Update on genitourinary cancers

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New horizons in the treatment of renal cell cancer

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introduction

The incidence of renal cell cancers (RCC) is increasing in the Western world. It increased by 35% and 25% between 1973–1991 and 1990–2000 respectively in North America. The incidence varies from around 12 per 100 000 of population in Italian and Estonian men to 1.5 in Indian men. The disease is 2.5 times more common in men than women. The mortality is between one third and a half of the incidence and there is no sign of the mortality decreasing.

Therapy has had little influence on mortality although there is some evidence of stage migration due to an increasing number of patients with the disease being discovered by ultrasound and computer tomography (CT) scanning done for reasons other than suspected cancer.

The median age of patients is around 60 years and aetiological factors include smoking, obesity, hypertension, exposure to asbestos and renal haemodialysis. About 5% of tumours are hereditary and the molecular basis of these syndromes has lead to a better understanding of the biology of the disease and has pointed the way to the development of novel therapeutic interventions. These genetic syndromes are summarised in Table 1.

The main histological sub-types and their incidence are also listed in Table 1. Previously it was believed that spindle cell (sarcomatoid) renal cell carcinoma was a separate entity but molecular studies have shown that this sub-type is an undifferentiated form of one of the other variants.

The von Hippel-Lindau (VHL) gene, located on the short arm of chromosome 3, encodes a tumour suppressor gene that interacts with hypoxia inducible factor 1-alpha (HIF-1α). Under normal oxygen tensions the VHL is expressed and binds to a complex of proteins containing HIF-1α targeting it for destruction. In hypoxic situations the VHL gene is not expressed and the amount of HIF 1α in the cell increases. This drives the expression of a number of so called hypoxia response genes which include: vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), transforming growth factor beta (TGFβ) and erythropoietin.

The VHL gene is mutated in 70% of patients with sporadic RCC and the gene is silenced by methylation in a further 20% [1]. These data have formed the basis for the development of many of the new targeted agents which are currently in clinical development. It also explains why these tumours are highly vascularised and patients sometimes present with polycythaemia.

treatment

surgery

Radical nephrectomy remains the mainstay of initial treatment for patients with renal tumours without evidence of metastatic disease. The role of debulking nephrectomy in patients with metastatic disease was controversial for many years. Two randomised trials [2–4] have addressed this issue. Both trials randomised patients to nephrectomy or not and all were subsequently given immunotherapy with interferon. In patients with a good performance status that are not thought to have rapidly progressive disease a debulking nephrectomy should be performed prior to immunotherapy.

It is currently unknown whether this procedure is of benefit in patients who are going to receive the new targeted agents. Many of the patients entered into the trials of these new agents had received prior immunotherapy and had therefore already undergone nephrectomy.

In patients with small tumours (T1,2a) laparoscopic nephrectomy or partial nephrectomy should be considered. This procedure is associated with much lower morbidity and shorter hospital stays than open nephrectomy with equivalent long-term survival [5]. Partial or nephron sparing nephrectomy is particularly important in patients with familial RCC because they are likely to develop multiple tumours and it is therefore important to preserve as much renal function as possible with each operation. In patients with small tumours, who are medically unfit for either laparoscopic or open removal of the tumour consideration should be given to radiofrequency ablation or cryosurgery.

radiotherapy

Many patients present with large primary cancers and have significant risk of local relapse. Because of this four randomised trials have addressed the role of radiotherapy following nephrectomy [6–9]. All of these trials were small and therefore not powered to detect meaningful differences in survival. None of the trials showed a significant benefit for radiotherapy and in three of them there was a non-significant trend for inferior survival for patients receiving radiotherapy.

chemotherapy

A review of 3502 patients with metastatic RCC treated with one of 72 chemotherapeutic agents demonstrated response rates of 2–6% [10]. RCC is intrinsically resistant to conventional
chemotherapy and this modality currently plays no role in the management of these patients.

**immunotherapy**

**interferon.** Recombinant interferons (IFNs) were introduced into the clinic at the beginning of the 1980s. Overall about 15% of patients will respond to interferon [11]. Complete remissions (CR) are, however rare. The median durations of response and survival are 6 and 15 months respectively. A Cochrane meta-analysis summarising data from trials comparing IFN with control showed significant benefit for interferon in terms of response (Peto odds ratio 4.89, P = 0.007) and survival at 1 year (relative reduction is risk of death (RR) 0.67, P = 0.007) [12]. Although some individual trials have shown that adding other drugs, such as vinblastine or retinoids, to IFN give superior results the Cochrane meta-analysis could not confirm this (Peto odds ratio 0.88, P = 0.1773).

