuvant therapy has been studied. There is no survival advantage demonstrated in patients treated with adjuvant IFN-α. Pizzocaro et al[22] in their multicenter trial randomized 264 patients with Robson stages II and III disease following nephrectomy to observation versus IFN-α 2a. After a median follow up of 62 months there were more relapses seen in the IFN-α arm (51/123 compared to 38/124 in the nephrectomy alone arm) although it did not reach statistical significance. The Eastern Cooperative Oncology Group (ECOG) carried out a phase III trial and randomized patients with pT3, T4a and/node positive disease after radical nephrectomy and lymphadenectomy to observation alone versus IFN-α.[23] IFN-α was given for 5 days every 3 weeks to a total of 12 cycles. The median survival was 7.4 years in the observation arm and 5.1 years in the treatment arm at a median follow up of 10.4 years ($p = 0.09$). In addition there was an increased incidence of grade 4 toxicities seen in the treatment arm.

A number of phase III trials evaluating the benefit of targeted therapies in the adjuvant setting are currently accruing patients. NCT00492258 is a randomized, placebo-controlled, double-blind multicenter study.[24] Patients are being randomized to placebo twice daily for 3 years, oral sorafenib twice daily for 1 year followed by oral placebo twice daily for 2 years or oral sorafenib twice daily for 3 years in the absence of disease progression or unacceptable toxicity. Patients in group 2 will receive sorafenib by mouth twice a day for 6 weeks and a placebo by mouth once a day for 4 weeks. Treatment may repeat every 6 weeks for up to nine courses. The primary outcome is disease free survival and secondary outcome is overall survival. NCT00326898/E2805 is a phase III randomized study of adjuvant sunitinib versus sorafenib in patients with resected RCC.[25] Patients in group 1 will receive sunitinib by mouth once a day for 4 weeks and a placebo by mouth twice a day for 6 weeks. Patients in group 2 will receive sorafenib by mouth twice a day for 6 weeks and a placebo by mouth once a day for 4 weeks. Patients in group 3 will receive one placebo by mouth twice a day for 6 weeks and another placebo by mouth once a day for 4 weeks. Treatment is repeated every 6 weeks for up to nine courses.

## Medical management

In patients with metastatic disease the various options for treatment include chemotherapy, immunotherapy, targeted therapies and antiangiogenic agents.

### *Chemotherapy*

The results of various trials involving chemotherapy in patients with clear cell renal cell cancer have been dismal. Yagoda et al[26] in their review of 72 different agents either alone or in a two drug combination revealed response rates of less than 6% in metastatic disease with no benefit in survival. Based on these studies clear cell RCC is generally considered refractory to chemotherapy. Non-clear cell RCC does not respond to immunotherapy. However, there are anecdotal reports of response to chemotherapy. The various agents that have shown some benefit include carboplatin with taxol,[27] gemcitabine with cisplatin[28] or gemcitabine with doxorubicin.[29]

### *Radiotherapy*

RCC is generally considered a radioresistant tumor. There is no established role of radiation therapy as primary treatment or in the adjuvant setting.[30] However, radiation therapy is used in metastatic setting for brain metastasis, painful bone metastasis and for painful recurrences in the renal bed.

### *Immunotherapy*

The immune system plays an important role in the pathogenesis of various malignancies. Spontaneous remission of disease and regression of metastatic disease following nephrectomy[18] or radiofrequency ablation of the kidney[31] suggests that RCC evokes an immune response. The idea behind the development of immunotherapy is to either reproduce or accentuate this response. There are various strategies by which this can be attempted. These include cytokines (interferons, interleukin-2), tumor vaccines, induction of graft versus tumor response and the use of monoclonal antibodies against tumor specific antigens. Interleukin-2 (IL-2) and interferons (IFN) are the two most widely studied agents. The exact mechanism of action of IL-2 and IFN's is poorly understood. However, it is known that they stimulate the tumor infiltrating lymphocytes (cytotoxic T cells) and natural killer cells (NK cells) to act on the tumor cells. IFN's also have anti-angiogenic effects leading to inhibition of tumor growth.

