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Advanced Renal Cell Carcinoma

Current and Emerging Management Strategies

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Contents

Abstract

Management of renal cell carcinoma (RCC) has made considerable progress in recent years, and new emerging strategies are being developed. On the basis of the results of two randomised studies in the early 2000s, nephrectomy has now become the standard as cytoreductive surgery before embarking on systemic treatment with cytokines. Interleukin (IL)-2 and interferon were the standard treatment in metastatic RCC (MRCC) until 2006. The efficacy of these two drugs, which have now been used for >20 years in MRCC, is still controversial. On the basis of many studies, these drugs should not be given to patients with a poor prognosis. In patients with good prognostic factors, a cytokine-based regimen should remain the standard as either a high-dose IL-2 or subcutaneous regimen. In patients with intermediate risk, the results of the French Percy Quattro study encourage the use of new targeted therapies as first-line therapy.

Development of targeted therapies in RCC has been necessary largely because the Von Hippel-Lindau (*VHL*) gene is often mutated in sporadic RCC. VHL protein abnormalities lead to accumulation of hypoxia-inducible factor (HIF)-α and activation of a series of genes, including vascular endothelial growth factor (VEGF), thus inducing angiogenesis. Results from many recent studies with new agents that block the VEGF pathway have been reported and offer new strategic options for patients with MRCC. Sunitinib and sorafenib, two tyrosine kinase

inhibitors, improve progression-free survival in RCC compared with standard treatment and have been recently approved. Temsirolimus, a mammalian target of rapamycin inhibitor regulating HIF-α, improves survival in RCC patients with poor risk features. Bevacizumab, a monoclonal antibody against VEGF, has shown very promising efficacy. Overall, treatment of MRCC is currently moving from the cytokine era to the targeted agent era. However, many questions still remain regarding the efficacy of combination treatments and on the best way to achieve complete remission, which is probably the best hope of curing MRCC.

The management of renal cell carcinoma (RCC) has made considerable progress in recent years, and new and emerging treatment strategies are being developed. Early diagnosis has greatly improved as a result of the development of new imaging techniques, such as spiralled CT scans, magnetic resonance imaging and positron emission tomography scanning. The histopathological classification of RCC was reviewed in 2004, and new pathological entities have been described with the help of molecular biology. Management of localised tumours is evolving to less aggressive treatments, and treatment of metastatic disease is moving from the cytokine era to a period of targeted agents. Prognostic factors for both localised and metastatic diseases have been reported and allow better prediction of the outcome for patients. New molecular factors have been described and will have to be incorporated in future staging systems, as already proposed by the University of California, Los Angeles group.[1,2]

This article focuses on current and emerging treatment strategies for advanced or MRCC. A literature search of MEDLINE was conducted.

1. Role of Nephrectomy in Metastatic Renal Cell Carcinoma

Approximately two-thirds of patients with RCC present with disease localised to the kidney that can often be cured by surgery. However, in 20–25% of patients, metastases are present at the time the disease is diagnosed. In this setting, the utility of nephrectomy has been a debate for many years. On the basis of the results of two randomised studies conducted in the early 2000s,[3,4] nephrectomy has now become the standard as cytoreductive surgery before embarking on systemic treatment with cytokines. Both trials recruited patients with good performance status (0 or 1) who were then randomised to nephrectomy followed by standard treatment with interferon (IFN)-α versus treatment with IFNα alone. Median survival increased from 8 to 11 months[3] and from 7 to 17 months,[4] respectively, in the nephrectomy groups. Currently, nephrectomy should be proposed in every patient with good Eastern Cooperative Oncology Group performance status.

However, some groups have reported that nephrectomy should not be offered when metastatic burden is high with a relatively small primary tumour, because high-dose interleukin (IL)-2 can be effective in these patients.[5] In addition, the role of cytoreductive surgery in the context of new targeted therapies needs to be reassessed.

2. Cytokine-Based Therapy

IL-2 and IFN were the standard treatment in metastatic RCC (MRCC) until 2006. These treatments are still the only approved drugs in many countries, although the dose and schedule of these agents may vary between countries.

The efficacy of these two drugs, which have now been used for >20 years in MRCC, is still controver-

sial. No studies have demonstrated that IL-2 improves survival despite the great enthusiasm generated by the initial report of Rosenberg et al.[6] Two studies have demonstrated an improvement in survival with IFN, either in comparison with medroxyprogesterone[7] or in combination with vinblastine in comparison with vinblastine alone.[8] On the basis of these two studies, IFN has become the standard for evaluation of new treatments in MRCC, even in the US where only high-dose IL-2 has been approved.

