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Prevalence and incidence of liver enzyme elevations in a pooled oncology clinical trial cohort

Sumitra Shantakumar [a, *], Sarah Landis [b], Andy Lawton [b], Christine M. Hunt [c]

[a] Worldwide Epidemiology, GlaxoSmithKline, Gateway West, Singapore
[b] Worldwide Epidemiology, GlaxoSmithKline, Stockley Park, United Kingdom
[c] Department of Veterans Affairs, Durham VA Medical Center, North Carolina, USA

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ABSTRACT

Few epidemiologic studies describe longitudinal liver chemistry (LC) elevations in cancer patients. A population-based retrospective cohort was identified from 31 Phase 2–3 oncology trials (excluding targeted therapies) conducted from 1985 to 2005 to evaluate background rates of LC elevations in patients (n = 3998) with or without liver metastases. Patients with baseline liver metastases (29% of patients) presented with a 3% prevalence of alanine transaminase (ALT) ≥ 3x upper limits normal (ULN) and 0.2% prevalence of bilirubin ≥ 3xULN. During follow-up, the incidence (per 1000 person-months) of new onset ALT elevations ≥3xULN was 6.1 (95% CI: 4.5, 8.0) and 2.2 (95% CI: 0.9, 4.5) in patients without and with liver metastases, respectively. No new incident cases of ALT and bilirubin elevations suggestive of severe liver injury occurred among those with liver metastases; a single case occurred among those without metastasis. Regardless of the presence of liver metastases, LC elevations were rare in cancer patients during oncology trials, which may be due to enrollment criteria. Our study validates uniform thresholds for detection of LC elevations in oncology studies and serves as an empirical referent point for comparing liver enzyme abnormalities in oncology trials of novel targeted therapies. These data support uniform LC stopping criteria in oncology trials.

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1. Introduction

For the last 50 years, liver safety issues have been the most frequent cause of safety-related drug marketing withdrawals (US FDA, 2009) warranting close monitoring of liver safety in drug development clinical trials. During oncology clinical trials, serious hepatic events may require immediate drug cessation and affect long-term outcomes. In addition to monitoring clinical symptoms, laboratory tests monitoring the presence of liver enzyme abnormalities allow for the timely detection of potential hepatotoxicity. Through liver chemistry monitoring, drug-induced functional impairment of the liver and irreversible injury may be avoided or minimized.

Most drugs associated with liver injury cause hepatocellular damage (Weil et al., 2008;Lee, 2003), which is detectable through elevated levels of aminotransferase enzymes leaked from injured liver cells (US FDA, 2009). Serum elevations of alanine aminotransferase (ALT) and bilirubin (BILI) are particularly sensitive for detecting suspected drug-induced liver injury (US FDA, 2009). ALT is also more specific for liver injury than aspartate transaminase (AST) (Green and Flamm, 2002). The elevation of ALT is generally crudely proportional to the degree of injury; elevations exceeding 3 times the upper limits normal (xULN) suggest modest liver injury (Kaplowitz, 2005). Though some drugs may increase liver enzyme levels, severe hepatocellular injury is accompanied by an impaired ability of the liver to clear plasma bilirubin. In severe drug-induced liver injury, simultaneous elevations in ALT and bilirubin indicate the potential for acute liver failure (Kaplowitz, 2005).

Small case series have reported marked liver chemistry elevations and fulminant hepatic failure in patients with liver metastases or infiltrating neoplasms (Rajvanshi et al., 2005; Rowbotham et al., 1998). This study's focus is to understand the distribution of liver

Abbreviations: ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate transaminase; BILI, bilirubin; xULN, upper limits normal.

* Corresponding author. Worldwide Epidemiology, R&D Glaxosmithkline 150 Beach Road, #26-00, Gateway West Singapore 189720 Singapore.
E-mail addresses: sumitra.y.shantakumar@gsk.com (S. Shantakumar), sarah.h.landis@gsk.com (S. Landis), andy.m.lawton@gsk.com (A. Lawton), christine.hunt@va.gov (C.M. Hunt).

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injury events associated with liver metastases or potential drug-induced mechanisms in oncology clinical trials. In oncology clinical trials, liver chemistry elevations also arise from viral hepatitis (Rajvanshi et al., 2005), hypotension/ischemia, sepsis, acute vascular events, and non-hepatic causes (Green and Flamm, 2002), but these factors are beyond the scope of this report.

In this study we pooled data from 31 oncology clinical trials to assess the rates of liver chemistry elevations among 3998 enrolled patients with and without baseline liver metastases. Pooling data is advantageous for assessing the risk of rare outcomes, such as laboratory indicators of mild, moderate and severe drug-induced liver injury, and for assessing whether risk varies across patient characteristics. Accounting for the presence of liver metastases at patient enrollment, our study seeks to establish the background prevalence and incidence rates of liver injury events in a large, representative population of patients with solid tumors. Select demographic, clinical, and nutritional risk factors were examined among those with elevated levels of ALT.

2. Materials and methods

This study includes 31 Phase 2 (n = 26) and Phase 3 (n = 5) oncology trials conducted by GlaxoSmithKline or its heritage companies between 1985 and 2005 (Supplementary Material); all trials included liver chemistry testing. Clinical trials of targeted cancer therapies were excluded from the pooled dataset since a primary objective was to establish background rates of potential liver injury in a representative sample of the general oncology population. All patients with at least one follow-up liver chemistry elevation had their maximal measured value described. The outcome of interest was a liver chemistry elevation greater than or equal to pre-defined upper limit of normal (ULN) threshold. Baseline was defined as the period between the initial study visit up to the day before the first administration of investigational product. If more than one set of laboratory values were available during the baseline period, the tests performed closest to the initiation of investigational product were used.

