New treatments for metastatic kidney cancer

Andrea Mancuso, MD, Cora N. Sternberg MD, FACP

Department of Medical Oncology, San Camillo and Forlanini Hospitals, Rome, Italy

MANCUSO A, STERNBERG CN. New treatments for metastatic kidney cancer. The Canadian Journal of Urology. 2005;12(Supp.1):66-70.

Renal cell carcinoma accounts for approximately 3% of adult malignancies and 90%-95% of neoplasms arising from the kidney. It is characterized by a lack of early warning signs, diverse clinical manifestations, resistance to radiation and chemotherapy, and infrequent but reproducible responses to immunotherapy with agents such as interferon alpha (IFN-α) and interleukin 2 (IL-2). International studies have shown objective response rates of < 15% in patients with advanced and metastatic disease, with 5-year disease-specific survival ranging between 0-20%. Considering these poor outcomes, renal cancers' very vascular nature and overexpression of receptors for vascular endothelial growth factor (VEGF), various biologic and angio-suppressive therapies are being evaluated in clinical trials. Promising results in terms of overall response rate and median time to progression have been reported especially as second-line therapy following cytokine failure, a setting where no effective systemic therapy has been recognized (SU011248, Bay 43-9006, Bevacizumab and Erlotinib). While confirmatory studies are ongoing, other novel treatments in first line trials (CCI-779, Infliximab, PTK-787, and Thalidomide) have drawn international attention. This review, analyzing basic translational research principles, will summarize the available data on the use of these new therapeutic approaches in RCC.

Key Words: renal cancer, new regimens, antiangiogenic therapy, targeted therapies

Introduction

Renal cell carcinoma (RCC) is the sixth leading cause of cancer death in the USA with about 31,900 new cases in 2003. Approximately 30% of patients present with metastatic disease at the time of diagnosis, and one-third will develop metastasis during follow-up.[1] Table 1

Choice of treatments in advanced/metastatic disease

Immunotherapy (IFN-α and IL-2)

RCC is known to be a refractory disease and modulations of host immune mechanisms regulating tumor growth have been extensively evaluated. Among the most widely used immunotherapeutic agents are IFN-α and interleukins administered at variable doses either alone or in combination.[2-3]

IFN-α is a pleotropic cytokine having multiple antiproliferative and immunomodulatory biologic effects. It has an immunostimolatory and anti-angiogenic anti tumoral mechanism of action by promoting a Th1 immune response, upregulating the IL-12 receptor on subsets of lymphocytes, and inducing IFN-α production by other effecter cells. IFN-α has an objective response rate of approximately 11%-15%, with complete responses in 2% of patients. Durable responses are rare and the median response duration is about 6 months. Two randomized trials have reported a small but significant improvement in survival (3-6 months) with IFN-α therapy when

Address correspondence to Cora N. Sternberg, MD, FACP, Department of Medical Oncology, San Camillo and Forlanini Hospitals , Circonvallazione Gianicolense, 87 Rome Italy

TABLE 1. **Renal cell carcinoma: general aspects and survival**

Renal cell carcinoma (USA): new cases: 30,000; deaths/year: 12,000

Renal cell carcinoma (USA)	**Initial incidence**	**5-year survival**
Localized disease (pT1, pT2, pN0)	20%-25%	>80%
Locally advanced disease, pN+ or with extracapsular spread	45%-50%	10%-25%
Metastatic disease	30%	0%-9%

compared either to medroxy-progesterone or vinblastine therapy.[4-5] In patients with a favorable risk, IFN-α confers a survival advantage and is a reasonable control arm for phase III trials, Figure 1.[4-9] It is also an excellent agent for combination therapy with IL-2 and other targeted agents.

