New challenges in kidney cancer therapy: sunitinib

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Introduction

The American Cancer Society estimates, based on the most recent data on cancer incidence, mortality and survival, that approximately 38,890 individuals will be diagnosed as having renal cell carcinoma (RCC) in the United States in 2006 and approximately 12,840 patients will die from the disease [1]. RCC is the most common malignant lesion of the kidney and accounts for 85% of all renal neoplasms and 3% of all adult malignancies [1]. The overall incidence of RCC has increased over the past 20 years from 2 to 4% per year [2]. Response rates to chemotherapy have rarely exceeded 6% [3]. Immunotherapy, including interleukin-2 (IL-2) and interferon-alpha (IFN-α), has been the standard treatment in advanced RCC during the past two decades. High-dose (HD) IL-2 has a significantly better overall and complete response rate, with the major benefit realized in the durable complete responses (5%). There is no proven benefit in disease-free survival or overall survival for the entire cohort receiving IL-2. Toxicity is substantial. Good performance status patients with access to centres that have expertise in HD IL-2 may appropriately receive HD IL-2 after consideration of the relative risks and benefits. A prospective trial is planned to select metastatic RCC patients based on biomarkers (including G250; also called CAIX) to increase the response rate. IFN-α confers a modest survival advantage over no/ineffective therapy [4]. Two randomized studies have demonstrated a modest impact on survival, while the PERCY Quattro trial has failed to show a significant median survival improvement over the control group (medroxyprogesterone).

Recent progress in understanding the biology of RCC has led to the identification of potential new targets for the treatment of metastatic disease. Some of the solid tumours and haematological malignancies are at least partially driven by dysregulated tyrosine kinase receptors such as stem-cell factor receptor (KIT) (e.g. in gastrointestinal stromal tumours) [5], platelet-derived growth factor receptor (PDGFR) (e.g. in dermatofibrosarcoma protuberans) [6], and fetal liver tyrosine kinase receptor 3 (FLT3) (e.g. in acute myelogenous leukaemia) [7]. In addition to their roles in cancer cell growth and survival, PDGFR and vascular endothelial growth factor receptor (VEGFR) facilitate the transmission of proliferation, migration, differentiation and survival signals from cancer cells and neighbouring host-derived stromal cells to the endothelial cells of the tumour neovascularity [8].

RCC biology provides the rationale for targeted approach including the inhibition of the pro-angiogenic pathway. The cloning of von Hippel–Lindau (VHL) tumour suppressor gene and demonstrating its role in regulation of growth factors associated with angiogenesis were important steps in the knowledge of RCC biology [9]. VHL syndrome is characterized by a germ-line mutation of chromosome 3p and development of RCC. Non-inherited clear cell RCC is characterized by VHL gene tumour suppressor gene inactivation. VHL gene inactivation leads to constitutive expression of an oxygen-regulated transcription factor (HIF-alpha) and induction of hypoxia-inducible genes including VEGF. Under normal conditions, HIF1-alpha is ubiquitinated by the VHL protein complex and degraded within proteasomes. Bi-allelic inactivation of VHL (as occurs in clear-cell RCC) prevents degradation of HIF-1 alpha HIF-1alpha accumulation increase the production of several pro-angiogenic factors by trans-activation of their promoters, including VEGF, PDGF and erythropoietin. Others factors induced by HIF-1alpha are involved in survival, pH regulation and glucose metabolism [10].

The identification of these alterations in clear-cell RCC is the basis for the development of molecular-targeted approaches against VEGF, PDGF and related pathways.

Mechanism of action

Sunitinib (sunitinib malate; SU11248; SUTENT®; Pfizer Inc, New York, NY) is a novel, orally bio-available, oxindole, multi-targeted tyrosine kinase inhibitor with anti-tumour and anti-angiogenic activities. Sunitinib is a multi-targeted agent and has been identified as a potent inhibitor of VEGFRs (types 1–3), PDGFR (α and β), as well as FLT3, KIT, colony-stimulating factor type 1 (CSF-1R) and glial cell-line-derived neurotrophic factor receptor (RET), in both biochemical and cellular assays [11].

Direct anti-tumour effects on tumour cells have also been suggested, such as wild-type and activated mutants of FLT3 expressed by acute myeloid leukaemia-derived cell lines [5], and small cell lung cancer-derived cell lines expressing KIT [12]. Indirect anti-tumour activity of sunitinib by inhibition of VEGFR expressed on endothelial cells, and PDGFR on pericytes or stromal cells has also been demonstrated [13] and its full anti-tumour efficacy was associated with prolonged (at least 12 of 24 h), but not continuous, inhibition of VEGFR2 and PDGFR.
clinical pharmacology

In vitro metabolism studies demonstrated that sunitinib is metabolized primarily by cytochrome CYP3A4, resulting in formation of a major, pharmacologically active N-desethyl metabolite, SU012662. This metabolite was shown to be equipotent to the parent compound in biochemical tyrosine kinase and cellular proliferation assays, acting toward VEGFR, PDGFR and KIT [14].

