Expanding the boundaries of clinical practice: building on experience with targeted therapies

C. N. Sternberg
Department of Medical Oncology, San Camillo Forlanini Hospital, Rome, Italy

Background: Advances in understanding of the mechanisms underlying cancers such as renal cell carcinoma (RCC) and gastrointestinal stromal tumour (GIST) have enabled the identification of therapeutic targets. Targeted agents have considerably improved the prognosis for patients with these cancers.

Design: This supplement reviews approaches to the management of metastatic RCC (mRCC) and advanced GIST using targeted agents and examines clinical evidence supporting these strategies. Future developments in RCC and GIST treatment are also considered.

Results: In a phase III trial in 750 treatment-naive mRCC patients, the multitargeted tyrosine kinase inhibitor sunitinib conferred median progression-free survival more than double that seen with interferon-alfa and median overall survival exceeding 2 years. Sunitinib is now considered the reference standard of care for first-line treatment of mRCC, and bevacizumab plus interferon-alfa is also recommended in this setting. As a result, the treatment algorithm has evolved to reflect the role of sunitinib and other targeted agents for mRCC. For advanced GIST, sunitinib has been shown to extend survival in patients with imatinib-resistant/-intolerant GIST and is licensed multinationally in this setting.

Conclusions: Developments with targeted agents may enhance the treatment of patients with advanced RCC and GIST and offer benefits in other settings, such as adjuvant and neoadjuvant therapies.

Key words: gastrointestinal stromal tumour, metastatic renal cell carcinoma, overall survival, progression-free survival, targeted therapies

introduction

Targeted therapies have significantly improved prognosis for patients with cancers such as metastatic renal cell carcinoma (mRCC) and gastrointestinal stromal tumours (GISTs). Fewer than 20% of patients with mRCC gained benefit from the previous standard of care, cytokine therapy, and median overall survival (OS) averaged only 13 months [1–3]. Median progression-free survival (PFS) in patients with mRCC has more than doubled with the introduction of targeted therapies compared with cytokines, and substantial improvements in objective response rates (ORRs) have been observed [4, 5].

Similarly, before the advent of targeted agents, the prognosis for patients with advanced GIST was poor, as chemotherapy and radiotherapy were generally ineffective [6]. Historical data show a median OS of 19 months for patients with metastatic GIST and 9 months for patients with metastatic GIST and local recurrence [7]. The 1-year OS rate in patients with advanced GIST has increased to almost 90% with the introduction of targeted agents [6, 8].

development and mode of action of targeted therapies in mRCC and GIST

Advances in knowledge of the molecular mechanisms and oncogenic processes associated with RCC and GIST have enabled rational targets for pharmacotherapy to be identified.

In clear-cell RCC, the most common subtype of RCC, inactivation of the von Hippel–Lindau (VHL) gene is associated with the accumulation of hypoxia-inducible factor 1 (HIF-1α), allowing transcriptional activation of several genes, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) [9–11]. VEGF and PDGF serve as agonists for their respective receptor tyrosine kinases, VEGFR and PDGR. Overexpression of these and other receptor tyrosine kinases is implicated in tumour angiogenesis and growth, providing a rationale for targeting these pathways in RCC and other solid tumours [12]. HIF-1α levels are also regulated by the phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (mTOR) signal transduction pathway and the Ras/Raf/mitogen-activated protein kinase pathway, and both of these pathways are also potential therapeutic targets in RCC [13].

In patients with GIST, mutations in the KIT gene result in the constitutive activation of the KIT protein tyrosine kinase and lead to enhanced cell proliferation and survival in the...
in the majority of GISTs [14]. KIT mutations occur at the highest frequency in exon 11 and, in fewer cases, in exons 9, 13 and 17 [15, 16]. In addition, ~5% of GISTs have a constitutively activating mutation in the PDGFRα gene encoding PDGFR-α, which is implicated in tumour angiogenesis and growth [15, 17]. The KIT tyrosine kinase also appears to be activated in many wild-type GISTs [17].

