An update on the systemic treatment of renal cell cancer

V. Kruse, N. Lumen, F. D'Hondt, S. Rottey

Renal cell carcinoma is a common malignancy affecting men and women sporadically or as part of an inherited syndrome. Upregulation of VEGF and other growth factors due to accumulation of HIF in combination with an activation of the mTOR pathway are known to be important parts of the pathogenesis. These signaling pathways are therapeutic targets of monoclonal antibodies, small-molecules kinase inhibitors (TKI's) and mTOR-pathway inhibitors and currently constitute the mainstay of metastatic RCC treatment. During the last decade, treatment options for patients with advanced renal cell carcinoma, a disease resistant to cytotoxic chemotherapy, have improved significantly with increasing survival rates. Several clinical trials are ongoing and new results are expected in the coming years. In Belgium, three TKI's, two mTOR-inhibitors and one anti-VEGF monoclonal antibody in combination with IFN-α are reimbursed for the treatment of advanced renal cell carcinoma. Sunitinib can be administered in first line and everolimus from second line on to patients with low- or intermediate risk disease. Therapy with bevacizumab/IFN-α is an alternative first line option. Temsirolimus is an option in first line for patients with high risk disease. Sorafenib has shown positive results in patients pretreated with cytokines. Recently, pazopanib has become available as a first line treatment for patients with advanced renal cell carcinoma.
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Introduction

Kidney cancer is among the 10 most frequently occurring cancers in Western societies. About 20-30% of all patients are diagnosed with metastatic disease. In addition, another 20% of patients undergoing nephrectomy will relapse and develop metastatic renal cell cancer (mRCC) during follow-up.[1] The estimated age-standardised kidney cancer incidences per 100,000 Europeans are 15.8 for males and 7.1 for females.[2]

The causes of renal cell cancer (RCC) are poorly understood, but specific life style factors such as cigarette smoking, obesity and hypertension are important etiological factors. Recent cohort studies show that moderate alcohol consumption reduces the risk of developing RCC. RCC is not a typical occupational disease, but some exposures, such as to lead, glass fibers and brick dust, are significantly associated with increased RCC risk. On the other hand, asbestosis does not seem to be a risk factor.[3] Overall, 2-3 % of RCCs are familial. The risk of RCC for a first-degree relative of a patient with RCC is

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about two-fold increased, suggesting a hereditary component. The best-known family syndrome for clear cell RCC is the von Hippel Lindau (VHL) syndrome, in which patients can also develop haemangioblastomas of the central nervous system, retinal angiomas and pheochromocytomas. The VHL gene is mutated or silenced in up to 75% of sporadic clear cell RCC, suggesting that genetic abnormalities involved in inherited RCC syndromes may also play a central role in sporadic RCC. Loss of function of the VHL gene leads to accumulation of hypoxia inducible factors (HIFs) and subsequent upregulation of vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), c-Met and other factors that promote angiogenesis and tumour growth. Signaling pathways initiated by these effecters, VEGF and PDGF in particular, are therapeutic targets of monoclonal antibodies and small-molecules kinase inhibitors (TKI's) that currently constitute the mainstay of metastatic RCC treatment.[4,5] Genetic abnormalities leading to activation of the mTOR pathway will, among other effects, cause increased synthesis and accumulation of HIF. A direct link between HIF/angiogenesis and the mTOR pathway to renal carcinogenesis is thus created. Because unregulated angiogenesis is a prominent feature of RCC, the inhibitions of mTOR are clinically relevant and may inhibit angiogenesis through a mechanistic approach that differs from that of VEGF receptor-targeted agents (*Figure 1*).[6]

Prognostic factors of Renal Cell Carcinoma

According to the World Health Organization (WHO) there are at least three major histological subtypes of RCC: clear cell (cRCC, 80-90%), papillary (pRCC, 10-15%) and chromophobe (chRCC, 4-5%).[7] Cancer-specific survival rates at 5 years for patients with clear cell, papillary, and chromophobe RCC are 68.9%, 87.4%, and 86.7% respectively. Patients with clear cell RCC generally have a poorer prognosis compared to patients with papillary and chromophobe RCC ($p < 0.001$).[8] Prognostic factors can be classified into: anatomical, histological, clinical and molecular. The anatomical factors are gathered in the TNM classification which is clinically and scientifically recommended to use. The histological factors include, among others, the Fuhrman nuclear grade and the RCC subtype. Clinical factors include patients performance status, localised symptoms, cachexia, anaemia end platelet counts. To date, several molecular markers have been investigated, including VEGF, HIF, Ki67 proliferation index, p53 and PTEN, but none of them has been shown to improve the predictive accuracy of current prognostic systems and their use is not recommended in routine practise.[9] A prognostic scoring system, combining different independent prognostic factors, has been proposed by the Memorial Sloan Kettering Cancer Centre, also called the MSKCC risk score or the Motzer Criteria. The MSKCC risk score assigns patients to favourable, intermediate and poor risk categories, based on performance status, time from diagnosis to treatment, serum haemoglobin levels, calcium levels and serum LDH. This score can help to guide the systemic treatment although the score dates from and was validated in the era of immunotherapy.[10]

