

Mini-reviews

It is important for us as urologists to keep up to date with new drugs being introduced for treating metastatic renal cancer, particularly in the era of the multidisciplinary team approach to cancer therapy. Authors from Rome cover this topic in this month's issue.

In other mini reviews in this section, the topics of ejaculatory disorders and cryosurgery are described. Both are relevant to modern management of common urological disorders.

Finally there is an historical contribution. There is no such section for these manuscripts, but occasionally subjects of interest are presented which are intended to be of general educational value to the reader. I believe that the paper on prisons presented in this issue to be such a case.

What's new in the treatment of metastatic kidney cancer?

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INTRODUCTION

RCC is the sixth leading cause of cancer death in the USA, and the incidence of RCC in Europe is increasing, with $\approx 20\,000$ new cases each year and an annual death rate from metastatic disease of ≈ 8000 per year. Surgery is the treatment of choice at initial presentation for patients with a good performance status, even though $\approx 30\%$ of patients present with metastatic disease and a third develop metastasis during the follow-up. Patients with metastatic disease have a median survival of 1 year and a 5-year survival of 0–20% (Table 1). Factors such as age, comorbidities and heterogeneous histology can complicate the decision of whether or not to treat aggressively or to pursue a supportive, symptom-directed approach [1].

FIRST LINE TREATMENTS IN ADVANCED/METASTATIC DISEASE

IMMUNOTHERAPY (INTERFERON- α , INTERLEUKIN-2 AND COMBINED TRIALS)

Before the introduction of immunotherapy the prognosis for most patients with metastatic RCC was dismal, with reported 1-year survival rates of 26% and 3-year

survival rates of 4% [2]. Interferon- α and various interleukins (-2, -4, -6, -12 and -18) have been advocated at variable doses either alone or in combined (interleukin-2 + interferon- α) [3,4]. Except for interferon- α and interleukin-2 the activity of the other molecules is limited or under investigation [5–8].

Interferon- α has immunostimulatory and anti-angiogenic antitumoral mechanisms of action, by promoting a Th1 immune response, up-regulating the interleukin-12 receptor on subsets of lymphocytes, and inducing interferon- α production by other effector cells. Interferon- α is approved in Europe for the treatment of RCC, with a reported objective response rate (RR) of 11–15%, with complete responses (CRs) in 2% of patients. Two randomized trials reported a small but significant ($P < 0.05$) improvement in survival with interferon- α therapy. In the first, interferon-interferon- α was compared to medroxy-progesterone, resulting in an improvement of 3 months in median survival [9]. In the second trial, interferon- α plus vinblastine was compared to vinblastine alone, and the combination showed a benefit in median survival of 6 months compared to interferon- α therapy alone [10].

Patient selection is extremely important in predicting both response and survival [11–14] (Fig. 1). Interferon- α is therefore considered to be an excellent control arm for phase III trials and a reasonable agent to be combined with interleukin-2 or new targeted agents.

Interleukin-2 is a glycoprotein secreted by activated T lymphocytes, which in addition to producing interleukin-2 also increases the expression of high-affinity interleukin-2 receptors. The mechanism of action of interleukin-2 is induction and activation of T lymphocytes and natural killer cells, and the secondary release of cytokines such as interferon- α , TNF, granulocyte-macrophage colony stimulating factor, interleukin-1 and -6.

Interleukin-2 is the only treatment approved by the USA Food and Drug Administration for metastatic RCC. The highest RR and greatest proportion of durable CRs were reported with a high-dose regimen (600 000–720 000 IU/kg intravenous bolus, every 8 h for 5 days) in patients with metastatic RCC. This regimen results in a 15% RR with 7% CRs. In the most recent update of these results, objective responses were confirmed with a median response duration of up to 84 months for responders [15,16].

Cytokine combination trials of interferon- α and interleukin-2 have failed to show a statistically significant benefit in terms of overall survival (OS) compared with single agents [17,18]. The Cytokine Working Group reported a randomized phase III trial to determine the value of outpatient interleukin-2 and interferon-2 β vs high-dose interleukin-2. This trial provided additional evidence that combined therapy was no better than high-dose interleukin-2, which the authors concluded should remain the preferred therapy for metastatic RCC [19].

