Exposure–response relationships in patients with metastatic renal cell carcinoma receiving sunitinib: maintaining optimum efficacy in clinical practice

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Targeted agents such as sunitinib, an oral, multitargeted receptor tyrosine kinase inhibitor, have greatly improved the prognosis for patients with metastatic renal cell carcinoma (mRCC). In this review we analyse data from sunitinib preclinical and clinical studies in detail and consider the key implications for the effective use of sunitinib in clinical practice. Sunitinib has shown efficacy and acceptable tolerability in patients with mRCC in phase II and III clinical studies. In a pivotal phase III study in treatment-naïve patients with mRCC, median progression-free survival for sunitinib-treated patients was double of that with interferon-α ($P<0.001$). Median overall survival was 26.4 versus 21.8 months, respectively ($P=0.0510$). In preclinical and phase I/II studies, sunitinib inhibits tyrosine kinase inhibitors in a dose-dependent manner, suggesting a correlation between increasing exposure and greater response. A pharmacokinetics/pharmacodynamics meta-analysis investigating the relationship between clinical end points and sunitinib exposure showed that increased sunitinib exposure was associated with a greater probability of objective response, longer time to tumour progression and overall survival, as well as some increased risk of specific adverse events. It is important to consider the relationship between exposure and response to maximize clinical benefit from sunitinib treatment. *Anti-Cancer Drugs* 22:377–383 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Sunitinib malate (SUTENT; Pfizer Inc., New York, New York, USA) is an oral, multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs-1, 2 and 3), platelet-derived growth factor receptors (α and β), stem cell factor receptor (KIT), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor and glial cell line-derived neurotrophic factor receptor (REarranged during Transfection) [1–6]. Sunitinib is approved multinationally for the treatment of advanced and/or metastatic renal cell carcinoma (mRCC) and gastrointestinal stromal tumour after disease progression on or intolerance to imatinib [7]. Recently, the Committee for Medicinal Products for Human Use adopted a positive opinion, recommending sunitinib for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults [8]. International treatment guidelines recommend sunitinib use as both first-line and second-line treatments for mRCC, and it is considered a reference standard of care in the first-line treatment setting [9,10]. The recommended starting regimen for sunitinib is 50 mg/day administered orally in 6-week cycles for 4 weeks on treatment followed by 2 weeks off treatment (Schedule 4/2) [7].

In several preclinical models, sunitinib has shown time-dependent and dose-dependent target inhibition and tumour regression. In a preclinical study in a mouse xenograft model, sunitinib inhibited vascular endothelial growth factor receptor-2 and platelet-derived growth factor-β phosphorylation, with greater changes in exposure, as evaluated by total exposure (area under the plasma concentration–time curve, AUC) or maximum plasma concentrations, resulting in greater inhibition [3]. Similarly, in an analysis of pharmacokinetics/pharmacodynamics (PK/PD) in a subcutaneous tumour and bone marrow engraftment models, inhibition of FLT3 phosphorylation was observed and led to tumour regression [5]. Building on these preclinical findings, a single-dose, phase I study in patients with acute myelogenous leukaemia [11] showed that in a clinical setting, sunitinib could inhibit the phosphorylation of FLT3 in a dose-dependent and PK-dependent manner [11].

The PK of sunitinib and its active metabolite, SU12662, has been characterized in several clinical studies. The AUC and maximum plasma concentration (C_{max}) increase dose proportionately in the dosing range of 25–100 mg/day after single and multiple dosing [7]. Plasma concentrations reach their maximum between 6 and 12 h

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after a single oral dose of sunitinib, and bioavailability is unaffected by food [7]. With repeated administration, steady-state concentrations of sunitinib and SU12662 are achieved in 10–14 days [7]. The elimination half-lives of sunitinib and SU12662 are approximately 40–60 and 80–110 h, respectively [7].

The demonstration that sunitinib inhibits tyrosine kinase receptors in a dose-dependent manner suggests that greater exposure to sunitinib may be associated with improved clinical responses [11]. In this review, we examine and interpret analyses that have been carried out to characterize the exposure–response relationship with sunitinib in patients with mRCC and discuss the practical implications of these findings with respect to the use of sunitinib in patients with mRCC.

