available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Advances in the Management of Metastatic Renal Cell Cancer

Cora N. Sternberg [a,*], *Joaquim Bellmunt* [b], *Viktor Grünwald* [c], *James Larkin* [d], *Peter Mulders* [e]

[a] *Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy*
[b] *Solid Tumor Oncology, Hospital Del Mar - IMIM, Barcelona, Spain*
[c] *Clinic for Hematology, Hemostaseology, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany*
[d] *Department of Medicine, Royal Marsden Hospital, London, United Kingdom*
[e] *Department of Urology, University Medical Centre St Radboud, Nijmegen, The Netherlands*

Article info

Keywords:
Bevacizumab
Everolimus
Renal cell carcinoma
Sorafenib
Sunitinib
Targeted therapy
Temsirolimus
Tyrosine kinase inhibitor

* Corresponding author. Department of Medical Oncology, San Camillo Forlanini Hospital, Circonvallazione Gianicolense 87, 00152 Rome, Italy. Tel. +39 06 66510620; Fax: +39 06 6630771.
E-mail address: cstern@mclink.it (C.N. Sternberg).

1. Introduction

Renal cell carcinoma (RCC) represents a therapeutic challenge. In 2008, an estimated 54 390 new cases of RCC were diagnosed, and the disease accounted for approximately 13 010 deaths in the United States [1]. RCC comprises multiple subtypes, each with a distinct phenotype, clinical course, and response to treatment [2]. Most research is focused on clear-cell RCC, which represents >75% of all histologic subtypes. Papillary RCC is the second most common subtype, followed by chromophobe RCC, accounting for 15% and 5% of all subtypes, respectively. Patients with von Hippel-Lindau (VHL) disease commonly develop RCC, specifically the clear-cell type [2,3].

With regard to the management of RCC, surgery is the primary treatment approach for localised RCC. Metastatic RCC (mRCC) is generally resistant to chemotherapy, radiation therapy and hormone therapy, and is associated with a poor prognosis. Immunotherapy using the cytokines interleukin-2 (IL-2) and/or interferon-α (IFN-α) has been the standard treatment for patients with mRCC over the past 20 yr. Cytokine therapy appears to be associated with low response rates of approximately 15% and a median overall survival (OS) of 10–12 mo, but only in patients with good prognostic features [4,5].

More recently, the role of the VHL/hypoxia-inducible factor (VHL/HIF) pathway has been strongly implicated in RCC. Several molecules of this signalling pathway, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-α (TGF-α), and the mammalian target of rapamycin (mTOR), have been identified. These molecules play a critical role in tumour angiogenesis and tumour cell proliferation and have led to the development of promising new, rationally designed, molecularly targeted agents for treatment of mRCC [6]. Targeted agents such as sunitinib, bevacizumab, temsirolimus, sorafenib, and everolimus have shown potential in randomised phase 3 trials for treatment of mRCC (Table 1). In these trials, IFN-α has been used as a baseline for assessment of new therapies, and patients were stratified according to the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic criteria [7].

This paper was based on presentations given at a symposium on advances in the management of mRCC that

1569-9056/$ – see front matter doi:10.1016/j.eursup.2009.06.004

Table 1 – Overview of randomised phase 3 clinical trials of targeted therapies for treatment of patients with metastatic renal cell carcinoma [8,9,11–15]

Author	No. patients	Regimen	Clinical setting	Efficacy (mo)
Motzer [8]	750	IFN-α vs sunitinib	First line	Median PFS: 5 vs 11 ($p < 0.001$)
Figlin [9]	750	IFN-α vs sunitinib	First line	Median OS: 26.4 vs 20.0 ($p = 0.0362$)*
Escudier [11]	649	Bevacizumab + IFN-α vs IFN-α	First line	Median PFS: 10.2 vs 5.4 ($p = 0.0001$)
Rini [12]	732	Bevacizumab + IFN-α vs IFN-α	First line	Median PFS: 8.5 vs 5.2 ($p < 0.0001$)
Hudes [13]	626	Temsirolimus vs IFN-α	First line	Median OS: 10.9 vs 7.3 ($p = 0.008$)
Escudier [14]	903	Sorafenib vs placebo	Second line (post-cytokines)	Median PFS: 5.5 vs 2.8 ($p < 0.01$)
Motzer [15]	410	Everolimus vs placebo	Second line (post-TKI)	Median PFS: 4.0 vs 1.9 ($p < 0.0001$)

IFN-α = interferon-α; PFS = progression-free survival; OS = overall survival; TKI = tyrosine kinase inhibitor.
*IFN-α patients who crossed over to sunitinib censored.

was held during the 2nd World Congress on Controversies in Urology (CURy) on 6 February 2009 in Lisbon, Portugal. Data were retrieved from original articles, review articles, and abstracts on the management of mRCC.