CHEMOTHERAPY

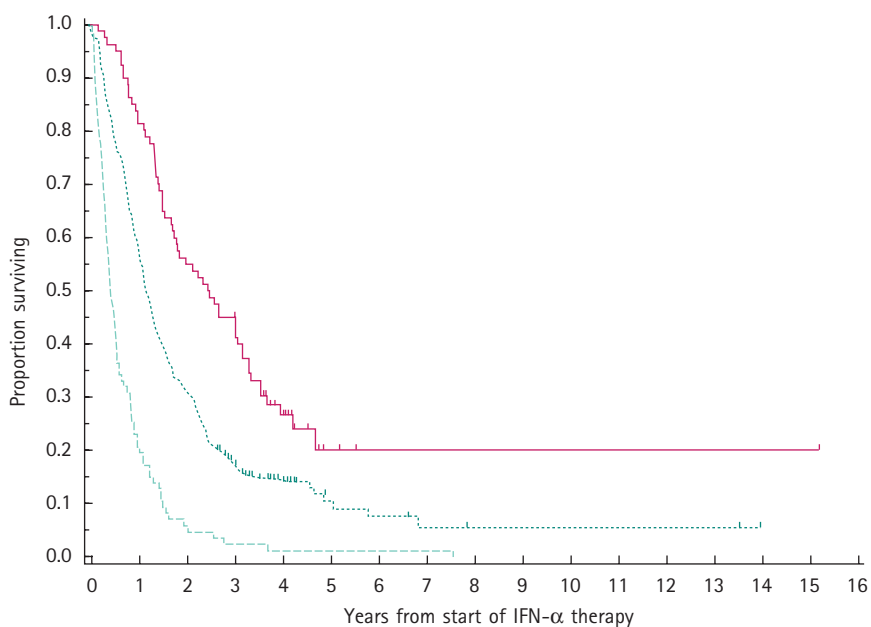
Chemotherapy has consistently shown disappointing results in the treatment of RCC. In a review of 83 trials in 4093 patients with advanced disease, the overall RR was only 6% [20]. Nonetheless, a review of phase II trials by Stadler *et al.* [21] showed that the combination of gemcitabine and fluorouracil had interesting activity, with RRs of 14–17% and an OS of \approx 12.5 months. These results are similar to those with cytokine-based therapy and likewise depend on prognostic factors.

In addition, there is preclinical evidence that drugs inhibiting platelet-derived growth factor receptor (PDGFR) could improve the efficacy of chemotherapy by reducing interstitial tumour fluid pressure and

Disease	Initial incidence, %	5-year survival, %
Localized (pT1, pT2, pN0)	20–25	>80
Locally advanced, pN+ or with extracapsular spread	45–50	10–25
Metastatic	30	0–9

TABLE 1
RCC in the USA (30000 new cases; 12000 deaths/year)

FIG. 1. Patients with RCC treated with interferon- α and related survival according to risk groups. Variables predicting poor outcome: low KPS, high lactate dehydrogenase, low haemoglobin, high corrected serum calcium, and time from diagnosis to start of interferon- α therapy < 1 year. Red solid line, 0 risk factors (80 patients, 21 alive); green dotted line, 1 or 2 risk factor (269 patients, 36 alive); light red dashed line, 3, 4 or 5 risk factors (88 patients, 0 alive). Favourable risk group: 0 poor prognostic factors; intermediate risk group: 1–2 poor prognostic factors; poor risk group: \geq 3 poor prognostic risk factors. Courtesy of [11].



increasing the concomitant uptake of chemotherapeutic agents such as 5-fluorouracil [22]. Second-generation taxanes (BAY 59–8862), and epothilones such as EP0906 are also under evaluation in RCC.

THE BIOLOGICAL BASIS OF NEW THERAPEUTIC APPROACHES

Recent developments in understanding the molecular biology of RCC have led to the development of new agents directed against tyrosine kinases (TKs), antigens and portions of the hypoxic response pathway (Table 2). Many studies show that overexpression of the epidermal growth factor receptor (EGFR) and its ligands EGF and TGF α occurs frequently in RCC and is associated with cancer

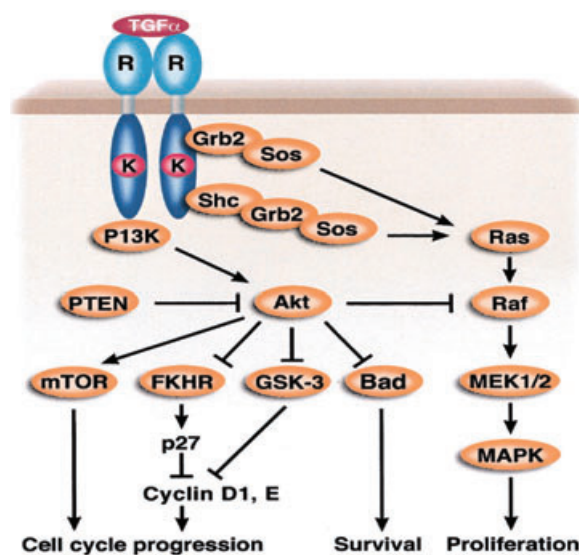
aggressiveness [23–28] (Fig. 2) [29]. EGFR signalling blockade decreases the proliferation of RCC cells *in vitro* and *in vivo*, which provides a sound basis for the clinical evaluation of EGFR inhibitors in RCC [30,31].