### *Interferon alfa*

IFN-α monotherapy has an overall response rate of approximately 15% in metastatic disease. The median time to response is about 4 months.[32] The majority of the responses are short lived and rarely last beyond 1 year. A daily dose of 5 MU to 10 MU subcutaneous three times a week of IFN-α has the most favorable therapeutic index. There are some studies that suggest a modest impact of IFN-α on survival. In the REO study[33] by Medical Research Council Renal Cell Cancer Collaborators 335 patients were randomized to subcutaneous IFN-α or oral medroxyprogesterone acetate (MPA). There was a 28% reduction in the risk of death in the IFN-α group. In addition, there was an improvement in 1-year survival of 12% (31% MPA and 43% IFN) and an improvement in median survival of 2.5 months (6 months MPA and 8.5 months in IFN group). However, a number of these patients had poor prognostic markers such as absence of nephrectomy (~42% in each arm) and performance status of 2 (one fourth of patients in each arm).

IFN-α in combination with chemotherapy has been used in recurrent and metastatic disease. The two commonly used agents are vinblastine and 5-fluorouracil. Neidhart et al[34] published their data of 165 patients randomly assigned to IFN-α alone or with vinblastine. The overall response rate was 10 % and median survival was 10 months with no difference between the two arms. In addition patients with pulmonary metastasis had a better response (44%) and overall survival. The Southwest Oncology Group (SWOG) conducted a phase II trial with interferon-α 2b and 5-FU. There were 13% partial responses and median duration of survival was 10 months.[35] However, the increased response rate in these studies has not translated into a prolonged disease free survival or overall survival. Multiple randomized trials have shown no benefit of addition of chemotherapy agents to IFN-α.

### *Interleukin-2*

In the mid 1980's high dose IL-2 in combination with lymphokine activated cells (LAK) showed promising results (response rates 16%-33%) in metastatic RCC. However, later studies with high dose IL-2 alone revealed equivalent efficacy to IL-2 plus LAK cells. Although the response rates were slightly lower (9%-30%).

Fyfe et al[36] in their study included 255 patients with metastatic RCC from seven phase II trials. IL-2 600000 IU/kg or 720000 IU/kg was administered by IV infusion every 8 hours to a maximum of 14 doses over 5 days. An additional 14 doses over 5 days were scheduled after a 5 to 9 day interval. Courses were repeated every 6-12 weeks in patients who remained stable or responded to treatment to a maximum of three cycles. Dose modification for toxicity was accomplished by omitting the dose and no attempts were made to make up for skipped doses. Majority of the patients had a performance status of zero (65%) or one (31%). The overall response rate was 14% (5% PR and 9% CR). The median duration of response for all patients was 20.3 months and for patients with PR was 19 months. However, the median duration of response for complete responders has not been reached. Baseline ECOG performance status was the single most important prognostic factor predictive of response (0.03). Majority of the toxicities occurred secondary to the capillary leak syndrome. There were treatment related deaths in 4% of patients. This landmark study led to the approval of IL-2 in metastatic RCC by the US food and drug administration (FDA). Follow up[37] data revealed the median survival of all patients to be 16.3 months and the median survival for complete responders had not been reached. The median duration of response was 54 months in all patients and 20 months in partial responders. While in complete responders the median duration of response had not been reached.

There is significant toxicity associated with the use of IL-2 that can result in treatment delays and reduction in dose. Flu like symptoms, fever, chills, capillary leak syndrome (CLS) and neurologic toxicity are some of the common adverse effects. CLS can cause hypotension, prerenal failure, fluid retention and pulmonary edema. Often patients require vasopressor support in an intensive care unit. The morbidity associated with Interleukin-2 led to an interest in low dose Interleukin-2. Yang et al[38] published the results of their randomized trial comparing high dose and low dose intravenous IL-2, Table 5.

There were no treatment related deaths in either arm. However, grade III and IV thrombocytopenia, malaise and hypotension was seen in the high dose arm. There was an increased incidence of infections in the low dose arm. Vasopressor support was required in 3% of the patients receiving low dose IL-2 compared to 52% of patients receiving high dose IL-2. They concluded that low dose IL-2 was an effective regimen in metastatic RCC with response rates , Table 5, comparable to high dose IL-2 but with significantly fewer complications, decreased use of vasopressor support and fewer admissions to ICU.