Clinical efficacy of sunitinib in patients with metastatic renal cell carcinoma

Sunitinib has been evaluated in several clinical trials in patients with mRCC, including two multicentre, phase II trials in patients with mRCC in whom earlier cytokine-based therapy had failed [12,13]. These studies showed the antitumour efficacy and tolerability of sunitinib 50 mg/day Schedule 4/2 in this setting [12,13].

In a subsequent randomized, multicentre, phase III trial, sunitinib 50 mg/day Schedule 4/2, administered as first-line therapy, was associated with superior efficacy compared with interferon-α (IFN-α) and an acceptable tolerability profile [14,15]. In this study, sunitinib-treated patients achieved median progression-free survival (PFS; primary end point) of 11 months [95% confidence interval (CI): 11–13], which was more than double of that seen with IFN-α [5 months; 95% CI: 4–6; hazard ratio 0.539 (95% CI: 0.451–0.643); $P < 0.001$] [15]. After the prespecified interim analysis when the primary end point of the study was met, patients in the IFN-α arm were allowed to crossover to receive sunitinib on documented disease progression [14,15]. Median overall survival (OS) in patients receiving sunitinib was 26.4 months (95% CI: 23.0–32.9) compared with 21.8 months (95% CI: 17.9–26.9) for patients treated with IFN-α [hazard ratio 0.821 (95% CI: 0.673–1.001); $P = 0.0510$] [15]. Censoring for patient crossover showed median OS of 26.4 months (95% CI: 23.0–32.9) for sunitinib-treated patients and 20 months (95% CI: 17.8–26.9) for IFN-α-treated patients [hazard ratio 0.808 (95% CI: 0.661–0.987); $P = 0.036$] [15]. A further subanalysis carried out in patients who received first-line treatment only showed median OS of 28.1 months (95% CI: 19–NA) for sunitinib-treated patients compared with 14.1 months for those treated with IFN-α [hazard ratio 0.647 (95% CI: 0.483–0.870); $P = 0.003$] [15].

In an expanded access study, sunitinib-treated patients achieved median PFS and OS of 10.9 (95% CI: 10.3–11.2) and 18.4 (95% CI: 17.4–19.2) months, respectively [16]. Patients achieved an objective response rate (ORR) of 17% and clinical efficacy was also observed in subgroups of patients, including those with brain metastases and those aged above or equal to 65 years [16]. Sunitinib has also been evaluated in a phase II study in patients with cytokine-refractory mRCC treated with a continuous daily dosing regimen of 37.5 mg/day [17]. The median PFS and OS were 8.2 months (95% CI: 6.4–8.4) and 19.8 months (95% CI: 16.2–24.9), respectively, and the clinical benefit rate (partial response plus stable disease > 3 months) was 53% in these patients [17].

These clinical findings clearly indicate that sunitinib is efficacious in patients with mRCC across a range of studies and patient population. It should be noted that the median OS with sunitinib of 2 years in the first-line setting compares favourably with median OS ranging between 13.3 and 18.8 months for the previous standard of care, immunotherapy [18–22]. This applies to the median OS observed with interleukin 2. As such, treatment expectations for mRCC have evolved and physicians are now able to offer patients a greatly improved prognosis. To ensure that the efficacy of sunitinib seen in clinical trials is achieved in clinical practice, it is important to consider the relationship between sunitinib exposure and response.

