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Hypertension (HTN) as a potential biomarker of efficacy in pazopanib-treated patients with advanced non-adipocytic soft tissue sarcoma. A retrospective study based on European Organisation for Research and Treatment of Cancer (EORTC) 62043 and 62072 trials

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Abstract ***Background:*** Reliable biomarkers of pazopanib's efficacy in soft tissue sarcoma (STS) are lacking. Hypertension (HTN) is an on-target effect of vascular endothelial growth factor (VEGF)-receptor inhibitors such as pazopanib. We evaluated the association of pazopanib-induced HTN with antitumour efficacy in patients with metastatic non-adipocytic STS.

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Methods: Associations between pazopanib-induced-HTN and antitumour efficacy were retrospectively assessed across 2 prospective studies (European Organisation for Research and Treatment of Cancer (EORTC) study 62043 and 62072) in metastatic STS patients who received pazopanib 800 mg daily. Only patients with baseline blood pressure (BP) $< 150/90$ mmHg, were included. BP was measured monthly. HTN was reported according to National Cancer Institute-Common Toxicity Criteria Adverse Events (NCI-CTC AE) grading (v3.0), and as absolute differences compared to baseline. The effect of HTN developing in patients without baseline anti-hypertensive medication was assessed on progression-free (PFS) and overall survival (OS) using a landmark analysis stratified by study; univariately using the Kaplan–Meier method and a log-rank test, and in a multivariate Cox regression model after adjustment for important prognostic factors.

Results: Of the 337 patients eligible for this analysis, 21.7% received anti-hypertensive medication at baseline and had a similar PFS and OS compared to those who did not. In patients without baseline anti-hypertensive medication, 38.6% developed HTN. As the majority of patients developing HTN did so within 5 weeks after initiation of pazopanib (68.6%), this time point was used as landmark. Univariately, there was no effect on PFS or OS from occurrence of HTN within 5 weeks of treatment expressed either in NCI-CTC AE criteria or as maximal differences from baseline in systolic and diastolic BP. Also in multivariate analysis, after adjusting for important prognostic factors, the occurrence of HTN expressed in the different parameters was not associated with PFS and OS.

Conclusions: In this retrospective analysis, pazopanib-induced HTN did not correlate with outcome in pazopanib-treated STS patients. The occurrence of HTN cannot serve as biomarker in this setting.

1. Background

Pazopanib is a tyrosine-kinase inhibitor (TKI) targeting several factors, including vascular endothelial growth factor (VEGF) receptors, platelet derived growth factor (PDGF) receptors, and c-kit. As VEGF-driven angiogenesis is involved in the tumour biology of many soft tissue sarcomas (STS) subtypes [1–6], pazopanib was tested for its efficacy in a phase II study and subsequently, in a placebo-controlled phase III study in patients with pretreated, advanced, non-adipocytic STS. This latter study showed that pazopanib yielded a threefold prolongation, of progression-free survival (PFS) over placebo [7] and led to market approval in metastatic non-adipocytic STS patients failing previous chemotherapy.

VEGF pathway inhibition is involved in many physiological processes and can lead to on-target side effects, such as hypertension, proteinuria, thromboembolic events and impaired wound healing [8]. Of these, hypertension (HTN) is the best documented toxicity. The incidence of drug-induced HTN seems to vary across the different VEGF-agents.

Concerning, VEGF-receptor targeting TKIs, the reported occurrence of HTN is 15% in patients treated with sorafenib, 25% with sunitinib [9–11], and up to 41% with pazopanib [7,12]. In patients treated with bevacizumab, a monoclonal antibody towards VEGF, 35% of the patients experiences HTN [13].

Several studies suggest that HTN induced by agents targeting the VEGF pathway, such as sunitinib [14,15] or sorafenib [16] correlates with the outcome to these drugs in metastatic renal cell cancer. Similar associations were observed with sorafenib in hepatocellular carcinoma [17], with sunitinib in metastatic GISTs [18,19], and more recently, with axitinib in melanoma and thyroid cancer [20]. However, a recent meta-analysis done by Hurwitz et al. [21] based on six phase III studies with bevacizumab in colorectal, breast and renal-cell carcinoma showed that treatment-induced HTN arising within 60 days of starting bevacizumab (defined by multiple criteria) was predictive of overall survival (OS) and PFS in only one of the six studies, while in the other studies no such relationship was revealed. Hence data on the association between the occurrence of treatment-induced HTN and outcome to VEGF pathway inhibitors are conflicting.

In addition to these conflicting data, most of these studies were affected by different forms of biases, and the results of these studies are therefore difficult to interpret [22]. For example, different definitions for hypertension were used, in many studies no absolute or relative changes in blood pressure (BP) were analysed but only National Cancer Institute-Common Toxicity Criteria Adverse Events (NCI-CTC AE) toxicity grades, patients using antihypertensive drugs prior to receiving an VEGF-pathway inhibitor, which attenuates BP rises, were frequently not excluded, and most of the studies were prone to time-to-event bias.

Since BP alterations induced by VEGF-targeting drugs might serve as a potential early marker for the efficacy of these drugs, and given the high need for such