Treatment of Renal Cell Carcinoma

Localised disease

Surgery

Surgical therapy is the only curative therapeutic approach for the treatment of local RCC. According to the guidelines from the European Association of Urology T1 tumours (tumours ≤7 cm in greatest dimension, limited to the kidney) nephron-sparing surgery should be performed whenever possible. Extended lymphadenectomy does not improve survival and can be restricted to staging purposes. Laparoscopic, whenever possible, or open radical nephrectomy is recommended from T2 renal cell cancer on (>7 cm in greatest dimension, limited to the kidney). Tumour nephrectomy is curative only if surgery can excise all tumour deposits. For patients with metastatic disease, tumour nephrectomy is palliative but can control disease.[9]

In patients with locally advanced renal cell carcinoma (venous tumour thrombi, extracapsular extension, adjacent organ involvement, nodal disease) currently the only curative treatment is aggressive surgical resection.[11]

Metastatic Disease

Surgery

Primary tumour removal is currently part of the

standard of care in mRCC, although recent studies suggest a limited role in poor-risk patients. For most patients with metastatic disease, tumour nephrectomy is palliative, and complementary systemic treatments are necessary.

Complete removal of metastatic laesions contributes to improvement of clinical prognosis. Therefore, surgical resection of metastases should be considered as a valuable therapeutic option, particularly in cases of delay between RCC diagnosis and occurrence of metastasis >1 year, young age, or favourable prognostic features, and when a complete resection is expected.[12]

Immunotherapy

For many years, the mainstay of treatment of metastatic renal cell cancer was immunotherapy with either IFN-α or interleukin-2. These treatments had modest overall response rates (ORRs) from 10%-20% with durable complete responses in only 6% of patients and a high incidence of toxic effects.[10] Side-effects of cytokine therapy included fatigue, peripheral neuropathy, mood disruption and endocrine dysfunction. The health-related quality of life was significantly lower in immunotherapy-treated mRCC.[13] Given the serious side-effects in combination with a small, but realistic chance of a long lasting complete response (CR), only selected patients (low risk disease, only lung metastases) should be considered for immunotherapy.

Bevacizumab and INF-α

Bevacizumab is an intravenous (IV) administered anti-VEGF monoclonal antibody given in combination with SQ injected IFN-α as first line therapy. Two clinical trials; AVOREN, comparing bevacizumab plus IFN-α to placebo plus IFN-α, and CALBG 90206, comparing bevacizumab plus IFN-α to IFN-α, showed that median progression-free survival (PFS) was significantly longer with bevacizumab plus IFN-α (AVOREN: 10.2 months versus 5.4 months respectively; p =0,0001; CALBG 90206: 8.5 months versus 5.2 months respectively p <0,0001). In the AVOREN trial, the ORRs were 31% with bevacizumab plus IFN-α and 13% with placebo plus IFN-α (p =0.0001); in the CALBG 90206 trials, the ORRs were 25.5% with bevacizumab plus IFN-α and 13.1% with IFN-α (p <0,0001). In both trials, bevacizumab showed

