Medical treatment options in patients with metastatic renal cell carcinoma

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Renal cell carcinoma (RCC) is a common urological tumour and accounts for ~3% of all human malignancies. Each year in Europe ~40 000 patients are newly diagnosed with RCC, and almost 20 000 people die of the disease. In the United States, in 2003, RCC accounted for 31 000 people diagnosed with the disease, 12 000 deaths, and was the 10th most common cause of cancer mortality in men [1]. It is estimated that ~25–30% of all patients with RCC have metastases at presentation, and even following complete resection of the primary tumour by radical nephrectomy, relapse occurs in 20–30% of patients. The overall 5-year survival rate is 60%. Those who present with metastases have a median survival of 6–12 months, with a 5-year survival of <10% [2].

Renal cell carcinomas generally arise in the epithelium of the proximal tubule. Approximately 80% are of clear cell histology and 15% are papillary.

Medical treatment options are generally offered for locally advanced or metastatic renal cell carcinoma, and much of the clinical experience with these approaches is in patients with clear cell histology.

Chemotherapy

Chemotherapy or radiation has only limited effects in metastatic RCC. A recent study reporting the effects of chemotherapy, published by Amato, reviewed more than 3600 patients with metastatic RCC and demonstrated the highest response rates for vinblastine (mean objective remission rate: 6.67%), 5-fluorouracil (mean objective remission rate: 6.57%) and floxuridine (mean objective remission rate: 9.66%) [3]. The impact of these cytotoxic agents is increased when combined with cytokine-based immunotherapies. In contrast, the combination of various chemotherapeutic agents (polychemotherapy) did not improve the antitumour effect compared with the monotherapies mentioned, whereas the side effects increased. The overexpression of multiple drug resistance genes (MDR, e.g. p-170), glutathione-S transferase and the down-regulation of topoisomerase-2 are mainly responsible for the meagre effects of the cytotoxic therapy [3,4].

Immunotherapy

The value of immunomodulatory therapy for renal clear cell carcinoma is supported by reports of occasional spontaneous tumour regression, infrequent complete regression of metastatic disease with cytokine therapies and promising early results of tumour vaccines.

At present, cytokine-based immunotherapy with interleukin 2 (IL-2) and/or interferon α (IFN-α) can be considered as the standard first-line treatment for metastatic RCC, although with limited enthusiasm. IL-2 serves as a crucial growth factor and activator of the cellular immune response, which is considered to play a central role in tumour rejection. IFN-α has several mechanisms of action: First, it stimulates the lytic capacity of natural killer cells. Second, it augments the expression of HLA class I on tumour cells, therefore enhancing the recognition by cytotoxic T cells. In addition to a role in the tumour immune response, it has direct antiproliferative effects and serves in low doses as an inhibitor of angiogenesis [5].

IL-2 monotherapy given intravenously in a high-dose bolus regimen has response rates reaching 21%, as compared with only 13% in patients who receive low-dose IL-2 [6]. This treatment is favoured by some because a proportion of the 5% of patients who enjoy complete remission survive long term [7]. The median duration of a partial response is 12–19 months, although in some studies the median duration of the complete response has not yet been reached. However, the response rates attained with intravenous IL-2 have been associated with considerable toxicity manifested...
as fever, malaise, weight loss, oedema, neurocortical effects and liver dysfunction [8].

IFNα monotherapy has an average response rate of up to 15%, with a response duration of 4–6 months. Complete responses are rare (≤5%), but may be long-lasting. Responses are seen predominantly in lung and lymph node metastases. Flu-like symptoms (fever, myalgia, asthenia) occur in almost all patients treated with IFNα and may be dose-limiting [9]. Two phase III studies have shown a significantly longer overall and progression-free survival when patients were treated with IFN. In the MRC Renal Cancer Collaborators’ Trial, a 2.5 months median overall survival gain was observed for the IFNα group compared with the medroxyprogesterone acetate (MPA) group [10]. In the trial conducted by Pyrhonen et al. [11] median overall survival was 15.7 months with IFN plus vinblastine compared with 8.2 months with vinblastine alone.

