Renal cell cancer: the unmet needs

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Back in the 1980s, experts in the field of genitourinary oncology expressed skepticism about any success in treating patients with advanced renal cell cancer (RCC). Not a single agent, hormonal manipulation, or combination of cytotoxics, could provide any benefit in terms of survival or quality of life [1,2]. Since then, we have witnessed impressive accomplishments with major advances, mostly in the last two decades. In 1992, the Food and Drug Administration approved, based on phase II data, the use of high-dose interleukin-2 to treat selected populations of patients with advanced RCC [3]. Only 1 year later, the von Hippel–Lindau tumor suppressor gene was isolated and its connection with some forms of hereditary and sporadic kidney cancer was described [4]. This knowledge led to very intense research in the field and the further development of several drugs that have progressively entered the clinical setting.

The understanding that von Hippel–Lindau mutations lead to an abnormal response to hypoxia and heightened angiogenesis in clear cell RCC led to the development of strategies targeting elements involved in this process such as the vascular endothelial growth factor (VEGF) and its receptor (VEGFR). In 2003, a randomized study showed that bevacizumab, a mononoclonal antibody against VEGF, improved time to progression in patients with advanced clear cell RCC, proving the concept that targeting angiogenesis was a therapeutically relevant approach in this disease [5]. Over the last few years, a plethora of clinical trials involving agents that target different components of the angiogenesis pathway have been conducted, leading to the approval of several agents to treat metastatic kidney cancer.

In a phase II randomized discontinuation trial, the tyrosine kinase inhibitor (TKI), sorafenib increased time to progression in patients with metastatic RCC as compared with placebo [6]. These results were subsequently confirmed in a randomized, placebo-controlled phase III trial, where sorafenib showed a statistically significant improvement in progression-free survival (PFS) from 2.8 to 5.5 months in RCC patients treated earlier with cytokines [7]. Similarly, early phase I and II studies with sunitinib showed a high response rate in the range of 30–40% [8,9]. In a phase III study, compared with interferon α (IFN-α), the agent showed a statistically significant improvement in PFS from 5.1 to 11 months in patients with advanced RCC not treated earlier [10]. Although in the overall population there was a borderline statistically significant improvement in median survival from 21.6 to 26.4 months ($P = 0.051$), in the subset of patients who did not receive any poststudy treatment on progression (no crossover confounding factor), the improvement in the overall survival (OS) for sunitinib was statistically significant (28.1 vs. 14.1 months, $P = 0.003$). More recently the TKI, pazopanib showed improvement in PFS when compared with placebo, for patients chemo naive (11.1 vs. 2.8 months, $P < 0.000\,0001$) as well as for those who had progressed to previous cytokine treatment (9.2 vs. 4.2 $P < 0.000\,0001$) [11]. Lastly, axitinib, a newer TKI targeting similar receptors, has resulted in 23% response rate in a single arm phase II study with RCC patients who were treated earlier [12]. Moreover, two randomized phase III studies compared the combination of bevacizumab and IFN-α versus only IFN-α in patients with advanced RCC not treated earlier. Both were positive showing an improvement in PFS and also showing a trend towards benefit in OS and therefore adding to the armamentarium in the first line setting [13,14].

Another intracellular target that has added to the therapeutics of RCC is the mammalian target of rapamycin (mTOR) pathway. The mTOR inhibitor temsirolimus showed preliminary evidence of activity in patients treated with RCC earlier, regardless of their risk group as per the Memorial Sloan–Kettering classification [15]. This study was followed by a randomized phase III trial specially addressed to first-line RCC poor prognosis patients that showed an improvement in the median survival in patients treated with temsirolimus versus those who received IFN-α (10.9 vs. 7.3 months) [16]. More recently, everolimus, another mTOR inhibitor, increased PFS from 1.8 to 4.9 months in a population of patients that had progressed to the therapy with TKIs earlier [17].

These results show a significant improvement in response rate, PFS, and OS from the cytokines era. However, despite these major advances in recent years there is still room for improvement. Most of the progress has been in the field of clear cell RCC. There is scarce information about the proper management of other histologies, and this represents an increasing number of patients. We still do not

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know the role of adjuvant or neoadjuvant approaches in RCC with the new therapeutic armamentarium, and the knowledge about good predictive markers is insufficient. Additional studies are needed to properly define how to combine all these new agents in sequential or parallel designs.

We recently conducted a survey among genitourinary oncologists in Spain on the management of patients with RCC (data not published). The results confirmed that there are areas of some controversy. Homogenous answers were obtained in general features such as first-line and subsequent treatments for patients with clear cell RCC. Sunitinb seems to be the preferred drug in first-line treatment for the majority of surveyed doctors (83%), whereas a switch-on mechanism of action on progression rotating to an mTOR inhibitor such as everolimus is the most common approach in second-line treatment (69% of surveyed doctors). Some heterogeneity was observed, however, in features such as adjuvant treatment and the management of patients with non-clear cell RCC. Only a minority of centers (20%) have access to adjuvant studies and approximately one-third of respondents would consider adjuvant strategies in a high-risk patient. None of the surveyed doctors would contemplate neoadjuvant approaches and approximately 10% conduct routinely predictive and/or prognostic studies through serum or tumor tissue collection. When asked about the patients with non-clear cell RCC, the physicians are almost equally divided between TKIs and mTOR inhibitors with approximately 40% each. Although surveyed oncologists acknowledged a large amount of information about hereditary syndromes in RCC, the way they incorporate this in their routine clinical practice varies.