In another randomized trial Yang and colleagues[39] compared three different regimens of IL-2, Table 5. There was a higher rate of response in the high dose arm (21%) versus the low dose arm (13%). Although no difference in overall survival was seen. In addition,

TABLE 5. **Selected studies of IL-2 in metastatic renal cell carcinoma**

| Study | No | Treatment schedule | Response rate (%) | Median overall survival |
|---|---|---|---|---|
| Fyfe et al[36] 1995 | 255 | IL-2 600000 or 720000 IU/kg IV over 15 min every 8 hrs to a max of 14 doses over 5 days* | 14% | |
| Yang et al[38] 1994 | 125 | High dose IL-2 (720000 IU/kg every 8 hrs to a max of 15 doses)** | 20% | No difference |
| | | Low dose IL-2 (72000 IU/kg every 8 hrs to a max of 15 doses)** | 15% | |
| Yang et al[39] 2003 | 400 | High dose IL-2 (720,000 IU/kg IV every 8 hrs) | 21% | No difference |
| | | Low dose IL-2 (72000 IU/kg IV every 8 hrs) | 13% | |
| | | Subcutaneous IL-2 (250000 IU/kg/ dose for 5 days in week 1 followed by 125000 U/kg/dose in the next 5 weeks) | 10% | |
| Negrier et al[40] 1998 | 425 | IL-2 (18 MIU/$m^2$/day Day1-5) | 6.5% | No difference |
| | | IFN-α (18 MIU/day 3 times a week) | 7.5% | |
| | | IL-2 (18 MIU/$m^2$/day Day1-5) + IFN-α (6 MIU/day 3 times a week) | 18.6% | |
| McDermott[42] 2005 | 192 | IL-2 (600000 U/kg every 8 hrs day 1-5 and day 15-19) | 23.2% | No difference |
| | | IL-2 (5 MIU/$m^2$ SC every 8 hrs for 3 doses on day 1, than daily for 5 days a week) + IFN-α (5MIU/$m^2$ three times a week for 4 weeks) | 9.9% | |

*Dose repeated after 5-9 days and in patients with stable disease or response same course repeated every 6-12 weeks.
**Dose repeated after 7-10 days and patients who had stable disease or response following treatment received a second course of treatment 5-6 weeks later.

patients who had a complete response with high dose IL-2 therapy had a longer duration of response and survival benefit.

The optimum dose and route of administration of IL-2 remains to be answered. However, based on the current data high dose IL-2 is favored due to the presence of durable complete responses despite the toxicity associated with it. Most of the adverse effects are reversible. Usually patients who respond show evidence of tumor regression after one to two cycles. In such patients IL-2 treatment can be continued until complete response or until IL-2 intolerance develops. In patients who do not respond usually treatment is stopped after two cycles.

### *Cytokine combination therapy*

Interleukin-2 and interferon-α have modest activity in metastatic RCC. Interest arose as to whether a combination of the two cytokines will lead to improved responses and survival benefit.

Negrier et al[40] from the Groupe Francaise d'Immunotherapie conducted a randomized control trial involving 425 patients who were randomized to intermediate dose IL-2 (group 1), IFN-α (group 2) or a combination of both (group 3). The response rate at week 10 was 6.5%, 7.5% and 18.6% in groups 1, 2 and 3 respectively ($p < 0.01$). Similarly 1-year event free survival was 20% in the combination arm compared to 15% and 12% in groups 1 and 2 ($p = 0.001$). There was no significant difference in overall survival between the groups ($p = 0.55$). However, there was no true high dose IL-2 arm in this study. Toxicities were more in the IL-2 arms as compared to the IFN-α arm.

Negrier et al reported the results of the Percy Quattro Study[41] in abstract form at the American Society of Clinical Oncology annual meeting in 2005. Four

hundred and ninety two patients with intermediate risk metastatic RCC were randomized. This was a four arm study comparing medroxyprogesterone, IFN-α, SC IL-2 with IFN-α and SC IL-2. The preliminary results indicate an improved survival in the combination arm (2.5%, 4.4%, 4.1% and 10.9% respectively).

