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Targeted therapy in metastatic renal cell carcinoma: efficacy, adverse-event management and key considerations

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Renal cell carcinoma (RCC) accounts for approximately 2% of all cancers worldwide, with the highest rates observed in North America, Australia and Europe.[1] In Europe, approximately 40,000 patients are diagnosed with RCC each year, leading to an estimated 20,000 deaths.[2]

RCC is often asymptomatic, or associated with non-specific symptoms such as fatigue, weight loss, malaise, fever and night sweats.[3] Approximately half of all cases are detected incidentally during abdominal imaging for other medical conditions,[4,5] and up to one-third of patients are initially diagnosed with locally invasive or stage IV disease.[2] A high proportion of patients with localised disease who undergo nephrectomy with curative intent subsequently develop metastases,[6–8] and approximately 25–30% of patients have metastatic disease at diagnosis.[3,9]

The 5-year relative survival rate for patients with RCC varies with disease stage at diagnosis, and is estimated to be approximately 90% for localised disease and 62% for regional disease.[10] Metastatic RCC (mRCC) is highly resistant to conventional chemotherapy, radiotherapy and hormonal therapy.[9,11,12] As a result, the prognosis is extremely poor, with a 5-year survival rate of generally $\leqslant$11%.[9,13]

However, the prognosis for patients with mRCC is improving. Early detection of disease is associated with improved outcome and in recent years, the rate of early, incidental, RCC diagnosis has increased with the growing use of radiographic diagnostic testing. Furthermore, there have been advances in the management of RCC: surgical techniques have been refined, perioperative care has improved, prognostic variables have been characterised and new therapeutic agents have become available.[14]

For several decades, cytokine therapy, using either interleukin-2 (IL-2) or interferon-alpha (IFN-α), was the only effective treatment available for patients with mRCC.[15–20] However, these agents provide only modest increases in survival in a limited subset of patients and are associated with substantial toxicity, particularly at high doses.[17,21–23] They should therefore be reserved for use in a highly selected population of patients with a good risk profile and clear-cell histology.[24,25]

IL-2 and IFN-α have now been largely superseded by novel agents targeted against specific components of the pathways involved in tumour growth and angiogenesis, such as vascular endothelial growth factor (VEGF). These agents include the multitargeted receptor tyrosine kinase inhibitors sunitinib (SUTENT®, Pfizer Inc.) and sorafenib (Nexavar®, Bayer HealthCare/Onyx Pharmaceuticals), the VEGF ligand-binding monoclonal antibody bevacizumab (Avastin®, Genentech, Inc.) and the mammalian target

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of rapamycin (mTOR) kinase inhibitor temsirolimus (Torisel™, Wyeth Pharmaceuticals).

Several of these agents have demonstrated clinical activity in patients with mRCC.[26–33] In particular, results from a randomised phase III trial showed that sunitinib is the new reference standard for first-line therapy of mRCC.[27] Median progression-free survival was significantly longer in patients treated with sunitinib (11 months) compared with those who received IFN-α (5 months), corresponding to a hazard ratio of 0.42 (95% confidence interval [CI]: 0.32–0.54; $p < 0.001$). Sunitinib was also associated with a higher overall response rate than IFN-α (31% versus 6%, $p < 0.001$).

In this supplement, we review current evidence for the use of targeted therapy in patients with mRCC, review strategies to manage adverse events and optimise treatment in key patient populations and examine evidence for the value of potential prognostic factors. The supplement focuses primarily on sunitinib, recently approved for first-line therapy of mRCC.

In the first article, I explore the efficacy of the targeted agents that have been evaluated in the first- or second-line treatment of mRCC. Recent trials examining sequential or combination therapy are discussed and data on the use of these agents in the adjuvant setting are also presented.

In the past few years, there has been greater understanding of the adverse-event profile of targeted agents and increased experience of strategies to minimise the impact of adverse events. In the second article, Professor Sylvie Négrier provides an update on the tolerability of sunitinib in patients with mRCC and discusses practical strategies to optimise treatment, such as proactive management of patient expectations and treatment-related toxicities, as well as changes to the dosing schedule or duration of treatment. Such strategies can help to maintain the optimal dose of sunitinib during patients' treatment, with the ultimate goal of delaying disease progression and minimising the risk of further metastasis during long-term care.

Prognostic variables identified in mRCC allow patients to be categorised according to risk, and assist in planning and implementing treatment to ensure patients achieve maximum benefit from the new targeted drugs available. In the third article, I explore the prognostic value of key patient- and tumour-related characteristics and provide recommendations for treatment based on the implications of these characteristics.

Finally, case reports of interest are presented to illustrate practical examples of therapy optimisation and management. These reports cover the use of sunitinib in a patient with pre-existing thrombocytopenia and leucopenia, management of cutaneous toxicity arising during treatment with sorafenib and sunitinib, and the management of patients with cerebellar metastases.

RCC management has changed considerably in recent years and is likely to continue to change with the availability of new clinical data and growing clinical experience with new therapeutic agents. This supplement provides a comprehensive update on the role of sunitinib in managing mRCC, incorporating updates from recent and ongoing trials and recommendations from experts in the field of RCC management.

Disclosure

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Conflict of interest

A. Ravaud: member of the Global, European and/or French advisory boards of Pfizer, Bayer, GSK and Wyeth. Member of RCC clinical trial steering committees for Pfizer and Novartis. Principal investigator for the S-TRAC trial sponsored by Pfizer.