2. Randomised phase 3 trials of targeted therapies for treatment of metastatic renal cell carcinoma

2.1. First-line treatment of metastatic renal cell carcinoma

Sunitinib is an orally administered tyrosine kinase inhibitor (TKI) with activity against VEGF receptors, PDGF receptors, c-kit, and FLT-3. In a landmark phase 3 trial, sunitinib demonstrated statistically superior efficacy over IFN-α as first-line treatment of good- or intermediate-risk patients with clear-cell mRCC (Table 1) [8]. Figlin et al. [9] presented at the American Society of Clinical Oncology (ASCO) 2008 annual meeting the final OS data of this phase 3 trial. Sunitinib appears to offer a statistically significant survival benefit compared with IFN-α in patients with previously untreated clear-cell mRCC (Table 1). According to a population-based analysis, the introduction of first-line treatment with sunitinib was associated with a doubling of OS compared with patients treated with IFN-α alone. Moreover, this advantage extended to patients with all MSKCC prognostic risk profiles [10].

Besides sunitinib, the combination of the humanised anti-VEGF monoclonal antibody bevacizumab with IFN-α has proven antitumour activity as a first-line treatment of clear-cell mRCC (Table 1) [11,12]. Temsirolimus, an intravenously administered inhibitor of mTOR, has shown a significant OS benefit over IFN-α in patients with previously untreated mRCC and poor-risk features (Table 1). The addition of temsirolimus to IFN-α did not improve survival [13].

2.2. Second-line treatment of metastatic renal cell carcinoma

Sorafenib, another oral multitargeted TKI, has shown antitumour activity in patients with mRCC who progressed on first-line cytokine treatment (Table 1) [14]. Escudier et al. [14] randomly assigned 903 patients with RCC resistant to standard therapy to receive either continuous treatment with sorafenib or placebo. As compared with placebo, treatment with sorafenib significantly prolonged progression-free survival (PFS) and increased overall responses. In addition, there was a trend towards a reduction in the risk of death among patients receiving sorafenib as compared with those receiving placebo.

Everolimus (ie, RAD001) is an orally administered mTOR inhibitor with structural and functional similarities to temsirolimus. Treatment with everolimus resulted in prolonged PFS compared with placebo in patients with mRCC that progressed on other antiangiogenic TKI-targeted therapies (Table 1) [15,16].

3. Sequential therapy versus combination therapy with targeted agents

There are now many potentially active agents in mRCC with different molecular targets, which raises important questions regarding sequencing and combination therapies. However, to date, few data have been reported supporting either strategy. Two retrospective studies demonstrated that sequential use of sorafenib–sunitinib appears to be more effective than sunitinib–sorafenib for treatment of advanced RCC [17,18]. Dudek et al. [17] recently hypothesised that drug resistance emerging after initial use of sorafenib would be overcome by sunitinib, whereas development of resistance to initial sunitinib would not be salvaged by sorafenib. Alternatively, it was reported that the observed differences could be the result of a higher potency of sunitinib salvage therapy. Moreover, phase 2 and 3 trials support a role of sunitinib, axitinib, and everolimus in patients with bevacizumab-, sorafenib- or TKI-refractory mRCC, respectively [15,16,19,20]. These data suggest lack of cross-resistance between targeted agents. Nevertheless, the majority of patients entering such sequential studies had a favourable or intermediate MSKCC prognostic score [21].

An alternative approach would be to use combinations of targeted agents. One way might be to combine agents that block the HIF–VEGF pathway at multiple levels (ie, a vertical strategy)—for example, the combined use of agents that block circulating VEGF and its receptor. Another way is to block multiple signalling pathways (eg, agents that block VEGF receptors and PDGF receptors) downstream of HIF and another pathway such as mTOR (ie, a horizontal strategy) [22]. However, the combination of sunitinib with other agents has resulted in severe toxicities in phase 1 studies [23,24], whereas the combined use of agents with IFN-α or bevacizumab seems

to be much better tolerated [25–27]. In contrast, a recently published case study reported that the bevacizumab–sunitinib combination in sunitinib-refractory patients seems active and has a tolerable toxicity profile [28]. In an era of multiple therapeutic options for patients with mRCC, phase 3 clinical trials should address the crucial question of the optimal sequence or combination of targeted agents.

4. Conclusions

There is a strong rationale for targeting angiogenesis and multiple pathways in mRCC. Currently, several targeted agents have been evaluated in randomised phase 3 trials and are available for treatment of mRCC. Sunitinib and bevacizumab plus IFN-α can be considered as a first-line treatment of mRCC with good or intermediate prognosis, whereas temsirolimus has proven antitumour activity in poor-risk patients. With regard to second-line treatment of mRCC, sorafenib and everolimus seem to significantly prolong PFS in cytokine-refractory and TKI-refractory RCC, respectively. Phase 2 and 3 clinical trials are ongoing to assess the potential benefits of sequencing or combination therapies with targeted agents in mRCC. In addition, more research should address the effect of targeted therapies on the immune system and investigate whether there is a role of other cytokines (eg, IL-6) combined with targeted agents. With regard to the most appropriate treatment option, clinical cases demonstrated the complexity and variables involved in management decisions for the individual patient. Working together with a dedicated multidisciplinary team is essential to improve patient outcomes.