IL-2 is a glycoprotein secreted by activated T lymphocytes, which in addition to producing IL-2 also increase the expression of high affinity IL-2 receptors. The mechanism of action of IL-2 is induction and activation of T lymphocytes and natural killer cells, and the secondary release of cytokines. IL-2 is the only FDA approved treatment in metastatic RCC. Innumerable different dose regimens and schedules for IL-2 have been described in the literature. The highest response rate and greatest proportion of durable complete responses has been reported with a high-dose regimen (600,000 to 720,000 IU/Kg IV bolus every 8 hours for 5 days) in patients with metastatic RCC. This regimen results in a 15% response rate with 7% complete responses. Toxicities are a consequence of immune activation and include fever, malaise, capillary leak with resultant hypotension, azotemia, metabolic and electrolyte abnormalities, and neurocortical toxicity.[10-11] Subcutaneous IL-2 administration results less toxic and more manageable with very similar response rates and survival.[12] Cytokine combination trials of IFN-α and IL-2 have revealed response rates (RR) of 20% with complete responses (CR) in 3%-5% without a significant benefit as compared to any of the two cytokines alone.[13]

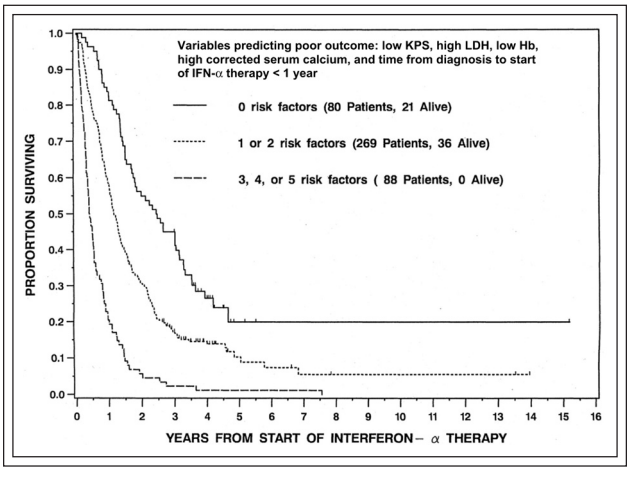

Figure 1. RCC patients treated with IFN-α and related survival according to risk groups.

Chemotherapy

The results with chemotherapy in the treatment of RCC are consistently disappointing. In a recent review, considering 83 trials and 4,093 patients with advanced disease, the overall RR was only 6%.[14] A review of phase II trials by Stadler showed that the combination of Gemcitabine and Fluorouracil has activity with a RR of 14%-17% and overall survival of 12.5 months, similar to what has been seen with cytokine based therapy and similarly depending upon prognostic factors.[15] These results need to be confirmed.

New therapeutic approaches

Recent developments in understanding of the molecular biology of RCC have led to the development of new agents targeting portions of the hypoxic response pathway. RCC is characterized by its frequent loss of the Von Hippel-Lindau (VHL) tumor suppressor gene which results in an increased concentration of hypoxia inducible factor-1 (HIF-1) determining neoangiogenesis stimulation. Tumor angiogenesis is also stimulated by growth factors through the PI3K-AKT-mTOR signal transduction pathway.[16]

SU011248

SU011248 is an oral multitargeted receptor tyrosine kinase (RTK) inhibitor with antitumor and antiangiogenic activities through targeting of platelet-derived growth factor receptor (PDGFR-ß), vascular endothelial growth factor receptor (VEGFR-2), KIT and Flt3 receptors.[17-18] In a multicenter trial, Motzer et al treated patients with metastatic renal cancer who

had failed IL-2 or interferon with SU011248, 50 mg per day. Of the 63 subjects enrolled, 21 (33%) demonstrated an objective partial response and 23 (37%) had stable disease for > 3 months, including a significant number of patients who had a minimal response that did not meet criteria for partial response. Of the 21 responding patients, 14 have maintained a durable response of 4+ to 12+ months. The median time to progression was 8.3 months, and 1-year survival was 65%. Fatigue was the most common non-hematologic toxicity in this study (grade 2, 25%; grade 3, 8%). Three patients were withdrawn from treatment because of a > 20% decrease in left ventricular ejection fraction. The trial provides evidence that inhibition of VEGF-Receptor (and PDGF-Receptor) mediated signaling is an appropriate therapeutic target for refractory RCC. SU011248 is well tolerated and active. The median time to progression compares favorably with the historical experience in cytokine-refractory renal cancer. Further investigation with SU011248 will include a confirmatory phase II study in the second-line setting and a phase III randomized study of IFN-α alone versus IFN-α plus SU011248 as first-line therapy for metastatic disease.

