Sunitinib side effects as surrogate biomarkers of efficacy

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Abstract

With the proliferation of treatment options for the management of metastatic renal cell carcinoma (mRCC) over the past decade, predictive markers of response to therapy are becoming increasingly important. Sunitinib is commonly used in the first-line treatment of mRCC. Common mechanism-based adverse events, including hypertension, hypothyroidism, hand-foot syndrome, and neutropenia, have been explored as potential biomarkers of the clinical efficacy of sunitinib in mRCC and are reviewed in this article.

Introduction

Over the past decade, agents that target vascular endothelial growth factor (VEGF) and its receptors have become a standard of care for the treatment of metastatic renal cell carcinoma (mRCC). The selection and sequencing of targeted treatment are driven largely by baseline prognostic factors, with patients classified into poor, intermediate, and favourable risk groups.[1,2] However, these risk categories are prognostic and not predictive, prompting the exploration of efficacy biomarkers that can be used during treatment to adjust prognosis as needed. Several potential serum, radiological, and tissue-based biomarkers have been evaluated for various agents;[3-9] however, none has been validated for clinical use in RCC.[10] As a practical alternative, on-treatment predictors of efficacy have emerged that focus on mechanism-based adverse events (AEs) that reflect the targeted effects of a molecularly targeted agent and its inhibition of a particular pathway.

The anti-VEGFR tyrosine kinase inhibitor (TKI) sunitinib has been available in Canada for the first-line treatment of mRCC since 2006. With more than 10 years of experience with this agent, there is increased understanding of the mechanism-based AEs associated with sunitinib, the most common of which are hypertension, hypothyroidism, hand-foot syndrome, asthenia/fatigue, neutropenia, and thrombocytopenia. These AEs can lead to dose reductions, interruptions, and discontinuations[11] — all of which may negatively impact outcomes in patients with mRCC. However, some, including hypertension, hypothyroidism, hand-foot syndrome, and neutropenia, have been explored as potential biomarkers of the clinical efficacy of sunitinib. Associations between the onset of toxicity and outcomes have been described with other targeted agents, including the skin toxicity associated with EGFR therapy in colorectal cancer[12] or pneumonitis with mTOR inhibitors.[13] This article reviews some of the mechanism-based AEs and their potential role as biomarkers of efficacy for sunitinib in patients with mRCC.

Hypertension

Hypertension is a common AE associated with agents that target the VEGF pathway, including sunitinib, bevacizumab, sorafenib, and axitinib.[14] The molecular mechanisms underlying VEGF inhibitor-induced hypertension are unclear. Proposed mechanisms include endothelial dysfunction and increased vascular resistance due to impaired nitric oxide signalling, reduced prostacyclin production, endothelin-1 (ET-1) upregulation, oxidative stress, and rarefaction.[15-17] Hypertension occurs in approximately one-third of patients treated with sunitinib.[18] The association between sunitinib-induced hypertension and antitumour efficacy was evaluated in a retrospective analysis of pooled efficacy and safety data from four studies of 4915 patients with mRCC treated with sunitinib 50 mg/day administered on a four-week-on/two-week-off schedule (four/two).[19] Hypertension was defined as a maximum systolic blood pressure (SBP) of at least 140 mmHg or a maximum diastolic blood pressure (DBP) of at least 90 mmHg. Systolic hypertension was associated with an objective response rate (ORR) of 54.8%, compared with an ORR of 8.7% in patients without systolic hypertension ($p<0.001$). Progression-free survival (PFS) (12.5 vs. 2.5 months; $p<0.001$) and overall survival (OS) (30.9 vs. 7.2 months; $p<0.001$) were also significantly higher in patients with systolic hypertension than in those without.