It is possible to select patients who will have a relatively good outcome when treated with IFN [13]. The model was based on 670 patients treated with first-line interferon at the Memorial Sloan Kettering Cancer Center (MSK). The model was then validated on an independent data set from ECOG trials consisting of 175 patients. The results are shown in Table 2. The five factors that independently predicted median survival were Karnofsky performance status < 80%, high lactate dehydrogenase (LDH) (>1.5 × upper limit of normal), low haemoglobin (< lower limit of normal), high serum calcium (>10 mg/dl) and no prior nephrectomy. This model was also validated with data from the Cleveland Clinic [14]. On the basis of these data I would not offer IFN to patients in the poor risk group.

**interleukin-2.** Interleukin-2 (IL-2) entered clinical trial in the mid 1980s. In the USA Rosenberg developed a high-dose bolus programme (BIV). This treatment is still the only FDA approved IL-2-based therapy in the USA. It produces responses in 20% of patients with a median duration of 54 months. The median survival of the 8% of patients that achieve CR has not yet been reached and 60% of these patients are alive at a median follow-up of >10 years [15]. This treatment is however very challenging for both patients and physicians requiring high dependency or intensive care support due to capillary leak syndrome [16].

Because of this a different approach was adopted in Europe. Trials were conducted with either continuously infused (CIV) or subcutaneous (SC) IL-2. Toxicity is certainly reduced with these regimens but question marks have been raised about the comparative efficacy of the various treatments. A recent meta-analysis [17] and a randomised clinical trial [18] have shed light onto this issue. The meta-analysis demonstrated that the number of complete remissions (CR) is similar between BIV and SC routes and that these are higher than for CIV schedules. The durability of the CRs induced by BIV appeared superior to those induced by SC IL-2 and definitely higher than with CIV protocols. In the trial a total of 156 patients were randomly assigned to BIV IL-2, and 150 patients to low dose bolus (LDIV) IL-2. Toxicities were less frequent with LDIV IL-2 (especially hypotension), but there were no IL-2-related deaths in either arm. There was a higher response rate with BIV IL-2 (21%) versus LDIV IL-2 (13%; P = 0.048) but no overall survival difference. The response rate of SC IL-2 (10%, partial and complete response) was similar to that of LDIV IL-2, differing from BIV (P = 0.033). Response durability and survival in completely responding patients was superior with BIV compared with LDIV therapy (P = 0.04). These data suggest that high dose BIV IL-2 should be offered to patients with a good performance status because it offers the greatest chance of cure. Reliable predictive markers of response and survival would be of great value in this setting.

Recently Atkins and colleagues [19] examined the relationship between positive staining of the RCC for carbonic anhydrase IX (CAIX) and outcome in 66 patients who had received IL-2. 78% of the responders had high CAIX staining and the survival curve had a plateau at around 40% beyond 5 years. These authors have proposed a model incorporating a predictive pathological model developed by Upton and colleagues [20] and CAIX staining (Table 3). On the basis of this one could certainly recommend high dose IL-2 for the patients in the good risk group because their chance of response is 26/44 (59%).

Combinations of IL-2 with other agents such as IFN, retinoids and 5-fluorouracil have been controversial. The Groupe Français d’Immunothérapie randomised patients to CIV IL-2 alone, CIV IL-2 + IFN or IFN alone [21]. Response rates were higher for the combination (18.6, 7.5 & 6.5%) and one year event-free survival was also superior (20, 12 & 15%). Overall survival was, however, no different between the arms.

