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Review

Will the dark sky over advanced renal cell carcinoma soon become brighter?

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Abstract

Until recently, immunotherapy has been the most efficient treatment for advanced renal cell carcinoma, but clinical results are largely unsatisfactory. More promising agents are being developed as a result of an improved understanding of the biology of the disease. Several agents that target known biological abnormalities of the disease are now being tested in the clinic. This review describes the encouraging clinical results obtained to date with these new drugs or combinations of drugs.

Keywords: Renal cell carcinoma; Molecular-targeted therapy; Anti-angiogenesis agents; Review; New drugs

1. Introduction

Kidney tumours account for about 3% of adult malignancies and about 80% of those consist of renal cell carcinoma (RCC) originating from the proximal tubule cells. Most cases occur in patients aged 60 years or more, but the disease has been observed in children as young as 6 months, with a male to female ratio of 6:1 [1]. Kidney cancer is mostly sporadic, but it can be hereditary. Until the early 1990s, its incidence had been increasing throughout Europe and the United States of America (USA) for about 60 years. In the European Union (EU), mortality from kidney cancer has declined recently, with a 10% decrease for both sexes. The reasons for these changes are unclear [2].

According to the data from the Surveillance, Epidemiology and End Results Registry (http://www.seer.cancer.gov), RCC is localised in 54% of patients, regionally advanced in 21% and distant in 25%, with corresponding 5-year survival rates of 89%, 61% and 9%, respectively. Despite the important stage-related risk of tumour recurrence, until now no effective adjuvant treatment after surgery has been established. Various adjuvant protocols (radiotherapy, interferon-α (IFN-α) and interleukin 2 (IL-2)) have failed to improve progression-free survival (PFS) and/or overall survival (OS) after nephrectomy. Recently, a trial including 558 patients with RCC, of whom only 379 were assessable, showed a reduction of the risk of tumour progression after nephrectomy using an adjuvant, individually prepared, autologous renal tumour cell vaccine [3]. Five-year PFS was statistically longer in the subgroup of patients with T3 tumours treated with the vaccine compared with the control group. OS was not assessed. Until now, however, the standard management for localised tumours after nephrectomy remains surveillance.

Twenty to 50% of patients will eventually develop metastatic disease after nephrectomy. A shorter interval between nephrectomy and the development of metastases is associated with a poorer prognosis. The median survival time of patients with metastatic RCC is only 6–12 months, and the 2-year survival rate 10–20%. The clinical management of patients with metastatic RCC is complicated by the low efficacy of available

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therapies. Neither single chemotherapeutic agents nor combinations of agents produce a significant clinical response.

Immune therapy with IL-2 or IFN-α achieves responses in 10–20% of patients, with durable responses occurring in a subset of patients [4]. IL-2 alone remains the only approved agent for the treatment of advanced kidney cancer in the USA, while in Europe IFN-α also is approved as a standard treatment, alone or in combination, on the basis of two randomised trials showing a survival benefit [5,6]. Both treatments are highly toxic, and the benefit of treatment must be weighed against the drugs' toxic effects. Another immunotherapeutic approach, allogeneic stem cell transplantation after non-myeloablative chemotherapy, has been reported to achieve complete and partial responses in metastatic RCC as a graft *versus* tumour effect [7,8]. This treatment is feasible, but responses are obtained at the cost of considerable toxicity. Moreover, the need for a compatible donor, and treatment-related morbidity and mortality are limitations of this approach.

The antigens eliciting an immune response are unknown. Immunological abnormalities are frequently detected in patients with kidney cancer. Reliable predictive markers of a patient's probability to respond to immune therapy are currently unavailable. New therapeutic approaches other than immunotherapy and chemotherapy are therefore urgently needed. Progress in the treatment of kidney cancer will come from new strategies developed to target cell growth, proliferation and angiogenesis pathways. Even though progress has recently been made in understanding and modifying biological pathways involved in neoplastic development, much remains to be done.

There is no stepwise progression model of kidney cancer as there is for colon cancer, for example. This may be due in part to the inaccessibility of the kidney to screening and, consequently, to late stage tumour detection. Major advances in our understanding of the biology of RCC during the past decade were made possible primarily by the identification and cloning of tumour suppressor genes and oncogenes responsible for hereditary renal carcinoma syndromes. Six clinically distinct types of inherited kidney cancer have been identified: von Hippel–Lindau disease, hereditary papillary renal carcinoma, familial renal oncocytoma/Birt–Hogg–Dube syndrome, hereditary leiomyomatosis RCC, familial renal carcinoma, and renal carcinoma associated with a constitutional chromosome 3 translocation [9].

