How to optimise treatment compliance in metastatic renal cell carcinoma with targeted agents

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Background: Targeted agents are being used increasingly for the treatment of metastatic renal cell carcinoma (mRCC). Targeted agents are associated with a distinct pattern of adverse events (AEs) in mRCC, which should be managed promptly to ensure that patients maintain tumour control without impacting quality of life.

Design: This article discusses the importance of maintaining patients on optimum doses of targeted therapy to maximise treatment benefit, and reviews the safety profiles of targeted agents in mRCC. Strategies for managing the AEs associated with targeted agents are presented.

Results: Higher exposure to targeted agents is positively associated with increased probability of achieving improved overall survival, underlining the importance of maintaining patients on appropriate doses to derive clinical benefit. Patients’ risk profiles should be assessed before commencing targeted therapy and patients should be educated about AEs to aid early identification and treatment and improve compliance. Practical steps can be taken to minimise the impact of AEs and maintain patients on targeted therapy.

Conclusions: Targeted agents are associated with predictable AE profiles in mRCC. Early detection of treatment-related AEs and effective implementation of management strategies can reduce patient discomfort, avoid the need for dose reductions and discontinuations, improve patient compliance and support optimal clinical outcomes.

Key words: adverse events, management, metastatic renal cell carcinoma, targeted agents, treatment compliance

introduction
Targeted therapies have proven efficacy in the treatment of metastatic renal cell carcinoma (mRCC) [1–4]. Sunitinib malate (SUTENT®; Pfizer Inc.) is the current reference standard of care for first-line treatment of mRCC [5, 6]. As discussed in detail in the article by Cora Sternberg [7], sunitinib was associated with median overall survival (OS) of >2 years in a phase III trial in patients with previously untreated mRCC, the first time that OS of this duration has been observed in this setting [8].

In addition to sunitinib, targeted therapies for mRCC approved in Europe include the receptor tyrosine kinase (RTK) inhibitor, sorafenib (Nexavar®; Bayer Healthcare), for cytokine-refractory mRCC; an inhibitor of the mammalian target of rapamycin (mTOR) protein, temsirolimus (Torisel®; Wyeth Pharmaceuticals), approved for use in selected poor-risk mRCC patients; and the vascular endothelial growth factor (VEGF) ligand-binding monoclonal antibody, bevacizumab (Avastin®; F. Hoffmann-La Roche), given in combination with interferon-alfa (IFN-α).

Targeted agents are associated with a distinct pattern of adverse events (AEs) in mRCC, which are different from those observed with conventional chemotherapy or immunotherapy. As such, it is important for physicians treating mRCC patients with targeted agents to be aware of potential associated AEs and to anticipate and/or initiate management strategies promptly to avoid deleterious effects on clinical outcome and patient quality of life (QoL). This article discusses the importance of therapy management in order to maximise treatment benefit in mRCC, and reviews strategies for optimising treatment compliance.

importance of maintaining patients at the optimum dose
Sustaining adequate drug levels is important to maintain tumour control. In an analysis of efficacy in a meta-analysis of two phase II studies and one phase III trial in mRCC (N = 192), higher sunitinib exposure (25–75 mg/day) was found to be positively associated with the increased probability of achieving a partial response, longer time to progression (TTP) and improved OS (Figure 1) [9]. In addition, pharmacokinetic modelling studies have predicted a greater decrease in tumour volume with sunitinib 50 mg compared with sunitinib 25 mg [10]. An evaluation of safety from the meta-analysis (N = 319) showed only minimal changes in blood pressure and neutrophil levels, as indicators of hypertension and neutropenia, with increasing sunitinib...
A phase II comparison of three dosage levels of temsirolimus (25, 75 and 250 mg) in treatment-refractory mRCC (N = 111) indicated similar tolerability and tumour response rates across the three dosage levels [13]. Further analyses are required to fully characterise the relationship between administered dose and AE severity with the targeted agents, but data highlight the importance of optimal dosing in order to achieve maximal clinical benefit.

**safety profiles of targeted agents**

A number of clinical trials and expanded-access studies have provided data on the tolerability of targeted agents in mRCC. Cross-trial comparisons should be performed with caution because of the potential use of different criteria between trials for the assessment and documentation of AEs. However, careful comparison of trial data can provide an indication of the relative frequencies and intensities of AEs associated with the targeted agents in mRCC.