In addition, >75% of RCCs (sporadic histology) are characterized by loss of the Von Hippel-Lindau tumour-suppressor gene, which results in an increased concentration of hypoxia-inducible factor-1 (HIF-1), a central transcriptional factor which regulates the expression of a battery of genes, the products of which are critical components of tumour angiogenesis (e.g. VEGF, PDGF, TGF α ; Fig. 3) [32]. Tumour angiogenesis is also stimulated by growth factors through the PI3K-AKT-mTOR signal transduction pathway [33] (Fig. 2).

TABLE 2 New drug trials for metastatic RCC

Agent	Mechanism of action/molecular target	Administration	Development stage
Anti-EGFR			
ABX-EGF	Binds EGFR	intravenous	Phase II
Cetuximab	Binds EGFR	intravenous	Phase II
IRESSA	TKI: EGFR	oral	Phase II
mAb approaches			
Bevacizumab	Binds VEGF	intravenous	Phase III
Infliximab	Binds TNF α	intravenous	Phase II
WX-G250	Binds G-250 antigen	intravenous	Phase II
Kinase inhibitors			
SU-11248	Multitarget TKI	oral	Phase III
BAY 43-9006	TKI: RAF	oral	Phase II/III
GW 572016	TKI: EGFR, ErbB 1-2	oral	Phase III
PTK-787	TKI: VEGFR	oral	Phase I
Imatinib	TKI: c-kit, PDGFR, Bcr-Abl	oral	Phase II
CCI-779	TKI: mTOR	intravenous	Phase III
SU-5416	TKI: VEGF	intravenous	Closed
Proteasome			
Bortezomib	26S proteasome inhibitor	intravenous	Phase II
Peptide			
ABT-510	Nonapeptide: mimics TSP-1	subcutaneous	Phase II
Immunomodulator			
Thalidomide	Multitarget anti-angiogenic activity	oral	Phase II
AE-941	Multitarget anti-angiogenic activity, MMP inhibitor	oral	Closed
Vaccine			
HSPCC-96	Generates cytolytic T cells	intradermal	Phase II/III

FIG. 2.
EGFR signalling. Courtesy of [29].



ANTI-EGFR THERAPIES

ABX-EGF is a high-affinity fully human IgG₂ monoclonal antibody against the human EGFR. It completely blocks binding of EGF and TGF- α to the EGFR, and induces profound and

rapid internalization of the receptor in EGFR-expressing human cancers. These actions abolish EGFR-dependent cellular responses, including EGFR tyrosine phosphorylation, extracellular acidification, angiogenesis and cell proliferation [34,35]. Phase I studies have

established that the most common toxicity was a dose-dependent skin rash, occurring in all patients treated with ABX-EGF at 2.0 mg/kg/week or 2.5 mg/kg/week, with no allergic reactions, human antihuman antibody formation or serious adverse events at doses of up to 2.5 mg/kg/week [36].

Rowinsky *et al.* [37] explored four dose levels of ABX-EGF (1.0, 1.5, 2.0 and 2.5 mg/kg/week) in a phase I/II trial. Although this monoclonal antibody was safe, the results were poor. Eighty-eight patients in whom either immunotherapy had failed or in whom it was contraindicated were evaluated. The investigators found a 6.6% RR with stable disease in half the patients. The median (95% CI) time to progression (TTP) was 100 (58–140) days. These results are somewhat disappointing considering that a 6.6% RR has even been reported in randomized trials of patients with metastases with no systemic treatment [38,39].

Patients with clear-cell histology were more likely to respond and had a longer median TTP (92 vs 56 days), although the latter comparison was not statistically significantly different. Moreover, all patients treated at the highest dose level developed an acneiform rash, with a trend toward a longer TTP in patients with a more severe rash [37]. The low RR and relatively short TTP in the study by Rowinsky *et al.* is consistent with the results of other phase II EGFR inhibitor studies (C225, Gefitinib) [40,41].

Cetuximab (Erbix, C-225) is a chimeric IgG1 monoclonal antibody that binds to the EGFR with high specificity and with a higher affinity than either EGF or TGF α (thus blocking ligand-induced phosphorylation of EGFR). Moreover, preclinical data suggest a direct inhibition of angiogenesis that is secondary to down-regulation of VEGF, interleukin-8 and basic fibroblast growth factor expression [42,43].

However, cetuximab had no activity as a salvage therapy in pretreated patients. Motzer *et al.* [41] reported on 55 patients with metastatic RCC treated in a multicentre phase II trial. Cetuximab was given intravenously at a loading dose of 400 or 500 mg/m² followed by weekly maintenance doses of 250 mg/m². None of the treated patients had an objective response, and the median TTP was 57 days. The most frequently reported grade 3 or 4 treatment-related adverse events were acne

(17%) and rash or dry skin (4%). These results were also rather disappointing.