Von Hippel–Lindau (VHL) disease, an autosomal dominant syndrome in which kidney cancer arises from multiple benign renal cysts, is the best characterised entity. It occurs in 1 of every 36,000 live births, and kidney cancer occurs in 28–45% of VHL-affected individuals. It is now clear that the VHL gene, which has a key role in regulation of angiogenesis, is inactivated (by mutation or hypermethylation) in 70% of sporadic cases of kidney cancer.

Besides the VHL gene, germ line mutations of the c-met proto-oncogene also are responsible for a genetic predisposition to certain papillary renal tumours. Although some information is known about the c-met signalling pathway, the critical elements leading to tissue-specific tumourigenesis are not known. The role of the tissue microenvironment (extracellular matrix, angiogenic molecules, growth factors and proteases) in tumour development remains under-explored.

This article reviews promising new agents, that are being developed in the clinic, and that are directed at the pathophysiological abnormalities of the disease.

2. Angiogenic and anti-angiogenic factors

2.1. Angiogenic pathways

The high prevalence of the VHL mutation, a key regulator of angiogenesis, and the high vascularity in RCC renders the study of angiogenesis inhibitors particularly relevant. The earliest developed new agents are inhibitors of vascular endothelial growth factor (VEGF) or its receptor. VEGF is a fundamental regulator of normal and abnormal angiogenesis [10–12]. It is a homodimeric glycoprotein that exists in at least 5 isoforms (VEGF A–E). VEGF-A predominates and is more potent than other isoforms as an endothelial growth factor. There are at least three receptors for VEGF, all with tyrosine kinase activity. Vascular endothelial growth factor receptor (VEGFR)-1 (or Flt-1) and VEGFR-2 (or Flk-1/KDR) are the two high affinity receptors. The importance of VEGFR-3 (or Flt-4) is less clear. Receptors for VEGF are expressed almost exclusively on endothelial cells and on some haematopoietic ones [13,14]. VEGF-A and VEGFR-2 are essential to embryonic vasculogenesis, as demonstrated by gene inactivation studies. VEGF knockout mice die in utero from defective vasculogenesis, for example. VEGF is under the control of the hypoxia-inducible factor (HIF), a labile transcription factor. Under hypoxic conditions, HIF activates the transcription of VEGF, platelet-derived growth factor-β (PDGF-β), transforming growth factor-α (TGF-α) and erythropoietin (EPO). The main regulator of HIF is the VHL gene product (pVHL). When oxygen is available, HIF is hydroxylated and pVHL binds to it. Once bound, pVHL attaches a polyubiquitin chain to HIF, which marks HIF for destruction. For these reasons, pVHL-defective tumours overproduce HIF and the product of the genes targeted by HIF. In von Hippel–Lindau disease, an inactivated copy of the pVHL is inherited. Inactivation of the remaining allele provokes the loss of an HIF inhibitor

and is linked to the development of tumours with multiple blood vessels (haemangioblastoma) in the central nervous system and retina and to the development of RCC. In 70% of sporadic RCC, pVHL is deficient and consequently involved in the carcinogenesis.

In pre-clinical models, the neutralisation of VEGF hindered the growth of various tumour cells by inhibiting angiogenesis, which resulted in a decrease in tumour blood flow and microvessel density [15,16].

2.2. Angiogenesis inhibitors (see also Tables 1 and 2)

2.2.1. Bevacizumab

One of the most developed clinical agents against VEGF or its receptor is a monoclonal antibody neutralising VEGF, bevacizumab (Avastin™). In a double-blind phase II trial, 116 patients with metastatic RCC were randomised to placebo ($n = 40$), to 3 mg/kg ($n = 37$) or to 10 mg/kg ($n = 39$) bevacizumab [17]. Time to progression (TTP) was significantly longer in the high-dose antibody group when compared with the placebo group (4.8 *versus* 2.5 months; $P < 0.001$). The difference in TTP in the low-dose antibody group when compared with the placebo was smaller and less significant (3 *versus* 2.5 months; $P = 0.041$). There was no difference in OS between groups, at least in part due to the allowed crossover from placebo to antibody treatment at time of disease progression. The only four partial responses (PR) obtained were observed in the 10 mg/kg bevacizumab group. Two patients who received therapy for the complete duration of the 2-year study responded, but stopped therapy at the end of the study. When they progressed again while off therapy, treatment was resumed with bevacizumab, and both responded a second time. The significant effect on TTP and the low response rate observed suggest mainly a cytostatic effect of the drug. Minimal toxicity was observed, mainly in the form of hypertension and asymptomatic proteinuria. A randomised phase III is now ongoing and it compares IFN-α to the association of IFN-α and bevacizumab (10 mg/kg) as first-line therapy in advanced RCC. The primary endpoint is OS.