Conflicts of interest

Cora N. Sternberg received honoraria from Novartis. Joaquim Bellmunt has participated in advisory boards of Roche and received honoraria from Novartis. Viktor Grünwald received honoraria from Roche, Pfizer, and Novartis; a research grant from Wyeth; and is a consultant for Roche, Pfizer, and Novartis. James Larkin received honoraria from Novartis. Peter Mulders received honoraria from AstraZeneca, Bayer, Roche, Novartis, Gen-Probe, Antigenics, and Pfizer.

Funding support

None.

Acknowledgments

The authors are grateful to Ismar Healthcare NV for their assistance in writing the manuscript.

References

[1] American Cancer Society: Cancer Fact & Figures 2008. http://www.cancer.org. Accessed June 8, 2009.
[2] Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. J Urol 2003;170:2163–72.
[3] Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. J Clin Oncol 2004;22:4991–5004.
[4] Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. Cancer J Sci Am 2000;6(Suppl 1):S55–7.
[5] Chowdhury S, Larkin JMG, Gore ME. Recent advances in the treatment of renal cell carcinoma and the role of targeted therapies. Eur J Cancer 2008;44:2152–61.
[6] Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. J Clin Oncol 2005;23:1028–43.
[7] Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289–96.
[8] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
[9] Figlin RA, Hutson TE, Tomczak P, et al. Overall survival with sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC). J Clin Oncol 2008;26:256s (abstract 5024).
[10] Heng DYC, Chi KN, Murray N, et al. A population-based study evaluating the impact of sunitinib on overall survival in the treatment of patients with metastatic renal cell cancer. Cancer 2009;115:776–83.
[11] Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370:2103–11.
[12] Rini BI, Halabi S, Rosenberg JE, et al. CALGB 90206: a phase III trial of bevacizumab plus interferon-alpha versus interferon-alpha monotherapy in metastatic renal cell carcinoma. Paper presented at: ASCO GU 2008 (abstract 350).
[13] Hudes G, Carducci M, Tomczak P, et al. A phase III, randomized, 3-arm study of temsirolimus (TEMSR) or interferon-alfa (IFN) or the combination of TEMSR + IFN in the treatment of first-line, poor-prognosis patients with advanced renal cell carcinoma. J Clin Oncol 2006;24:2 (abstract LBA4).
[14] Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125–34.
[15] Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449–56.
[16] Escudier B, Ravaud A, Oudard S, et al. Phase-3 randomised trial of everolimus (RAD001) vs placebo in metastatic renal cell carcinoma. Ann Oncol 2008;19:viii45 (abstract 720).
[17] Dudek AZ, Zolnierek J, Dham A, Lindgren BR, Szczylik C. Sequential therapy with sorafenib and sunitinib in renal cell carcinoma. Cancer 2009;115:61–7.
[18] Sablin MP, Bouaita L, Balleyguier C, et al. Sequential use of sorafenib and sunitinib in renal cancer: retrospective analysis in 90 patients. J Clin Oncol 2007;25:241s (abstract 5038).
[19] Rini BI, Michaelson MD, Rosenberg JE, et al. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. J Clin Oncol 2008;26:3743–3748.
[20] Rini BI, Wilding GT, Hudes G, et al. Axitinib (AG-013736; AG) in patients (pts) with metastatic renal cell cancer (RCC) refractory to sorafenib. J Clin Oncol 2007;25:242s (abstract 5032).
[21] Eichelberg C, Heuer R, Chun FK, et al. Sequential use of the tyrosine kinase inhibitors sorafenib and sunitinib in metastatic renal cell

carcinoma: a retrospective outcome analysis. Eur Urol 2008;54: 1373–8.

[22] Kaelin WG Jr. The von Hippel-Lindau tumor suppressor gene and kidney cancer. Clin Cancer Res 2004;10:S6290–5.

[23] Fischer P, Patel P, Carducci MA, et al. Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma. J Clin Oncol 2008;26:672s (abstract 16020).

[24] Feldman DR, Ginsberg MS, Baum M, et al. Phase I trial of bevacizumab plus sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol 2008;26:274s (abstract 5100).

[25] Ryan CW, Goldman BH, Lara PN Jr, et al. Sorafenib with interferon alfa-2b as first-line treatment of advanced renal carcinoma: a phase II study of the Southwest Oncology Group. J Clin Oncol 2007;25:3296301.

[26] Gollob JA, Rathmell WK, Richmond TM, et al. Phase II trial of sorafenib plus interferon alfa-2b as first- or second-line therapy in patients with metastatic renal cell cancer. J Clin Oncol 2007;25:3288–95.

[27] Whorf RC, Hainsworth JD, Spigel DR, et al. Phase II study of bevacizumab and everolimus (RAD001) in the treatment of advanced renal cell carcinoma (RCC). J Clin Oncol 2008;26:252s (abstract 5010).

[28] Medioni J, Banu E, Helley D, et al. Salvage therapy with bevacizumab–sunitinib combination after failure of sunitinib alone for metastatic renal cell carcinoma: a case series. Eur Urol 2009;56: 207–11.