Exposure–response relationships with targeted agents in metastatic renal cell carcinoma

Characterization of the sunitinib exposure–response relationship

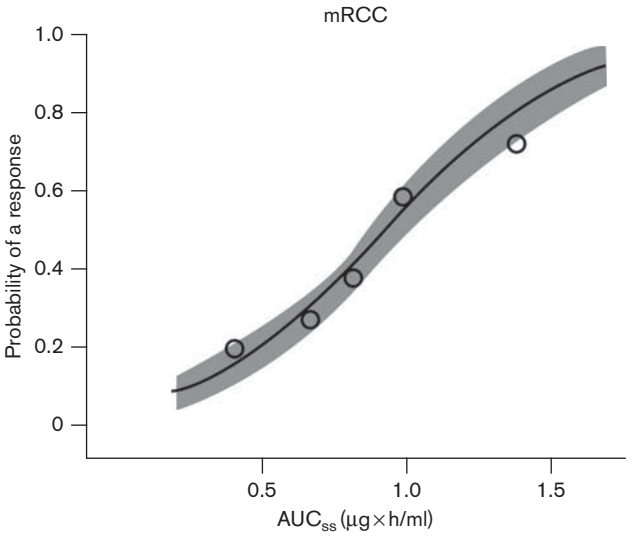
A population PK analysis of sunitinib and its primary metabolite in healthy volunteers and oncology patients has showed that covariates such as sex, age, Eastern Cooperative Oncology Group performance status and weight affect the PK for both compounds; however, the changes in exposure are not considered to be clinically significant and did not necessitate dose adjustments [23]. Nevertheless, an important aspect to ensure favourable treatment outcomes is a consideration of how particular patients with such covariates, and especially those with a combination of these, may vary in exposure. An understanding of the exposure–response relationship in patients with regard to efficacy and tolerability end points is thus critical.

The relationship between sunitinib exposure, efficacy and safety in patients with mRCC has been evaluated by a PK/PD meta-analysis [24]. The analysis included 169 patients from two phase II studies in cytokine-refractory mRCC who received treatment with sunitinib and had the appropriate PK/PD data available [12,13], as well as patients with gastrointestinal stromal tumour and solid tumours [24]. The mRCC study protocols were designed to administer sunitinib at 50 mg once daily on Schedule 4/2; however, in practice, due to dose adjustments based on safety and tolerability, the doses ranged from 25 to 75 mg [24]. The analysis considered sunitinib exposure–response relationships in terms of both efficacy and adverse events (AEs).

An exposure–response model was constructed as described earlier [24]. Individual patient PK parameters were estimated using 24-h postdose plasma samples using a population PK model, as described earlier [23]. The estimated exposure measures calculated for sunitinib, its primary active metabolite SU12662 and total drug included trough plasma concentrations over time (C_{trough}, taking into account the patient's dosing history); cumulative area under the concentration–time curve (AUC_{cum}, also taking into account the patient's dosing history); a 28-day 'windowed' cumulative AUC (AUC_{28day}, including only doses taken over the previous 28 days); and steady-state AUC based on the patient's last dose level (AUC_{last}) or mean daily AUC at steady state (AUC_{ss}).

These PK parameters were evaluated against four efficacy end points: objective tumour response, based on the Response Evaluation Criteria in Solid Tumors (RECIST); time to tumour progression (TTP); OS and tumour size changes. In addition, four tolerability end points were also analysed in the context of the PK data, based on those treatment-related AEs deemed by clinical study investigators to be related to sunitinib treatment: diastolic blood pressure (DBP) and associated hypertension; absolute neutrophil count (ANC) and associated neutropenia; fatigue and increased lipase. AEs were graded, where appropriate, according to the National Cancer Institute – Common Terminology Criteria for Adverse Events Version 3.0.

Fig. 1



Probability of a partial or complete response (by RECIST criteria) in mRCC versus average daily exposure (mean daily AUC at steady state, AUC_{SS}) to sunitinib [24]. Lines represent model prediction, shaded area represents 95% confidence interval and open circles represent observed percentage of patients in each quartile of AUC_{SS}. Modelling results only displayed relationships showing statistical significance. AUC, area under the plasma concentration–time curve; AUC_{SS}, AUC at steady state; mRCC, metastatic renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

Efficacy

The analysis showed that increased exposure to sunitinib resulted in greater efficacy; AUC at steady state (AUC_{SS}) was significantly associated with longer TTP and OS in patients with mRCC [24]. There was also a significant relationship between the probability of a partial or complete response according to Response Evaluation Criteria in Solid Tumors ($P = 0.00001$) and mean daily sunitinib exposure in patients with mRCC (Fig. 1) [24]. The relationship between the probability of stable disease and exposure to sunitinib (mean daily AUC_{SS}) was also significant ($P = 0.002$) [24]. In addition, simulations of tumour volume changes at expected exposures for doses between 25 and 50 mg/day on Schedule 4/2 indicated greater changes in tumour size at a dose of 50 mg/day (Fig. 2), with 38% more patients with mRCC expected to achieve a 30% reduction in tumour size when administered this dose of sunitinib compared with 25 mg/day [24].