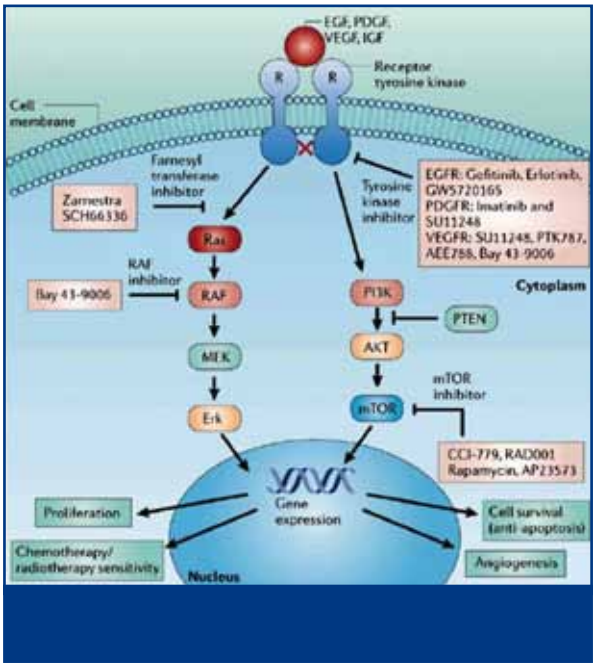

Figure 1. Current development of mTOR inhibitors as anticancer agents.[41]

a tendency towards a longer overall survival (OS) time, but the differences were not statistically significant. However, in both phase III studies, the overall toxicity was greater in patients receiving combination therapy. Toxicities included grade 3 hypertension, anorexia, fatigue and proteinuria.[14-17] Toxicities were significantly greater with bevacizumab plus interferon than with interferon alone. The overall incidence of grade 3 or 4 cardiac ischaemia/infarction, left ventricular dysfunction and gastrointestinal perforation were less than 1%. Due to the risk of hypertension (11% in the bevacizumab/IFN group versus 0% in the IFN group) and proteinuria (15% in the bevacizumab/IFN group versus 0% in the IFN group) routine blood pressure monitoring every 2-3 weeks and urine analysis to quantify urine protein are recommended.[18]

TKI's

Sunitinib has emerged as the current standard of care for first or second line therapy for patients with good or intermediate risk RCC. Sunitinib is an oral inhibitor of receptor tyrosine kinases (TKI), c-kit and Flt-3. The full approval of sunitinib was based on a phase III study that compared single agent sunitinib to IFN-α in 750 previously untreated patients with mRCC. Patients received oral sunitinib,

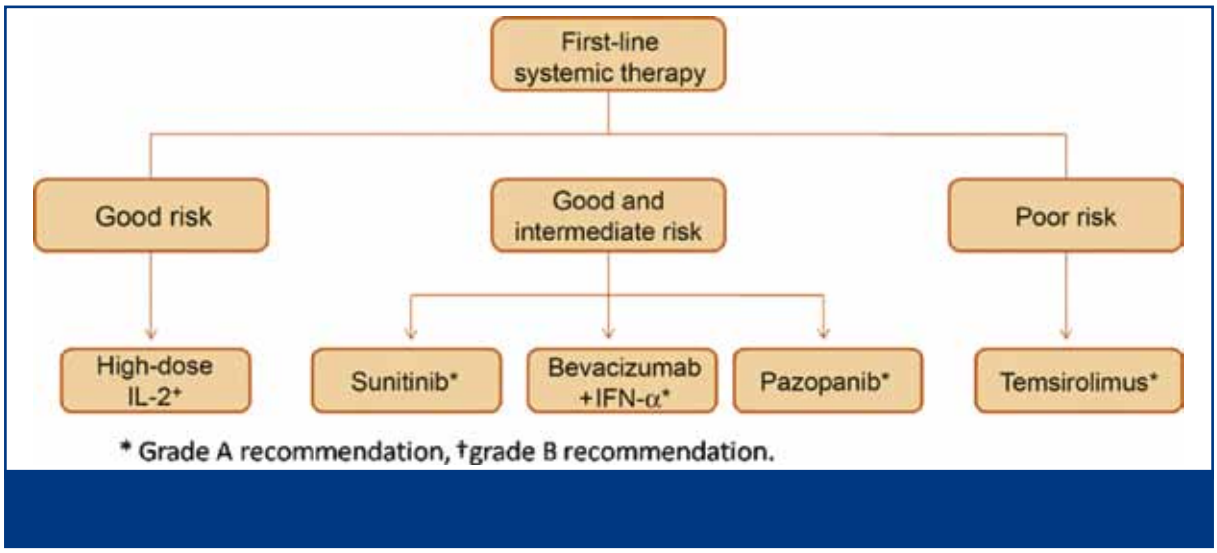

Figure 2a. Treatment regimens in first and second line.[12]