**targeted therapies for RCC and GIST**

Sunitinib malate (SUTENT®, Pfizer Inc.), an oral multitargeted receptor tyrosine kinase (RTK) inhibitor, targets a range of receptors including VEGFR-1, -2 and -3; PDGF-α and -β; glial cell line-derived neurotrophic factor receptor (REarranged during Transfection; RET), the receptor for macrophage colony-stimulating factor 1 (CSF-1R), FMS-like tyrosine kinase 3 receptor (FLT3) and c-KIT [18–23]. Due to its multitargeted nature, sunitinib has potential for use in a range of solid tumours. Sunitinib is approved multinationally for the first- or second-line treatment of mRCC and for patients with advanced GIST who have experienced failure on or intolerance to imatinib mesylate (Glivec®; Novartis).

Other targeted agents that are available for the treatment of mRCC include sorafenib tosylate (Nexavar®; Bayer Healthcare), temsirolimus (Torisel®; Wyeth Pharmaceuticals) and combination therapy with bevacizumab (Avastin®). Sorafenib is an oral multitargeted RTK inhibitor that targets VEGFR-2 and -3, PDGFR-β, FLT3, c-KIT, RET, B-Raf and Raf-1/C-Raf [24]. Temsirolimus is an mTOR kinase inhibitor [25], while bevacizumab is a humanised monoclonal antibody that binds to and neutralises all major isoforms of VEGF-A [13].

Imatinib is the standard first-line treatment for advanced GIST. Imatinib inhibits several RTKs, including KIT, PDGFR-α and -β, ABL, BCR-ABL and ABL-related gene (ARG), and the macrophage colony-stimulating factor c-FMS [16, 26]. Sunitinib has demonstrated antitumour activity in patients with GIST who have experienced disease progression on imatinib therapy [27].

**targeted treatments for mRCC**

Several targeted agents have demonstrated efficacy for the treatment of mRCC. Sunitinib is recommended in international treatment guidelines as the reference standard of care for the first-line treatment of mRCC in patients at favourable or intermediate prognostic risk, with temsirolimus recommended for poor-risk patients [4, 5]. Combination therapy with bevacizumab plus IFN-α has also shown activity in this setting. For second-line treatment, sunitinib or sorafenib are options dependent upon prior treatment [4, 5] and evidence supports activity with the novel agents everolimus and axitinib in this setting [28–30].

Table 1 presents a treatment algorithm for the management of mRCC according to prognostic risk status and prior therapy.

**sunitinib**

In a phase III trial in 750 patients with previously untreated mRCC, sunitinib demonstrated superior efficacy in comparison with IFN-α [32, 33]. Assessment by independent central review indicated that median PFS was 11 months (95% CI 10–12) for sunitinib versus 5 months (95% CI 4–6) for IFN-α [hazard ratio (HR) 0.42; 95% CI 0.32–0.54; P < 0.001] (Figure 1, Table 2) [32]. In an update of the final results of this trial, the ORR, by investigator review, was 39% (95% CI 34–44) for sunitinib compared with 8% (95% CI 6–12) for IFN-α (P < 0.001). By investigator review, the ORR was 47% (95% CI 42–52) for sunitinib as compared with 12% (95% CI 9–16) for IFN-α (P < 0.001) [33].

Importantly, sunitinib demonstrated median OS of >2 years, the first time that OS of this duration has been observed during the first-line treatment of mRCC [26.4 months (95% CI 23.0–32.9)] for sunitinib compared with 21.8 months (95% CI 17.9–26.9) for IFN-α, corresponding to an HR of 0.821 (95% CI 0.673–1.001; P = 0.051) [33]. After the interim analysis of the trial, which showed a significant PFS benefit for sunitinib relative to IFN-α, patients were permitted to cross over to sunitinib from IFN-α treatment. Two additional analyses of median OS have been conducted to take into account patients who changed therapies. When patients who crossed over to sunitinib were omitted, median OS with sunitinib [26.4 months (95% CI 23.0–32.9)] was found to be significantly superior to that seen with IFN-α [20.0 months (95% CI 17.8–26.9); HR 0.808 (95% CI 0.661–0.987); P = 0.0362] [33]. Furthermore, among patients who received first-line therapy only and no subsequent treatments, median OS in sunitinib-treated patients was double that observed in patients treated with IFN-α [28.1 months (95% CI 19.5–NA) with sunitinib compared with 14.1 months (95% CI 9.7–21.1) with IFN-α; HR 0.647 (95% CI 0.483–0.870); P = 0.0033] [32]. It should be noted that the OS of 14.1 months reported with IFN-α in this analysis is consistent with a report of OS of 13.3 months in a Cochrane review of cytokine therapy [3].