Tolerability

Overall, relationships between sunitinib exposure and certain AEs were observed. Results of the AE analysis indicated that changes in lipase correlated less than 5% with any of the exposure measures; these were not evaluated further as a function of exposure [24]. In contrast, the incidence of fatigue, but not its severity, correlated positively with total drug (sunitinib and its primary active metabolite, SU12662) exposure (AUC_{SS}) across tumour types, including mRCC [24]. Simulations were carried out to model the incidence and probability of fatigue. These indicated that the half-life for the appearance of fatigue was 8 days and patients were likely to experience the maximum level of fatigue after one treatment cycle. The probabilities of experiencing grade greater than or equal to 1 fatigue in patients with mRCC treated with sunitinib 25 and 50 mg/day were 57 and 74%, respectively [24].

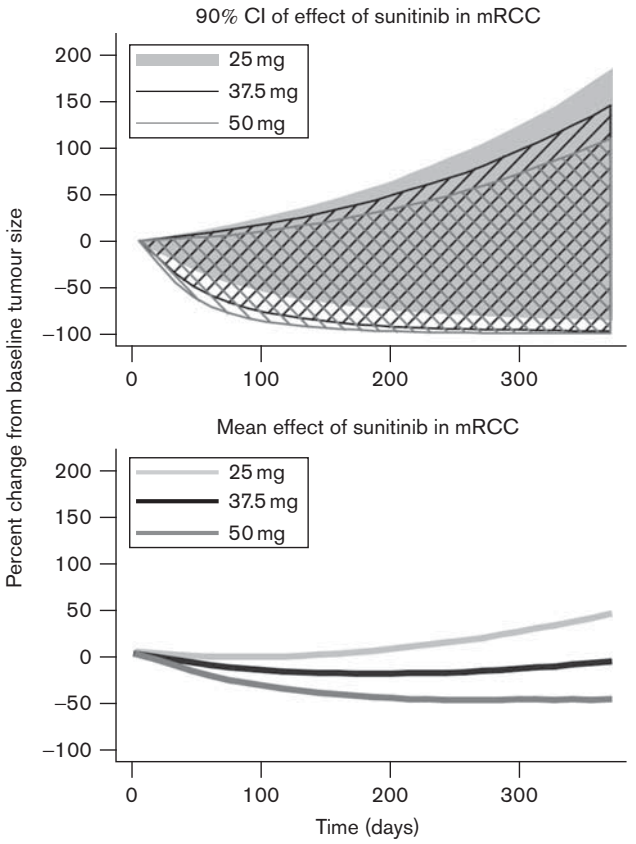
The meta-analysis also indicated a positive relationship between changes in DBP and sunitinib exposure (trough plasma concentration for total drug, $C_{troughTot}$) across tumour types [24]. Mean maximum increases in DBP of 5 mmHg with sunitinib 25 mg/day and 8 mmHg with sunitinib 50 mg/day were predicted. Overall, the estimated maximum drug-mediated change in DBP for the population analysis was 17 mmHg (with an interindividual variability of approximately 36% of this value).

There was an inverse relationship between ANC and sunitinib exposure (28-day cumulative AUC for total drug, $AUC_{Cum28Tot}$) across all tumour types, including mRCC (Fig. 3) [24]. The slope of this exposure–response relationship was significantly greater ($P < 0.05$) in those patients with the highest ANC at baseline: for a 10% increase in baseline ANC, there was an approximately

3.5% greater ANC reduction during treatment. Changes in ANC occurred predominantly after one cycle of sunitinib treatment and did not progress in subsequent cycles [24]. The estimated percentage reduction in ANC from baseline for patients with mRCC (from a baseline ANC of 5 counts/nl) was 15% at a sunitinib dose of 25 mg/day, 30% at a dose of 50 mg/day and 45% at 75 mg/day. Patients with mRCC had a 16% greater reduction in ANC reduction relative to patients with solid tumours [24].

