A Review of Regulatory Guidance for Conducting Hepatic Impairment Studies: A Case Study in Oncology

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Review Article

ABSTRACT

The liver is a vital organ that plays a central role in the metabolism and elimination of drug molecules. Impairment of this vital organ can lead to increased accumulation of parent drug or active metabolites, affecting systemic drug disposition, clinical efficacy, safety and tolerability. Hepatic disease in cancer patients is generally associated with the metastatic spread of the primary tumor to or near the liver, or by toxicities associated with treatment using chemotherapeutic agents. Over the last decade, the understanding of cancer has changed the field of drug development and has resulted in novel, oral targeted therapies that interfere with dysregulated pathways in cancer. Many of these orally administered agents are dependent on the liver for drug metabolism and so understanding hepatic impairment in cancer is imperative to achieve appropriate dose adjustments and to avoid toxicity. This mini-review will focus on how published guidance from the US Food & Drug Administration (FDA) and European Medicines Agency (EMEA) on hepatic impairment studies can be tailored to guide study design and subsequent dosage modification in cancer patients with varying degrees of hepatic dysfunction.

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INTRODUCTION

The liver is a vital organ that plays a central role in the metabolism and elimination of drug molecules through various oxidative and conjugative metabolic pathways, and through biliary excretion \(^1\). Hepatic impairment alters normal hepatic function which can adversely influence drug pharmacokinetics (PK) by changing the intrinsic hepatic clearance of drugs, reducing hepatic metabolic capacity, and altering the biliary excretion of drugs. Hepatic impairment can lead to increased accumulation of parent drug or active metabolites, thus affecting systemic drug disposition, clinical efficacy, safety and tolerability \(^2\).

Normal hepatic function can decline through a number of pathophysiological mechanisms, such as hepatic parenchymal injury, cell death and pathological repair processes, changes in the hepatic microcirculation and changes in the endothelial lining of the sinusoids \(^3\). Perpetrators of liver disease include chronic liver infection from conditions such as hepatitis B or C, chronic and excessive alcohol ingestion, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune chronic active hepatitis and metabolic syndromes \(^4\,^5\). In contrast, hepatic disease in cancer patients is generally associated with the metastatic spread of the primary tumor to or near the liver, or caused by toxicities associated with the treatment using chemotherapeutic agents. According to a Surveillance, Epidemiology, and End Results (SEER) annual report, between 1992 to 2005, 2 in every 1000 patients being treated for the four most common cancers, breast, colorectal, lung and prostate cancer, had concurrent liver disease \(^6\).

Over the last decade, the understanding of cancer has changed the field of drug development and has resulted in novel, oral targeted therapies that interfere with dysregulated pathways in cancer. Many of these orally administered target agents are dependent on the liver for drug metabolism and so understanding hepatic impairment in cancer is important to ensure appropriate dose adjustments to avoid toxicity in these patients.

2. Mechanisms of liver disease due to malignancy

The mechanisms by which malignancies cause hepatic dysfunction are complex and include direct reduction in the volume of the functional healthy liver, or by intrahepatic and/or extrahepatic biliary obstruction \(^7\). Further, cancer-associated humoral and immunological factors may increase cholestasis and inflammatory damage, and parenchymal infarction may result from portal-vein thrombosis as a consequence of a hypercoagulable state or tumor thrombi \(^7\,^8\). Singling out the right dosage regimen for the management of patients with serious malignancies presenting with hepatic dysfunction is difficult and is further complicated by the fact that the cause of dysfunction may or may not be directly related to their malignancy \(^8\). Increased risk of chemotherapy-induced hepatotoxicity in these patients adds to this challenge. More recently, with the rise of use of immunotherapy, the risk of autoimmune toxicities to the liver has become a major concern. This mini-review will focus on how the guidance for hepatic impairment studies published by the US Food & Drug Administration (FDA) and European Medicines Agency (EMEA) can be tailored to guide study design and subsequent dosage modification in cancer patients with varying degrees of hepatic dysfunction.