The Cytokine Working Group[42] conducted a randomized phase III trial to evaluate the value of low dose IL-2 with IFN-α 2b versus high dose IL-2, Table 5. One hundred and ninety two patients were randomized between the two arms. The overall response rate to HD IL-2 was 23.2% compared with 9.9% for IL-2/IFN-α arm. The median duration of response was 14 months in HD IL-2 arm versus 7 months. There was no significant difference in overall survival. Survival was superior in the HD-IL-2 arm in patients who had bone or liver metastasis ($p = 0.001$) or a primary tumor in place ($p = 0.040$).

### *Allotransplant*

Graft versus tumor (GVT) effect occurs as a result of transplantation of the donor immune cells along with the allograft, which can kill malignant cells that survive conditioning regimens. This effect is well estabilished in hematological malignancies.

Childs et al[43] demonstrated the GVT effect of nonmyeloablative allogeneic stem cell transplant in patients with refractory metastatic RCC. Nineteen patients received cyclophosphamide and fludarabine preparative regimen followed by peripheral blood stem cell infusion. Ten patients (53%) had regression of their disease with three complete responses. The tumor response was delayed and occurred usually after the withdrawal of cyclosporine at a median of 4 months following transplantation. Acute graft versus host disease was the only factor that predicted response and was associated with increased survival. Responses were observed in patients with clear cell RCC only. A large European study[44] involving 124 patients revealed a partial response in 24 patients and complete response in 4 patients. Transplant related mortality was 16% at 1 year. In multivariate analysis responses were seen more in patients with acute GVHD, HLA mismatched donor and < 1 year from diagnosis of metastatic disease to transplantation. Multivariate analysis revealed an increased overall survival in the presence of chronic GVHD, history of DLI post transplant and the presence of less than three metastatic sites.

Despite regression of refractory metastatic RCC the overall response rate to allogeneic transplant remains low. Currently due to the risk of transplant related mortality and morbidity and the delay seen in response, transplant has limited use.

### *Vaccines*

The hypothesis behind the development of vaccines for RCC is to enhance innate immunity leading to T-cell mediated antitumor effect. The majority of studies for metastatic RCC have shown no response to vaccines.[45]

## Targeted therapies

In metastatic RCC the response to cytokine treatment has been seen in less than one fourth of the patients. In addition there is significant toxicity associated with this treatment. Therefore in the last decade there has been an increased interest in targeted therapies at the molecular level. The various therapies include bevacizumab, sorafenib, sunitinib and temsirolimus, Figure 2 and Table 6.

Bevacizumab is a monoclonal antibody directed against VEGF. Yang et al[46] in their randomized double blind phase II trial assigned 116 patients to placebo, high dose bevacizumab (10 mg/kg body weight) and low dose bevacizumab (3 mg/kg body weight). Majority of the patients had received prior treatment with IL-2. The median duration of follow up was 27 months. There was a significant difference in progression free survival in the high dose arm compared to placebo (4.8 months versus 2.5 months, $p < 0.001$). The difference in progression free survival was marginal in the low dose arm and placebo ($p = 0.041$). Patients who progressed in the placebo arm could cross over to the bevacizumab arm. There was no difference in overall survival between the three groups. No grade 4 toxicity or deaths were noted secondary to bevacizumab. The major side effects were hypertension and proteinuria in the bevacizumab arm which were treated with standard antihypertensive medications. Escudier et al[47]

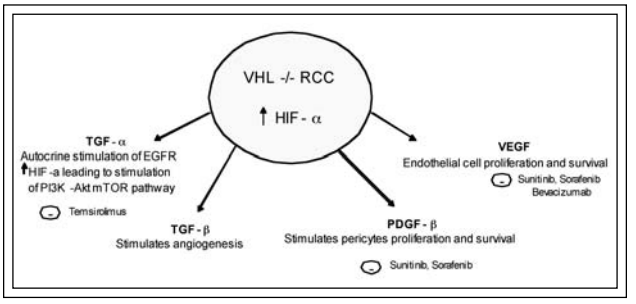


**Figure 2.** Renal cell carcinoma caused by deleted/mutated VHL gene results in elevated levels of HIF-α which causes a cascade of events leading to an increase in the levels of TGF-α, TGF-β, VEGF and PDGF-β. These molecules are targets for a number of agents.