50 mg, once daily in 6-weeks cycles (4 weeks of treatment and 2 weeks of no treatment; n =350) or SQ IFN-α three times a week (dose escalating from 3-6 MU per dose; n =350). The median PFS interval was significantly longer with sunitinib than with IFN-α (11 months versus 5 months, p <0,001) and this result was unaffected by patients' age, sex or MSKCC risk score. In the final analysis ORRs were 47% and 12% respectively (p <0.001). Results of the final analysis showed a marginally greater median OS time with sunitinib than with IFN-α (26.4 months versus 21.8 months, respectively, p =0.051). An exploratory analysis, accounting for confounding effects and cross-over, showed that OS time was significantly longer with sunitinib than with IFN-α (26.4 months versus 20 months respectively; p =0.036). In addition, quality of life (QOL) with sunitinib was superior to that with IFN-α; scores indicated clinically meaningful differences in kidney cancer-related symptoms and overall QOL (p <0,001). The most frequent adverse events included hypertension (12%), fatigue (11%), diarrhoea (9%) and hand-foot skin reaction (9%).[19,20] Recent data have shown that cardiotoxicity is a greater problem associated with sunitinib than was first expected. Left ventricular dysfunction is the main cardiac side effect of sunitinib and might be a result of cardiomyocyte toxicity exacerbated by hypertension.[21] Therefore, blood pressure and cardiac function have to be closely monitored during treatment with sunitinib for patients with a history of cardiac disease. For patients without risk factors, a baseline evaluation of the ejection fraction should be considered.

Sorafenib is an oral multikinase inhibitor that inhibits signalling by Raf serine/threonine kinase, VEGF receptors (VEGFRs) and platelet-derived growth factor receptors (PDGFRs). Nine hundred and three patients who failed one prior systemic therapy, with favourable or intermediate risk factors were randomised to receive oral sorafenib (400mg twice daily; n =451) or placebo (n =453). The PFS time was significantly longer with sorafenib than with placebo (5.5 months versus 2.8 months respectively, p>0,0001), regardless of age, MSKCC risk score, prior cytokine therapy, the presence of metastases at baseline, and time since diagnosis. Based on these results, patients assigned to receive placebo were allowed to cross-over to the other study arm to receive sorafenib in May 2005. The final analysis of OS did not reach statistical significance, with a median OS time of 17.8 months with sorafenib and 15.2 months with placebo. A preplanned secondary analysis, accounting for confounding effects of cross-over, showed that OS time was significantly longer with sorafenib than with placebo (17.8 months versus 14.3 months, p =0.0287). The most common adverse events during treatment with sorafenib were fatigue, diarrhoea, anorexia, nausea, mucositis and palmoplantar erytrhodysethesia (PPE).[22,23]