3. Classification of hepatic impairment

The severity of hepatic dysfunction can be defined using a number of validated scales. The Child-Pugh classification has been widely used in clinical practice to categorize chronic cirrhotic patients based on the severity of liver function impairment \(^9\,^10\). This classification system consists of five components that assess the degree of impairment, including laboratory parameters: serum bilirubin, serum albumin, and prothrombin time, and clinical symptoms: presence of encephalopathy and presence of ascites \(^11\). Based on disease severity, patients are categorized into groups defined as mild (class A), moderate (class B) or severe (class C), corresponding to 5-6, 7-9
and 10-15 scores, respectively \cite{11}. Although the Child-Pugh score is very helpful in classifying patients and monitoring disease course over time, it assigns a score of 5 for normal subjects and thus, does not accurately differentiate between normal subjects and patients with mild impairment. Furthermore, the Child-Pugh classification scale assigns points based on the presentation of clinical symptoms - ascites and encephalopathy - which may not be applicable to cancer patients with hepatic disease due to differences in the hepatic dysfunction etiology.

The National Cancer Institute (NCI) classification has been adopted to characterize the severity of hepatic dysfunction in cancer patients. This scale stratifies patients into five groups or cohorts (A: normal, B: mild dysfunction, C: moderate dysfunction, D: severe dysfunction, E: liver transplant) according to their hepatic function based on total bilirubin and serum aspartate aminotransferase (AST or SGOT) levels \cite{12}. Based on Younis’s work comparing the sensitivity of liver function classification systems for exposure changes, the NCI scale appears to be the most precise for indicating exposure changes in hepatically impaired cancer patients \cite{13}. Multiple studies have used the NCI scale to classify cancer patients according to the degree of hepatic impairment and to inform dosing recommendations in these subpopulations \cite{14-17}. Recently, the FDA suggested using the NCI scale as an alternative to the Child-Pugh scale for hepatic impairment classification in oncology trials \cite{18}.

4. Guidelines for conduct of hepatic impairment studies

Considering the importance of the effects of liver function impairment on PK during drug development, the FDA published a guidance document in May 2003 on the design, conduct, analysis, and reporting of hepatic impairment studies and their impact on dosing and labeling \cite{19}. Soon after, the EMEA provided guidelines in August 2005 for PK evaluation of medicinal products in patients with impaired hepatic function \cite{5}. Recently, an unofficial presentation by a representative from the FDA specifically discussed hepatic impairment studies in cancer patients and the labeling changes in the 2011 FDA hepatic guidance revision \cite{18}.

In general, a hepatic impairment study should be conducted if the drug is likely to be used in hepatically impaired patients. Both the FDA and EMEA guidelines recommend a dedicated PK study in patients with impaired hepatic function if hepatic metabolism and/or excretion accounts for a substantial portion of the elimination of a parent drug or active metabolite, defined as > 20% of the absorbed drug. If drug labeling or literature sources suggest that a drug has a narrow therapeutic range, the guidance recommends conducting a hepatic impairment study even if the drug and/or active metabolite is eliminated to a lesser extent (<20 %). The FDA also recommends conducting a study if drug metabolism is unknown and information is inadequate to suggest that hepatic elimination accounts for a minor percentage of total drug elimination. A valid justification needs to be provided if hepatic function impairment is not likely to significantly alter drug PK and a study is not conducted. Rationale for not performing these studies can include no necessity to administer the drug to hepatically impaired patients, the majority of drug elimination occurring through renal routes, less than 20% of the drug being metabolized in the liver with a wide therapeutic range, or the drug being eliminated primarily by the lungs.