EGFR TK inhibitors such as gefitinib (Iressa, ZD1839), have been evaluated in RCC. Drucker *et al.* [40] reported negative results in 18 patients; 13 had progression of disease within 4 months of the start of therapy.

SMALL ORALLY ADMINISTERED KINASE INHIBITOR MOLECULES

SU11248

SU11248 is an oral multitargeted receptor TK (RTK) inhibitor with antitumour and anti-angiogenic activities through targeting of PDGFR-β, VEGFR-2, KIT and Flt3 receptors [44,45]. SU11248 has shown antitumour activity by inhibiting RTKs expressed by cancer cells directly involved in cancer proliferation and survival, and RTKs expressed on endothelial or stromal cells (pericytes) which support cancer growth [46]. VEGFR-2 is expressed in the endothelium of blood vessels [47] and PDGFR-β in the tumour stroma [48]. The targets of SU11248 are thought to be important in the growth and survival of human RCC, especially considering its very vascular nature.

In a multicentre trial, Motzer *et al.* [49] reported a phase II trial of SU11248 50 mg/day in patients with metastatic RCC in whom cytokine therapy with interleukin-2 or interferon had failed. Patients received treatment in 6-week cycles, with 4 weeks on and 2 weeks off therapy. All patients were selected who had a good or intermediate prognosis. Of 63 enrolled, 21 (33%) had an objective partial response (PR). A significant number of patients had a minimal response that did not meet the criteria for PR and 23 (37%) had SD for >3 months. Of 21 responding patients, 14 maintained a durable response for ≥4 to ≥12 months. The median TTP was 8.3 months and 1-year survival 65%.

Fatigue was the most common nonhaematological toxicity in this study (grade 2, 25%; grade 3, 8%). Three patients were withdrawn from treatment because of a >20% decrease in left ventricular ejection fraction. There were no reports of haemorrhage or development of hypertension. About a third of patients required dose reductions for increased pancreatic enzymes, although not of clinical

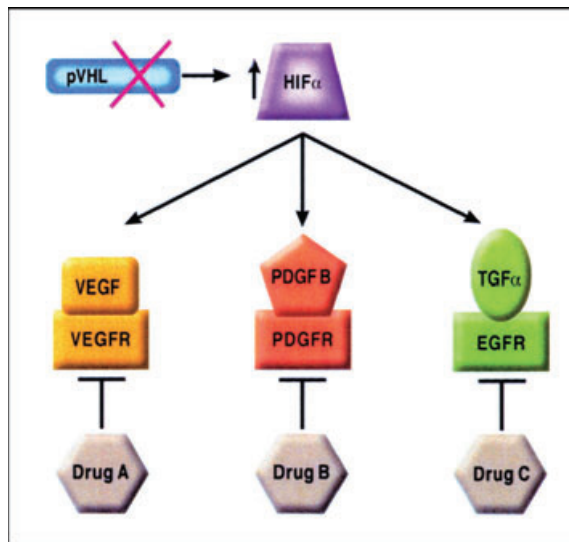


FIG. 3. Therapeutic targets of the von Hippel-Lindau tumour suppressor protein (pVHL) pathway. Courtesy of [32].

TABLE 3 SU-11248; activity vs other second-line agents

	N patients	Objective RR, %	TTP, months
SU-11248	63	33	8.3
Interleukin-2*	65	5	NA
interferon-α*	48	2	NA
Avastin (high dose)†	39	10	4.8
Placebo‡	40	0	2.5
Multiple agents in phase II trials‡	137	3	2.9

*[50]; †[51]; ‡[52]; NA, not applicable.

significance. Inhibition of VEGFR (and PDGFR)-mediated signalling is an appropriate therapeutic target for refractory RCC. SU11248 is well tolerated and active. The overall RR of 33% and the median TTP seemed better than what has been reported in other studies in patients with cytokine-refractory RCC (Table 3) [50–52]. Further investigation with SU11248 includes a confirmatory phase-2 study in the second-line setting, and a phase III randomized study of interferon-α alone vs SU011248 as first-line therapy for metastatic disease.

PTK787/ZK222584

PTK787/ZK222584, another VEGF RTK inhibitor, is under development as an angiogenesis inhibitor for treating various cancers. In metastatic refractory RCC, a phase I trial established that it was generally well tolerated at dose levels of 300–1500 mg, with partial or minor responses in 19% of patients, while 60% attained stable disease [53]. In this

trial, the median TTP was 5.3 months and the median estimated OS was 21.5 months. Changes in tumour blood flow evaluated with DCE-MRI significantly correlated with improved clinical outcomes but these data need to be confirmed in a larger phase II study.

