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Original Research

Is change in blood pressure a biomarker of pazopanib and sunitinib efficacy in advanced/metastatic renal cell carcinoma?

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Abstract ***Aim:*** Pazopanib, an oral antiangiogenic agent, is associated with improved outcomes in patients with metastatic renal cell carcinoma. In this retrospective analysis, we explore hypertension, an on-target adverse event, as a predictive marker.
Methods: Data from the pazopanib arm of the phase III COMPARZ trial (NCT00720941) comprised the test set. Pooled data from phase II (NCT00244764) and III (NCT00334282) pazopanib trials comprised the validation set. Data from the sunitinib arm of COMPARZ were analysed separately. Measures of efficacy were response rate, progression-free survival (PFS), and overall survival (OS). Mean arterial blood pressure (MAP) was the primary metric, and systolic hypertension (S-HTN) and diastolic hypertension (D-HTN) were secondary metrics; 4- and 12-week landmark analyses were performed.
Results: Analyses revealed no significant associations at the landmarks between response and MAP. We observed a trend towards improved PFS with S-HTN at week 4 (hazard ratio [HR] = 0.79, $P = 0.060$) and week 12 (HR = 0.75, $P = 0.073$) among pazopanib-treated patients in COMPARZ. This trend was not confirmed at week 12 in the validation set or in

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sunitinib-treated patients. In the test set, there was a trend towards increased OS in patients with S-HTN by week 4 (HR = 0.76, $P = 0.062$) and with D-HTN by week 4 (HR = 0.71, $P = 0.016$) but not by week 12. No significant differences in OS were observed in sunitinib-treated patients for S-HTN or D-HTN.

Conclusion: Neither hypertension nor any blood pressure elevation above baseline was associated with efficacy outcomes of pazopanib or sunitinib. Accordingly, management of tyrosine kinase inhibitor-induced hypertension is unlikely to compromise outcome.

1. Introduction

Angiogenesis inhibitors dominate the treatment landscape in metastatic renal cell carcinoma (RCC). Although many patients benefit from therapy, identification of clinically useful biomarkers of efficacy has remained elusive. Angiogenesis inhibitors either bind vascular endothelial growth factor (VEGF) or block the VEGF receptor (VEGFR). VEGF induces nitric oxide synthase and leads to vasodilation and decreased vascular resistance, and VEGF pathway inhibition leads to hypertension [1-5]. In patients treated with targeted antiangiogenic agents, the incidence of any-grade and high-grade hypertension varies (9–30% and 6.5–8.3%, respectively) [6-9].

Because hypertension is an on-target effect of VEGF inhibition, it has been explored as a potential predictive biomarker. In a retrospective analysis of sunitinib-treated patients with metastatic RCC, patients with systolic or diastolic hypertension (≥140 or ≥90 mm Hg, respectively) experienced significantly improved progression-free survival (PFS) and overall survival (OS) versus patients without hypertension [10]. Similar observations have been reported for patients treated with axitinib, another VEGFR tyrosine kinase inhibitor (TKI) [11].

Pazopanib, an oral antiangiogenic TKI targeting VEGFR, is associated with improved PFS in patients with locally advanced/metastatic RCC [12]. Hypertension was reported in 40–41% of pazopanib-treated patients; incidence of grade III hypertension was 4–9% [12,13]. We explore hypertension as a predictive biomarker of treatment benefit with pazopanib or sunitinib using data from the COMPARZ trial [14] in which each drug was evaluated and integrated with data from the original phase II and III pazopanib trials [12,13].

2. Patients and methods

2.1. Patients

Data from clinical trials of pazopanib 800 mg/d monotherapy for metastatic RCC were analysed; the phase III COMPARZ trial analysis population (NCT00720941) was the test set, and pooled data from phase II (NCT00244764/VEG102616) and the pivotal phase III (NCT00334282/VEG105192) trials were the validation set. Sunitinib data from COMPARZ were analysed separately. Additional patient information is available in Supplementary Methods (Appendix A).

2.2. Study design

This retrospective analysis evaluated the relationship between changes in blood pressure (BP) and the efficacy of pazopanib and sunitinib in the test set. Key relationships were reevaluated in a validation set of pazopanib-treated patients. Measures of efficacy were response rate (RR), PFS, and OS; all efficacy analyses were conducted using independent radiologic review data only. Additional study design details are available in Supplementary Methods (Appendix A).

The principal analyses were landmark analyses at 4 and 12 weeks, with 4 weeks as the primary landmark. The week 4 landmark was defined as day 35 and the week 12 landmark was defined as day 91 after initiation of therapy, to allow for a visit window of ±7 d.

In this report, 'response to treatment' is defined as an increase in BP; survival is defined separately as both PFS and OS. Only patients who were on-study and event free (PFS analysis included patients who were alive and progression free; OS analysis included patients who were alive) at the landmark time are included in the analysis, separated into two categories based on response (whether they experienced a BP increase) at any point before the landmark. Patients who discontinued treatment before the landmark for any reason (e.g. toxicity) were excluded. Patients in both groups are compared from the landmark forward, ignoring all BP changes after and all events before the landmark.

The primary metric for change in BP was maximum change from baseline in mean arterial pressure (MAP) ≥10 versus <10 mm Hg by the landmark, where MAP is defined as (2 × diastolic blood pressure [DBP] + systolic blood pressure [SBP])/3 [15]. Secondary metrics were maximum change from baseline in SBP ≥10 versus <10 mm Hg, observation of systolic