4.1. Hepatic impairment study design and dose administration

With regard to study design, normal PK drug properties have to be taken into account and the implications of hepatic dysfunction on drug PK needs to be assessed prior to choosing a study design and including subjects. According to the FDA guidance, hepatic impairment studies consist of three study designs: a basic full study design, a modified study design and reduced study design. The full study design should enroll patients belonging to all three Child-Pugh categories, mild, moderate and severe, as well as normal controls. The reduced design includes subjects with normal hepatic function and moderate hepatic impairment, and the modified design includes subjects with normal hepatic function (controls) and subjects with mild and moderate hepatic impairment. The
EMEA recommends starting with the reduced study design to screen for significant effects of hepatic impairment on PK, and enrolling subjects with milder and severe degrees of impairment if a significant effect is detected. Both guidance documents recommend matching control subjects to hepatically impaired subjects based on age, weight and gender. Depending on the drug being investigated, factors like smoking, alcoholic intake, and genetic polymorphism should also be controlled for. For a full study design at least 6 subjects should be included per group, and at least 8 subjects per group for the modified or reduced study designs.

These studies can be designed as a single-dose or multiple-dose study with assessment of both the parent drug and any active metabolites, depending on the PK of the drug. Both guidance documents recommend a single dose study when the parent drug and its active metabolite demonstrate linear and time-independent PK. However, a multiple dose study should be conducted at steady state when the parent drug or its active metabolite is known to exhibit nonlinear or time-dependent PK. Although the regular clinical dose is usually employed as an appropriate starting dose in these studies, doses administered to hepatically impaired patients in a multiple dose study may have to be lowered to avoid drug accumulation to harmful blood levels. The population for hepatic impairment studies generally consists of volunteers with hepatic dysfunction but no other significant diseases. For similar studies in oncology, non-cancer and otherwise healthy subjects can be used for single dose studies however ethical concerns arise in using non-cancer subjects for multiple dose studies. Hence, multiple dose studies in oncology may need to be carried out in the representative disease population.

Both FDA and EMEA encourage using simulations to identify suitable doses and dosing intervals in hepatically impaired patients. For PK sampling, the duration of blood sampling has to be sufficient to determine the terminal half-life of the drug and its active metabolite(s), with the supposition that these times will most likely be extended in hepatically impaired patients compared to the control population. Furthermore, if the drug or metabolite exhibits high plasma protein binding, PK has to be analyzed relative to unbound concentrations in addition to total plasma concentration.

4.2. Data analysis, dosing recommendations and labeling

Data analysis for hepatic impairment studies is mainly carried out to determine at risk patients and to suggest suitable posology adjustments depending on the degree of hepatic impairment. Estimation of PK parameters should include plasma concentration data for the drug and its metabolites for a single dose study, plasma concentration data at steady state for a multiple dose study, and unbound plasma concentration data where relevant. The estimation can be carried out using either non-compartmental and/or compartmental modeling approaches. Linear and nonlinear models can be used to determine the relationship between hepatic functional abnormalities (e.g., hepatic blood flow, overall impairment scores such as Child-Pugh, or NCI categories), and selected PK parameters.

The FDA guidance describes the general approach that should be used to develop dosing recommendations. If there is a significant change in drug PK due to hepatic impairment, administration of reduced doses should be recommended in labeling. However, for a prodrug, these adjustments might involve administration of higher doses and shorter dosing intervals. If a conclusion of no effect is made, it should be based on a priori specified no effect boundaries or the employment of a 90 percent confidence interval. According to the FDA guidance, a general labeling approach is a dose reduction in the Child-Pugh population in which a significant PK change was observed. The drug might be contraindicated or must be used with caution in severely hepatically impaired patients, depending on drug's indication and its therapeutic range. On the contrary, if no significant impairment of drug clearance is observed in the moderately impaired patients, it can be assumed that the drug can be administered in both mildly and moderately impaired patients without dose modification. Almost always, labeling will indicate
caution for severely impaired patients if the drug undergoes significant hepatic clearance and there is an absence of evidence to aid a lesser labeling restriction.

5. 