BAY 43-9006 (SORAFENIB)

Sorafenib is an oral agent designed as a c- and b-raf kinase inhibitor. The Ras/Raf signalling pathway is a mediator of tumour cell proliferation and angiogenesis. Recently, sorafenib was found to inhibit several RTKs, among them VEGFR-2, PDGFR-β, FLT-3 and c-KIT. A randomized discontinuation study of sorafenib 400 mg twice daily permitted enrichment of the population by initially treating all patients for 12 weeks with the drug, and continuing treatment in responding patients (defined as ≥25% tumour shrinkage) while randomizing stable patients to sorafenib vs placebo [54]. Patients who had

progression ($\geq 25\%$ tumour growth) were discontinued from the study. Enrolment to this study was open to a wide variety of patients with refractory solid tumours, while accrual of patients with RCC comprised 42% of the total (203/484).

These patients were heavily pre-treated; 47% had received one previous systemic therapy, 39% two or more and 87% had had a previous nephrectomy. Response data at 12 weeks were available for 89 patients with RCC; 37 (42%) showed $\geq 25\%$ tumour shrinkage, 45 (51%) had SD, including several who had tumour shrinkage of $< 25\%$ that did not meet the RECIST criteria for PR. Of the 37 patients with $\geq 25\%$ tumour shrinkage who continued to receive sorafenib, 88% were progression-free at 24 weeks.

Dermatological toxicity was the most common adverse event, followed by fatigue and diarrhoea. Hand-foot syndrome was the most common grade 3 toxicity, but with an incidence of $< 10\%$. Hypertension was reported in $< 10\%$ of patients and was manageable with oral medications. Sorafenib showed interesting antitumour activity in RCC, with an acceptable toxicity profile for long-term chronic administration [54]. The agent is currently being evaluated in an international, randomized, placebo-controlled study as a second-line treatment for metastatic RCC. Phase II studies in combination with cytokines as first-line treatment are being planned in the cooperative groups.

GW572016 (LAPATINIB)

GW572016 (lapatinib) is an oral TK inhibitor (member of the 4-anilinoquinoline class) that is a potent dual inhibitor of the EGFR, ErbB-1 and ErbB-2 [55]. It has oral bioavailability (45–60%), hepatic metabolism, activity in several preclinical models and clinical trials, and no evidence of cardiac toxicity. A phase III trial is ongoing in which patients who express either the EGFR or Her-2 by centralized immunohistochemistry and who have had one line of previous immunotherapy are randomized between lapatinib and hormonal therapy. Results are too premature to be reported.

IMATINIB MESYLATE (GLEEVEC)

The mechanism of action of Imatinib consists of inhibition of the constitutively active

kinase activity of Bcr-Abl by binding to the nucleotide-binding site, thereby blocking access to ATP and inhibiting signalling pathways associated with proliferation. Moreover, Imatinib mesylate selectively inhibits two other TKs, c-kit and PDGF receptor. This latter finding has provided the rationale for treating patients with RCC. Notably, high expression of the PDGFR and c-kit are also reported in sarcomatoid-specific subtypes [56]. Despite this background, results have been somewhat disappointing. There were no major responses in a phase II study, with a median TTP of 3 months; adverse events were tolerable. Notably, only one tumour of 12 expressed c-kit by immunohistochemistry. Given the minimal toxicity of this regimen, combination trials of imatinib mesylate with pegylated interferon- α are in progress [57].

SMALL INTRAVENOUSLY ADMINISTERED KINASE INHIBITOR MOLECULES

CCI-779 (TEMSIROLIMUS)

Temsirolimus is a rapamycin analogue that inhibits mTOR kinase, a regulator of HIF-1 (causing G1 cell-cycle arrest) [58]. A phase II dose-escalation study of single-agent temsirolimus in 110 patients with refractory RCC evaluated doses of 25–250 mg. Despite a RR of only 7%, the overall tumour growth control was 70% and TTP 6 months. At least 15 patients remained on study for > 1 year. There was a suggestion of improved survival in patients with intermediate and poor prognostic risk factors, according to Motzer's classification of prognostic groups [59] (Fig. 1). At the 40th ASCO meeting a phase I study reported the results of temsirolimus combined with interferon- α . This was a dose-escalation study in patients with advanced RCC, who had received no more than two previous systemic therapies. In all, 71 patients were enrolled; 96% had had a previous nephrectomy, and 55% immunotherapy. The maximum tolerated dose was 15 mg of temsirolimus weekly in combination with 6 mIU of interferon- α subcutaneously three times weekly. Dose-limiting toxicities were fatigue, stomatitis, and nausea and vomiting. Among all treated patients, there were eight (11%) PRs and 21 (30%) with SD; the median TTP was 9.1 months [60]. Temsirolimus appears promising and is currently in phase III testing in patients with previously untreated poor-prognosis metastatic RCC as a single

agent vs combined therapy with interferon- α vs interferon- α alone.