Baseline prevalence and incidence estimates for liver chemistry thresholds of alanine transaminase (ALT), aspartate transaminase (AST), bilirubin (BILI) and alkaline phosphatise (ALP) were examined. The baseline prevalence of selected liver chemistry tests above the ULN threshold was defined as the proportion (%) of patients with an elevation greater than or equal to pre-defined ULN threshold levels among all patients with laboratory values during the baseline period. The incidence proportion (%) and incidence rates per 1000 person-months of new onset elevations while on treatment were calculated. For incidence analyses, patients were considered at-risk if they had normal baseline liver chemistries and at least one follow-up test. Person-time at-risk was censored at either the date of reaching a particular elevation threshold or the date of the final administration of investigational product among patients who did not experience the outcome. Analyses of prevalence and incidence were conducted separately for each liver chemistry and each threshold definition; an individual could contribute to the numerator in more than one analysis of different liver chemistry tests and thresholds. A combination endpoint suggesting possible severe liver injury (ALT or AST $\geq$ 3xULN and BILI $\geq$ 2xULN and ALP < 2xULN) was also evaluated (US FDA, 2009). Lastly, for patients with at least one follow-up elevation, the distribution of maximal measured liver chemistry elevations was described. All prevalence and incidence analyses were stratified by the presence of baseline liver metastases. Assessment of metastatic progression varied across the 31 trials. Our pooled study did not require confirmation of baseline liver metastases by medical imaging.

Lastly, demographic, clinical, and nutritional factors potentially associated with ALT elevations were examined. The baseline prevalence and incidence proportion of ALT $\geq$ 3x ULN were stratified by these covariates and risk ratios (RR) comparing each level of the covariate to a referent group were calculated. The cancer type with the lowest incidence at follow-up was chosen as the referent group (breast cancer) for tumour type analyses. Corresponding confidence intervals using an approximate method were calculated (Armitage et al., 2002). All analyses were conducted using SAS version 9.1.

3. Results

Liver chemistries were examined in 3998 patients in 31 Phase 2 and 3 oncology trials. The aggregated dataset included clinical trials of lung cancer (n = 10 trials), colorectal cancer (n = 6), breast cancer (n = 5), ovarian cancer (n = 5), prostate cancer (n = 1), non-Hodgkin lymphoma (n = 1), Kaposi sarcoma (n = 1), and leukemia (n = 2). In these trials, baseline laboratory values for ALT, AST, ALP, and bilirubin were obtained in 81% (n = 3223), 61% (n = 2451), 86% (n = 3424) and 92% (n = 3665) of patients respectively. The median patient age was 61 years (range: 18–90 years). The median length of follow-up was 119 days (range: 1–1111 days). At baseline, the majority of patients had locally advanced or metastatic disease and 29% had liver metastases. In most trials, liver chemistry inclusion criteria were specified, and typically required levels of transaminases and bilirubin $\leq$2x ULN in the absence of liver metastases and $\leq$5x ULN in the presence of liver metastases.

Across all liver chemistries and threshold levels, there was a higher baseline prevalence of enzyme elevations among patients with liver metastases, compared to patients without liver metastases. Elevations <10x ULN were generally twice as common among those with baseline liver metastases compared to those without metastases (Table 1). At baseline, transaminases (ALT, AST) at $\geq$ 3xULN affected 5% or less of patients with liver metastases and less than 2% of patients without liver metastases (Table 1). Baseline ALP $\geq$ 3x ULN was more common, identified in 17.1% of those with liver metastases and 3.7% of patients without liver metastases. Baseline bilirubin $\geq$2x ULN affected fewer than 1% of those with or without liver metastases (with most patients exceeding this threshold excluded from trials). Potentially severe liver injury is identified by concomitant transaminase and bilirubin elevations. At baseline, a single patient without liver metastases exhibited concomitant transaminase and bilirubin elevations (ALT or AST $\geq$ 3xULN and BILI $\geq$ 2xULN and ALP < 2xULN), yielding a prevalence of 0.04% (95%CI: 0%–0.2%); no such combination occurrence was observed among those with baseline liver metastases.

Overall during follow-up, an incident elevation of ALT $\geq$ 3xULN affected 2.8% of patients without metastases, and only 1.2% of patients with liver metastases (Table 2). The incidence of AST $\geq$ 3xULN, a nonspecific injury marker, was twice as common among subjects without liver metastases (10.6%) compared to subjects with baseline liver metastases (5.1%). An incident elevation of ALP $\geq$ 3xULN affected 1% or less of all patients. Bilirubin $\geq$ 3xULN, the threshold for clinical jaundice, affected 0.6% of those without liver metastases and 2.0% of those with baseline liver metastases. Regardless of liver metastases, the incidence of moderate liver chemistry elevations (i.e. $\geq$5xULN) was less than 1%. Bilirubin was the only analyte with higher incidence rates among patients with liver metastases. The incidence of ALT or AST elevations of 1-5xULN was higher for patients without liver metastases, compared to those with metastases. Only one patient without liver metastases exhibited concomitant transaminase and bilirubin elevations (ALT or AST $\geq$ 3xULN and BILI $\geq$ 2xULN and ALP < 2xULN)

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