The OS benefit with sunitinib extended across subgroups of patients stratified according to baseline factors of Eastern Cooperative Oncology Group performance status [ECOG PS

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Table 1. Treatment algorithm for metastatic renal cell carcinoma, according to patient prognostic risk and prior therapy [31–41: Adapted with permission from 31]

<table>
<thead>
<tr>
<th>Setting</th>
<th>Patients</th>
<th>Therapy (level 1)</th>
<th>Other options (level 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previously untreated</td>
<td>Good-/intermediate-risk</td>
<td>Sunitinib + IFN-α</td>
<td>HD IL-2, Sorafenib</td>
</tr>
<tr>
<td>Poor-risk</td>
<td>Temsirolimus</td>
<td>Clinical trial</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>Treatment refractory</td>
<td>Prior cytokine</td>
<td>Sorafenib</td>
<td>Sunitinib</td>
</tr>
<tr>
<td>Prior VEGF–TKI</td>
<td>mTOR</td>
<td>Everolimus + IFN-α</td>
<td>Clinical trial</td>
</tr>
</tbody>
</table>

IFN-α, interferon-alfa; HD IL-2, high-dose interleukin-2; VEGF–TKI, vascular endothelial growth factor-tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin.
0 versus 1; HR 0.515 (95% CI 0.417–0.636); *P < 0.0001*, time from diagnosis to treatment [21 year versus <1 year; HR 0.574 (95% CI 0.461–0.715); *P < 0.0001*], haemoglobin [lower limit of normal versus <lower limit of normal; HR 0.304 (95% CI 0.401–0.634); *P < 0.0001*], corrected calcium ([≤10 mg/dl versus >10 mg/dl; HR 0.466 (95% CI 0.327–0.664); *P < 0.0001*] and lactate dehydrogenase (LDH) levels ([≤1.5 upper limit of normal versus >1.5 upper limit of normal; HR 0.500 (95% CI 0.337–0.742); *P = 0.0006*] [33]. Sunitinib was also associated with OS benefit compared with IFN-α according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic risk status. Median OS was 5.3 months (95% CI 4.2–10.0) with sunitinib versus 4.0 months (95% CI 2.7–7.2) with IFN-α in poor-risk patients (HR 0.660; 95% CI 0.360–1.207), 20.7 months (95% CI 18.2–25.6) with sunitinib versus 15.4 months (95% CI 13.6–18.2) with IFN-α (HR 0.787; 95% CI 0.617–1.004) in intermediate-risk patients, and was not reached with either treatment in the favourable-risk prognostic group [34].

Sunitinib has also shown efficacy in an international open-label expanded-access study. This study was initiated to enable a broad, heterogeneous population of patients with mRCC who are ineligible for participation in clinical trials to receive sunitinib, including those who have been heavily pre-treated or who have poor performance status [42–44]. In 4185 evaluable patients in the intention-to-treat population, median PFS of 10.8 months (95% CI 10.2–11.1) was observed, with median OS reaching 19.8 months (95% CI 19.1–21.1) [42]. It is important to note that the median PFS observed here is in line with that reported from the phase III trial, indicating that sunitinib provides consistent efficacy during first-line treatment for mRCC. Furthermore, substantial antitumour activity was demonstrated with sunitinib in patients with brain metastases [42]. The safety profile reported with sunitinib was consistent with that reported previously in the literature [44], and there was no indication of long-term cardiovascular safety concerns. These results are encouraging given the heterogeneous nature of this patient population, which included elderly and poor-risk patients.