Pharmacokinetic data indicate good oral absorption, a prolonged half-life for sunitinib (~40 h) and its active metabolite, SU12662 (~80 h) and linear kinetics at the doses administered. A dose-proportional increase in both maximum concentration (C\text{max}) and area under the curve (AUC) of Sunitinib was observed with increasing doses from 50 to 350 mg. Similar linearity was observed for the active metabolite SU12662 (10–15%). Across all dose levels, the time to plasma peak (T\text{max}) was generally observed at 4–6 and 8–12 h, for both sunitinib and its metabolite.

These results indicate that a single dose of sunitinib exhibits dose-dependent pharmacokinetics in humans. Drug plasma protein binding rate is estimated to be 90% (SU12662) to 95% (Sunitinib) with a largest volume of distribution of 2230 L.

Radiolabeled, orally administrated sunitinib in preclinical species was primarily excreted in the faeces (70–84%; investigator brochure). Only 16% of parent drug was excreted in the urine (Table 1). Pharmacokinetic/pharmacodynamic data from animal studies showed that target plasma concentrations of sunitinib plus SU012662 capable of inhibiting PDGFR\beta and VEGFR2 phosphorylation were established in the range of 50–100 ng/ml. Interestingly, those data were consistent with those observed in patients with several cancers.

In acute myeloid leukaemia, treatment led to a sustained inhibition of FLT3 phosphorylation in blast cells. From two phase II advanced RCC trials including 169 patients, a population pharmacokinetic analysis was performed to assess the exposure–response relationship between pharmacokinetics and tumour volume changes, clinical response and time to tumour progression (TTP). Plasma clearance decreased by an average of 28% in metastatic RCC patients relative to healthy volunteers. Improved clinical response and longer time to progression were associated with greater AUCs. Within 12 weeks of treatment, mean tumour volume decreased by 24–32% in each trial. The authors concluded that over the first 12 weeks of treatment at 50 mg daily on schedule 4/2, increased exposure was associated with improved clinical response and decreased tumour volumes [15]. However, at higher doses (275 mg/d), tumour responses were often associated with reduced intra-tumoural vascularization and central tumour necrosis, eventually resulting in organ perforation or fistula [16].

clinical experience in renal cell carcinoma (table 2)

Objective responses have been observed in the phase I study conducted in Gustave-Roussy Institute [16]. In this early phase of development including 22 patients, objective responses have been documented in 3 out of 6 patients with metastatic RCC. Based both on this report and a solid biological background, two single-arm consecutive studies involving patients with advanced RCC who had experienced failure of prior cytokine-based therapy [17, 18] have been conducted by Motzer et al. Patients received the Gustave-Roussy schedule (50 mg/day continuously for 4 weeks, followed by 2 weeks off) until they met withdrawal criteria or had progressive disease.

In the first study [17], 63 patients with advanced RCC were enrolled. The majority of patients had clear cell-carcinoma (55 patients; 87%), but the study included small minorities of patients with papillary cell subtype (4 patients; 6%), sarcomatoid variant (1 patient; 2%), and unspecified (3 patients; 5%). An outstanding response rate of 40% (using RECIST criteria) was reported with a duration of response of 8.7 months. Median duration of treatment was 9 months and median time to progression was 8.7 months. Stable disease lasting more than 3 months in an additional 17 patients (27%) was also reported. Of the 25 patients with partial responses, 2 discontinued treatment, 15 experienced progression and 8 remained progression-free more than 20 months from the initiation of therapy.

To confirm the anti-tumour activity and safety observed in the first phase II trial, a second larger study [18] involving 106 patients with clear-cell metastatic RCC was conducted. The objective response rate was 39%. Of the 106 patients that were evaluable for efficacy analyses, 36 patients achieved partial response [34%; 95% confidence interval (CI), 25–44%], and a median progression-free survival of 8.3 months as evaluated by an independent third-party assessment. No complete responses were reported in those two studies.

A randomized phase III international trial [19] compared the efficacy and safety of sunitinib to IFN-α in first-line treatment of patients with advanced RCC. Results demonstrated a statistically significant improvement in progression-free survival and a better objective response rate for sunitinib over IFN-α in first-line treatment of patients with metastatic RCC. 690 untreated patients with clear-cell advanced RCC were randomized 1:1 to receive sunitinib (375 patients) (6-week cycles: 50 mg orally once daily for 4 weeks, followed by 2 weeks off) or IFN-α (375 patients) (6-week cycles:...
subcutaneous injection 9 MU given three times weekly). Ninety percent of patients had prior nephrectomy. Median progression-free survival was 47.3 weeks (95% CI 40.9) for sunitinib versus 24.9 weeks (95% CI 21.9, 37.1) for IFN-α [hazard ratio 0.394 (95% CI 0.297, 0.521) (P < 0.000001)]. The objective response rate by third-party independent review was 37% for sunitinib versus 4.9% for IFN-α (P < 0.000001). The objective response rate by investigator assessment was 31% (95% CI 30.9, 40.8) for sunitinib versus 6 versus 8.8% (95% CI 6.1, 12.1) for IFN-α (P < 0.000001). 632 patients (85%) are alive, with 49 deaths on sunitinib arm and 65 deaths (95% CI 30.9, 40.8) for sunitinib versus 6 versus 8.8% (95% CI 6.1, 12.1) for IFN-α (P < 0.000001). The objective response rate by investigator assessment was 31% (95% CI 30.9, 40.8) for sunitinib versus 6 versus 8.8% (95% CI 6.1, 12.1) for IFN-α (P < 0.000001). 632 patients (85%) are alive, with 49 deaths on sunitinib arm and 65 deaths (95% CI 30.9, 40.8) for sunitinib versus 6 versus 8.8% (95% CI 6.1, 12.1) for IFN-α (P < 0.000001). The toxicity profile was similar to that reported in second-line trials. All prognostic sub-groups benefited from sunitinib. Based on this large phase III study, sunitinib is standard therapy for first-line treatment of metastatic RCC.