There are some similarities in the types of AE observed with the targeted agents, although the specific profiles and relative severities vary by agent, as shown in Table 1. For example, administration of first-line bevacizumab with IFN-α in a phase III trial was associated with grade 3–4 fatigue in 37% of mRCC patients [15]. Grade 3–4 fatigue was reported in 7% and 11% of mRCC patients receiving first-line sunitinib and temsirolimus, respectively, in phase III randomised clinical trials [3, 4], and in 5% of patients receiving second-line sorafenib in a phase III trial [1].

In addition to clinical trial results, data are now available evaluating the impact of targeted agents over the longer term (i.e.,>6 months). In a large, international, expanded-access study with sunitinib, no new or unexpected long-term toxicities were identified during long-term use (N = 1263), and there was no evidence of serious cumulative toxicity and no apparent increase in the incidence of grade ≥3 cardiac toxicities [16]. A lack of long-term cumulative toxicity has also been reported in Japanese mRCC patients (N = 61) receiving long-term sorafenib [17], and in mRCC patients (N = 95) receiving bevacizumab plus IFN-α followed by bevacizumab alone for >12 months [18].

As stated above, all of the targeted agents available for the treatment of mRCC are associated with fatigue/asthenia to varying degrees [1–4]. Fatigue is an AE that places a substantial burden on patients in terms of its impact on QoL and is a clinical symptom of mRCC that may be related to the tumour burden. The severity of fatigue may be affected by patient age, comorbidities and nutrition. Furthermore, fatigue may be caused by thyroid function abnormalities and hypothyroidism, which have been observed in patients treated with sunitinib and, less frequently, in those administered sorafenib [19–21]. In a study in 66 patients receiving sunitinib therapy with available thyroid function test data, 85% of patients exhibited one or more post-treatment thyroid function test (TFT) abnormalities [19], compared with 41% of mRCC patients receiving sorafenib in a small retrospective study of TFT abnormalities (N = 39) [20]. In total, 70% and 18%, respectively, of patients receiving sunitinib and sorafenib in the two studies experienced post-treatment elevations in thyroid-stimulating hormone [19, 20].

Data from a small study evaluating sunitinib in mRCC (N = 40) have suggested that sunitinib-induced thyroid dysfunction was correlated with patient outcomes, indicating the potential of hypothyroidism as a biomarker of treatment response [21]. Typically, hypothyroidism occurs 2–3 months after the initiation of treatment but time of onset can vary from patient to patient.

Skin toxicity, and specifically hand–foot syndrome (HFS), has been observed with the RTK inhibitors sunitinib and sorafenib (Table 1) [1, 4]. HFS is characterised by erythema, numbness, dysaesthesia and/or paraesthesia, and desquamation on the palms of the hands or soles of the feet. HFS often occurs during the third or fourth week of the first treatment cycle [22].

**Figure 1.** Correlation between sunitinib exposure and (A) time to progression and (B) overall survival in patients with metastatic renal cell carcinoma [reproduced with permission from 9]. AUC, area under the curve.

Supporting these results, a study with sorafenib (N = 44) showed that dose escalation [400 mg twice daily (b.i.d.) on days 1–28, 600 mg b.i.d. on days 29–56, 800 mg bid on day 57 onwards, as tolerated] was associated with improved response rates, according to Response Evaluation Criteria In Solid Tumors (RECIST), but not with prolonged progression-free survival (PFS) [11, 12]. The same study reported a mild-to-moderate AE profile with dose escalation and suggested greater efficacy with higher exposure [11, 12]; however, these findings require confirmation in a larger study.

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with these agents, and may necessitate dose reduction for a period of time.

Several targeted agents, particularly bevacizumab plus IFN-α, sorafenib and sunitinib, have been associated with hypertension [1, 2, 4], which may be due to the inhibition of VEGF. Indeed, one study suggested that hypertension may act as a marker for the activity of VEGF-targeted agents [22]. Hypertension can occur rapidly after the initiation of targeted therapy, therefore patients should be assessed for individual risk before treatment is initiated. It is important to note, however, that the overall incidences of cardiovascular toxicities associated with both sunitinib and sorafenib appear to be low [23, 24].