Better results have been obtained by combining VEGF and EGFR inhibition. The combination of bevacizumab (10 mg/kg every 2 weeks) and erlotinib (150 mg daily) was evaluated in advanced RCC in a phase II trial [18], the results of which were presented at the 2004 ASCO meeting. Of the 62 patients included in this trial, 57 received at least 8 weeks of treatment and were evaluable for response. Twelve (21%) patients experienced PR and 38 (66%) had stable disease (SD). Among the latter group, 12 showed a minor response. PFS was 67% at 6 months and 50% at 1 year, with an OS of 81% at 1 year. Toxicity was mostly grade I/II, consisting of rash, diarrhoea, nausea and vomiting. Two patients stopped treatment due to toxicity (rash). The activity of combining VEGF and EGFR inhibition appears superior to the activity of either agent used alone. This synergy can be explained by complementary targeting of two different mechanisms involved in cancer growth: tumour cell proliferation and angiogenesis.

2.2.2. SU011248

Another target for anti-angiogenic therapy is the VEGF receptor. SU011248 is an orally available tyrosine kinase inhibitor that is active against receptors for VEGF, PDGF and against KIT and FLT3. SU011248 showed promising anti-tumour activity in several tumour types in phase I studies.

In a phase II trial, 63 patients with immune-pre-treated metastatic RCC received repeated cycles of SU011248 orally at 50 mg/day for 4 weeks followed by a 2-week rest period [19]. Results were reported at the 2004 ASCO meeting. Twenty-one (33%) patients experienced a PR and 23 (37%) had SD. Toxicity consisted mostly of asthenia, nausea, diarrhoea and stomatitis and was usually grade I/II. Thirty percent of patients experienced grade III lymphopaenia. Median duration of therapy was 9 months with a median TTP of 8.3 months. This promising agent is now being tested in a randomised phase III trial comparing SU011248 with IFN-α.

2.2.3. Thalidomide

Thalidomide is a drug with anti-angiogenic properties. Initially developed as a sedative, it produced teratogenic effects in pregnancy, which were attributed to the inhibition of blood vessel growth in the developing foetal limb bud. The exact mechanism by which it inhibits endothelial function is not fully understood although it is known to reduce the expression of angiogenic factors such as VEGF, basic fibroblast growth factor (bFGF), tumour necrosis factor-α (TNFα), and interleukin-6 (IL-6) [20]. In humans, these anti-angiogenic properties may be mediated by a metabolite rather than by thalidomide itself. The drug also modifies cell adhesion molecule expression [21] and promotes T-helper cell response switch from Th1 to Th2 [22]. Several studies have shown anti-tumour activity in myeloma, with a dose-limiting neurological toxicity [23].

Phase II studies of thalidomide as a single agent in patients with metastatic RCC refractory to cytokine therapy have shown limited results with respect to response and stable disease [24–29]. There is no clear dose–response relationship. The limiting toxicities were lethargy, constipation and peripheral neuropathy (the latter being seen only after prolonged therapy) (see Table 1).

Thalidomide has also been studied in combination with IFN-α. In one study of metastatic RCC, thalidomide (from 100–400 mg/d) was combined with high dose IFN-α (9 MIU, 3 times per week). Five of 13 patients

Table 1
Thalidomide phase II studies in advanced RCC

Reference	Thalidomide daily dose (mg)	Number of evaluable patients	PR	SD	Toxicity
Eisen et al. [24]	100	18	3 (17%)	3 (17%)	–
Stebbing et al. [25]	100–600	22	2 (9%)	12 (54%) Of note: 7 for ⩾6 months	Lethargy Constipation Neurotoxicity
Minor et al. [26]	400–1200	24	1 (4%)	3 (12%)	Lethargy Constipation
Escudier et al. [27]	400–1200	40	2 (5%)	9 (22%) for 6 months	Lethargy Constipation Neuropathy (EMG): 70% at 6 months 100% at 1 year Venous thrombo-embolism
Motzer et al. [28]	200–800	25	–	16 (64%) Of note: 3 for >16 months	Neurotoxicity Dyspnoea
Daliani et al. [29]	200–1200	19	2 (10%)	9 (47%)	Constipation Somnolence Fatigue Peripheral neuropathy after prolonged therapy

RCC, renal cell carcinoma; EMG, electromyography; SD, stable disease; PR, partial response.