**Case study: Hepatic Impairment Study in Oncology**

We present the crizotinib hepatic impairment study (NCT01576406) as a case example to discuss the application of regulatory guidance in the design of a hepatic impairment study. Crizotinib (Xalkori®) is an ATP-competitive small-molecule inhibitor of anaplastic lymphoma kinase (ALK), Recepteur d’Origine Nantais (RON), and ROS1 receptor tyrosine kinases [20-22]. In a Phase 3 randomized clinical study in patients previously treated for ALK-positive non-small cell lung cancer (NSCLC), crizotinib significantly improved progression-free survival (PFS) by about 4.7 months compared to the standard of care chemotherapy with either pemetrexed or docetaxel [23]. In a meta-analysis involving six clinical studies, crizotinib treatment demonstrated a 1-year overall survival (OS) of 66.8% and PFS of 8.6 months [24]. Based on the efficacy findings and overall favorable side effect profile, crizotinib 250 mg administered orally twice daily (BID) has been approved for the treatment of advanced ALK-positive and ROS1-positive NSCLC.

Crizotinib’s PK in cancer patients was determined from a Phase 1 dose escalation study. Following a single oral dose, the time to peak plasma concentration of crizotinib (Tmax) was determined as around 4 hours after dosing, followed by a multi-exponential decline with mean terminal half-life of 42 hours [25]. Following repeated oral administration, steady state was reached within 15 days. Across the dose range of 200 mg to 300 mg, steady-state crizotinib exposure appeared to increase in a more-than-dose-proportional manner. The mean oral clearance (CL/F) of crizotinib was estimated at about 100 L/h following a single dose as compared to 60 L/h at steady state, demonstrating nonlinear PK [26].

In vitro studies with human liver microsomes, demonstrated crizotinib as a cytochrome P450 (CYP) 3A4/5 substrate. This was confirmed in human drug interaction studies with co-administration of either ketoconazole or rifampin, which demonstrated a change in crizotinib area under the curve (AUC) by 216% increase and a 84% decrease, respectively [25-27]. Crizotinib is also an inhibitor and inducer of CYP3A4/5 with net time-dependent auto-inhibition effect at steady state.

The effect of hepatic impairment on the PK of crizotinib was evaluated in a Phase 1, open-label, non-randomized clinical study [28, 29]. The primary outcomes for this study were determining crizotinib steady-state exposures (area under the concentration-time curve during one dosing interval, AUCτ and maximum plasma concentration, Cmax) for different hepatic impairment groups. Since crizotinib follows nonlinear PK, a multiple dose study was designed for the PK assessment of the parent drug and its active metabolite. This study enrolled crizotinib-naïve patients with advanced NSCLC, who were ≥18 years of age and had an Eastern Cooperative Oncology Group (ECOG) status 0-2, with mild, moderate or severe liver dysfunction alongside control patients with normal liver function [28, 30]. Patients were classified, based on liver function using the NCI scale, into normal (groups A1 and A2) with aspartate aminotransferase (AST) and total bilirubin (TB) levels ≤ the upper limit of normal (ULN), mildly impaired (group B) with AST > ULN and TB ≤ ULN, or AST any value and TB > 1.0 – 1.5 × ULN, moderately impaired (groups C1 and C2) with AST any value and TB > 1.5 – 3 × ULN, and severely impaired (group D) with AST any value and TB > 3 × ULN, patients with hepatic dysfunction [12, 28, 29]. Patients in the control groups, A1 and A2, were matched on the basis of weight, age, gender, race and ECOG status to patients in groups B and C2, respectively.

The starting dose for groups A1 and B was the clinically administered dose of 250 mg BID. This dose was reduced for patients in the moderately impaired groups C1 and C2, to 250 mg once a day (QD) and 200 mg BID, respectively [28, 29]. Patients in the second control group, A2, received 250 mg QD. Group C was not matched to any control group but received a dose of 250 mg QD. Although no rationale was provided for the reduced doses for the
patients with moderate and severe hepatic impairment, the reduction is probably best explained by the extensive hepatic metabolism of crizotinib which might lead to toxic plasma concentrations in these patients. It is unknown whether selection of doses is based on the use of simulations as suggested in the EMEA guidelines.