Similar correlations were seen between diastolic hypertension and efficacy. In this retrospective analysis of nearly 5000 sunitinib-treated patients with mRCC, the incidence of hypertension-associated cardiovascular, cerebrovascular, ocular, and renal AEs was low.[19] Comparable results have been observed in other studies and other VEGFR-TKIs.[20-22] Donskov et al demonstrated that hypertension and neutropenia influenced outcomes in each IMDC group.[20] Although not all patients required hypertension to gain a clinical benefit from sunitinib, these results support the hypothesis that hypertension may be a viable biomarker of antitumour efficacy in patients with mRCC and may be used to adjust prognosis during first-line therapy. Treatment of hypertension should follow the regular hypertension guidelines.[23] Importantly, use of antihypertensive medications does not reduce the antitumour activity of sunitinib.[19] In one small prospective study, patients undergoing treatment with sunitinib for mRCC underwent aggressive blood pressure monitoring and algorithmic treatment for hypertension according to European guidelines rather than common toxicity criteria.[24] Nine of the 10 patients were able to achieve uninterrupted, full-dose sunitinib treatment. Such a management approach could complement the use of hypertension as a biomarker — maximizing the therapeutic benefits of sunitinib while minimizing the risk of hypertension-associated complications. Some studies even indicate that the type of antihypertensive treatment may also have an influence on outcomes.[25]

Hypothyroidism

Hypothyroidism is a common AE associated with sunitinib and other agents in this class.[26] The potential role of hypothyroidism as a predictive marker of outcomes has been explored. In a prospective analysis of 87 consecutive patients with mRCC treated with sunitinib or sorafenib, subclinical hypothyroidism during treatment was associated with a significant increase in the rate of objective remission compared with euthyroid patients (28.3% vs. 3.3%; p<0.001), as well as an increase in the median duration of survival (not reached vs. 13.9 months; p=0.016).[27] In a meta-analysis of 11 retrospective and prospective studies of 500 patients treated with sunitinib or sorafenib for mRCC,[28] there was no significant difference in PFS between patients who acquired hypothyroidism during sunitinib treatment and those who did not. OS was longer in patients who developed hypothyroidism during sunitinib therapy compared with patients who did not (hazard ratio [HR] 0.52; p=0.01); however, the authors urged caution in interpreting these results due to the retrospective nature of the study.

Other mechanism-based AEs

Other mechanism-based AEs secondary to VEGRF inhibitors have been studied as potential biomarkers of treatment efficacy. Sunitinib induces neutropenia and thrombocytopenia in approximately 20% of non-Asian patients and hand-foot syndrome in approximately 30% of patients.[29] A pooled retrospective analysis of patients from five prospective clinical trials evaluated the development of hypertension, neutropenia, thrombocytopenia, hand-foot syndrome, and asthenia/fatigue during treatment with sunitinib for mRCC as predictors of PFS and OS.[20] Neutropenia was associated with significantly longer PFS and OS (p=0.013 and p=0.0122, respectively), while hypertension and hand-foot syndrome were associated with significantly longer OS (p=0.004 and p=0.022, respectively). In a multivariate analysis, hypertension, neutropenia and hand-foot syndrome remained as independent prognostic factors of OS.

Recently, an Italian centre evaluated the prognostic role of cumulative toxicity in 104 patients with mRCC treated with first-line sunitinib or pazopanib.[30] Cumulative toxicity — defined as having more than one selected AE of any grade — was associated with a significantly greater median OS (61.2 months vs. 18.7 months; HR 0.23; p<0.001) and PFS (27.6 vs. 7.2 months; HR 0.31; p<0.001) compared with those who experienced one or no AEs. In this analysis, both OS and PFS were significantly higher in those who experienced hypertension, hypothyroidism, and hand-foot syndrome while on treatment compared with those who did not experience these AEs.

Maximizing quality of life in patients undergoing treatment with sunitinib

Higher exposure of sunitinib has been shown to correlate significantly with a higher probability of overall response rate, longer time to progression, and increased OS.[31] Although several frequently occurring AEs of sunitinib, including hypertension, hypothyroidism, neutropenia, and hand-foot syndrome are potentially associated with better clinical outcomes, these AEs can affect patient quality of life, leading to dose reduction or even discontinuation, which may affect patient outcome. Schedule changes, e.g., a two-week-on/one-week-off schedule, are in many cases a good choice to avoid dose reduction. Early effective management of these AEs is vital to maximizing the patient's quality of life and time on treatment.

Conclusions

mRCC is a heterogeneous disease, and optimal management is driven largely by the patient's prognosis. Reliable and

clinically validated predictive biomarkers for response to antiangiogenic therapy are still lacking. The ideal biomarker would be available prior to treatment start, simple, easy to measure, and affordable. To date, treatment-induced hypertension has been the best studied on-therapy biomarker, and is relatively easy to manage. Prospective trials are needed to validate this and other mechanism-based AEs as biomarkers for efficacy.

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