**bevacizumab plus IFN-α**

Bevacizumab, in combination with IFN-α, has demonstrated activity in the first-line setting in mRCC in two phase III studies (Table 2) [35, 36]. Median PFS by investigator assessment was superior for bevacizumab plus IFN-α versus IFN-α alone (10.2 months compared with 5.4 months, respectively, in the first study and 8.5 months compared with 5.2 months, respectively, in the second cooperative group CALGB study) [35, 36]. ORR by investigator assessment was also superior in patients treated with bevacizumab plus IFN-α compared with IFN-α (Table 2) [35, 36]. OS data are not yet mature for either of these studies.

**temsirolimus**

In a randomised, multicentre phase III trial, temsirolimus monotherapy was compared with temsirolimus plus IFN-α and IFN-α alone in 626 patients with previously untreated poor-prognosis mRCC [38]. The definition of poor risk in this study utilised the five MSKCC criteria (low haemoglobin, high corrected calcium, high lactate dehydrogenase, poor performance status, interval of <1 year from diagnosis to treatment [45]), as well as a sixth characteristic, the number of metastatic sites [38]. Median PFS and OS were significantly longer in patients treated with temsirolimus monotherapy compared with IFN-α alone (Table 2) [38].

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**Figure 1.** Kaplan–Meier estimate of progression-free survival (by independent central review) with sunitinib versus interferon-alfa (IFN-α) in previously untreated patients with metastatic renal cell carcinoma [Reproduced with permission from 32].

**Table 2.** Median progression-free survival, overall survival and objective response rates reported with key targeted agents in randomised controlled trials in first-line and second-line settings in patients with mRCC [28, 29, 32–36, 38–40]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sunitinib versus IFN-α [32–34]</td>
<td>750</td>
<td>11.0 versus 5.1*</td>
<td>26.4 versus 21.8</td>
<td>47 versus 12*</td>
</tr>
<tr>
<td>Bevacizumab + IFN-α versus IFN-α [35]</td>
<td>649</td>
<td>10.2 versus 5.4*</td>
<td>IFN-α: 19.8 Bev + IFN-α: NR</td>
<td>31 versus 13*</td>
</tr>
<tr>
<td>Bevacizumab + IFN-α versus IFN-α [36]</td>
<td>732</td>
<td>8.5 versus 5.2*</td>
<td>NR</td>
<td>26 versus 13*</td>
</tr>
<tr>
<td>Temsirolimus versus IFN-α [38]</td>
<td>626</td>
<td>5.5 versus 3.1*</td>
<td>10.9 versus 7.3*</td>
<td>8.6 versus 4.8</td>
</tr>
<tr>
<td><strong>Second-line setting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib versus placebo [39, 40]</td>
<td>903</td>
<td>5.5 versus 2.8*</td>
<td>17.8 versus 15.2</td>
<td>10 versus 2</td>
</tr>
<tr>
<td>Everolimus versus placebo [28, 29]</td>
<td>410</td>
<td>4.9 versus 1.9*</td>
<td>Placebo: 13.0 Everolimus: NR</td>
<td>1 versus 0</td>
</tr>
</tbody>
</table>

*Statistically significant.

PFS, progression-free survival; OS, overall survival; ORR, objective response rate; IFN-α, interferon-alfa; Bev, bevacizumab; NR, not reported.
previously untreated patients with metastatic renal cell carcinoma [33, 34]. Imatinib demonstrated efficacy in a phase III study in which patients with GIST received imatinib at either 400 mg/day or 800 mg/day [48]. OS was estimated at 85% at 1 year and 69% at 2 years in patients treated with the 400 mg/day dose and 86% and 74%, at 1 and 2 years, respectively, in patients receiving the 800 mg/day dose. Overall, 5% of patients achieved a complete response. Of the patients treated with imatinib 400 mg/day, 56% experienced disease progression compared with 50% of patients treated with imatinib 800 mg/day [HR 0.82 (95% CI 0.69–0.98); P = 0.026].