This study included cancer patients with all degrees of hepatic impairment and followed the full study design as recommended by FDA. Since crizotinib is likely to be used in patients with hepatic impairment, conducting a study in this subset of patients and including patients with all degrees of hepatic impairment is crucial for its safe administration. Additionally, the NCI scale was used to classify patients in terms of hepatic impairment. Given that crizotinib is intended for use in metastatic NSCLC patients, it is justifiable and desirable to use the NCI classification over the Child-Pugh classification.

Crizotinib has been reported to exhibit nonlinear PK behavior, such that steady-state plasma levels increase in a less than dose-proportional manner. Hence, a multiple dose study would be the most appropriate dose administration scheme for crizotinib, in accordance with the FDA and EMEA guidance. Currently, it is not well understood how hepatic dysfunction can disrupt the inhibition and induction capabilities of CYP enzymes. Crizotinib exhibits both inhibition and induction effects with the net auto-inhibition in patients with normal hepatic function; thus it is unclear how hepatic impairment may disrupt the balance of its inhibition and induction capabilities.

Given the reduced dose and dosing interval in more severely impaired patients, it appears that the labeling for crizotinib might require reduced dose recommendations for patients with moderate and severe hepatic impairment and caution might have to be exercised with the use of this agent in patients with hepatic dysfunction.

6. Challenges in Conducting Hepatic Impairment Studies in Oncology

Although hepatic impairment studies are important in oncology and the information obtained is critical for the management of advanced cancer patients, conducting these clinical trials can be challenging. The eligibility criteria for cancer patients are more restrictive for hepatic impairment studies than other clinical studies. Thus, recruiting cancer patients with moderate and severe hepatic impairment who meet the strict inclusion/exclusion criteria represents the biggest challenge in completing study enrollment. The crizotinib hepatic impairment case study began in May 2012 and data collection was completed in June 2016 [28]. It is critical, particularly for hepatic impairment studies, that subjects are not also renally impaired to rule out renal impairment as the cause of any changes in PK if the drug is eliminated by both organs. Besides this, ethical issues arise with regards to enrolling subjects for these studies. Chemotherapeutic drugs cannot be administered to non-cancer patients with hepatic dysfunction due to safety and toxicity concerns, and hence cancer patients need to be enrolled. With cancer patients, there is a concern whether dosing of investigational agents are optimized for efficacy and minimizing toxicities. Therefore, administering reduced treatment doses to cancer patients in the control group who have normal hepatic function in order to compare with hepatically impaired patients prompts questions about reduced efficacy. Other considerations for conducting hepatic impairment studies in cancer patients include: disease progression and serious treatment-related toxic events or death, which not only prolongs study completion, but may also require enrolling high numbers of patients to fulfill the regulatory recommendations of 6-8 subjects per hepatic impairment group.

SUMMARY

The FDA and EMEA guidance on hepatic impairment studies provide important considerations for conducting studies, study design, data interpretation and labeling implications. Although these guidance documents have not been written specifically for studies in patients with malignancies, we have tried to tailor our review so it could be
utilized as a reference to conduct hepatic impairment studies in oncology. The complex etiology of cancer and stringent inclusion/exclusion criteria makes it difficult to carry out these studies in cancer patients. In addition, ethical concerns of safety and efficacy arise since cancer agents are cytotoxic and cannot be administered to healthy volunteers, and cancer patients with hepatic dysfunction have to be enrolled for multiple dose studies. Nonetheless, simulations have been used successfully to guide the design of clinical studies and to select appropriate doses in cancer patients with varying degrees of hepatic impairment \cite{31, 32}.

More recent publications have helped to clarify how to apply regulatory guidance to the development of cancer therapeutics. The Child-Pugh system has commonly been employed to classify patients with hepatic impairment but more recently the NCI scale has been adopted since it provides an objective way of assessing hepatic dysfunction and has more discriminatory power to segregate patients accurately \cite{33, 34}.

With the increased development of oral targeted agents in oncology and with hepatic metabolism being the major elimination route for these agents, identification of accurate dosing regimens for disease management in this specific population is becoming increasingly important.

**DECLARATION OF CONFLICTING INTEREST**

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