TABLE 6. **Major studies of targeted agents in metastatic renal cell carcinoma**

| Study | No. | Schedule | PFS (months) | OS (months) |
|---|---|---|---|---|
| Yang et al[46] 2003 | 116 | Placebo (40)<br>Bevacizumab 3 mg/kg (37)<br>Bevacizu mab 10 mg/kg (39) | 2.5*<br>3<br>4.8* ($p < 0.001$)* | No difference |
| Escudier et al[49] 2007 | 903 | Sorafenib 400 mg twice daily (451)<br>Placebo (452) | 5.5<br>2.8 ($p < 0.01$) | Not reached |
| Motzer et al[54] 2007 | 750 | Sunitinib 50 mg once daily for 4 weeks followed by 2 weeks off (375)<br>IFN-α 3 MU per dose three times a week in week 1. Increase dose to 6 MU SQ thrice a week in week 2 and 9 MU thrice a week thereafter (375) | 11<br>5 ($p < 0.001$) | Not reached |
| Hudes et al[56] 2007 | 626 | Temsirolimus 25 mg IV weekly (209)<br>Interferon-α 3 MU SQ three times a week (Increase to 18 MU three times a week) (207)<br>Temsirolimus 25 mg IV + Interferon-α 6 MU three times a week (210) | 3.8<br>1.9<br>3.7 | 10.9*<br>7.3*<br>8.4 ($p = 0.008$)* |

presented the early results of their phase III trial comparing interferon-α with placebo or bevacizumab as first line treatment in metastatic RCC at the 2007 ASCO annual meeting. Six hundred and forty nine patients with metastatic RCC who had undergone nephrectomy and had no evidence of CNS metastasis were randomized to receive IFN-α 2a (9 million IU three times a week up to a year) with bevacizumab (10 mg/kg every 2 weeks) or placebo until disease progression. In the IFN-α plus bevacizumab arm the objective tumor response rate was 30.6% versus 12.4% ($p < 0.0001$). The PFS in the bevacizumab arm was 10.2 months versus 5.4 months in the placebo arm (HR 0.63, $p < 0.0001$). In addition a trend towards improved OS was seen in the bevacizumab arm ($p = 0.0670$). There were no unexpected toxicities seen with the addition of bevacizumab to IFN-α.

Sorafenib is a tyrosine kinase inhibitor. It targets the pathway downstream of VEGF and TGF-α. It inhibits angiogenesis and stimulates apoptosis of tumor cells. The early results of the randomization discontinuation trial of sorafenib were presented at ASCO 2005.[48] In this phase II study 202 patients with metastatic RCC were treated with sorafenib 400 mg twice a day for 12 weeks. Response to treatment was assessed at week 12 and patients who had a greater than 25% reduction in tumor size were continued on sorafenib. Patients who had a less than 25% reduction in tumor size were randomized to sorafenib (400 mg twice a day) or placebo for 12 weeks. Patients with a 25% increase in tumor size were taken off the study. At 12 weeks after randomization 50% patients on sorafenib had stable disease as compared to 18% in placebo arm. The median progression free survival from the time of randomization was 24 weeks in the sorafenib group and 6 weeks in the placebo group. Escudier et al[49] published results of their phase III randomized controlled trial (TARGET) comparing sorafenib to placebo in patients who were previously resistant to standard therapy. Eligible patients had clear cell RCC, had progressed on one systemic treatment within the previous 8 months and were intermediate or low risk based on the MSKCC prognostic score. Patients with brain metastasis or prior exposure to VEGF inhibitors were excluded. Crossover of patients from placebo to drug arm was allowed if disease progressed. Survival analysis was done prior to the crossover to avoid compromising survival data. Sorafenib was given at a dose of 400 mg twice a day. The median duration of treatment was 23 weeks in the sorafenib group and 12 weeks in the placebo group. There were 43 (10%) partial responses in sorafenib arm (versus 2%) and 74% had stable disease on treatment (versus 53% in placebo arm). The median progression free survival was 5.5 months in the sorafenib arm versus 2.8 months in the placebo arm ($p < 0.001$, HR 0.44). The benefit in progression free survival was independent of age, MSKCC score, previous therapy, presence or absence of lung or liver metastasis and time since diagnosis