Pazopanib is an oral multikinase angiogenesis inhib-

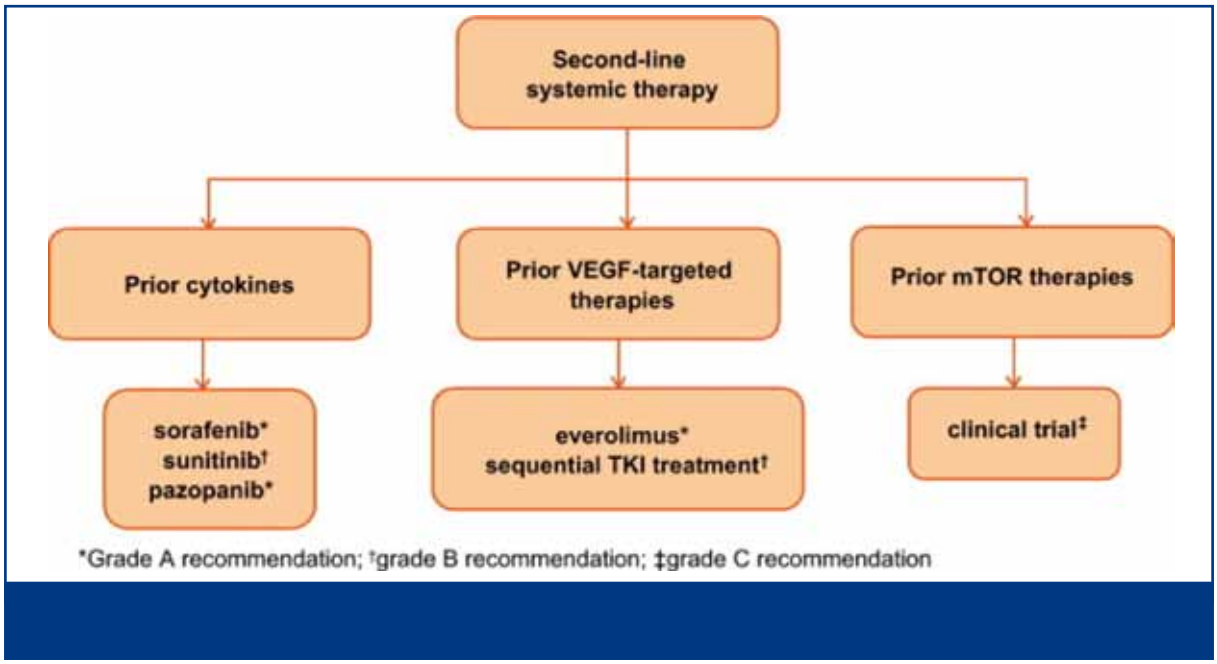

Figure 2b. Treatment regimens in first and second line.[12]

itor that inhibits signalling by VEGFRs, PDGFRs and c-Kit. It was approved by the Food and Drug Administration (FDA) in 2009 for the first line treatment of patients with advanced/metastatic RCC. In a randomised, double-blind, placebo-controlled phase III trial, 453 patients were enrolled; 233 were treatment naïve (54%) and 202 were cytokine pre-treated (46%). PFS was significantly longer with pazopanib compared to placebo in the overall study population (PFS 9.2 months versus 4.2 months respectively, p <0,0001), in the cytokine pre-treated (7.4 months versus 4.2 months respectively; p <0,0001) and in the treatment-naïve (11.1 months versus 2.8 months respectively; p <0,0001). The objective response rate was 30% with pazopanib compared to 3% with placebo (p <0.0001). The median duration of response was longer than a year. The most common adverse events were diarrhoea, hypertension, hair colour changes, nausea, anorexia and vomiting. There was no evidence of clinically important differences in quality of life for pazopanib versus placebo.[24]

mTOR pathway inhibition

Temsirolimus, an inhibitor of mammalian target of rapamycin (mTOR) has demonstrated prolonged survival and PFS compared to IFN-α in patients with advanced RCC and poor prognostic features. Patients with advanced disease, no prior systemic therapy, and three or more of six poor-risk factors according to the modified Motzer criteria, referring to the classical five Motzer Criteria (performance status, time from diagnosis to treatment, serum haemoglobin levels, calcium levels and serum LDH) and the criterion more than one metastatic site, were randomly assigned to receive IFN up to 18 MU thrice weekly, temsirolimus 25 mg weekly IV or temsirolimus 15 mg weekly plus interferon SC 6 MU thrice weekly. The median PFS intervals were 3.8 months with temsirolimus alone, 1.9 months with IFN-α alone and 3.7 months with the combination. The ORRs were 8.6% with temsirolimus alone, 4.8% with IFN- α alone and 8.1% with the combination. The median OS time was significantly longer with temsirolimus alone than with IFN-α alone (10.9 months versus 7.3 months respectively; p =0,008). Combination therapy with temsirolimus and IFN-α did not lead to significantly longer median OS. The most common temsirolimus-related grade 3-4 adverse events are anaemia (13%), hyperglycaemia (9%) and asthaenia (8%). Grade 3-4 hypercholesterolaemia (1%), hypertriglyceridaemia (3%) and hypophosphataemia (4%) were also observed.[25,26] A few lethal cases of pneumonitis/interstitial lung disease have been reported in phase I and II trials. Therefore, patients developing respira-

tory symptoms during a treatment course with temsirolimus have to be monitored with chest X-ray, CT scan and lung function, and the treatment has to be stopped immediately when deterioration of the clinical symptoms occurs.[27]

The RECORD-1 trial investigated the use of the single agent everolimus versus placebo among patients with advanced RCC progressing after treatment failure with sunitinib and/or sorafenib. Next to this major inclusion criterion, prior treatment with other anti-cancer agents (e.g. chemotherapy, immunotherapy, bevacizumab) was allowed. Everolimus treatment resulted in a significantly longer median PFS interval (4.9 months versus 1.9 months, p <0.0001). There was no difference based on prior therapy or MSKCC risk score, and clinical benefit maintained across all subgroups. Everolimus had a positive effect on patient survival despite cross-over design. When cross-over patients were censored from the analysis, the estimated median survival time of the everolimus-treated patients was 14.8 months compared to 10.0 months for the patients treated with placebo. The safety profile of everolimus was good. The most common adverse events of any grade included stomatitis (40%), rash (25%) and fatigue (20%). A few cases of grade 3 severity pneumonitis have also been described in the literature.[27] Given the risk of hyperglycaemia, hyperlipidaemia and a raise in serum creatinine, blood results have to be followed during a treatment course.

