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Effect of small angiokinase inhibitor nintedanib (BIBF 1120) on QT interval in patients with previously untreated, advanced renal cell cancer in an open-label, phase II study

Summary

Purpose Some targeted anticancer agents are associated with serious ventricular tachyarrhythmias, which may be predicted by electrocardiographic evaluation of drug-related QT prolongation. We studied the effects of nintedanib (BIBF 1120; an oral, triple angiokinase inhibitor targeting vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor receptors) on the QT interval in patients with renal cell carcinoma (RCC) participating in an open-label phase II trial. *Methods* Treatment-naïve, adult patients with unresectable/metastatic, clear cell RCC received nintedanib 200 mg twice daily. QT intervals were evaluated at baseline (day −1), on day 1 (after the first dose), and on day 15 (steady state) by 12-lead electrocardiograms (ECGs) performed in triplicate. Pharmacokinetic sampling was also undertaken. *Results* Among 64 evaluable patients, the upper limits of the 2-sided 90 % confidence intervals for the adjusted mean time-matched changes in QTcF interval (corrected for heart rate by Fridericia's method) from baseline to day 1 and 15 (primary ECG endpoint) were well below the regulatory threshold of 10 ms at all times. No relationship between nintedanib exposure and change from baseline in QTcF was seen. Nintedanib was generally well tolerated with no drug-related cardiovascular adverse events. *Conclusion* Nintedanib administered at 200 mg twice daily was not associated with clinically relevant QT prolongation.

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PHASE II STUDIES

Effect of small angiokinase inhibitor nintedanib (BIBF 1120) on QT interval in patients with previously untreated, advanced renal cell cancer in an open-label, phase II study

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Keywords Nintedanib · BIBF 1120 · Renal cell carcinoma · RCC · QT interval · Phase II · Angiogenesis inhibitor

Electronic supplementary material The online version of this article (doi:10.1007/s10637-013-9962-7) contains supplementary material, which is available to authorized users.

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Introduction

Targeting tumor angiogenesis through inhibition of vascular endothelial growth factor (VEGF) signaling has proven clinically beneficial in several solid tumors [1, 2]. However, compensatory signaling via fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) pathways can result in the development of resistance to therapies that inhibit only VEGF receptors [3, 4]. Nintedanib (BIBF 1120), a new, potent, orally available triple angiokinase inhibitor, has the potential to overcome this problem, as the drug can specifically inhibit all subtypes of VEGF [1–3], FGF [1–3], and PDGF (α and β) receptors [5], along with RET and Flt3. Early clinical studies conducted to date suggest that nintedanib has an acceptable general safety profile, with rare reports of hypertension or thromboembolic events, and is usually well tolerated [6–9]. As a consequence of these positive safety signals and its broad mechanism of action, nintedanib is currently under investigation for the treatment of multiple solid tumor types, including renal cell cancer (RCC), hepatocellular carcinoma, ovarian/endometrial cancer, lung cancer, breast cancer, prostate cancer, gliomas, and colorectal cancer.

Cardiac toxicity, particularly QT prolongation (an electrocardiographic measure of the total duration of ventricular activation and recovery), is a potential short- or long-term complication of some anticancer therapies. Most significantly, agents that prolong the QT interval can induce ventricular arrhythmias, including torsade de pointes, which are associated with a risk of sudden cardiac death [10]. Because of this risk, prolongation of the QT interval has become the most common cause of delays in drug development, nonapprovals, and post-marketing withdrawals by the US Food and Drug Administration (FDA) [11]. Consequently, QT risk assessment has become a global regulatory requirement [12–14]; according to the International Conference on Harmonisation (ICH) E14 guideline, all drugs must undergo a formal clinical evaluation prior to marketing authorization dedicated to exploring their effect on cardiac repolarization (i.e., a thorough QT study) [12].

Assessment of QT interval prolongation is particularly relevant in the current era of targeted anticancer therapy, given that several classes of these novel agents are associated with this phenomenon, including the multitargeted tyrosine kinase inhibitors (TKIs) and Src/Abl protein kinase inhibitors. For example, nilotinib and vandetanib both have FDA boxed warnings relating to the increased risk of QT prolongation and sudden deaths observed in patients receiving these medications [15, 16]. Lapatinib and pazopanib can also cause QT prolongation in some patients, and should be administered with caution to patients who have or may develop prolongation of QTc [17, 18]. In a dedicated QT study designed to assess the cardiac effects of high concentrations of sunitinib in patients with advanced solid tumors, sunitinib was shown to have a dose-dependent effect on QT interval [19]. A phase I study evaluating the cardiac safety of sorafenib in patients with advanced cancer also showed modest QTc prolongation [20]. Additionally, mild QTc prolongation has been noted with dasatinib in a phase I, dose-escalation study in patients with chronic myeloid leukemia and acute lymphoblastic leukemia [21].

QT risk assessment for anticancer drugs is challenging since new therapies are typically tested in patients with advanced cancers, who may have underlying heart disease, risk factors for cardiac morbidity, multiple concomitant medications, and a pre-existing prolonged QT/QTc interval [22]. Furthermore, for reasons related to safety and tolerability (i.e., a high potential for side effects with many anticancer therapies), which prohibit supratherapeutic dosing, it is rarely possible to conduct formal, positive-controlled 'thorough QT/QTc' trials in healthy volunteers [12]. A modified study design is therefore necessary following published recommendations (including FDA guidance) regarding the assessment of QT risk in situations where a traditional QT trial is not appropriate [14, 23–25].

Following in-vitro studies demonstrating that nintedanib has no effect on myocardial repolarization at expected therapeutic concentrations (Boehringer Ingelheim, data on file), this study was undertaken to evaluate the potential effects of nintedanib on the QT interval (corrected for heart rate [HR] by Fridericia's method; QTcF) [26] when administered at the recommended dose of 200 mg twice daily [27] to patients with previously untreated, advanced RCC. This prospective analysis was part of a randomized, controlled study designed to compare the efficacy and safety of nintedanib with sunitinib in the same patient population. Additional objectives were to assess the pharmacokinetics of nintedanib.

Patients and methods

Study design and treatment

As part of a randomized, phase II, multicenter, open-label study to evaluate the efficacy and safety of nintedanib versus sunitinib in patients with advanced RCC (NCT01024920), electrocardiogram (ECG) data from patients in the nintedanib treatment arm were collected to assess the effects of nintedanib on the QT/QTcF interval. Nintedanib 200 mg was administered twice daily (400 mg/day) until disease progression or intolerable side effects. The data presented here are from an analysis evaluating ECG variables (particularly the QTcF interval), the pharmacokinetic (PK) characteristics of nintedanib and its major metabolites BIBF 1202 and BIBF 1202-glucuronide, and adverse events (AEs) observed until day 15 of the first treatment course with nintedanib.

Within this Article

Related Content

Supplementary Material (1)

- 10637_2013_9962_MOESM1_ESM.doc (276KB)
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