SU5416 (SEMAXANIB)

SU5416 is a small organic molecule that noncompetitively inhibits the phosphorylation of the VEGF TK receptor, Flk-1. Whereas PTK787/ZK222584 inhibits all three isoforms of VEGFR, SU5416 inhibits VEGFR-1 and VEGFR-2. It is delivered intravenously twice weekly. In phase I/II studies, single-agent SU5416 was well tolerated, but the antitumour response was low, particularly in patients with RCC (no PRs, 25% SD) [61]. In combination with interferon- α the drug has biological activity, as shown by significant declines in serial VEGF and plasminogen activator inhibitor-1 plasma levels, but the 1-year relapse-free survival of 6% and an adverse toxicity profile (three on-study deaths) have diminished enthusiasm for new additional studies [62].

BEVACIZUMAB (AVASTIN) AND OTHER MONOCLONAL ANTIBODY APPROACHES

Extensive preclinical studies showed that treatment with anti-VEGF antibodies was effective in suppressing kidney tumours. Bevacizumab, an anti-VEGF humanized monoclonal antibody, is promising in the treatment of metastatic RCC [63]. A randomized phase II double-blind clinical trial evaluated cytokine-refractory RCC. Patients were randomized to receive either bevacizumab at 3 mg/kg (low dose), or 10 mg/kg (high dose) or placebo. After 116 patients were enrolled, the trial was stopped because patients on the high dose of bevacizumab showed a significant prolongation in the TTP. The probability of being progression-free for patients given high- or low-dose antibody and placebo was 64%, 39% and 20%, respectively, at 4 months, and 30%, 14% and 5% at 8 months ($P < 0.001$) [64]. Only four patients had responses (all of which were PRs) and all of these had received high-dose bevacizumab. The mean (95% CI) RR for high-dose bevacizumab was 10 (2.9–24.2)%. Survival analysis showed no significant differences between the groups ($P > 0.20$), but the trial was closed early. For this reason two randomized phase III single-agent confirmatory trials are in progress in the CALGB and in Europe in the first-line setting.

Considering the overexpression of VEGF, EGFR, TGF α and PDGF- β by clear cell RCC, a

multicentre phase II trial tested the combination of bevacizumab and the oral EGFR inhibitor erlotinib [65]. Eligibility criteria for this study included metastatic RCC ($\geq 75\%$ clear cell) and no more than one previous systemic regimen (no previous angiogenesis or EGFR inhibitors, including thalidomide). Treatment consisted of bevacizumab 10 mg/kg intravenously every 2 weeks and erlotinib 150 mg orally each day. Sixty-two patients were enrolled. At a median follow-up of 11 months, 92% had received at least two courses (8 weeks) of treatment and were evaluable for response. According to Motzer's prognostic risk groups, 42% were low risk, 32% were intermediate risk and 26% were high risk. All patients had had a nephrectomy and 68% had received no previous systemic therapy; 58 were evaluable. Twelve (21%) patients had a PR and 38 (66%) SD, including 12 (21%) who had a minor response. The progression-free survival was 67% at 6 months and 50% at 12 months. Grade 3–4 toxicity associated with this regimen included rash (13%), diarrhoea (10%), nausea/vomiting (10%), hypertension (8%) and bleeding (5%). The results provide early evidence that targeting both VEGF and EGFR pathways may be an effective strategy in RCC. The association was well tolerated and appears to be greater than the activity of either agent used alone, with 45% of patients having SD or a minor response for ≥ 6 months.

A randomized phase II study of bevacizumab and erlotinib or placebo is being planned as a confirmatory study. There should be a comparison of this regimen with standard treatments for advanced RCC.

Maisey *et al.* [66] reported results with infliximab, a monoclonal antibody against TNF α , in patients with RCC who had progressed after first-line cytokine therapy. TNF α is an autocrine growth factor for RCC and an inducer of T-cell apoptosis. In a phase II study, there were three responses in 19 patients, and one had a late response after progressing and discontinuing the study. An additional three patients had SD. The drug was well tolerated except by one patient who developed an allergic reaction. Infliximab could be a potential new target drug for treating RCC, but confirmatory studies are needed.

The G250 antigen (which is the same as the cellular protein MN/CA9) is specifically expressed on most RCC cells [67]. Small trials

with WX-G250, a chimeric monoclonal antibody directed against this tumour-specific, heat-sensitive surface antigen have reported SD [68,69]. Bleumer *et al.* [70] showed in a multicentre phase II trial the results of safety and efficacy for this approach in 36 patients with metastatic RCC. WX-G250 was given weekly by intravenous infusion for 12 weeks. There was one CR and a significant regression during the treatment, and five patients with progressive disease at study entry were stable for > 6 months. The median survival was 15 months. None of 36 enrolled patients had any drug-related grade III or IV toxicity and only three had grade II toxicity possibly related to the study medication. To improve the activity of WX-G250-specific antibody-dependent cellular cytotoxicity and the clinical response rate, currently combinations of WX-G250 with cytokines are in phase II trials.