In this supplement to Anticancer Drugs, these controversial topics have been addressed. Homicsko *et al.* [18] have conducted an extensive review on the current evidence on adjuvant and neoadjuvant strategies. There are currently many studies in progress and others to be initiated shortly. Different approaches are being tested, with various drugs and different lengths of treatment. However, none of the studies are mature, and our current practice should remain unchanged. Observation or inclusion in a clinical trial after nephrectomy remains the standard of care at this time until further data is available. The researchers raise a critical topic: selection of patients. There is no doubt that the future management of RCC will be determined by predictive and prognostic markers. This knowledge will assist in an appropriate treatment selection. Multiple studies have been published recently exploring potential genetic and molecular markers, although none of these had conclusive results that would imply a change in current practice [19,20].

Another very important aspect revised in this supplement is the hereditary syndromes linked to RCC. García-Donas *et al.* [21] present an extensive but very practical review of this topic. The oncologist treating RCC should be familiar with these clinical entities, and should be able to recognize them and manage them appropriately. We are probably missing some of these patients because of the lack of familiarity with these syndromes.

Lastly, Sánchez *et al.* [22] review another current controversial topic: the management of non-clear cell RCC. One out of every four patients seen in our clinics with renal cancer will have a non-clear cell histology [23]. There is no consensus in the literature on the best management of these patients. Starting from the molecular and genetic basis of each subtype, the available treatments are summarized, as are the multiple ongoing studies. Further data are needed to be able to make formal recommendations, although the increased knowledge about the molecular basis of each subtype has clearly helped to direct further research. It is likely that in the next few years we will be able to better define the therapeutics of these patients.

In conclusion, over the last 20 years we have been able to change a paradigm of a disease that was perceived as resistant to any systemic treatment and had very poor outcomes. Yet, despite great improvements, we still have some 'unmet needs' in this patient population. The coming years will hopefully provide us with the appropriate answers to the current unresolved scientific questions.

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References

1 Harris DT. Hormonal therapy and chemotherapy of renal-cell carcinoma. *Semin Oncol* 1983; **10**:422–430.
2 Yagoda A, Abi-Rached B, Petrylak D. Chemotherapy for advanced renal-cell carcinoma: 1983–1993. *Semin Oncol* 1995; **22**:42–60.
3 Atkins MB, Sparano J, Fisher RI, Weiss GR, Margolin KA, Fink KI, *et al.* Randomized phase II trial of high-dose interleukin-2 either alone or in combination with interferon alfa-2b in advanced renal cell carcinoma. *J Clin Oncol* 1993; **11**:661–670.
4 Latif F, Tory K, Gnarra J, Yao M, Duh FM, Orcutt ML, *et al.* Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science* 1993; **260**:1317–1320.
5 Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, *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.
6 Ratain MJ, Eisen T, Standler WM, Flaherty KT, Kaye SB, Rosner GL, *et al.* Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24**:2505–2512.
7 Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, *et al.* Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007; **356**:125–134.
8 Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, *et al.* Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2006; **24**:16–24.
9 Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, *et al.* Sunitinib in patients with metastatic renal cell carcinoma. *JAMA* 2006; **295**:2516–2524.
10 Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, *et al.* Sunitinib versus interferon alpha in metastatic renal-cell carcinoma. *N Engl J Med* 2007; **356**:115–124.
11 Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, *et al.* Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010; **28**:1061–1068.

12 Rini BI, Wilding G, Hudes G, Stadler WM, Kim S, Tarazi J, *et al.* Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. *J Clin Oncol* 2009; **27**:4462–4468.
13 Escudier B, Bellmunt J, Négrier S, Bajetta E, Melichar B, Bracarda S, *et al.* Phase III trial of bevacizumab plus interferon alpha-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J Clin Oncol* 2010; **28**:2144–2150.
14 Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, *et al.* Phase III trial of bevacizumab plus interferon alpha versus interferon alpha monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J Clin Oncol* 2010; **28**:2137–2143.
15 Atkins MB, Hidalgo M, Stadler WM, Logan TF, Dutcher JP, Hudes GR, *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.
16 Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, *et al.* Temsirolimus, interferon alpha, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007; **356**:2271–2281.
17 Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, *et al.* Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008; **372**:449–456.
18 Homicsko K, Berthold DR. Neoadjuvant and adjuvant strategies in renal cell carcinoma: more questions than answers. *Anti-Cancer Drugs* 2011; **22** (**suppl 1**):S4–S8.
19 Arsanious A, Bjarnason GA, Yousef GM. From bench to bedside: current and future applications of molecular profiling in renal cell carcinoma. *Mol Cancer* 2009; **8**:20.
20 Gossage L, Eisen T. Alterations in VHL as potential biomarkers in renal-cell carcinoma. *Nat Rev Clin Oncol* 2010; **7**:277–288.
21 García-Donas J, Hernando S, Romero N, Jara C. Knowledge of hereditary renal cancer syndromes: a pending issue for oncologists. *Anti-Cancer Drugs* 2011; **22** (**suppl 1**):S15–S20.
22 Sánchez P, Calvo E, Durán I. Non-clear cell advanced kidney cancer: is there a gold standard? *Anti-Cancer Drugs* 2011; **22** (**suppl 1**):S9–S14.
23 Motzer RJ, Russo P, Nanus DM, Berg WJ. Renal cell carcinoma. *Curr Probl Cancer* 1997; **21**:185–232.