Table 1. Selected phase III safety data for targeted agents in the treatment of patients with metastatic renal cell carcinoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients, n</th>
<th>Most frequently reported all-grade adverse events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib versus IFN-α [4, 7]</td>
<td>375</td>
<td>Diarrhoea (53), fatigue (51), nausea (44)</td>
</tr>
<tr>
<td>Bevacizumab/IFN-2α versus IFN-2α/placebo [2]</td>
<td>327</td>
<td>Fatigue (51), pyrexia (34), nausea (33)</td>
</tr>
<tr>
<td>Bevacizumab/IFN-α versus IFN-α/placebo [13]</td>
<td>369</td>
<td>Pyrexia (45), anorexia (36), fatigue (33)</td>
</tr>
<tr>
<td>Temsirolimus versus IFN-α</td>
<td>209</td>
<td>Pyrexia (43), anorexia (30), asthenia (28)</td>
</tr>
<tr>
<td>versus temsirolimus/IFN-α [3]</td>
<td>210</td>
<td>Fatigue (37), anorexia (17), proteinuria (15)</td>
</tr>
<tr>
<td>Second-line treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib versus placebo [1]</td>
<td>451</td>
<td>Diarrhoea (43), rash/desquamation (40), fatigue (37)</td>
</tr>
<tr>
<td>Everolimus versus placebo [14]</td>
<td>272</td>
<td>Fatigue (28), nausea (19), rash/desquamation (16)</td>
</tr>
<tr>
<td></td>
<td>138</td>
<td>Asthenia (64), fever (50), anorexia (44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthenia (62), fever (60), anaemia (61)</td>
</tr>
</tbody>
</table>

*Grade 3–4 adverse events reported.
AE, adverse event; IFN-α, interferon-alfa.

Note: The table above presents patient numbers and most frequently-reported AEs for six targeted agents in phase III trials. The corresponding patient number and AEs for the comparator treatment(s) in each trial are presented in the row below.

strategies to optimise compliance with targeted agents

Widespread use of targeted agents in the clinic has enabled the development of practical AE management techniques to enable patients to derive the greatest benefit from treatment. Based on clinical experience, specific strategies and recommendations to manage the AEs associated with targeted agents are summarised in Table 2 [23].

Before commencing treatment, a full assessment of the patient’s risk profile should be conducted, including, in particular, blood pressure, cardiovascular risk and thyroid function tests. Any comorbidities and risk factors should be stabilised before treatment is initiated. It is important to note that general practitioners are typically unfamiliar with the AE profiles of targeted agents and may not be equipped for their management. Specialists with experience in prescribing targeted agents have a key role to play to ensure that these agents are administered correctly and that patients are managed appropriately during treatment.

It is also important to educate patients and their caregivers about AEs that might occur with targeted therapy and to provide accessible support and counselling, particularly during the first two treatment cycles. Educating patients can help in the early identification and management of AEs, which may minimise patient discomfort and dissatisfaction with therapy and could reduce the need for dose reductions or treatment interruptions. Patient education may also improve the patient’s ability to manage uncomfortable AEs that may be non-relevant clinically, so that they can achieve prolonged exposure to targeted therapy. Illustrative aids may be particularly useful to help patients to recognise particular AEs, such as HFS. Frequent monitoring and assessment of patients undergoing treatment with targeted agents is essential and patients should be made aware of the importance of regular follow up.

fatigue and hypothyroidism

Fatigue rarely leads to dose reductions or treatment interruptions if managed appropriately. Factors contributing to the onset and exacerbation of fatigue, including pain, anaemia, depression and hypothyroidism, should be monitored carefully.

Patient counselling should be provided to help motivate patients to remain on therapy and daily activities may need to be adapted. When QoL is severely affected by fatigue, it may be necessary to modify the dosage of the targeted agent; as symptoms stabilise, it may then be possible to increase the dose.
Baseline laboratory measurement of thyroid function is recommended. All patients should be observed for signs and symptoms of hypothyroidism during treatment with sunitinib, and such strategies may also be considered for sorafenib. Monitoring of thyroid-stimulating hormone is recommended every two cycles, when symptoms occur. Once detected, hypothyroidism can be managed easily through standard medical practice.

**Hand–foot syndrome**

Any pre-existing plantar hyperkeratosis should be treated before the commencement of therapy with a targeted agent.