Sequencing and combination regimens

Two different concepts of combination targeted therapy for RCC have been presented. *Horizontal blockade* is where numerous target molecules downstream from HIF-α are individually or jointly inhibited. In *Vertical blockade* the same pathway is targeted at two or more different levels by two or more different agents. By combining different treatments, resistance would be reduced. Several phase I/II trials have investigated combination therapy with TKI's and other targeted agents. The combination of sunitinib with bevacizumab was poorly tolerated in full doses and this combination is not recommended for use in clinical practice.[28] Also, the combination of temsirolimus with sunitinib, investigated in a phase I trial, was terminated because of dose-limiting toxicity observed at low starting doses of both agents.[29] The combination of sorafenib and bevacizumab also resulted in an unexpected level of toxicity at lower doses.[30] Interestingly, the combination therapy with full doses of IV temsirolimus and bevacizumab was active and well-tolerated, and further trials are ongoing, investigating the comparison of this regimen to bevacizumab plus IFN. Combination therapy with everolimus and the VEGFR TKI's showed promising results in initial studies. The combination of sorafenib plus everolimus was safe and feasible in a phase I trial of patients with advanced RCC. Also, the combination of everolimus with bevacizumab was well-tolerated.[31] Several trials investigating the different regimens are ongoing and currently recruiting new patients.[32] Sequential therapy can be beneficial, ensuring that optimal drug levels are achieved without the additional toxicity that often occurs with combination approaches. Sunitinib and sorafenib have shown activity among patients refractory to bevacizumab.[33,34] Recently, pazopanib has also demonstrated a significant improvement in PFS and tumour response compared to placebo in cytokine-pretreated patients.[23] The sequential use of two TKI's has been investigated as well. Some preliminary trials suggest that OS may be longer in patients treated with sorafenib followed by sunitinib, rather than the reverse sequence. These studies suggest that sequential TKI therapy improves response without cross resistance.[35] Numerous ongoing trials address these topics (*Figure 2a and 2b*).

Neoadjuvant and adjuvant therapy

Neoadjuvant Treatment

Several studies have been performed to evaluate the neo-adjuvant treatment approach to patients with renal cell tumours. Small prospective trials and retrospective studies of different VEGF pathway targeted agents with widely varied durations of therapy prior to surgery demonstrated that the neoadjuvant approach was feasible.[36,37] Further investigation is necessary to determine the patient groups most likely to benefit from neoadjuvant treatment, and whether risk for disease recurrence can be reduced by adding neoadjuvant systemic treatment. In addition, the optimal duration of treatment prior to

Key messages for clinical practice

1. About 20-30 % of all patients with kidney cancer are diagnosed with metastatic disease.
2. Surgery is the only curative therapeutic approach for treatment of localised RCC.
3. No clear benefit of neoadjuvant or adjuvant treatment has been identified to date. Several trials are ongoing.
4. In Belgium, three TKI's, two mTOR-inhibitors and one anti-VEGF monoclonal antibody are reimbursed for the treatment of advanced renal cell carcinoma:
   - Sunitinib or pazopanib can be administered in first line.
   - Bevacizumab/IFN-α is an alternative first line option.
   - Temsirolimus can be used in first line for patients with high risk disease.
   - Sorafenib has shown positive results in patients pre-treated with cytokines.
   - Everolimus is reimbursed from second line onwards.
   - Immunotherapy, a treatment with important side-effects, provides a small, but realistic chance of a long-lasting complete response.

surgery has to be defined. Several trials are addressing this topic.

Adjuvant Treatment

Many adjuvant trials have been performed to establish a reduction in risk of recurrence among patients undergoing surgical resection for locally advanced renal cancer. However, no clear benefit has been identified to date. Several trials with vaccine therapy, immunotherapy, cytotoxic chemotherapy and hormone therapy failed to show an overall survival benefit.[38] Given the positive results of using targeted agents in the metastatic setting, trials have been designed to test these agents in the adjuvant setting. The S-TRAC study evaluates sunitinib compared to placebo as adjuvant therapy following nephrectomy in high risk patients. The ASSURE trial investigates sorafenib, sunitinib and placebo as adjuvant therapy in patients with intermediate or very high risk disease after radical or partial nephrectomy. The SORCE trial investigates high or intermediate risk patients with completely resected clear cell RCC, randomised to receive one or three years of sorafenib at standard dose or placebo. The PROTECT study compares pazopanib to placebo in the adjuvant setting. The SURTIME trial investigates the optimal timing of nephrectomy (sunitinib prior to nephrectomy followed by re-administration of sunitinib versus nephrectomy followed by sunitinib).[39]