In the past decade, various studies have been designed to determine if the combination of IFN with IL-2 and/or chemotherapy could improve outcomes in MRCC. Some very important studies have been reported. The French group reported that the combination of IL-2 and IFN improves response rate and progression free survival (PFS) over IL-2 or IFN alone,[9] and that switching from one cytokine to the other was not useful.[10] The German group reported that a triple combination of IL-2, IFN and fluorouracil was very active.[11] Furthermore, they reported that this triple combination improved survival compared with IFN plus vinblastine. The Cytokine Working Group ran different studies with high-dose IL-2, but none of them demonstrated improvement in overall survival, despite the fact that response rate and PFS is significantly better with high-dose IL-2.[5,12]

However, recent studies have been reported that might change the way patients will be offered these treatments.

Bolus intravenous IL-2 is the gold standard in the US. This treatment, despite its toxicity, provides some long-lasting complete remissions but no proven benefit in terms of survival over subcutaneous IL-2 or IFN.[5] Recent studies from the Cytokine Working Group show that high expression of carbonic anhydrase (CA) IX is a good predictor of response to IL-2.[13] The same group has also described some pathological features that could help to better determine those patients who are the most likely to respond to treatment. A specific study aiming to validate these predictors for response will start soon in the US, and might help us to fully understand if high-dose IL-2 will remain a standard for MRCC in selected patients.

A recent study reported at the American Society of Clinical Oncology (ASCO) conference 2005 by the French group[14] studied the role of IL-2 and IFN in the intermediate prognostic group, as defined by the French group.[9,15] In this study, called the Percy Quattro study, patients were randomised to medroxyprogesterone, IL-2, IFN or a combination of both cytokines. This study failed to demonstrate any survival benefit for IL-2 or IFN in the patients who did receive these cytokines over those who did not receive them. Thus, continuing to administer cytokines to such patients (with intermediate prognosis) becomes questionable, and should be considered only on a case-by-case basis.

Overall, there is a general consensus on the current treatment with cytokines:

- These drugs should not be given to patients with poor prognosis (bad performance status, poor risk groups). In these patients, new therapies should be given as first-line therapy
- In patients with good prognostic factors, a cytokine-based regimen remains a therapeutic option, either with a high-dose IL-2 or subcutaneous regimen. This option is supported by the small number of long-lasting complete remissions with this treatment, mainly with high-dose IL-2.
- In patients with intermediate risk, the results of the French Percy Quattro study encourage the use of new targeted therapies in first-line treatment, but these results will have to be confirmed.

However, this consensus may well change in the coming months with the results of randomised studies comparing new targeted agents with cytokine-based therapy.

3. Targeted Therapies

The development of targeted therapies in RCC has been necessary largely because the Von Hippel-Lindau (*VHL*) gene is often mutated in sporadic RCC. This gene has initially been described in VHL disease, an autosomal dominant condition characterised by a predisposition to heamangioblastomas of the retina and CNS (most commonly the cerebellum and spinal cord) and to clear cell carcinoma of the kidney. The VHL protein is involved with cellular responses to hypoxia. In normoxic conditions, the VHL protein binds to hypoxia inducible factor (HIF)-1α and HIF-2α, which consequently become ubiquinated and tagged for degradation in the proteasome.[16] In hypoxic conditions or in the absence of VHL, HIF-1α accumulates; this stimulates the production of growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-α, which binds to endothelial growth factor receptor (EGFR), and platelet-derived growth factor (PDGF). Through the interaction with the VEGF pathway, these targeted therapies block angiogenesis and can induce tumour shrinkage and/or tumour necrosis, leading to a delay in tumour growth. The decrease in tumour vascularisation has been observed by different radiological approaches, including Doppler ultrasound[17] and dynamic CT scans.[18] Results from studies with these new agents have been recently reported and offer new strategic options for patients with MRCC.