BAY 43-9006 (Sorafenib)

Sorafenib is an oral agent designed as a c-and b-raf kinase inhibitor. The Ras/Raf signalling pathway is a mediator of tumor cell proliferation and angiogenesis. Recently, Sorafenib has also been found to inhibit several receptor tyrosine kinases, among them VEGFR-2, PDGFR-beta, FLT-3 and c-KIT. A "randomized discontinuation design" study of Sorafenib in patients with refractory solid tumors was presented at the 40th annual ASCO meeting. Enrolment to this study was open to a wide variety of refractory solid tumors, and accrual of renal cell was 42% of the total patients enrolled (203/484). Week-12 response data were available for 89 RCC patients. Thirty-seven (42%) subjects demonstrated ≥ 25% tumor shrinkage. Forty-five (51%) patients demonstrated stable disease, including a number of patients who had tumor shrinkage; < 25% that did not meet Recist Criteria for partial response (PR). Of the 37 patients with ≥ 25% tumor shrinkage who continued to receive Sorafenib, 88% were progression-free at 24 weeks. In this study design all patients were treated upfront and then responding patients were continued on therapy while patients with stable disease were randomized between drug or placebo. This design has the advantage of enriching the treated population for responders.[19]

Dermatologic toxicity was the most common adverse event associated with this agent, followed by fatigue and diarrhea. Sorafenib has meaningful antitumor activity in renal cell carcinoma and other diseases, with an acceptable toxicity profile for long-term chronic administration.[20] The agent is currently being evaluated in an international, randomized, placebo-controlled study as second-line treatment for metastatic renal cancer. Phase II studies in combination with cytokines as first-line treatment are being planned through the cooperative groups.

Bevacizumab (Avastin) and erlotinib (Tarceva)

Extensive preclinical studies have demonstrated that treatment with anti-VEGF antibodies was effective in suppressing kidney tumor. Based on preclinical data, phase I/II/III programs with bevacizumab are actually ongoing.[21] A randomized phase II double-blind clinical trial, with a cross-over design, was performed to evaluate the activity of bevacizumab in metastatic refractory RCC. Patients were randomized to receive either bevacizumab at 3 mg/kg (low dose, LD), or bevacizumab 10 mg/kg (high dose, HD) or placebo. After 116 patients were enrolled, the trial was stopped because patients on the high dose of bevacizumab arm showed a significant prolongation in time to progression. The probability of being progression-free for patients given high-dose or low dose antibody and placebo was 64%, 39% and 20% respectively at 4 months and 30%, 14% and 5% at 8 months ($p<0.0001$).[22] Two randomized phase III confirmatory trials are in progress in the CALGB and in Europe.

Considering this single agent activity and clear cell renal cancer's overexpression of VEGF, TGF-α and PDGF-β, a multicenter phase II study combining the anti-VEGF monoclonal antibody bevacizumab with an oral EGFR inhibitor, erlotinib was performed.[23] Eligibility criteria for this study included metastatic renal cancer (at least 75% clear cell component) and no more than one prior systemic regimen. Treatment consisted of bevacizumab 10 mg/kg intravenously every 2 weeks and erlotinib 150 mg orally daily. Sixty-two patients were enrolled and the median follow-up was 11 months at the time of the report. Among the subjects, 92% received at least two courses (8 weeks) of treatment and were evaluable for response. All patients had prior nephrectomy, and 68% had received no previous systemic therapy. Fifty-eight patients were evaluable for response. Twelve (21%) patients demonstrated a PR, and 38 (66%) had stable disease, including 12 (21%) who had a minor response (MR). Progression-free survival was 67% at 6 months and 50% at 12 months. Grade 3-4 toxicity associated with this regimen included rash (13%), diarrhea (10%),

