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Review

Characterisation of liver chemistry abnormalities associated with pazopanib monotherapy: A systematic review and meta-analysis of clinical trials in advanced cancer patients

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Abstract Drug-induced liver chemistry abnormalities, primarily transaminase elevations, are commonly observed in pazopanib-treated patients. This meta-analysis characterises liver chemistry abnormalities associated with pazopanib. Data of pazopanib-treated patients from nine prospective trials were integrated ($N = 2080$). Laboratory datasets were used to characterise the incidence, timing, recovery and patterns of liver events, and subsequent rechallenge with pazopanib. Severe cases of liver chemistry abnormalities were clinically reviewed. Multivariate analyses identified predisposing factors. Twenty percent of patients developed elevated alanine aminotransferase (ALT) >3×ULN. Incidence of peak ALT >3–5×ULN, >5–8×ULN, >8–20×ULN and >20×ULN was 8%, 5%, 5% and 1%, respectively. Median time to onset for all events was 42 days; 91% of events were observed within 18 weeks. Recovery rates based on peak ALT >3–5×ULN, >5–8×ULN, >8-20×ULN and >20×ULN were 91%, 90%, 90% and 64%, respectively. Median time from onset to recovery was 30 days, but longer in patients without dose interruption. Based on clinical review, no

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deaths were associated with drug-induced liver injury. Overall, 38% of rechallenged patients had ALT elevation recurrence, with 9-day median time to recurrence. Multivariate analysis showed that older age was associated with development of ALT >8×ULN. There was no correlation between hypertension and transaminitis. Our data support the current guidelines on regular liver chemistry tests after initiation of pazopanib, especially during the first 9 or 10 weeks, and also demonstrate the safety of rechallenge with pazopanib.

1. Introduction

Pazopanib, a multi-targeted vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI), is an effective treatment for advanced renal cell carcinoma (RCC) and soft tissue sarcoma (STS) [1]. While hepatotoxicity is an adverse event (AE) associated with a majority of approved TKIs, it appears to be particularly significant for lapatinib, pazopanib, ponatinib, regorafenib and sunitinib, each requiring a boxed label warning [2]. The precise mechanism of liver injury with TKIs is poorly understood [3–5] and requires further investigation.

Hepatotoxicity associated with pazopanib treatment commonly presents as isolated transaminase or total bilirubin elevations. The observed incidence of alanine aminotransferase (ALT) elevations in pazopanib-treated patients ranged from 46% to 60% for all grades (NCICTCAE v3.0), 8–15% for grade 3 and <1–2% for grade 4; similar rates were observed for aspartate aminotransferase (AST) elevations [1,6–8]. Total bilirubin elevations associated with pazopanib treatment were primarily grade 1 or 2, isolated hyperbilirubinemia that was considered to be associated with pazopanib inhibition of uridine-diphosphoglucuronate glucuronosyltransferase 1A1 (UGT1A1) combined with polymorphism of the *UGT1A1* gene, such as Gilbert's syndrome [9,10]. Approximately 2% of pazopanib-treated patients versus ⩽1% of placebo-treated patients met laboratory criteria for Hy's law [1,8].

Hy's law cases, defined as concurrent ALT elevation of greater than 3 times the upper limit of normal (>3×ULN) and total bilirubin ⩾2×ULN with no evidence of biliary obstruction (i.e. without significant elevation of alkaline phosphatase [ALP]), and with other causes excluded, harbour significant risk of developing severe drug-induced liver injury (DILI) and have been associated with ~10% fatality rate [11–13].

Although some features of pazopanib-induced hepatotoxicity have been identified, such as early occurrence and reversibility [1], much remains to be elucidated, including mechanisms of induction, factors predictive of development, and other features. More detailed characterisation of the onset, recovery, and rechallenge of liver events based on severity categories are also needed to help clinicians optimise treatment management for patients. Our meta-analyses address these issues using integrated data from 2080 patients with advanced cancer who received pazopanib in clinical studies.

2. Methods

2.1. Data source

Nine prospective Phase II and III GlaxoSmithKline-sponsored clinical studies that evaluated efficacy and safety of pazopanib monotherapy in patients with advanced cancer were selected [6–8,14–16] (Supplementary Table A1); data were integrated for all patients who received ⩾1 pazopanib dose (Table 1).

2.2. Liver chemistry monitoring

Most studies had ALT/AST entry criteria of ⩽2.5×ULN and total bilirubin entry criteria of ⩽1.5×ULN. Routine liver chemistry panels included ALT, AST, ALP, and total bilirubin with bilirubin fractionation required when total bilirubin was >1.5×ULN or >2×ULN. Post-baseline liver chemistry tests were generally performed every 3 or 4 weeks. Earlier studies included Day 8 testing. For isolated ALT >3–8×ULN, study treatment could continue with liver chemistry monitored until normalisation or stabilisation; for isolated ALT >8×ULN, dose would be interrupted and liver chemistry properly monitored, with rechallenge attempted only if clinical benefit had been observed. For concurrent ALT >3×ULN and total bilirubin ⩾2×ULN with >35% direct bilirubin or with hypersensitivity (i.e. potential Hy's law cases), dosing was permanently discontinued and patients were further evaluated to exclude other causes.

2.3. Data analyses

2.3.1. Characterisation of liver chemistry abnormalities

Incidence of ALT, AST, total bilirubin and ALP elevations was based on peak values calculated as a multiple of ULN. Per FDA guidance on drug-induced liver injury, transaminases >3×ULN were considered events of clinical significance [17] and were further categorised based on peak values of >3–5×ULN, >5–8×ULN, >8–20×ULN and >20×ULN. Because ALT is considered hepatic specific, ALT was used instead of AST for