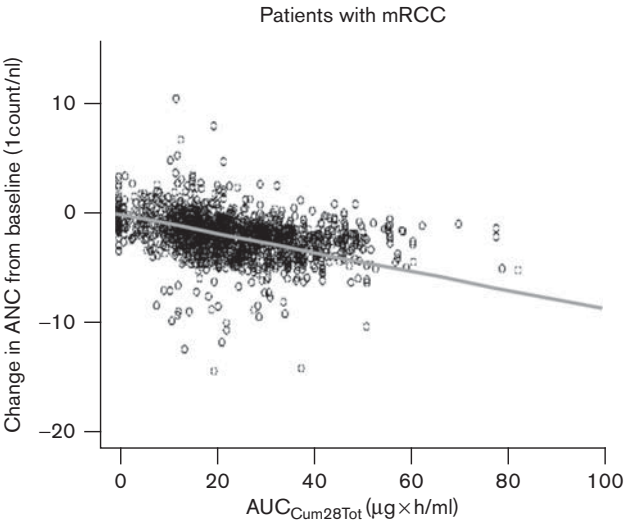
Although the analysis between sunitinib exposures and adverse relationships was limited due to the small dose range and limited placebo data, tentative relationships were still identified between sunitinib exposure and fatigue, raised DBP and neutropenia [24]. This is consistent with the observed clinical AE profile of sunitinib. However, at a dose of 50 mg/day Schedule 4/2, these AEs have been shown to be generally mild-to-moderate in severity and manageable with standard medical intervention including temporary sunitinib dose reductions or interruptions, as well as other clinical measures [7,13–16].

Fig. 2



Simulated tumour size changes in patients with metastatic renal cell carcinoma (mRCC) at doses between 25 and 50 mg once daily on Schedule 4/2 [24]. CI, confidence interval.

Fig. 3



Changes in the absolute neutrophil count (ANC) [measured and population-predicted (straight line)] in patients with mRCC treated with sunitinib [24]. $AUC_{Cum28Tot}$, 28-day cumulative area under the concentration–time curve for total drug; mRCC, metastatic renal cell carcinoma.

Maximizing sunitinib response in clinical practice: therapy management

The exposure–response analyses highlight the importance of achieving and maintaining maximum possible sunitinib exposure to support greater antitumour activity. As such, therapy management is important for ensuring that patients achieve the efficacy benefits observed with sunitinib in clinical trials. Therapy management focuses on three interlinked factors related to sunitinib exposure–response relationships in order that patients achieve maximum clinical benefit: dosing level; treatment duration and management of side effects to ensure that patients remain on treatment [25].

Sunitinib dosing

The correlation of efficacy measures (partial or complete responses, TTP, OS and changes in tumour size) with sunitinib dose exposure in the meta-analysis discussed above [24] emphasizes the need to use the optimal sunitinib dose to maximize sunitinib exposure, and therefore clinical outcome. Treatment with 50 mg/day was associated with significantly longer TTP and OS, indicating that this is an appropriate dose for initiating treatment in most patients. In addition, this dose was associated with a probability of AEs of interest occurring at low-to-moderate intensities, providing further support for treatment with a starting dose of 50 mg/day Schedule 4/2.

Of interest, due to dose adjustments, and in some instances, differences in starting doses used in the studies included in the meta-analysis, the doses administered ranged from 25 to 75 mg in some patients [24]. The safe

administration of doses above the recommended 50 mg/day and the variability in PK may indicate the potential for some patients to tolerate higher doses of sunitinib without significantly impacting the frequency or severity of AEs in these patients. However, this remains hypothetical at present and insufficient data are available to support this. As such, administration of higher doses requires evaluation in a clinical trial setting before implementation in clinical practice.