(39%) experienced serious adverse events. These included 4 severe neurological toxicities, after which the study was stopped [30]. In a study combining lower doses of IFN-α (0.9 MIU 3 times daily initially and 1.2 MIU after 1 month) and thalidomide (from 100–300 mg/d), toxicity was much milder. Among 27 evaluable patients, 6 (22%) PR and 17 (63%) SD for 3 months or longer were observed [31]. An Eastern Cooperative Oncology Group (ECOG) randomised phase III study compared the combination of high-dose thalidomide (dose escalation from 200 to 1000 mg/d) and low-dose IFN-α (1 MIU bid) (I + T) with IFN-α alone (I) in 353 previously untreated patients with advanced RCC. There was no difference in response rates and OS between the groups. PFS was 1 month longer in the I + T arm than in the I arm (3.8 *versus* 2.8 months, $P = 0.04$) [32]. In a phase I/II study, the combination of thalidomide (200–600 mg/d) and IL-2 (7 mIU on days 1–5 for 4 weeks of a 6-week cycle) was tested in 15 patients with advanced RCC. After 12 weeks of therapy, 1 (7%) complete response (CR), 5 (33%) PR and 2 (13%) SD were observed [33]. A phase III trial of IL-2 with or without thalidomide is now being planned.

Other combinations with thalidomide have also been tested. Thalidomide with chemotherapy consisting of gemcitabine and prolonged continuous 5-fluorouracil (5-FU) was shown to be too toxic, with 9 out of 21 patients (43%) experiencing venous thromboembolism [34]. Another study combining thalidomide, IFN-α and capecitabine produced a high rate of hand-foot syndrome and a 15% rate of deep vein thrombosis [35].

All these studies suggest a suboptimal benefit *versus* risk ratio for thalidomide as a single agent in RCC. Efficacy in combination with IFN-α also seems limited. The

Table 2
Clinical results of new drugs in RCC (phase II trials except for thalidomide + IFN-α: phase III trial)

Agent (targets)	RR	PFS (months)
Bevacizumab (VEGF) [17]	10% PR	Median: 4.8 (*versus* 2.5 for placebo)
SU 011248 (VEGFR, PDGFR) [19]	33% PR	Median: 8.3
Thalidomide (several pathways) [35]	7% PR	Median: 4.6
AE-941 240 ml/day (several pathways) [36]	14% PR	NA Median survival: 16.3
Bay 43-9006 (VEGFR, Raf kinase) [43]	35% PR	PFS at 6 months: 50%
CCI-779 (mTOR) [44]	7% CR + PR	Median: 5.8
Bevacizumab (VEGF) + erlotinib (EGFR) [18]	21% PR	PFS at 6 months: 67%
Thalidomide + IFN-α [32]	6.5% CR + PR	Median: 3.8

RCC, renal cell carcinoma; SD, stable disease; CR, complete response; PR, partial response; IFN-α, interferon-α; PFS, progression-free survival; NA, not applicable; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor.

results from other combination phase III trials are being awaited to better define thalidomide's role in RCC. Analogues of thalidomide with a better therapeutic index are currently in development.

2.2.4. AE-941

AE-941 (Neovastat™) was developed based on the observation that shark cartilage may contain biologically active inhibitors of angiogenesis. At the molecular level, AE-941 has various potential mechanisms of action: modulation of matrix proteases; inhibition of VEGF binding to its receptor; induction of endothelial cell apoptosis; and stimulation of angiostatin production. In pre-clinical models, AE-941 has shown antitumour activity.

Clinical data with AE-941 in RCC are as follows: in a phase II trial, 22 patients with refractory RCC received either 60 ml/d ($n = 8$) or 240 ml/d ($n = 14$) of oral AE-941 [36]. Two PR were observed at the 240-ml dose level. Survival was significantly longer in patients treated with 240 ml/d than in those receiving 60 ml/d (16.3 *versus* 7.1 months; $P = 0.01$). The results of a phase III trial conducted in more than 300 patients with metastatic RCC are pending [37].