3.1 Bevacizumab

Bevacizumab is a monoclonal antibody directed against VEGF. This drug significantly improved PFS[19] at a dosage of 10 mg/kg every 2 weeks compared with placebo in patients who did not respond to treatment with high-dose IL-2. Promising response rates have been reported with bevacizumab in combination with erlotinib and gefitinib.[20] However, a recent randomised study that failed to show a benefit with the addition of erlotinib over bevacizumab alone in untreated patients has been reported.[21] It should be noted that, in this randomised phase II study, PFS with bevacizumab was 8.5 months, which might reflect a good activity of the drug in a first-line setting. The results of two large randomised studies in untreated MRCC comparing the combination of IFN and bevacizumab with IFN alone (CALCB [Cancer and Leukemia Group B] study) or with a placebo (European study) are expected later in 2007, and should help to better determine the role of this antibody in the treatment of RCC.

3.2 Sunitinib

Sunitinib (SU11248) is the first multi-targeted tyrosine kinase inhibitor (TKI) that has shown activity in MRCC. Sunitinib is administered orally and inhibits the receptor tyrosine kinases VEGFR2, PDGFR, FMS-like tyrosine kinase 3 (FLT-3) and c-KIT with 50% inhibitory concentrations (IC_{50}) in the nanomolar range.

Motzer et al.[22,23] reported the results from two consecutive phases II in >160 patients with MRCC whose first-line, cytokine-based therapy had failed. In these studies, sunitinib 50 mg/day for 4 weeks followed by a 2-week rest period, produced a high response rate of around 40%, with an overall survival of approximately 16 months. The most common adverse event was fatigue, which was categorised as grade 3 severity in seven patients (11%). The most frequently occurring grade 3–4 laboratory abnormalities included lymphopenia without infection (32%) and elevated serum lipase (21%) without clinical signs or symptoms of pancreatitis. The activity of this promising drug has been confirmed through a large phase III study that compared sunitinib with IFN in untreated patients. In this 750-patient study,[24] PFS was 5 months in the IFN arm compared with 11 months in the sunitinib arm ($p < 0.001$). A high response rate was confirmed with

37% of the patients achieving a partial response by Response Evaluation Criteria in Solid Tumours (RECIST) criteria compared with 9% for IFN. Preliminary analysis of overall survival shows a difference in the curves of survival, but it is not yet statistically significant.

Although sunitinib has been developed with an intermittent administration, there is a strong rationale for blocking angiogenesis in a continuous manner. Recently, data with a continuous administration of 37.5mg have been presented.[25] The response rate was 14.6% with an additional 66% rate of stable disease and a promising 8.3 months for PFS, which is similar to that reported previously by Motzer et al.,[22] with the intermittent administration in the same patient population.

3.3 Sorafenib

Sorafenib (BAY 43-9006) is another multitargeted TKI. Initially developed because of its inhibitory effect on the non-receptor serine threonine kinases BRAF and CRAF, sorafenib also inhibits the receptor tyrosine kinases VEGFR2, VEGFR3, FLT-3, c-KIT and PDGFR with IC_{50} values in the nanomolar range.

This oral agent has shown promising activity and a good safety profile in MRCC in phase I/II studies, and also in a multicentre phase II randomised discontinuation trial.[26] In this study, patients with stable disease after 12 weeks of sorafenib were randomised between sorafenib continuation or placebo. PFS was 24 weeks in the sorafenib arm versus 6 weeks with placebo. These encouraging results have been the rationale for a large randomised study, TARGET (Treatment Approaches in Renal cancer Global Evaluation Trial), in patients whose first-line treatment had failed.[27] In this 903 patient study, patients were randomised between sorafenib 400mg twice daily and placebo. Tumour shrinkage was observed in a large majority of patients and PFS was significantly improved from 3 to 6 months ($p < 0.0001$). Survival data show that patients treated with sorafenib had a 39% increase in overall survival compared with placebo.[28] This difference has not yet reached the O'Brien-Fleming boundary for statistical significance. Final analysis will be performed after 540 deaths. Drug-related toxicities for sorafenib versus placebo were rash (34% vs 13%), diarrhoea (33% vs 10%), hand-foot skin reaction (27% vs 5%), fatigue (26% vs 23%) and hypertension (11% vs 1%). Grade 3 or 4 adverse events were reported in 30% of patients receiving sorafenib compared with 22% of patients receiving placebo.

The efficacy of sorafenib as a first-line treatment in MRCC is currently under investigation through a randomised phase II study comparing sorafenib 400mg twice daily with IFN 9MU three times per week. Data from this study will be presented at ASCO 2007.