New Drugs

Axitinib, a small molecule indazole derivative, is an oral, potent multitargeted tyrosine kinase receptor inhibitor, which selectively inhibits vascular endothelial growth factor receptors (VEGFR)-1, -2, and -3 at subnanomolar concentrations, in vitro. The Phase III AXIS 103 study showed that Axitinib significantly extended PFS in patients with previously treated advanced RCC in comparison to sorafenib (Nexavar®). Axitinib demonstrated a generally manageable safety profile. Common adverse events with axitinib versus sorafenib were hypertension (40% versus 29%, all grades), fatigue (39% versus 32%), dysphonia (31% versus 14%), and hypothyroidism (19% versus 8%). More frequent adverse events with sorafenib were hand-foot syndrome (27% versus 51%), rash (13% versus 32%), alopecia (4% versus 32%), and anaemia (4% versus 12%). A randomised phase III clinical trial is ongoing to determine the efficacy of axitinib in patients with mRCC in the first line setting. These results will help to deter-

mine the place of axitinib in the mRCC treatment algorithm.[40]

In addition, regorafenib and tivozanib (amongst others) are investigated in RCC.

The Belgian Situation

Based on the clinical trials mentioned above, there is evidence that the targeted agents are well tolerated and that the treatment can be started at diagnosis of metastatic disease in order to achieve the expected survival benefit for patients with an advanced RCC. However, the best moment to start systemic therapy has to be decided individually, depending on disease burden, localisation of metastases, age of the patient, co-morbidity, personal expectations etcetera. In Belgium sunitinib, pazopanib, the combination bevacizumab with IFN-α and temsirolimus can be used as first line treatment for patients with advanced RCC. More specifically, temsirolimus is a possible first line treatment for patients with high risk disease according to the modified Motzer criteria explained above.

The combination bevacizumab with IFN-α is limited in Belgium to patients presented with at least one adverse event grade III or IV during the first 4 weeks of sunitinib administration. Sunitinib, pazopanib and sorafenib remain a useful option for patients pre-treated with interleukins. Everolimus can be prescribed from second line onwards for patients with an advanced cRCC pre-treated with VEGF-targeted therapy. After the use of an mTOR-inhibitor (e.g. temsirolimus in first line) there is no standard treatment and patients should be referred to clinical trials whenever possible.

References

1. Gupta K, Miller JD, Li JZ, et al. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008;34:193–205.

2. Levi F, Ferlay J, Galeone C, et al. The changing pattern of kidney cancer incidence and mortality in Europe. BJU Int 2008;101:945-58.

3. Ljungberg B, Campbell S, Cho HY, et al. The Epidemiology of Renal Cell Carcinoma. European Urology 2011;60:615-21.

4. Nathanson KL, Stephenson AJ. Diagnosis and management of inherited renal cancer. In: Rini BI, Campbell SC, eds. Renal cell cancer. Shelton, CT: Peoples Medical Publishing House; pp. 25-40.

5. Kaelin WG Jr. The von Hippel-Lindau tumor suppressor protein and clear cell renal carcinoma. Clin Cancer Res 2007;13:680s-4s.

6. Milella M and Felici A. Biology of Metastatic Renal Cell Carcinoma. J Cancer 2011;2:369-73.

7. Eble JN, Sauter G, Epstein JI, Seesterheen I1 (eds). In: Pathology and genetics of tumours of the urinary system and male genital organs. World Health Organisation Classification of Tumours. Lyons: IARC Press, 2004: p7.

8. Cheville JC, Lohse CM, Zincke H, et al. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Update 2010. Am J Surg Pathol 2003;27(5):612-24.

9. Ljungberg B, Cowan N, Hanbury DC et al. EAU Guidelines on Renal Cell Carcinoma. Update 2010. European Association of Urology 2010;3:398-406.

10. Lombardi G, Zustovich F, Donach M et al. An update on targeted therapy in metastatic renal cell carcinoma. J Urol Oncl 2010. (Epub ahead of print).

11. Margulis V, Master VA, Cost NG, et al. International consultation on urologic diseases and the European association of urology international consultation on locally advanced renal cell carcinoma. European Urology 2011;60(4):673-83.