3. Growth factor receptor inhibitors

Epidermal growth factor (EGF) expression is common in RCC, and the poor prognosis of these patients has prompted the study of a number of strategies to block or downregulate this pathway. These include monoclonal antibodies directed against epidermal growth factor receptor (EGFR) and tyrosine kinase inhibitors (TKI).

Among monoclonal antibodies, C225 (Cetuximab™) showed interesting pre-clinical activity in VHL-positive RCC cell lines [38]. However, no objective response was observed in a phase II study involving 55 patients with metastatic RCC [39].

Low activity has been observed with ABX-EGF, a fully human anti-EGFR monoclonal antibody, in 88 previously treated patients with metastatic RCC [40]. In this study, 4 dose levels (1, 1.5, 2 or 2.5 mg/kg) were tested. Ninety-one percent of the analysed tumours stained positively (2+ or 3+) by immunochemistry for EGFR in at least 10% of the cells. Three (3.4%) objective responses (1 CR and 2 PR) and 2 minor responses were observed, and 44 (50%) patients had stable disease. Patients with non-clear cell histology seemed to have a better overall outcome than those with clear cell histology.

Among TKI, pre-clinical activity was observed in RCC lines and in a xenograft model with ZD1839 (Iressa™), a TKI of the EGFR [41], but neither objective responses nor improvement in TTP were observed in a phase II study that included 18 patients with RCC [42]. Erlotinib (Tarceva™), another TKI of EGFR, has shown a probable synergistic effect in combination with bevacizumab in a phase II trial with a 21% PR rate (see above). These results emphasise the potential of combining inhibitors of various pathways.

4. Signal transduction inhibitors (see also Table 2)

Many transduction inhibitors that downregulate cell growth pathways have been developed in the clinic, and some suggest interesting clinical activity in RCC.

4.1. BAY 43-9006

So far, more than 20 agents that target the RAS/RAF pathway have been tested. One of these is BAY 43-9006, which inhibits the Raf kinase involved in the downstream signalling of the RAS pathway, as well as platelet-derived growth factor receptor (PDGFR)-b, VEGFR-2 and FLT3.

In a phase II study, 203 patients with advanced RCC were included [43]. The study consisted of a 12-week induction phase, during which patients received oral BAY 43-9006 400 mg bid, followed by a randomisation phase. Patients with progressive disease (PD) at re-evaluation (target lesion >25%) were discontinued from the study. Responding patients (target lesion <25%) continued BAY 43-9006 in an open label phase until PD or toxicity. Patients with SD (target lesion within 25% of baseline) were randomised to receive BAY 43-9006 or placebo. At the time of the 2004 ASCO meeting, 106 patients had been assessed at 12-weeks. Thirty-seven (35%) of the patients were responders continuing on open label BAY43-9006 who had a median PFS of 48 weeks; 38 (36%) patients with SD were randomised to BAY 43-9006 or placebo. Half of the BAY 43-9006 randomised patients had rapidly progressing disease. This randomisation design provides a rapid way to screen for disease stabilising activity resulting from the natural evolution of the disease or from the drug. Side-effects were mostly cutaneous, with hand-foot syndrome being the most frequent grade III toxicity, as well as fatigue, anorexia and stomatitis. Only 5% of patients experienced dose reduction due to toxicity. Because of these very good clinical results, a randomised phase III study comparing BAY43-9006 with placebo is ongoing and will evaluate the potential for this drug to improve survival in patients for whom first-line immunotherapy failed.

4.2. CCI-779

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase, a member of the phosphatidylinositol 3-kinase (PI3-K), which plays a pivotal

regulatory role in multiple cellular functions, such as the transduction of proliferative signals by growth factors and the response of cells to nutrients. Rapamycin, an inhibitor of mTOR, has been known for years to have immunosuppressive, antifungal and antiproliferative effects. Among rapamycin-like drugs, CCI-779, an ester of rapamycin, has been selected for clinical development.

In a phase II trial, 111 patients with immunotherapy refractory advanced RCC were randomised to receive 25, 75 or 250 mg CCI-779 weekly [44]. The objective response rate was 7%: one patient at the 250-mg dose level had a CR, 7 patients had PR (2 at the 25-mg, 3 at the 75-mg and 2 at the 250-mg dose level). An additional 29 (26%) patients had minor response (MR). For the total population, 51% had CR, PR, MR or SD for 24 weeks or more. Median TTP was 5.8 months, and median survival was 15 months. The most frequent side-effects were cutaneous rash, mucositis, asthenia and nausea. Neither toxicity nor efficacy was significantly influenced by CCI-779 dose level.