nausea/vomiting (10%), hypertension (8%), and bleeding (5%). The results provide early evidence that targeting both VEGF and EGFR may be an effective strategy in renal cell carcinoma. A randomized phase II study of bevacizumab plus erlotinib or placebo is being planned as a confirmatory study. A comparison of this regimen with standard treatments for advanced RCC should be performed.

CCI-779 (temsirolimus)

Temsirolimus (CCI-779) is a rapamycin analogue that inhibits mTOR kinase, a regulator of HIF-1α. In a recently published phase II dose escalation study of single-agent temsirolimus (110 patients with refractory RCC, doses tested 25 mg-250 mg), overall tumor growth control was 70%, while the overall objective RRs was only 7%, with time to progression of 6 months. A suggestion of improved survival was shown for patients with intermediate and poor prognostic risk factors according to Motzer's classification of prognostic groups.[24] At the 40th ASCO meeting a phase I study reported the results of temsirolimus in combination with IFN-α. This was a dose escalation study in advanced renal cancer patients who had received no more than two prior systemic therapies. A total of 71 patients were enrolled; 96% had undergone prior nephrectomy, 55% had prior immunotherapy. The maximum tolerated dose was 15 mg of temsirolimus once weekly in combination with 6 mIU of IFN-α subcutaneously 3 times weekly. Dose-limiting toxicities were fatigue, stomatitis, and nausea/vomiting. Among all treated patients, there were 8 (11%) PRs and 21 (30%) patients with stable disease. The median time to progression was 9.1 months.[25] Considering this data, the agent appears promising and is currently in phase III testing for patients with poor-prognosis metastatic renal cell cancer (previously untreated), as a single agent versus combined therapy with IFN-α versus IFN-α alone.

GW572016 (lapatinib)

GW572016 (lapatinib) is an oral tyrosine kinase inhibitor that is a potent dual inhibitor of the epidermal growth factor receptors (EGFR, ErbB-1) and ErbB-2.[26] A phase III international trial is ongoing in which patients who express either the EGFR or Her-2 by centralized immunohistochemistry and who have had one line of prior immunotherapy; they are randomized between lapatinib and hormonal therapy. Results are too premature to be reported.

Other novel treatments

Maisey has reported results with infliximab, a monoclonal antibody against tumor necrosis factor (TNF-α), in patients with RCC who had progressed after first-line cytokine therapy.[27] In a phase II study, 3 (16%) responses were seen among 19 patients, and one patient had a late response after progressing and discontinuing the study. An additional three patients had stable disease. The drug was well tolerated with the exception of one patient who developed an allergic reaction. Infliximab could be a potential new target drug for the treatment of renal cancer but confirmatory studies are needed.

In recent years, Thalidomide has received attention for its potential activity against renal cancer through its effect on cytokines as well as its antiangiogenic properties. One of its potential mechanisms of action may be through down-regulation of TNF-α. Phase II studies have reported response rates from 0% to 17%,[28-29] and in combination with IFN-α to 21%.[30] A phase III randomized study of IFN-α at antiangiogenic low doses (1 mIU subcutaneously twice a day) with or without thalidomide (200 mg/day with escalation to 400-1000 mg/day) in previously untreated metastatic renal cancer was presented at the ASCO 2004 meeting. This trial found an overall objective RR of 7.6% in the IFN-α alone arm and of 3.1% in the combination arm.[31] There was no difference in overall survival and these results add to a building literature that thalidomide has minimal, activity in the treatment of renal cancer.