12. Patard JJ, Pignot G, Escudier B, et al. ICUD-EAU International Consultation on Kidney Cancer 2010: treatment of metastatic disease. Eur Urol. 2011;60(4):684-90.

13. Cella D. Beyond Traditional Outcomes: Improving Quality if Life in Patients with Renal Cell Carcinoma. The Oncologist 2011; 16 (suppl 2): 23-31.

14. Escudier B, Pluzanska A, Koralewski P et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: A randomised double-blined ohase III trial. Lancet 2007; 370: 2103-2111.

15. Escudier B, Bellmunt J, Négrier S et al. Bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): Final analysis of overall survival. J Clin Oncol 2010; 28: 2137-2143.

16. Rini BI, Halabi S, Rosenberg JE et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: Final results CALBG 90206. J Clin Oncol 2008; 26: 5422-5428.

17. Rini BI, Halabi S, Rosenberg JE et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALBG 90206. J Clin Oncol 2008; 26: 5422-5428.

18. Ravaud A. Treatment-Associated Adverse Event Management in the Advanced Renal Cell Carcinoma Patient Treated with Targeted Therapies. The Oncologist 2011; 16 (suppl 2): 32-44.

19. Motzer RJ, Hutson TE, Tomczak P et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 3584 – 3590.

20. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal cell carcinoma. N Engl J Med 2007; 356: 115-124.

21. Clu TF, Rupnick MA, Kerkela R et al. Cardiotoxicity associated with the tyrosine kinase inhibitor sunitinib. Lancet 2007; 370, 2011-2019.

22. Escudier B, Eisen T, Stadler WM et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007; 356: 125-134.

23. Escudier B, Eisen T, Stadler WM et al. Sorafenib in treatment of renal

cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cell cancer global evaluation trial. J Clin Oncol 2009; 27: 3312-3318.

24. Sternberg CN, Davis ID, Mardiak J et al. Pazopanib in Locally Advanced or Metastatic Renal Cell Carcinoma: Results of a Randomised Phase III Trial. J Clin Oncol 2011; 28 (6), 1061-1068.

25. Hudes G, Garducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal cell carcinoma. N Engl J Led 2007; 356: 2271-2281.

26. Bellmunt J, Szczylik C, Feingold J et al. Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. Ann Oncol 2008;19:1387 - 92.

27. Motzer RJ, Escudier B, Oudard S et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. Cancer 2010;116(18):4256-65.

28. Feldman DR, Ginsberg MS, Baum M et al. Phase I trial of bevacizumab plus sunitinib in patients with metastatic renal cell carcinoma. In: Poster presented at the 44th annual meeting of the American society of clinical oncology, Chicago, Illinois, 2008.

29. Patel PH, Senico PL, Curiel RE, Motzer RJ. Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma. Clin Genitourin Cancer 2009;7:24-7.

30. Azad NS, Posadas EM, Kwitkowski VE et al. Combination targeted therapy with sorafenib and bevacizulmab results in enhanced toxicity and antitumor activity. J Clin Oncol 2008; 26: 3709-14.

31. Sammons B. Targeted Therapies for the Treatment of Metastatic Renal Cell Carcinoma: Clinical Evidence. The Oncologist 2011; 16 (suppl 2): 14-22.

32. www.clinicaltrials.gov.

33. Rini Bin 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;26:3743-8.

34. Tamaskar I, Garcia JA, Elson P et al. Antitumor activity and biomarker analysis of sunitinib in patients with metastatic renal cell carcinoma who received prior antiangiogenetic therapy. J Urol 2008;179: 81-6.Discussion 6.

35. Oudard S, Beuselinck B, Decoene J, Albers P. Sunitinib for the treatment of metastatic renal cell carcinoma. Cancer Treatment Reviews 2010. In progress.

36. Thomas AA, Rini BI, Stephenson AJ, Garcia JA et al. Surgical resection of renal cell carcinoma after targeted therapy. J Urol 2009;182:881-6.

37. Amin C, Wallen E, Pruthi RS, et al. Preoperative tyrosine kinase inhibition as an adjunct to debulking nephrectomy. Urology 2008;72:864-8.

38. Scherr A, Lima JP, Sasse EC et al. Adjuvant therapy for locally advanced renal cell cancer: A systematic review with meta-analysis. BMC Cancer;11:115.

39. http://www.clinicaltrials.gov.

40. Rini B.I, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC): Results of phase III AXIS trial. J Clin Oncol 29: 2011 (suppl; abstr 4503)

41. Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. Nat Rev Drug Discov 2006;5(8):571-88.