In a phase I dose-escalating study combining weekly CCI-779 with IFN- α given subcutaneously 3 times weekly, 71 patients with RCC were enrolled [45]. The maximum tolerated dose was selected as 15 mg CCI-779 and 6MU IFN-α. Preliminary tumour responses were assessed in 55 patients. Seven (13%) patients presented PR, and 39 (71%) had SD. Based on these encouraging results, a phase III trial comparing the combination of CCI-779 and IFN-α to each agent alone has been initiated.

5. Proteasome inhibitor

The ubiquitin-proteasome pathway is an essential pathway for intracellular protein degradation. Many regulatory proteins undergo ubiquitin-dependent proteolysis. Additionally, the ubiquitin-proteasome pathway plays an important role in tumour growth and metastasis. Proteasome inhibitors trigger apoptosis as a result of effects on several pathways, including cell cycle regulation, p53 and nuclear factor κB.

PS-341, a reversible proteasome inhibitor, has shown promising clinical activity in a variety of tumours and is registered for use in myeloma. It was tested in a phase II trial including 23 patients with metastatic RCC [46]. Among the 21 assessable patients, 1 (5%) experienced a PR and 6 (28%) had SD. Grade III and IV toxicity included mostly haematotoxicity, gastrointestinal toxicity and neurotoxicity. In a preliminary report of another phase II trial including 32 patients with metastatic RCC, 3 patients (9%) presented a PR and median TTP was 1.4 months [47]. This quite modest clinical activity did not encourage further evaluation of PS-341 in this disease.

6. Conclusion

New stars have begun to appear in the dark sky of advanced RCC treatment. Innovative therapies are being developed with biological agents targeting cell growth and proliferation pathways. The most promising drugs include, at present, bevacizumab, SU11248, BAY 43-9006 and CCI-779. Some with low activity as a single agent, such as erlotinib, appear promising in combination. Others are under evaluation.

Accurate understanding of the biological pathways modified by these drugs and of the mechanisms of resistance is needed. Translational research during phase I/II drug development is therefore essential. Simultaneously, the endpoints of trials should be adapted to the new biological drugs that sometimes stabilise tumour growth for a long period of time while producing low rates of objective tumour responses.

The development of synergistic or additive combinations of drugs from various classes, rationally based on mechanisms of action, will eventually allow for further improvement in tumour growth control. Much more remains to be elucidated, however. For instance, the recent evidence that microvascular endothelial cells within B-cell lymphomas express markers of the neoplasm demonstrates that the tumour microenvironment is more complex and unpredictable than initially thought [48].

Further progress in kidney cancer therapy, based on the selection of the right drug at the right time for individual patients, will depend on the availability of predictive factors of response or of resistance to each drug or combination of drugs. High throughput techniques such as microarray gene profiling and proteomics are new powerful tools that may help developing multimarker models for treatment individualisation.

Conflict of interest statement

None declared.

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References

1. Jemal A, Murray T, Samuels A, *et al.* Cancer statistics, 2003. *CA Cancer J Clin* 2003, **53**, 5–26.
2. Levi F, Lucchini F, Negri E, *et al.* Declining mortality from kidney cancer in Europe. *Ann Oncol* 2004, **15**, 1130–1135.
3. Jocham D, Richter A, Hoffman L, *et al.* Adjuvant autologous renal tumour cell vaccine and risk of tumour progression in