(< 1.5 years or > 1.5 years). There was no significant difference in overall survival. The most common side effects were rash, hand foot skin reaction, alopecia, pruritus and diarrhea. These adverse effects were predominantly grade 1 or 2. Dose reduction occurred in 13% patients in the sorafenib group compared to 3% in the placebo group ($p < 0.001$). The most serious drug related adverse event was hypertension seen in 1% patients in the sorafenib arm and none in the placebo group. Follow up data[50] from this trial revealed a 39% improvement in OS for sorafenib compared to placebo (p 0.018, HR= 0.72). After 6 months of crossover there was a 30% improvement in OS for sorafenib compared to placebo (p 0.015, HR = 0.77). However, final overall survival analysis indicated a 13.5% benefit in the sorafenib arm which was not statistically significant (HR = 0.88, p 0.146). Secondary analysis after adjusting for crossover revealed an overall survival benefit for sorafenib (HR = 0.78, p 0.0287) indicating that crossover had confounded the results. Also baseline high VEGF levels were associated with a poor prognosis and showed a greater PFS benefit with sorafenib.

Knox et al[51] presented the safety and efficacy results of sorafenib 400 mg twice a day in patients with advanced RCC who were excluded from prior sorafenib trials. The eligibility criteria included patients with ECOG performance status of 0-2 (some pts with PS 3-4 were included), age greater than 15 and adequately treated prior brain metastasis. Two thousand four hundred and eighty eight patients were enrolled. Almost half of these patients had prior treatment with IFN-α (54%), IL-2 (43%), bevacizumab (23%), thalidomide (12%) and sunitinib (2%). Unconfirmed partial response was seen in 17.5% patients, 3.6% had confirmed partial response, 79.9% had stable disease and 16.4% had progressive disease. The major grade 3 or 4 adverse events included hand foot reaction, fatigue, hypertension, rash, dehydration, dyspnea and diarrhea. The toxicity and response rates were similar to the prior published data. However, efficacy data was limited since many patients were enrolled in the last 2 months of the study.

Sunitinib is an orally administered tyrosine kinase inhibitor that acts on the VEGF and PDGF receptors. Phase II studies had encouraging results with respect to response to this agent as a second line agent.[52,53] A phase III trial[54] was conducted which compared sunitinib with interferon-α as first line treatment in patients with metastatic RCC. Seven hundred and fifty patients were randomized to six weekly cycles of sunitinib at a dose of 50 mg orally for 4 weeks followed by 2 weeks off and interferon-α 9 MU given subcutaneously three times a week. Majority of the patients had previous nephrectomy (~90%) and majority (> 90%) had favorable and intermediate risk prognosis based on the MSKCC prognostic score. The objective response rate was 31% in the sunitinib group and 6% in the IFN-α group ($p < 0.001$). The median progression free survival was 11 months in the sunitinib group compared to 5 months in IFN-α group. ($p < 0.001$, HR = 0.42). The median progression free survival in the favorable risk group on sunitinib has not been reached and was 8 months in the IFN-α group. The median PFS in the intermediate and poor risk groups receiving sunitinib was 11 months and 4 months respectively (versus 4 months and 1 month in the IFN-α group). Hence the benefit of sunitinib in prolonging PFS was present regardless of the prognostic group. The median overall survival had not been reached at the time of analysis although there was a trend towards improved survival with sunitinib. Diarrhea, hypertension, hand-foot syndrome and neutropenia were the grade 3 or 4 adverse events seen more in the sunitinib arm as compared to the IFN-α arm ($p < 0.05$). The quality of life as reported by patients was better in the sunitinib group than in the IFN-α group. This is the first phase III trial that has compared an oral agent with cytokine treatment and has encouraging results. Although a longer duration of follow-up is required to assess the durability of response and to clarify the survival benefit.