PTK787/ZK222584, a VEGF receptor tyrosine kinase inhibitor, is under development as an angiogenesis inhibitor for the treatment of various cancers. In metastatic refractory kidney tumors, a phase I trial established that it was generally well tolerated at dose levels of 300 mg-1500 mg with partial or minor responses in 19% of patients, and 60% attained stable disease.[31] In this trial, the median time to progression was 5.3 months and the median estimated survival was 21.5 months. These data need to be confirmed in large phase II study.

Conclusions

Molecular profiling appears to be the future for patient prognostication, staging and treatment. There is increasing awareness that validation of therapeutic targets is necessary for the discovery of new drugs and for verification of their success. Several targeted agents appear to have activity. These agents are providing some, although modest, hope for patients with renal cell carcinoma. The next few years should be characterized by new rational treatment strategies based on inhibition of specific biologic pathways which will hopefully culminate in a better understanding of the causes of renal cancer, its prevention, and, perhaps its cure. □

References

1. Linehan WM, Zbar B. Focus on kidney cancer. *Cancer Cell* 2004;6(3):223-228.
2. Sternberg CN. Metastatic renal cell cancer treatments. *Drugs Today (Barc)* 2003;39(Suppl C):39-59.
3. Sternberg CN, Vogelzang NJ. Gemcitabine, paclitaxel, pemetrexed and other newer agents in urothelial and kidney cancers. *Crit Rev Oncol Hematol* 2003;27(46Suppl):S105-115.
4. Medical Research Council Renal Cancer Collaborators. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. *Lancet* 1999;353(9146):14-17.
5. Pyrhonen S, Salminen E, Ruutu M, Lehtonen T, Nurmi M, Tammela T, Juusela H, Rintala E, Hietanen P, Kellokumpu-Lehtinen PL. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. *J Clin Oncol* 1999;17(9):2859-2867.
6. Robert J Motzer, Jennifer Bacik, Barbara A Murphy, Paul Russo, Madhu Mazumdar. Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies Against Advanced Renal Cell Carcinoma. *JCO* 2002;20:289-296.
7. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, Caton JR Jr, Munshi N, Crawford ED. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001;345(23):1655-1659.
8. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R, European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001;358(9286):966-970.
9. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol* 2004;171(3):1071-1076.
10. Atkins MB, Regan M, McDermott D. Update on the role of interleukin 2 and other cytokines in the treatment of patients with stage IV renal carcinoma. *Clin Cancer Res* 2004;10(6342):S-6S.
11. Yang JC, Sherry RM, Steinberg SM, Topalian SL, Schwartzentruber DJ, Hwu P et al. Randomized Study of High-Dose and Low-Dose Interleukin-2 in Patients With Metastatic Renal Cancer. *JCO* 2003:15:3127-3132.
12. Geertsen PF, Gore ME, Negrier S, Tourani JM, von der Maase H, Safety and efficacy of subcutaneous and continuous intravenous infusion rIL-2 in patients with metastatic renal cell carcinoma. *Br J Cancer* 2004;90(6):1156-1162.
13. Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, Ravaud A, Mercatello A, Peny J, Mousseau M, Philip T, Tursz T. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie. *N Engl J Med* 1998;338(18):1272-1278.
14. George CM, Stadler WM. The role of systemic chemotherapy in the treatment of kidney cancer**.** *Cancer Treat Res* 2003;116:173-182.
15. Stadler WM, Huo D, George C, Yang X, Ryan CW, Karrison T, Zimmerman TM, Vogelzang NJ. Prognostic factors for survival with gemcitabine plus 5-fluorouracil based regimens for metastatic renal cancer. *J Urol* 2003;170(4 Pt 1):1141-1145.