patients with renal-cell carcinoma after radical nephrectomy: a phase III, randomized controlled trial. *The Lancet* 2004, **363**, 594–599.
4. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. *J Urol* 2000, **163**, 408–417.
5. Medical Research Council Renal Cancer Collaborators. Interferon-α and survival in metastatic renal carcinoma: early results of a randomized controlled trial. *The Lancet* 1999, **353**, 14–17.
6. Pyrhönen S, Salminen E, Ruutu M, *et al*. Prespective randomized trial of interferon alfa-2a plus vinblastine alone in patients with advanced renal cell cancer. *J Clin Oncol* 1999, **17**, 2859–2867.
7. Childs R, Chernoff A, Contentin N, *et al*. Regression of metastatic renal cell carcinoma after nonmyeloablative allogeneic peripheral blood stem cell transplantation. *N Engl J Med* 2002, **343**, 750–758.
8. Rini B, Zimmerman T, Stadler W, Gajewski TF, Vogelzang NJ. Allogeneic stem cell transplantation of renal cell cancer after non myeloablative chemotherapy: feasibility, engraftment, and clinical results. *J Clin Oncol* 2002, **20**, 2017–2024.
9. Jones P, Vogelzang N. Priorities of the kidney/bladder cancer progress review group. Bethesda, MD, National Cancer Institute 2002. Available at: http://prg.nci.nih.gov/kidney/final report.html.
10. Shweiki D, Itin A, Stoffer D, *et al*. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature* 1992, **359**, 843–845.
11. Gnarra JR, Zhou S, Merrill MJ, *et al*. Post-transcriptional regulation of vascular endothelial growth factor mRNA by the product of the VHL tumor suppressor gene. *Proc Natl Acad Sci USA* 1996, **93**, 10589–10594.
12. Iliopoulos O, Levy AP, Jiang C, *et al*. Negative regulation of hypoxia-inducible genes by the von Hippel–Lindau protein. *Proc Natl Acad Sci USA* 1996, **93**, 10595–10599.
13. Ziegler BL, Valtieri M, Porada GA, *et al*. KDR receptor: a key marker defining haematopoietic stem cells. *Science* 1999, **285**, 1553–1558.
14. Veikkola T, Karkkainen M, Claesson-Welsh L, *et al*. Regulation of angiogenesis via vascular endothelial growth factor receptors. *Cancer Res* 2000, **60**, 203–212.
15. Kim KJ, Li B, Winer J, *et al*. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. *Nature* 1993, **362**, 841–844.
16. Borgstrom P, Bourdon MA, Hillan KJ, *et al*. Neutralizing anti-vascular endothelial growth factor antibody completely inhibits angiogenesis and growth of human prostate carcinoma micro tumors in vivo. *Prostate* 1998, **35**, 1–10.
17. 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**, 427–434.
18. Hainsworth JD, Sosman JA, Spigel DR, *et al*. Phase II trial of bevacizumab and erlotinib in patients with metastatic renal cell carcinoma (RCC). *Proc Am Soc Clin Oncol* 2004, **23**. [abstr 4502].
19. Motzer RJ, Rini BI, Michaelson MD, *et al*. SU011248, a novel tyrosine kinase inhibitor, shows antitumor activity in second-line therapy for patients with metastatic renal cell carcinoma: results of a phase 2 trial. *Proc Am Soc Clin Oncol* 2004, **23**. [abstr 4500].
20. D'Amato RJ, Loughnan MS, Flynn E, *et al*. Thalidomide is an inhibitor of angiogenesis. *Proc Natl Acad Sci USA* 1994, **94**, 4082–4085.
21. Geitz H, Handt S, Zwingenberger K. Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. *Immunopharmacology* 1996, **31**, 213–221.
22. McHugh SM, Rifkin IR, Deighton J, *et al*. The immunosuppressive drug thalidomide induces T helper cell type 2 (Th2) and concomitantly inhibits Th1 cytokine production in mitogen- and antigen-stimulated human peripheral blood mononuclear cell cultures. *Clin Exp Immunol* 1995, **99**, 160–167.
23. Singhal S, Mehta J, Desikan R, *et al*. Antitumor activity of thalidomide in refractory multiple myeloma. *N Engl J Med* 1999, **341**, 1565–1571.
24. Eisen T, Boshoff C, Mak I, *et al*. Continuous low dose thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer. *Br J Cancer* 2000, **82**, 812–817.
25. Stebbing J, Benson C, Eisen T, *et al*. The treatment of advanced renal cell cancer with high-dose oral thalidomide. *Br J Cancer* 2001, **85**, 953–958.
26. Minor DR, Monroe D, Damico LA, *et al*. A phase II study of thalidomide in advanced metastatic renal cell carcinoma. *Invest New Drugs* 2002, **20**, 389–393.
27. Escudier B, Lassau N, Couanet D, *et al*. Phase II trial of thalidomide in renal cell carcinoma. *Ann Oncol* 2002, **13**, 1029–1035.
28. Motzer R, Berg W, Ginsberg M, *et al*. Phase II trial of thalidomide for patients with advanced renal cell carcinoma. *J Clin Oncol* 2002, **20**, 302–306.
29. Daliani DD, Papandreou CN, Thall PF, *et al*. A pilot study of thalidomide in patients with progressive metastatic renal cell carcinoma. *Cancer* 2002, **95**, 758–765.
30. Nathan PD, Gore ME, Eisen TG. Unexpected toxicity of combination thalidomide and interferon alfa-2a treatment in metastatic renal cell carcinoma. *J Clin Oncol* 2002, **20**, 1429–1430.
31. Hernberg M, Virkunnen P, Bono P, *et al*. Interferon alfa-2b three times daily and thalidomide in the treatment of metastatic renal cell carcinoma. *J Clin Oncol* 2003, **21**, 3770–3776.
32. Gordon MS, Manola J, Fairclough D, *et al*. Low dose interferon-α 2b (IFN) + thalidomide (T) in patients (pts) with previously untreated renal cell cancer (RCC). Improvement in progression-free survival (PFS) but not quality of life (QoL) or overall survival (OS). A phase III study of the Eastern Cooperative Oncology Group (E2898). *Proc Am Soc Clin Oncol* 2004, **23**. [abstr 4516].
33. Amato RJ, Breheny S, Tracy E. Phase I/II study of thalidomide + interleukin 2 (IL-2) for patients with metastatic renal cell carcinoma. *Proc Am Soc Clin Oncol* 2002, **21**. [abstr 759].
34. Desai AA, Vogelzang NJ, Rini BI, Ansari R, Krauss S, Stadler WM. A high rate of venous thromboembolism in a multi-institutional phase II trial of weekly intravenous gemcitabine with continuous infusion fluorouracil and daily thalidomide in patients with renal cell carcinoma. *Cancer* 2002, **95**, 1629–1636.
35. Amato RJ. Thalidomide therapy for renal cell carcinoma. *Critical Reviews in Oncology/Hematology* 2003, **46**(suppl 1), 59–65.
36. Batist G, Patenaude F, Champagne P, *et al*. E. Neovastat (AE-941) in refractory renal cell carcinoma patients: report of phase II trial with two dose levels. *Ann Oncol* 2002, **13**, 1259–1263.
37. Bukowski RM. AE-941, a multifonctional angiogenic compound: trials in renal cell carcinoma. *Expert Opin Investig Drugs* 2003, **12**, 1403–1411.
38. Perera AD, Kleymenova EV, Walker CL. Requirement for the von Hippel–Lindau tumor suppressor gene for functional epidermal growth factor receptor blockade by monoclonal antibody C225 in renal cell carcinoma. *Clin Cancer Res* 2000, **6**, 1518–1523.
39. Motzer RJ, Amato R, Todd M, *et al*. Phase II trial of antiepidermal growth factor-receptor antibody C225 in patients with advanced renal cell carcinoma. *Invest New Drugs* 2003, **21**, 99–101.
40. Rowinsky EK, Schwartz GH, Gollob JA, *et al*. Safety, pharmacokinetics, and activity of ABX-EGF a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. *J Clin Oncol* 2004, **22**, 3003–3015.
41. Asakuma J, Sumimoto M, Asano T, *et al*. Modulation of tumor growth and tumor induced angiogenesis after epidermal growth factor receptor inhibition by ZD1839 in renal cell carcinoma. *J Urol* 2004, **171**, 897–902.
42. Drucker B, Bacik J, Ginsberg M, *et al*. Phase II trial of ZD1839 (Iressa) in patients with advanced renal cell carcinoma. *Invest New Drugs* 2003, **21**, 341–345.