References

1. Parkin DM, Bray F, Ferlay J, *et al.* Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55(2):74–108.
2. Schoffski P, Dumez H, Clement P, *et al.* Emerging role of tyrosine kinase inhibitors in the treatment of advanced renal cell cancer: a review. *Ann Oncol* 2006;17(8):1185–96.
3. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. *N Engl J Med* 1996;335(12):865–75.
4. Porena M, Vespasiani G, Rosi P, *et al.* Incidentally detected renal cell carcinoma: role of ultrasonography. *J Clin Ultrasound* 1992;20(6):395–400.
5. Jayson M, Sanders H. Increased incidence of serendipitously discovered renal cell carcinoma. *Urology* 1998;51:203–5.
6. Rabinovitch RA, Zelefsky MJ, Gaynor JJ, *et al.* Patterns of failure following surgical resection of renal cell carcinoma: implications for adjuvant local and systemic therapy. *J Clin Oncol* 1994;12(1):206–12.
7. Antonelli A, Cozzoli A, Zani D, *et al.* The follow-up management of non-metastatic renal cell carcinoma: definition of a surveillance protocol. *BJU Int* 2007;99(2):296–300.
8. Janzen NK, Kim HL, Figlin RA, *et al.* Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. *Urol Clin North Am* 2003;30(4):843–52.
9. Godley P, Taylor M. Renal cell carcinoma. *Curr Opin Oncol* 2001;13:199–203.
10. US National Institutes of Health. Surveillance, Epidemiology and End Results (SEER) Cancer Statistics Review. Kidney and renal pelvis cancer. 5-year relative survival rates, 1996–2002. <http://seer.cancer.gov/cgi-bin/csr/1975_2003/search.pl#results> (accessed September 2006).
11. Lilleby W, Fossa SD. Chemotherapy in metastatic renal cell cancer. *World J Urol* 2005;23(3):175–9.

12. Rohrmann K, Staehler M, Haseke N, *et al.* Immunotherapy in metastatic renal cell carcinoma. *World J Urol* 2005;23(3):196–201.
13. Sachdeva K, Makhoul I, Javeed M, *et al.* Renal cell carcinoma. *eMedicine* 2006;1–23.
14. Feldman DR, Motzer RJ. Novel targets and therapies for metastatic renal cell carcinoma. *Oncology (Williston Park)* 2006;20(14):1745–53.
15. Law TM, Motzer RJ, Mazumdar M, *et al.* Phase III randomized trial of interleukin-2 with or without lymphokine-activated killer cells in the treatment of patients with advanced renal cell carcinoma. *Cancer* 1995;76(5):824–32.
16. Négrier S, Escudier B, Lasset C, *et al.* 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):1272–8.
17. Négrier S, Perol D, Ravaud A, *et al.* Do cytokines improve survival in patients with metastatic renal cell carcinoma (MRCC) of intermediate prognosis? Results of the prospective randomized PERCY Quattro trial. *J Clin Oncol* 2005;23(16S):LBA4511.
18. Vogelzang NJ, Lipton A, Figlin RA. Subcutaneous interleukin-2 plus interferon alfa-2a in metastatic renal cancer: an outpatient multicenter trial. *J Clin Oncol* 1993;11(9):1809–16.
19. Wirth MP. Immunotherapy for metastatic renal cell carcinoma. *Urol Clin North Am* 1993;20(2):283–95.
20. Wirth M. The current use of interferons, interleukin-2 and tumor necrosis factor in renal cell cancer. *Urol Int* 1991;47(4):219–30.
21. Coppin C, Porzsolt F, Awa A, *et al.* Immunotherapy for advanced renal cell cancer. *Cochrane Database Syst Rev* 2005;(1):CD001425.
22. Rosenberg SA, Lotze MT, Yang JC, *et al.* Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. *J Natl Cancer Inst* 1993;85(8):622–32.
23. Fyfe G, Fisher RI, Rosenberg SA, *et al.* Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol* 1995;13(3):688–96.
24. Ljungberg B, Hanbury D, Kuczyk M. Renal cell carcinoma guideline. *Eur Urol* 2007;51(6):1502–10.
25. Négrier S, Escudier B, Gomez F, *et al.* Prognostic factors of survival and rapid progression in 782 patients with metastatic renal carcinomas treated by cytokines: a report from the Groupe Francais d'Immunotherapie. *Ann Oncol* 2002;13(9):1460–8.
26. Motzer RJ, Rini BI, Bukowski RM, *et al.* Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006;295(21):2516–24.
27. Motzer RJ, Hutson TE, Tomczak P, *et al.* Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356(2):115–24.
28. Escudier B, Eisen T, Stadler WM, *et al.* Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356(2):125–34.
29. Ratain MJ, Eisen T, Stadler WM, *et al.* Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006;24(16):2505–12.
30. Escudier B, Koralewski P, Pluzanska A, *et al.* A randomized, controlled, double-blind phase III study (AVOREN) of bevacizumab/interferon-α2a vs placebo/interferon-α2a as first-line therapy in metastatic renal cell carcinoma. *J Clin Oncol* 2007;25(18S):3.
31. 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(5):427–34.
32. 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(5):909–18.
33. Hudes G, Carducci M, Tomczak P, *et al.* A phase 3, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alpha (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-risk patients with advanced renal cell carcinoma (adv RCC). *J Clin Oncol* 2006;24(18S):LBA4.