OTHER NOVEL TREATMENTS

Bortezomib (Velcade, PS-341) is part of a new class of therapeutic agents targeting the 26S proteasome of the ubiquitin-proteasome degradation system. This system is the major extra-lysosomal pathway responsible for intracellular protein degradation in eukaryotes, and is important in regulating the cell cycle and in the development and growth of tumour cells. Many phase I/II trials of bortezomib in patients with metastatic RCC have been conducted on the basis of observed antitumour activity and the potential role of this agent in anti-angiogenesis. In a phase II trial, Kondagunta *et al.* [71] reported an 11% PR rate (95% CI, 3–25%) and SD in 14 (38%; 23–55%) of 37 assessable patients. The four patients with PR had a response duration of 8, > 8 , > 15 and > 20 months. Grade 2 or 3 sensory neuropathy was present in 10 patients (53%); one in the 1.5 mg/m² group had grade 3 sensory neuropathy.

Two other independent phase II trials of PS 341 confirm the drug's activity (5–10%) in patients with refractory RCC. However, considering the modest activity and toxicity profile (fatigue in half and neurotoxicity in 28%) other studies with single-agent bortezomib are probably not warranted [72,73]. However, it may still be interesting to explore the activity in combined therapies with interferon- α or new agents targeting the VEGF pathway.

ABT-510 is a substituted nonapeptide that potentially inhibits angiogenesis by blocking multiple pro-angiogenic signals and causing apoptosis in endothelial cells. In preclinical studies ABT-510 mimics the anti-angiogenic activity of an endogenous protein, thrombospondin-1, by competing for its cellular receptor CD36, thereby inhibiting spontaneous tumour growth and blocking activated endothelial cells. In a small, randomized, phase IB trial of ABT-510, its safety profile was presented for six different cancer types, with preliminary data of antitumour activity [74]. Given these encouraging results, a phase III trial in RCC has been initiated.

In recent years thalidomide has received increasing attention for its potential anti-angiogenic mechanism of action through down-regulation of TNF α . Phase II/III studies have reported RRs of 0–17% [75,76], with no benefit in OS when compared with medroxy progesterone [77]. In combined therapy with interferon- α or interleukin-2, thalidomide had a higher RR (20–40%) with a questionable benefit on OS [78–80]. An Eastern Cooperative Oncology Group phase III randomized study of interferon- α at anti-angiogenic low doses (1 mIU subcutaneously twice a day) with or without thalidomide (200 mg/day with escalation to 400–1000 mg/day) in previously untreated metastatic RCC was disappointing. This trial found a RR of 7.6% in the interferon- α -alone arm and of 3.1% in the combined arm (no statistically significant difference), and no differences in OS [79]. Amato *et al.* [80] presented better results in a phase II study with the combination of interleukin-2 and thalidomide. Patients with no previous chemotherapy or immunotherapy received thalidomide 200–400 mg and interleukin-2 at 7 mIU/m². This regimen was very well tolerated, with no grade 3 or 4 adverse events. Of 36 patients, there was one CR, 14 PRs and 11 who achieved SD. The time on therapy was 3–15 months; 26 patients (69%) remain on treatment with either an OR or SD. Based on the negative results with interferon, the viability of a proposed phase III randomized trial of thalidomide plus interleukin-2 vs interleukin-2 vs thalidomide is questionable.

Similar to thalidomide, AE-941 (Neovastat), a mixture of molecules with molecular weights of < 500 kDa derived by homogenization and purification of shark cartilage, is an agent with pleiotropic anti-angiogenic activities. A

phase III international randomized study of AE-941 vs placebo in 302 patients with refractory metastatic clear cell RCC showed RRs of 5%, a TTP of 56 days and OS of 12.3 months, none of which were different from values in placebo-treated patients. These results have limited the clinical utility and development of this drug [81].

ALLOGENEIC STEM-CELL TRANSPLANTATION

RCC is susceptible to immunological therapy and therefore allogeneic peripheral-blood stem cell transplantation has been considered for patients with refractory metastatic disease [82]. A low-intensity conditioning regimen provides sufficient immunosuppression to permit engraftment of the donor's immune cells (CD34), avoiding the substantial side-effects of conventional myelo-ablative regimens. The existence of full donor chimerism is essential. The antitumour effect is mediated by the donor's T cells and the evidence that regression can occur via a graft-vs-tumour effect is compelling.