43. Ratain MJ, Flaherty KT, Stadler WM, *et al*. Preliminary antitumor activity of BAY 43-9006 in metastatic renal cell carcinoma and other advanced refractory solid tumors in a phase II randomized discontinuation trial (RDT). *Proc Am Soc Clin Oncol* 2004, **23**. [abstr 4501].
44. 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**, 909–918.
45. Smith JW, Ko YJ, Dutcher J, *et al*. Update of a phase I study of intravenous CCI-779 given in combination with interferon-α to patients with advanced renal cell carcinoma. *Proc Am Soc Clin Oncol* 2004, **23**. [abstr 4513].
46. Davis NB, Taber DA, Ansari RH, *et al*. Phase II trial of PS-341 in patients with renal cell cancer: a University of Chicago phase II consortium study. *J Clin Oncol* 2004, **22**, 115–119.
47. Drucker BJ, Schwartz L, Bacik J, *et al*. Phase II trial of PS-341 shows response in patients with advanced renal cell carcinoma. *Proc Am Soc Clin Oncol* 2003, **22**. [abstr 1550].
48. Streubel B, Chott A, Huber D, *et al*. Lymphoma-specific genetic aberrations in microvascular endothelial cells in B-cell lymphomas. *N Engl J Med* 2004, **351**, 250–259.