sunitinib
Approximately 12–14% of patients with GIST develop primary resistance to imatinib and 4% exhibit intolerance to imatinib [6, 26, 49]. In a phase III study in patients with advanced imatinib-resistant or -intolerant GIST, sunitinib treatment significantly increased TTP in comparison with placebo [27,3 weeks (95% CI 16.0–32.1) compared with 6.4 weeks (95% CI 4.4–10.0); HR 0.33; P < 0.0001] [27]. Updated data from this analysis are discussed in more detail by Jean-Yves Blay later in this supplement [30].

conclusions
As experience with the use of targeted agents in clinical practice grows, strategies are being developed to maximise benefits for patients. This includes ensuring optimal use of available targeted agents for different patient profiles, based on available clinical evidence, as well as approaches to manage treatment-related adverse events.

This supplement provides an overview of the current state of the art in mRCC management, including approaches to therapy management with targeted agents such as sunitinib, the standard of care for the first-line treatment of mRCC. We also examine future developments in RCC treatment. The tolerability profile of targeted agents in patients with mRCC and strategies to manage treatment-related adverse events to improve compliance is discussed by Alain Ravaud [51]. In his article, Joaquim Bellmunt reviews future developments in RCC treatment, including optimal use of targeted agents in sequence, and potential use of targeted agents in the adjuvant and neoadjuvant settings [52].

The management of GIST with targeted agents is reviewed by Jean-Yves Blay [50], including a discussion of ongoing clinical trials that will further define the role of these agents in the future. Finally, case studies describing the use of sunitinib in patients with mRCC and GIST in clinical practice are presented in the article by Patrick Schoffski, Ronald Bukowski, Per Flodgren and Alain Ravaud [53].

Targeted agents have considerably improved the prognosis of patients with mRCC and GIST; the recent and future developments described here may enhance the treatment of patients who already receive therapy with targeted agents, in addition to offering potential additional benefits in other settings.

disclosures
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sorafenib
Sorafenib has shown efficacy in the second-line treatment of mRCC, among patients in whom prior cytokine therapy had failed (Table 2) [39]. In a randomised phase III trial in 903 patients, median PFS was significantly longer with sorafenib therapy compared with placebo treatment (Table 2) [39]. In the final analysis of this study, in a pre-planned analysis accounting for crossover from placebo to sorafenib, median OS was 17.8 months for sorafenib versus 14.3 months for placebo (P = 0.0287) [40].

targeted agents in development
In a phase III study (N = 416), the oral mTOR inhibitor, everolimus, demonstrated clinical efficacy in the treatment of patients with mRCC who had shown disease progression in response to prior therapy with sunitinib or sorafenib or sunitinib and sorafenib or other therapies (e.g. bevacizumab or cytokines) [28, 29]. More than 70% of the patients enrolled in the study had received prior treatment with sunitinib, sorafenib or both. Patients treated with everolimus achieved significantly longer median PFS compared with placebo (Table 2) [29]. There was no OS benefit due to crossover [41].

Two phase II trials have investigated the efficacy and safety of the oral VEGF inhibitor, axitinib [30, 46]. Axitinib showed clinical activity and acceptable toxicity in 52 patients with cytokine-refractory mRCC. The ORR was 44.2%, median time to progression was 15.7 months and median OS was 29.9 months [46]. In 62 patients with mRCC refractory to sunitinib and sorafenib, cytokines and sorafenib, or sorafenib alone, axitinib demonstrated antitumour activity, indicating an absence of cross-resistance [30].

The VEGF inhibitor pazopanib has shown activity in a phase II study of 225 patients with advanced RCC. The ORR was 34.7% and median PFS was 11.9 months [47].

targeted treatments for GISTs
imatinib
Imatinib demonstrated efficacy in a phase III study in which patients with GIST received imatinib at either 400 mg/day or
references