3.4 Axitinib

Axitinib (AG013736) is a third TKI that inhibits the receptor tyrosine kinases VEGFR1, VEGFR2, PDGFR and c-KIT. Axitinib is an oral agent that is given at a dosage of 5mg twice daily, with an impressive activity shown in 52 patients with MRCC (46% response rate).[29] As with the other TKIs, this targeted agent has a good safety profile. Reported grade 1 or 2 toxicities were nausea (29%), fatigue (29%), diarrhoea (27%), hoarseness (19%), anorexia (17%) and weight loss (15%). Hypertension was reported in 17 patients (33%); 12% of patients had grade 3 or 4 hypertension and 6% of patients had aggravated hypertension. The activity of this drug needs to be confirmed in larger randomised studies.

3.5 Temsirolimus

Temsirolimus (CCI 779) is a mammalian target of rapamycin (mTOR) inhibitor, which acts directly on HIF production, a driver for the VEGF pathway. The mTOR is a non-receptor tyrosine kinase; mTOR

activation has various downstream effects, including increasing HIF-1α gene expression at the level of messenger RNA translation.

The activity of temsirolimus was reported by Atkins et al.[30] in 2004. In this randomised phase II study, 111 patients were randomly assigned to receive temsirolimus 25mg, 75mg or 250mg as a weekly intravenous infusion. Most patients had previously received therapy, and the response rate was 7%, with 51% of the patients having stable disease or better after 24 weeks. The most frequent grade 3 or 4 toxicities were hyperglycaemia (17%), hypophosphataemia (13%), anaemia (9%) and hypertriglyceridaemia (6%). Recently, the results of a large phase III trial in MRCC patients with poor risk features were reported.[31] In this 626-patient study, IFN 9–18MU three times per week was compared with intravenous temsirolimus 25mg weekly monotherapy and temsirolimus 15mg weekly combined with IFN 6MU three times per week. Overall survival was significantly better with temsirolimus alone than IFN alone with a 49% improvement from 7.3 to 10.9 months ($p = 0.0069$), whereas the combined arm did not demonstrate better overall survival than IFN alone. It must be underlined that this study was restricted to a group of patients with poor risk characteristics, and thus the activity of this drug needs to be confirmed in the good and intermediate prognostic groups.

3.6 Summary

Therefore, evidence of the efficacy of targeted therapy in advanced RCC has been demonstrated, with two recently registered drugs (sorafenib and sunitinib) and probably two additional drugs in the near future (temsirolimus and bevacizumab). The respective role of these drugs in the algorithm for treatment of RCC has been beautifully discussed by Atkins during the ASCO 2006 plenary session (table I). On the basis of reported phase III data from 2006, the gold standard for advanced RCC should be according to risk group:[32]

Table I. Algorithm for treatment of renal cell carcinoma based on phase III data (adapted from Atkins, plenary session American Society for Clinical Oncology [ASCO] 2006)

Setting	Therapy
First-line therapy	
Good and intermediate risk	Sunitinib
Poor risk	Temsirolimus
Second-line therapy	
After first-line therapy (cytokines or chemotherapy)	Sorafenib
After tyrosine kinase inhibitors	Unknown

- In a first-line setting, sunitinib should be the therapy in good and intermediate risk groups, with temsirolimus used in poor risk groups. In the good risk group, the role of cytokines might remain in the hope of reaching complete remission, especially with high-dose IL-2.
- In a second-line setting, after failure of cytokines or chemotherapy, sorafenib should be the standard therapy.

However, many questions remain and should be resolved in the next coming years. One of the most important questions is whether targeted therapy can be active after failure of a first regimen. The first study that addressed this question has been recently reported.[33] In a phase II study of sunitinib in 60 patients with MRCC refractory to bevacizumab, partial response was observed in 16% of the patients with an additional 56% with some tumour shrinkage, leading to an encouraging median PFS of 24 weeks. Anecdotal reports also demonstrate that sorafenib or sunitinib can be active in patients for whom the other TKI has failed. These findings will have to be confirmed through prospective studies.

4. Conclusion

The treatment of MRCC is currently moving from the cytokine era to the targeted agent era. Both sorafenib and sunitinib have been recently approved by the US FDA and the European Agency for the

Evaluation of Medicinal Products, and are becoming the standard of care. Temsirolimus should also be approved in the future based on the large randomised study showing survival benefit. These drugs have tremendously improved the prognosis of patients with MRCC, although considerable effort is still required to reach complete remission in a significant number of patients.

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