16. Pantuck AJ, Zeng G, Belldegrun AS, Figlin RA. Pathobiology, prognosis, and targeted therapy for renal cell carcinoma: exploiting the hypoxia-induced pathway. *Clin Cancer Res* 2003;9(13):4641-4652.
17. Tinya J Abrams, Lesley J Murray, Enrico Pesenti, Vicky Walker Holway, Tina Colombo, Leslie B Lee, Julie M Cherrington, Nancy K Pryer. Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with "standard of care" therapeutic agents for the treatment of breast cancer. *Mol Cancer Ther* 2003;2:1011-1021.
18. O'Farrell AM, Abrams TJ, Yuen HA, Ngai TJ, Louie SG, Yee KWH, Wong LM, Hong WM, Lee LB, Town A, Smolich BD, Manning WC, Murray LJ, Heinrich MC, Cherrington JM. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. *Blood* 2003;101:3597–3605.
19. Motzer RJ, Rini BI, Michaelson MD et al. SU011248, a novel tyrosine kinase inhibitor, shows antitumor activity in second-line therapy for patients with metastatic renal cell carcinoma: Results of a phase 2 trial. *Proc Am Soc Clin Oncol* 2004;23:381. Abstract 4500
20. Ratain MJ, Flaherty KT, Stadler WM et al. Preliminary antitumor activity of BAY 43-9006 in metastatic renal cell carcinoma and other advanced refractory solid tumors in a phase II randomized discontinuation trial (RDT). *Proc Am Soc Clin Oncol* 2004;23:381. Abstract 4501
21. Warren RS, Yaun H, Matli MR. Regulation by vascular endothelial growth factor of human colon cancer tumorigenesis in a mouse model of experimental liver metastasis. *J Clin Invest* 1995;95:1789–1797
22. 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* 2003;349:427-434.
23. Hainsworth JA, Sosman DR, Spigel RC, Schwert DL et al. Phase II trial of bevacizumab and erlotinib in patients with metastatic renal carcinoma. *Proc Am Soc Clin Oncol* 2004;23:381. Abstract 4502.
24. Atkins MB, Hidalgo M, Stadler WM et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004;22:909-918.
25. Smith JW, Yo K-J, Dutcher J et al. Update of a phase I study of intravenous CCI-779 given in combination with interferon-a to patients with advanced renal cell carcinoma. *Proc Am Soc Clin Oncol* 2004;23:384. Abstract 4513
26. Wood ER, Truesdale AT, McDonald OB, Yuan D, Hassell A, Dickerson SH, Ellis B, Pennisi C, Horne E, Lackey K, Alligood KJ, Rusnak DW, Gilmer TM, Shewchuk LA. A unique structure for epidermal growth factor receptor bound to GW572016 (Lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells. *Cancer Res* 2004;64(18):6652-6659.
27. Maisey NR, Hall K, Lee C et al. Infliximab: A phase II trial of the tumour necrosis factor (TNFa) monoclonal antibody in patients with advanced renal cell cancer (RCC). *Proc Am Soc Clin Oncol* 2004;23:384. Abstract 4514
28. Motzer RJ, Berg W, Ginsberg M et al. Phase II trial of thalidomide for patients with advanced renal cell carcinoma. *J Clin Oncol* 2002;20:302-306.
29. Escudier B, Lassau N, Couanet D et al. Phase II trial of thalidomide in renal-cell carcinoma. *Ann Oncol* 2002;13:1029-1035.
30. Sella A, Sternberg C, Yarom N, Sava T, Calabrò F, Zisman A, Lindner A, Cetto GL. Phase II Study of Low dose Thalidomide and Interferon-a in Metastatic Renal Cell Carcinoma (RCC). *Amer Soc Clin Oncol* 2003;22:402,Abstract 1614.
31. Gordon MS, Manola J, Fairclough D et al. Low dose interferon-alpha2b (IFN) + thalidomide (T) in patients (pts) with previously untreated renal cell cancer (RCC). Improvement in progression-free survival (PFS) but not quality of life (QOL) or overall survival (OS). A phase III study of the Eastern Cooperative Oncology Group (E2898). *Proc Am Soc Clin Oncol* 2004;23:384. Abstract 4516
32. Potti A, George DJ. Tyrosine Kinase Inhibitors in Renal Cell Carcinoma. *Clin Cancer Res* 2004;10:6371S-6376S.