Gore et al[55] presented the results of their expanded access trial at the 2007 ASCO annual meeting. Four thousand patients with metastatic RCC who had progressed on at least one prior systemic therapy received sunitinib 50 mg/day in 6 week cycles (4 weeks on treatment and 2 weeks off). Two thousand one hundred and fifty eight patients were included in the analysis. Brain metastasis were present in 8% patients, 13% had an ECOG PS of 2, 7% had prior anti angiogenic treatment. The median duration of treatment was 128 days. Treatment was interrupted in 17% patients and dose reduction was done in 30% patients. Treatment was discontinued in 12% patients secondary to adverse events. The most common treatment related adverse events were diarrhea (39%), fatigue (35%) and nausea (33%). The adverse events were similar in patients regardless of age and site of baseline metastatic disease. Their results indicate an acceptable tolerability of sunitinib in metastatic RCC regardless of age or site of metastases.

Temsirolimus (CCI-779) is an inhibitor of mammalian target of rapamycin (mTOR) kinase. It binds to an intracellular protein FKBP12 and forms

a complex that inhibits mTOR signaling. This in turn inhibits cell growth and angiogenesis. In their multicenter trial Hudes et al[56] randomized 626 patients with untreated poor risk metastatic renal cell carcinoma to temsirolimus, interferon-α or a combination of both. Patients had to have at least three of the six predictors associated with decreased survival i.e. serum LDH greater than 1.5 times the upper limit of normal, hemoglobin less than the lower limit of normal, corrected serum calcium of more than 10 mg/dl, time from initial diagnosis to randomization of less than 1 year, Karnofsky performance status of 60-70 and metastasis to multiple organs. Patients with brain metastasis were included if they were adequately treated and neurologically stable. About two thirds of patients in each group had undergone a nephrectomy in the past. The median overall survival in the temsirolimus group was 10.9 months as compared to 7.3 and 8.4 months in groups given IFN-a and combination therapy respectively (p = 0.008, HR = 0.73). The median PFS was 3.8 months in temsirolimus group, 3.1 months in IFN-α and 4.7 months in combination group. Serious adverse effects were more common in the IFN-α group. The common side effects in the temsirolimus group included rash, peripheral edema, stomatitis and hyperlipidemia. Asthenia was the most common side effect in the group receiving IFN-α alone or in combination with temsirolimus. Hence temsirolimus improved overall survival in patients with poor risk metastatic RCC with fewer adverse effects compared to IFN-α.

Targeted therapies seem very attractive agents because of their ease of administration and fewer severe adverse effects as compared to cytokine therapy. However, longer follow-up is required to assess the durability of responses and to assess the impact on overall survival.

### *Other agents*

Thalidomide is an immunomodulatory agent with antiangiogenic properties. It reduces the expression of VEGF and TNF-α. In a phase II/III study patients with metastatic RCC who were refractory to cytokine treatment or were ineligible for cytokine treatment were randomized to thalidomide or medroxyprogesterone.[57] There were no objective responses seen in the thalidomide arm. However, there was stabilization of disease in 3 out of 29 (10.3%) patients for longer than 5 months in the thalidomide group whereas all patients in the medroxyprogesterone acetate group progressed. None of the patients could tolerate a dose of 400 mg/day secondary to side effects. There was no difference in overall survival.

Lenalidomide is a structural and functional analogue of thalidomide that has enhanced immunomodulatory properties and a more favorable toxicity profile as compared to thalidomide. Phase II data[58] has been encouraging however further data is required to evaluate its role in metastatic RCC.

## Conclusions

Metastatic renal cell carcinoma continues to be a therapeutic challenge. There is no single agent that has shown significant anti tumor activity. Interleukin-2 remains the only agent that has produced complete and durable responses. However, IL-2 treatment is very toxic and only patients with excellent performance status are able to tolerate this treatment. Oncologists are challenged as to how to better identify patients who will benefit the most from cytokine therapy. There are now a number of alternate treatments which are FDA approved for the treatment of metastatic RCC including sunitinib, sorafenib and temsirolimus. In addition agents such as bevacizumab and thalidomide have also been demonstrated to have activity in this disease. These targeted therapies are novel agents that are easily administered and well tolerated by the majority of patients. Recent data support an overall survival benefit for temsirolimus and sorafenib. However, the true magnitude of their impact on overall survival remains to be seen as these agents have shown only occasional complete responses. Ongoing extended access studies with sorafenib and sunitinib should provide additional data from which to draw conclusions concerning the magnitude of the survival benefit with these agents. □

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