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Cardiovascular events among 1090 cancer patients treated with sunitinib, interferon, or placebo: A comprehensive adjudicated database analysis demonstrating clinically meaningful reversibility of cardiac events ☆

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Abstract ***Purpose:*** To define cardiovascular (CV) risk and reversibility of cardiac events in patients who received sunitinib versus comparator treatment (interferon-alfa or placebo).
Patients and methods: We performed a retrospective adjudication of comprehensive CV adverse events (AEs) from two phase 3 trials. Components of the comprehensive CV AE end-point comprised hypertension, symptomatic and asymptomatic left ventricular ejection fraction decreases (SD-LVEF; AD-LVEF) and extent of reversibility, heart-failure symptoms, thromboembolic events, dysrhythmia and CV death. Three cardiologists and one oncologist, blinded to treatment allocation, adjudicated suspected CV AEs in the pooled trial database ($N = 1090$).
Results: Incidence rates (IR) for sunitinib versus Interferon-alfa (IFN-α)/placebo were hypertension: 6.9 versus 2.6 (hazard ratio (HR), 3.1; 95% confidence interval (CI), 2.4–4.0); SD-LVEF: 0.4 versus 0.2 (HR, 2.5; 95% CI, 1.0–6.2); AD-LVEF: 1.1 versus 0.8 (HR, 2.1; 95% CI, 1.3–3.4); and composite CV AE end-point: 10.1 versus 4.8 (HR, 2.5; 95% CI, 2.0–3.1), however reversibility, not previously quantified, was found to be clinically meaningful.

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Conclusions: Hypertension and SD-LVEF/AD-LVEF were significantly higher with sunitinib versus IFN-α/placebo. Among patients who experienced a cardiac event, symptomatic and asymptomatic instances of decreased cardiac dysfunction were adjudicated as reversible in 47 of 83 (56%) and 17 of 30 (57%), respectively. Among sunitinib-treated patients, many were able to resume sunitinib dosing following resolution of events, a finding that is important for clinical care. In comparator groups, symptomatic and asymptomatic instances were adjudicated as reversible in 4 of 6 (66.7%) and 11 of 21 (52%), respectively. Thromboembolic, dysrhythmic and/or CV deaths were not significantly higher in sunitinib-treated patients.

1. Introduction

Antiangiogenic agents targeting the vascular endothelial growth factor (VEGF) signalling pathway are associated with a variety of cardiovascular adverse events (CV AEs), including heart failure (HF), hypertension, infarction, left ventricular dysfunction and thromboembolic events [1–7]. Sunitinib malate (SUTENT, Pfizer Inc., New York, NY) is a multi-kinase inhibitor with potent antiangiogenic activity approved for the treatment of advanced renal cell carcinoma (RCC) and imatinib-resistant/intolerant gastrointestinal stromal tumour (GIST). The two pivotal phase 3 trials [8–11] are summarised in Table 1. We performed a comprehensive independently adjudicated analysis using pooled data from these randomised controlled RCC and GIST trials in order to describe the incidence of CV AEs, associated risk factors and to define the extent of reversibility of cardiac adverse events in sunitinib-treated patients.

2. Materials and methods

2.1. Patients and studies

To ensure clinical significance, the present analysis utilised data from single-agent phase 3 studies in the two approved sunitinib indications at the time the analysis was performed (RCC and GIST). General eligibility criteria for these studies have been described previously [8,10]. Interferon-alfa (IFN-α) was the comparator in the RCC study, and placebo, the comparator in the GIST study; both studies allowed crossover to sunitinib (Table 1).

Safety was analysed at regular intervals in both studies by assessing AEs (Common Terminology Criteria for Adverse Events version 3), physical examinations and laboratory abnormalities. Blood pressure (BP) measurements were made on days 1 and 28 of each treatment cycle at a minimum. Left ventricular ejection fraction (LVEF) was assessed by multigated acquisition scanning at screening on day 28 of odd-numbered treatment cycles, at study withdrawal, at post-treatment assessment if necessary to follow up on ongoing abnormalities from the time of withdrawal, or if otherwise clinically indicated in the RCC study; and at screening, on day 28 of even-numbered cycles, and at study withdrawal in the GIST study; ejection fraction data were limited to those available from protocol records.

2.2. Adjudicated CV AE analysis

A panel of three independent cardiologists (MSE, TMS and DJL) and one oncologist (RJM) adjudicated the CV AEs using data provided by Pfizer, but without Pfizer involvement and without remuneration.

The CV-AE adjudication criteria were defined broadly so as to minimise under-reporting; an over-inclusion bias was assumed by design. In contrast to previously published reports that focused on one or more type(s) of CV AE, the primary composite CV-AE endpoint was defined to include a broad spectrum of CV AEs to comprehensively define the CV-AE profile (Table 2). Wide time windows were used to define concomitant symptoms and to assess reversibility or recovery. All CV events except hypertension were adjudicated by the panel. Data presented to the panel were tabulated and blinded by a third-party data-management organization (Harvard Clinical Research Institute, Boston, MA): none of the panel members knew the patients' treatment allocations. These data (derived from both AE and laboratory-test databases) comprised BP readings, reported LVEF estimations and symptoms. Dyspnea, pitting oedema and weight gain were reviewed in a targeted manner, but the entire data set (with all symptom listings) was available and was used when needed. Integration of the adjudications with treatment allocations was performed by the third-party organization. The adjudicated dataset was analysed by the authors and Pfizer, and the analysis was replicated and validated by the third-party organization.

2.3. Statistical analysis

Data from patients who received at least one dose of assigned study drug (safety-assessable population) were