<table>
<thead>
<tr>
<th>AE</th>
<th>Management</th>
<th>During therapy</th>
<th>Sunitinib treatment adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/asthenia</td>
<td>Counsel on expectations from treatment Offer psychological support Encourage modification of daily activities to conserve energy Advise that physical exercise may help to reduce levels of fatigue</td>
<td>Monitor patients for underlying factors: hypothyroidism, anaemia, pain, depression, emotional distress, sleep disturbance Treat underlying factors according to standard treatment</td>
<td>Dose modifications (required infrequently) when fatigue is disruptive to QoL</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Monitor for baseline thyroid function (exacerbation of asthenia) and treat according to standard practice</td>
<td>Monitor for TSH every two cycles, when symptoms occur Patients should be treated when clinical signs occur and when biological disturbances are observed Manage according to standard medical practice</td>
<td></td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>Educate patients regarding AEs using visual illustrations and leaflets Conduct full foot exam and consult with podiatrist Advise patients to reduce pressure on affected areas Any pre-existing plantar hyperkeratosis should be treated before commencement of therapy</td>
<td>Advise patients to wear thick-soled shoes Recommend shock absorbers and hydrocolloidal bandages (for grade 2–3 HFS) Podiatrist consultations, as required Emollient creams and topical treatments containing urea or salicylic acid. Topical corticosteroids for patients experiencing painful erythema</td>
<td>Treatment interruption or dosage reduction may be required where HFS of grade ≥2 affects patient QoL until resolution to grade 0 or 1</td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>Conduct a full cardiovascular assessment Monitor patients for hypertension and control according to standard medical practice BP should be stabilized at ~130/80 mmHg before treatment initiation</td>
<td>Monitor for signs and symptoms of CHF and LVEF, particularly in patients with cardiac risk factors Monitor patients regularly for BP (daily or three times per week) Treat with individualised anti-hypertensive therapy and monitor in case of dose reduction/interruption of targeted therapy</td>
<td>Dose reduction/discontinuation to reverse change in LVEF if &lt;50% and &gt;20% below baseline If BP exceeds 170/100 mmHg, treatment interruption or dose reduction may be required until hypertension is controlled</td>
</tr>
<tr>
<td>Oral changes and mucositis</td>
<td>Educate patients on possible symptoms Consult dietician for diet modification Switch to paediatric toothpaste and a soft toothbrush Advise patients to avoid consuming alcohol</td>
<td>Advise use of bicarbonate mouthwashes containing paracetamol with morphine or codeine to help symptom control Tetracain-hydrochloride gels, camomile, sage, arnica and zinc may also be beneficial</td>
<td>Dose delay/reduction may be required to reduce grade 3 or 4 mucositis to grade ≤1</td>
</tr>
</tbody>
</table>

*Information based on data from the SUTENT® Summary of Product Characteristics (2008) and the author’s opinion.

AE, adverse event; QoL, quality of life; TSH, thyroid-stimulating hormone; HFS, hand–foot syndrome; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; BP, blood pressure.
During treatment, it may be advisable to consult a podiatrist according to individual patient requirements. Emollient creams can be used to manage HFS, and other topical treatments containing urea or salicylic acid may be of benefit. For patients experiencing painful erythema, topical corticosteroids can be utilised. Patients may also be advised to use shock absorbers and hydrocolloidal bandages (for grade 2 and 3 HFS). Treatment may need to be interrupted or the dosage reduced if patients experience HFS of grade 2 that affects their QoL. As symptoms resolve to grade ≤1, it may be possible to resume treatment or increase the dosage.

**hypertension and cardiovascular symptoms**

Blood pressure should be stabilised before commencing patients on targeted treatment, in accordance with standard clinical practice, and patients should be monitored regularly during treatment (daily or three times per week dependent on the patient). Anti-hypertensive therapy should be individualised according to each patient’s profile, and carefully monitored in case of dose reduction or interruption of the targeted therapy. Patients should be monitored carefully for clinical signs and symptoms of congestive heart failure, particularly those with existing cardiac risk factors. Dose reduction or discontinuation may be implemented to minimise changes in left ventricular ejection fraction (LVEF).

**oral changes and mucositis**

For patients experiencing mucositis, switching to a paediatric toothpaste and/or a soft toothbrush may help to reduce irritation and discomfort. Patients may also be advised to avoid alcohol and to use bicarbonate-based mouthwashes (containing paracetamol with morphine or codeine in the event of pain) to help with symptom control. The use of topcal anaesthetics, such as tetracain hydrochloride, and herbal products containing camomile, sage, arnica and zinc may also be beneficial to reduce discomfort.

**conclusions**

Targeted agents are cytostatic rather than curative, thus continued treatment over long periods is likely to be required to ensure that disease control is maintained for as long as possible. Targeted agents for mRCC have been studied in a number of clinical trials and expanded-access studies, as well as in clinical practice, and this has enabled the identification of distinct and predictable AE profiles. With the widespread and increasing use of targeted agents in mRCC, strategies have been developed to help manage treatment-related AEs. In addition to reducing patient discomfort, early detection of AEs and prompt intervention can avoid the need for dose reductions and treatment interruptions, and minimise the impact of AEs on patient compliance and clinical outcomes.

**disclosures**

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**references**