The combination of IFNα and IL-2 (with the possible addition of 5-fluorouracil) appears to result in higher response rates than the monotherapies, but the effects on overall survival remain unclear. While Atzpodien et al. [12] were able to demonstrate a significant median overall survival benefit with 25 months for the IFNα/IL-2/5-FU group compared with 16 months for the IFNα/vinblastine group in their phase III study; others could not confirm these results [13–15]. Data from the French Immunotherapy Intergroup’s PERCY Quattro Trial, a phase III study, showed no significant improvement in median progression-free and overall survival with the use of cytokines, alone or in combination, when compared with an MPA control. Median survival was 14.9 months with MPA, 15.2 months with IFNα, 15.3 months with subcutaneous IL-2 and 16.8 months with IFNα plus IL-2.

In addition to the questionable effect on overall survival, the toxicity of the combined IFNα/IL-2 therapy is higher. Culine et al. [16] reported that 78% of the patients treated with the cytokine combination developed at least one episode of grade 3 toxicity.

Although cytokine-based immunotherapy is up to now first-line systemic treatment, only a small subset of patients with metastatic RCC is likely to benefit from treatment. As toxicity is significant, this has to be taken into consideration when treating patients.

Targeted therapies

A growing understanding of the underlying molecular biology of RCC has identified a number of pathways pertinent to the pathophysiology of the most common histological form of this disease, clear cell RCC. Inactivating mutations or methylation of the von Hippel–Lindau (VHL) tumour suppressor gene have been found in over 75% of sporadic clear cell RCCs, resulting in an activation of the hypoxia response pathway [17]. VHL is a tumour suppressor gene that encodes for a 213-amino-acid protein (pVHL), which interacts with hypoxia-inducible factor 1α (HIF-1α). The complex of pVHL and HIF-1α mediates ubiquitination-mediated, oxygen-dependent proteosomal degradation of HIF-1α. Hypoxia or mutated pVHL leads to accumulation of HIF-1α and binding to HIF-1β. This complex increases the transcription of hypoxia-inducible genes encoding several growth factors. These include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), erythropoietin, transforming growth factor (TGF)-β and the cellular membrane antigen carbonic anhydrase (CA) IX.

VEGF is overexpressed throughout clear-cell renal carcinoma tissue and may be the most important angiogenic factor contributing to the typical hypervascular tumour histology. TGF-β is also overexpressed and is a potent growth factor for epithelial cells acting through the epidermal growth factor receptor (EGFR), which is a tyrosine kinase.

Inhibitors targeting various aspects of these pathways have recently undergone clinical testing in metastatic RCC: Sunitinib (Sutent, Pfizer, New York, NY, USA) is an orally bioavailable small molecule tyrosine kinase inhibitor of VEGF receptor-2 (VEGFR-2) and PDGF receptor-β (PDGFR-β). Two phase II trials using sunitinib in cytokine-refractory metastatic RCC have been conducted [18,19]. Sunitinib was administered as 50mg/day for the first 4 weeks of repeated 6-week cycles. The first trial included all histological subtypes, the second only clear-cell histology. One complete response and around 40% partial responses (trial 1:40%, trial 2:39%) have been observed. Median time to progression was 8.7 months [19]. Toxicity in these trials, most commonly grades 1 and 2, included fatigue/asthenia, nausea, diarrhoea, stomatitis and cytopenia. A 750-patient phase III trial of sunitinib as first-line treatment in metastatic RCC patients vs IFN-α has demonstrated a significantly longer median progression-free survival in the sunitinib group with 47.3 weeks compared with 24.8 weeks in the IFN-α group with objective response rates of 24.8% for sunitinib vs 4.9% for IFN-α [20].

Sorafenib (Nexavar, Bayer Pharmaceuticals, Leverkusen, Germany) is an orally bioavailable Raf-1 kinase inhibitor belonging to a class of bis-aryl ureas. In addition to the effects on Raf, sorafenib inhibits receptor kinases of VEGFR-2, VEGFR-3 and PDGFR-β. A 903-patient phase III trial of sorafenib in cytokine-refractory metastatic RCC patients vs placebo has demonstrated an overall survival advantage of 5 months in the treatment arm (19.3 months for sorafenib vs 14.3 months for placebo) despite a 2% RECIST-defined objective response rate [21]. Sorafenib was administered as 400 mg bid. Side effects, mainly in grades 1 and 2 (grades 3/4 in 8.2%), include diarrhoea, fatigue, fever, hypertension, nausea, hand–foot skin reaction and rash/desquamation, hypophosphataemia and lipase elevation [22]. Sorafenib has also been evaluated in a phase II study as first-line therapy in combination with IFN-α.
The overall objective response rate of 19% for the combination of sorafenib and IFN-α was greater than that expected with either IFN-α or sorafenib alone [23].