Sunitinib treatment duration

Results from the pivotal phase III study with sunitinib highlight the importance of maintaining patients on treatment while efficacy is observed [14,15]. In this study, the ORR was greater with longer sunitinib treatment duration and follow-up. At the preplanned interim analysis, after 6 months of treatment (range, 1–15 months), sunitinib-treated patients achieved an ORR based on blinded central radiological assessment of 31% (95% CI: 26–36) and of 37% based on investigator assessment [14]. At the final OS analyses for this study, at a median treatment duration of 11 months (range, < 1–41 months), the ORR based on investigator assessment was 47% (95% CI: 42–52) in sunitinib-treated patients [15].

Adverse event management

Maintaining patients on sunitinib at the optimal dose is dependent on the effective management of AEs. In clinical trials and an expanded access study, sunitinib has shown a consistent and predictable tolerability profile, with the majority of AEs being mild or moderate in intensity [14,16,26]. The most common nonhaematological grade 3–4 AEs reported in the large pivotal phase III clinical trial with sunitinib in mRCC were hypertension, fatigue, diarrhoea and hand-foot syndrome [14]. An ongoing expanded access trial has enrolled more than 4000 patients with mRCC, including those with poor performance status or brain metastases [16]. The safety profile observed in this study was similar to that observed in other clinical trials. The most common nonhaematological grade 3–4 treatment-related AEs were fatigue, hand-foot syndrome, asthenia, hypertension and diarrhoea [16,26]. In addition, no new or unexpected toxicities were observed with longer-term use of sunitinib and there was a lack of serious cumulative toxicity in this group of patients [26].

As the AE profile of sunitinib is well characterized, it is possible to anticipate potential AEs in clinical practice and consider management strategies [12–14,16,26]. Many of the AEs occurring with sunitinib may be managed with standard medical intervention and patient education [25,27]. Before starting treatment, patients should have a good understanding of their disease and the treatment course, including AEs that they might experience. The importance of receiving an optimal dose of sunitinib should be explained [28].

An overview of potential management strategies for the AEs reported with sunitinib are described in detail elsewhere [25,27–29] and is also summarized in Table 1.

Conclusion

Targeted agents such as sunitinib have been shown to provide substantial efficacy for patients with mRCC in clinical trials. A recent elegantly designed meta-analysis has shown a clear and direct correlation between sunitinib exposure and clinical response in mRCC. Tentative relationships were also established between increasing exposure to sunitinib and the risk of certain AEs. Although drug exposures vary from patient to patient, population PK analysis did not identify clinically meaningful changes in exposure as a result of sex, age, Eastern Cooperative Oncology Group performance status or weight. Nevertheless, exposures may vary from patient to patient and dose adjustments and interruptions may play an important role in maintaining patients at an acceptable dose for the longest duration possible. The approved sunitinib dose of 50 mg/day on Schedule 4/2 seems to be an appropriate starting dose for the majority of patients, providing clinical benefit with an acceptably low risk of AEs.

It is important to ensure that patients achieve the optimal sunitinib exposure to maximize efficacy through effective therapy management. The key therapy management strategies focus on maintaining an optimally effective dose of sunitinib for as long as efficacy is observed, through proactive side effect management. Dose interruptions and adjustments have also been shown to reduce both the frequency and severity of AEs. Alternative sunitinib dosing schedules, such as continuous daily dosing, are currently being evaluated in clinical trials. These may provide additional treatment options for patients to maximize exposure, reduce AEs and thus provide benefit to patients with mRCC treated with sunitinib.

A phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory mRCC showed that PK for sunitinib and its metabolite were similar to those observed with the intermittent dosing schedule of 4 weeks followed by 2 weeks off treatment [17]. In addition, the efficacy and safety profiles of sunitinib in this study were also similar to those observed with studies in which sunitinib was administered on Schedule 4/2, with most patients requiring neither dose reduction nor treatment delays [17]. In addition, the results of a recently completed clinical study comparing continuous versus intermittent sunitinib dosing [the Randomized Phase II Study of the Efficacy and Safety of Sunitinib Malate Schedule 4/2 vs. Sunitinib Malate Continuous Dosing as First-Line Therapy for Metastatic Renal Cell Cancer (Renal

Table 1 Commonly observed adverse events in patients treated with sunitinib and associated management strategies [25,27–29]

	Management strategies	
Adverse event	Pretreatment	During treatment
Fatigue and asthenia	Educate patients regarding possible occurrence and provide psychological support Encourage modification of daily activities to conserve energy Recommend moderate physical exercise to help reduce levels of fatigue	Assess for underlying factors: hypothyroidism, anaemia, depression, emotional distress, sleep disturbance Treat underlying factors according to standard treatment Provide supportive counselling as required; educating patients on viewing fatigue in the wider context of benefit from treatment Dose modifications are infrequently or rarely required
Thyroid dysfunction	Monitor for baseline thyroid function and treat according to standard practice	Monitor for thyroid hormone levels on a regular basis Treat according to standard medical practice when clinical signs or biological disturbances occur
Skin disorders	Educate patients using visual illustrations and leaflets and brochures regarding possible occurrence Advise patients on possible depigmentation of hair and skin Conduct full foot examination and consult with podiatrist – treat any preexisting hyperkeratosis before commencing therapy Advise patients to reduce pressure on affected areas	Advise patients to wear thick-soled shoes Recommend shock absorbers and hydrocolloidal bandages (grade 2–3 hand–foot syndrome) Podiatrist and dermatologist consultations as required for supportive treatment Use emollient creams and topical treatments containing urea or salicyclic acid. Topical creams with corticosteroids may be used for patients experiencing painful erythema Treatment interruption or dose reduction may be required if hand–foot syndrome grade ≥ 2 affects patients until resolution to grade 0 or 1
Oral changes, stomatitis and mucositis	Educate patients on possible occurrence and symptoms Consult dieticians for modification of diet Switch to paediatric toothpaste and soft toothbrush Advise patients to avoid alcohol	Advise patients to use bicarbonate mouthwashes containing paracetamol with morphine or codeine to help symptom control Tetracain-hydrochloride gels, camomile, sage, arnica and zinc may also be beneficial Dose delay or reduction may be required to reduce grade 3 or 4 mucositis to grade ≤ 1
Gastrointestinal toxicity	Educate patients about possible symptoms Advise patients to reduce intake or discontinue use of stool softeners, fibre supplements or laxatives to help prevent diarrhoea Consultation with a dietician may be beneficial for patients Nausea and vomiting may be prevented by a low dose of a single agent such as corticosteroid	Antiemetic medication may be used as secondary prophylaxis Bulking agents or antidiarrhoeal medication may be used Severe diarrhoea may be managed by treatment interruption until severity decreases Dose reduction may be used at recurrence of grade 3 diarrhoea and should be used at recurrence of grade 4 diarrhoea
Hypertension and cardiovascular events	Conduct a full cardiovascular assessment before starting treatment Monitor for hypertension and treat according to standard medical practice Stabilize blood pressure before initiating treatment	Monitor cardiovascular status, including blood pressure, regularly during treatment Monitor for signs and symptoms of congestive heart failure or changes in ejection fraction, particularly in patients with cardiac risk factors Treat with antihypertensive therapy according to normal management protocols Dose adjustments or interruptions may be necessary until hypertension is controlled or if the left ventricular ejection fraction is <50 and $>20\%$ below baseline Treatment may need to be discontinued in patients with symptoms of congestive heart failure
Haematological toxicity	Advise patients on possible occurrence, good diet and eliminate hypothyroidism as a cause	Monitor blood counts regularly Manage and treat according to local guidelines Dose delay or reduction may be required in patients with low neutrophil and granulocyte counts

EFFECT Trial)] will also provide further information regarding the efficacy and safety of both dosing schedules [30].

Finally, dose–response relationships are also likely to be important considerations for the other targeted agents available for the treatment of mRCC. No specific correlations between efficacy and safety measures and exposure have been established for these agents to date; however, this warrants further investigation.

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