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**Table 1.**

<table>
<thead>
<tr>
<th>Sporadic renal cell carcinomas</th>
<th>Inherited renal cell cancer syndromes</th>
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<tbody>
<tr>
<td><strong>Histology</strong></td>
<td><strong>Gene (frequency)</strong></td>
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<tr>
<td>Clear cell</td>
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</tr>
<tr>
<td>Papillary</td>
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<td>Chromophobe</td>
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</tr>
<tr>
<td>Oncocytoma</td>
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<td>Collecting duct</td>
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<tr>
<td>Unclassified</td>
<td>3–5</td>
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</table>

*VHL*, von Hippel-Lindau; *PRC*, familial clear cell renal cancer; *SDHB*, succinate dehydrogenase B; *HPRC*, hereditary papillary renal cell carcinoma; *HLRCC*, hereditary leiomyomatosis and renal cancer; *FH*, fumarate hydratase.
A phase II study Ratain and colleagues included 112 patients with RCC [27]. Those with progressive disease (PD) at 12 weeks discontinued treatment whilst those that experienced a >25% reduction in size continued (40% of patients). Those with stable disease (15 patients (24%)) were randomised to either continue drug or receive placebo. Further patients were then entered and an analysis of 63 randomised patients was presented at the 2005 ASCO meeting [28]. 24-week PFS was superior for Sorafenib (50 vs. 18%; \( P = 0.0077 \)) and median PFS was also longer (23 vs. 6 weeks; HR 0.29, \( P = 0.0001 \)). Of 25 patients who progressed on placebo and started Sorafenib the median PFS was 24 weeks. Common adverse reactions included rash (62%), hand-foot syndrome (61%) and fatigue (56%). Grade 3/4 reactions were hypertension (24%), hand-foot reactions (13%) and fatigue (5%) but only 2% of patients having to discontinue treatment due to toxicity. There is some evidence of tachyphylaxis with this agent as some patients who had to dose reduce could be re-escalated some time later.

Motzer and colleagues have recently published the results of the phase 2 evaluation of SU11248 (SUTENT or Sunitinib) [29]. Of 63 patients treated the median duration of treatment was 7 months and 40% responding using RECIST criteria, one of which achieved CR. A further 27% had stable disease lasting >3 months. Median PFS was 8.7 months. Grade 3/4 toxicities included fatigue 11%, diarrhoea 3%, nausea/vomiting 3%, skin reactions 2%, hypertension 2%, lymphopenia 32%, neutropenia 13%, anaemia 10%, hyperlipaesaemia 21% and hyperamylasaemia 8%. A randomised trial comparing SU11248 with interferon as first-line therapy is currently underway.

Temsirolimus is an mTOR inhibitor which has been investigated in phase 2 trials [30] and is currently undergoing phase III assessment. 111 patients with advanced refractory RCC were randomised to one of three doses of Temsirolimus. RR was 7% with one patient achieving CR and 26% evaluated as minor response. Median PFS and overall survivals were 5.8 and 15 months respectively.

AG-013736 targets the VEGF-1, VEGF-2 and PDGF receptors. In 52 patients with cytokine refractory RCC, 5 mg orally twice daily, produced responses in 46% of patients with a further 40% having stable disease. Median time to progression had not been reached at 12 months. Grade 3 hypertension occurred in 15% but other grade 3 toxicities occurred in less than 10% of patients.

Pazopanib is a multi-targeted tyrosine kinase inhibitor that selectively inhibits VEGFR-1, -2, -3, PDGFR-alpha and beta and c-kit. Twelve patients with metastatic RCC were included in a phase I study of this agent. One of these patients achieved a partial remission (duration 69+ weeks) and six others disease stabilisation (median duration 40 weeks). The comparative toxicities of Pazopanib, Sorafenib and sunitinib are shown in Table 4.
Table 4. Comparison of the toxicities of three multi-targeted receptor tyrosine kinase inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sorafenib</th>
<th>Sunitinib</th>
<th>Pazopanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>17</td>
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<td>36</td>
</tr>
<tr>
<td>Fatigue</td>
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<td>Diarrhoea</td>
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<tr>
<td>Rash/desquamation</td>
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<tr>
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<tr>
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<td>4</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>15</td>
<td>26</td>
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</tbody>
</table>

**conclusion**

From going to a position of only having immunotherapy as a treatment for metastatic RCC we are now in possession of a wealth of new therapies. Some of these produce significant numbers of objective responses whereas others seem to stabilise the disease for long periods. There seems little doubt that the survival of patients who are refractory to immunotherapy is prolonged by treatment with these new targeted agents. On the basis of the data available to date it is difficult to decide whether one agent is superior to another. There are, however differences in the toxicity profiles of the drugs which may influence choice of agent. Ultimately randomised trials will be needed to assess which of these drugs is superior, whether combinations produce better results and whether immunotherapy will become obsolete.

**references**

12. Cochrane Library.
18. Yang JC et al.