**toxicity, practical consideration and discontinuation of drug treatment**

In the two phase II RCC trials [17, 18], the most common side effects that were noted, compared with those observed in the GIST study, are fatigue (74%), diarrhoea (55%), nausea (54%), and mucositis and stomatitis (53%). In most instances, symptoms improved with dose modification. In the first phase II study, however, in 12 patients (11%), sunitinib was discontinued due to adverse events [17]. Also, two patients were taken off study for asymptomatic decreases in left ventricular ejection fraction of >20% compared with baseline. The exact mechanisms of sunitinib toxicities are not well understood. Hypertension and asthenia are thought to be associated with inhibition of VEGF and VEGFRs. Skin and/or hair depigmentation or discolouration are attributed to a direct anti-VEGFR and/or PDGFR effect on dermal endothelial cells, as well. Reversible hair depigmentation was associated with modulation of tyrosinase-related protein 1 genes and tyrosinase, related to the KIT signalling pathway [16].

A subset of patients may develop thyroid dysfunction, which may account, in part, for fatigue previously described with sunitinib. Thyroid dysfunction is not dose-limiting and patients could be treated effectively with thyroid hormone replacement, with rapid clinical improvements and resolution of thyroid-stimulating hormone (TSH) elevation. The mechanism by which sunitinib affects thyroid function is being investigated and may account for documented objective responses to this drug [20].

**Conclusion and perspectives**

In addition to sunitinib there are several other VEGFR inhibitors developed in RCC, including sorafenib which completed phase III evaluation and had been recently registered. Additional agents including AG-013736 [22] and pazopanib [23] have demonstrated promising activity and could complete in the next future the arsenal for the treatment of metastatic RCC. Furthermore, other strategies to inhibit the major iso-forms of VEGF-A (using bevacizumab or VEGF-trap) or mTOR activity, a downstream component of the PI3K/Akt pathway (using temsirolimus or everolimus) have shown significant activity.

Sunitinib has clearly revolutionized the treatment of metastatic RCC and was approved based on two single-arm studies compared with historical controls. Several major questions need to be addressed in prospective trials to enhance efficacy; combination studies with agents that target non-VEGF pathways need to be extensively explored; combination with mTOR inhibitors are warranted; quest for identification of predictive factors of sunitinib activity are currently explored including clinical

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**Table 2. Sunitinib activity in metastatic renal carcinoma**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Phase of development</th>
<th>Response rate (RECIST)</th>
<th>TTP (Median, Mo)</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fairev et al. 2006 [16]</td>
<td>22</td>
<td>I</td>
<td>3 out 6 patients with metastatic RCC</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Motzer et al. 2006 [17]</td>
<td>63</td>
<td>II</td>
<td>40%</td>
<td>8.7</td>
<td>NA</td>
</tr>
<tr>
<td>Motzer et al. 2006 [18]</td>
<td>106</td>
<td>II</td>
<td>39%</td>
<td>8.3</td>
<td>NA</td>
</tr>
<tr>
<td>Motzer et al. 2007 [19]</td>
<td>690</td>
<td>III</td>
<td>31%</td>
<td>11</td>
<td>NR</td>
</tr>
</tbody>
</table>

Mo. months; NA, not applicable; NR, not reached.
(e.g. hypertension) or biological parameters (e.g. erythropoietin level, proteomic or genomic analysis).

Patient management after sunitinib failure is another remaining question. Second- and third-line therapies are under evaluation to study efficacy and mechanism(s) of cross-resistance among targeted agents. Preliminary data suggest the putative absence of constant cross-resistance between anti-angiogenic compounds. In a phase II study evaluating the activity of sunitinib in bevacizumab-refractory metastatic RCC, 26 out of 32 patients (81%) demonstrated some degree of tumour shrinkage, including 4 patients with an objective response [24].

The role of sunitinib in the adjuvant setting will be evaluated in Europe in a large phase III study in a selected population (high-risk) compared with observation, which remains the standard of care in this indication.

The role of initial cytoreductive nephrectomy in de novo metastatic patients and the resection of metastases in responding patients should be evaluated in specific trials.

Finally, the activity of sunitinib in non-clear-cell RCC is warranted. c-Met alterations in this histology subtype constitute a robust rationale to support the initiation of exploratory studies in this setting [25].

references

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