Based on the second-line data presented earlier, sunitinib and sorafenib have been approved by the FDA for the treatment of advanced RCC and by the EMEA for the treatment of cytokine refractory RCC.

In addition to the multi-kinase inhibitors mentioned above, earlier studies attempted to block tumour vasculature with bevacizumab (Avastin, F. Hoffmann-La Roche, Basel, Switzerland), a recombinant monoclonal antibody that binds VEGF, thus blocking its interaction with the VEGF receptor. A phase II study demonstrated a 10% objective response rate in a high-dose (10 mg/kg bodyweight) antibody group with a significant prolongation of the progression-free survival, but failed to show a benefit in overall survival [24].

Similar limited antitumour effects have also been described with either monoclonal antibodies or small molecules that block EGF receptor tyrosine kinase (RTK) [25]. Contrary to these single pathway blockers, the combination of agents that block VEGF (bevacizumab) and EGFR (erlotinib) have demonstrated tumour growth inhibition in a phase II trial: 25% of patients had objective responses to the combined treatment with a median progression-free survival of 11 months. Overall survival after 18 months was 60%. The most significant reported side effects of the combined regimen included hypertension, proteinuria, diarrhoea and acne-like rash [26].

Other approaches to treat metastatic RCC include temsirolimus, a selective inhibitor of the mammalian target of rapamycin (mTOR). mTOR is a serine/threonine kinase and is involved in many critical cell cycle functions. mTOR acts in the downstream signalling of phosphatidylinositol 3-kinase and the AKt pathway. Essentially, mTOR regulates signal transduction pathways involving the coupling of growth stimuli to cell cycle progression, cell proliferation, survival and mobility and angiogenesis. Moreover, mTOR activity results in increased HIF-1α activity, which plays an important role in the pathogenesis of RCC as mentioned earlier.

A 626-patient phase III study has been conducted, randomizing poor risk patients with advanced RCC into three groups: IFN-α alone, temsirolimus alone and IFN-α plus temsirolimus. Patients treated with temsirolimus alone had a significantly longer overall survival of 10.9 months, compared with 7.3 months for IFN-α. There was no additional effect of the combined temsirolimus and IFN-α therapy [27]. Side effects included asthenia, anaemia and dyspnoea.

In summary, there is currently no role for chemotherapy alone in metastatic RCC. Cytokine-based immunotherapy is at present the first-line systemic treatment, although only a small subset of patients is likely to benefit from treatment and toxicity is significant. Targeted therapies using recombinant monoclonal antibodies and RTK inhibitors offer new treatment options with limited toxicity and reasonable response rates. Since RCC tumour proliferation is often driven by stimulation of multiple RTK pathways, it seems that substances that simultaneously inhibit multiple RTKs are more efficient than single pathway blockers. Unfortunately, the clinical response to the substances used so far is not permanent, with a time to progression of 6–12 months. This makes further research which combines inhibitors against various pathways or possibly adds cytokine-based immunotherapy necessary.

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References
In memoriam ‘analgesic nephropathy’ (circa 1972–2006)

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Throughout the last decades, analgesic nephropathy (AN) has remained a subject for controversy, leading to a series of epidemiological studies, reviews, statements by more or less officially appointed committees and appeals to public health authorities. In contrast, the ‘Obituary to Analgesic Nephropathy’ which appeared in the November issue of NDT [1] reports only a decisive new fact: 20 years after the removal of phenacetin from the freely available analgesics, the typical lesions of AN are no longer found at autopsy in Basel. How does this new evidence fit into the other available pieces of the puzzle?

It all started in the 50s, with localized epidemics of chronic renal failure in Sweden, in Swiss watch factories, in the Flanders region of Belgium and in Australia. All had in common a compulsive craving for analgesic mixtures, usually powders containing phenacetin combined with other antipyretic analgesics, caffeine and sometimes codeine. The description of capillary sclerosis as a pathognomonic lesion later completed the picture. As phenacetin was the only ‘common’ ingredient present in all the mixtures, the new disease became known as phenacetin nephropathy. As a consequence, phenacetin was progressively removed from most popular mixed analgesics and usually replaced by its principal metabolite, paracetamol.

In the 70s, the exclusive role of phenacetin became increasingly questioned when it appeared that paracetamol and not phenacetin accumulated in the papilla [2]. In addition, phenacetin had always been