Childs *et al.* [83] reported results on 19 consecutive patients with refractory metastatic RCC, who had suitable donors and received non-myelo-ablative allogeneic peripheral-blood stem-cell transplantation. A mean (95% CI) of 53 (31–75)% of the patients had tumour regression in three there was total regression of all metastases and the tumour burden was reduced by at least half in seven. Remarkably, three patients with a CR remained in remission for 27, 25 and 16 months after transplantation. The onset of tumour regression was typically delayed, occurring a median (range) of 4 (1–8 months) after transplantation. Development of acute graft-vs-host disease was the only factor that predicted response. Tumour regression occurred more often in patients with grade II, III or IV acute graft-vs-host disease of (nine of 10) than in those with no grade II, III or IV graft-vs-host disease (one of nine; $P=0.005$). Regression of metastases was delayed, and often followed the withdrawal of cyclosporin and the establishment of complete donor-T-cell chimerism. Other investigators have confirmed regressions of metastatic RCC with this approach, with a RR of 40–50% [84,85].

Non-myeloablative allogeneic stem-cell transplantation is feasible for a minority of patients with RCC but is extremely costly,

labour-intensive and toxic. Most patients have had PRs and not CRs. The requirement for a compatible donor, and treatment-related morbidity and mortality, and delayed treatment effect are recognized limitations of this approach. Difficulty with toxicity, insurance reimbursement and rapid progression while awaiting a response has diminished some of the enthusiasm surrounding this approach. More investigation is warranted to further evaluate this promising technique and to improve its safety. To date this therapy remains investigational.

TUMOUR VACCINES AND GENE THERAPY

Vaccination strategies have been used in RCC, both in the adjuvant and metastatic setting. Early approaches used whole-tumour cells or cell lysates with or without nonspecific adjuvants like BCG. Current strategies include tumour cells modified with genes encoding molecules necessary to stimulate a cytotoxic T cell response, such as cytokine genes, foreign HLA genes, tumour-associated antigen genes, and co-stimulatory molecules. Dendritic cell-based vaccines are increasingly used as cancer vaccines. They are capable of stimulating immunological and clinical responses. Hybrid cell vaccines are another promising approach [86]. However, to date no clear clinical benefit has been shown in randomized phase III trials in the metastatic setting [87].

A randomized phase III trial using an autologous renal tumour cell vaccine in 553 patients with stage pT2–3b pN0–3 M0 RCC showed a reduction in the risk of progression in patients undergoing radical nephrectomy for RCC of >2.5 cm; the 5-year progression-free survival was 77% in the vaccine group and 68% in the control group ($P=0.0204$). The vaccine was well tolerated, with only 12 adverse events reported [88].

Two other studies described this approach with different conclusions. Repmann *et al.* [89] evaluated an autologous tumour cell lysate vaccine in an adjuvant post-nephrectomy non-randomized study; there were benefits in 5-year progression-free survival and OS, but in another randomized study of 120 patients, Galligioni *et al.* [90] found no significant improvement.

Heat-shock protein-peptide complex vaccine (HSPPC-96) has been evaluated, with

encouraging results especially in association with interleukin-2. In one study, 30% of patients were alive at 2 years [91,92]. Notwithstanding these positive results, other randomized phase III trials are mandatory to confirm the usefulness of vaccination strategies in the adjuvant setting.

Since the first introduction of gene-marking technology to the clinical field in 1989 by Rosenberg (cited in [93]), more than 4000 patients have participated in gene therapy clinical trials worldwide. Gene therapy is a promising new method for treating RCC, whereby transfer of immunomodulatory tumour suppressor or suicide genes may alter the natural course of the disease. The great majority of clinical trials are still in the phase I-II setting, and to date there are very few ongoing phase II/III studies. Gene therapy strategies are limited by the difficulty of replication-defective vectors to efficiently infect solid tumours.

Gene therapy protocols have been shown to be feasible and safe. Whether or not these clinical trials produce durable clinical benefit must still be established. Early available results indicate SD for >1 year in 30–40% of patients. Further trials are necessary to firmly establish the benefits of these approaches.

CONCLUSIONS

There is an increasing awareness that validating therapeutic targets is necessary for the discovery of new drugs and to verify their success. Molecular profiling is heralding the future of prognosis, staging and treatment. Further exploration of biological targets, angiogenesis inhibition, and EGFR antagonists are providing new possibilities. Vaccination strategies such as dendritic cell-based therapies and allogeneic transplantation are complicated, but may be effective for a selected subset of patients. Efforts to improve results include identifying prognostic factors, which allow treatment to be better directed towards patients most likely to benefit. The next few years should be characterized by new rational treatment strategies based on inhibition of specific biological pathways, which will hopefully culminate in a better understanding of the causes of RCC, its prevention, and hopefully its cure.

CONFLICT OF INTEREST

None declared.

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Abbreviations: RR, response rate; CR, PR, OR, complete, partial, objective response; OS, overall survival; PDGFR, platelet-derived growth factor receptor; TK, tyrosine kinase; EGF(R), epidermal growth factor (receptor); TTP, time to progression; SD, stable disease; HIF-1, hypoxia-inducible factor-1.