Clinical Cancer Research

The Effect of Hepatic Impairment on Outcomes in Phase I Clinical Trials in Cancer Subjects

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Abstract

Purpose: The NCI Cancer Therapy Evaluation Program sponsors hepatic dysfunction phase I clinical trials (HDCT) and phase 1 clinical trials (P1CT) to determine safe doses and schedules of antineoplastic therapeutics. We sought to compare clinical outcomes between these trial types while stratifying by hepatotoxic agents.

Experimental Design: Individual subject data were extracted from the records of 51 NCI-sponsored HDCT and P1CT. The NCI's Organ Dysfunction Working Group's hepatic impairment categorization and two drug-induced liver injury (DILI) scales (FDA R ratio and Hy's law) were used to classify subjects. The number of cycles administered and treatment discontinuation reason were also evaluated and compared between groups.

Results: There were 513 and 1,328 subjects treated on HDCT ($n = 9$) and P1CT ($n = 42$), respectively. There were differing patterns of DILI with significant worsening of total bilirubin in subjects on HDCT, and worsening of alanine aminotransferase (ALT) in subjects on P1CT. Cholestatic peak patterns of liver impairment (predominant increases in alkaline phosphatase rather than transaminases) were more frequent in HDCT. Criteria for Hy's law were met by 11 subjects on P1CT, but not by any subjects on HDCT. Disease progression was the most common reason for treatment discontinuation, followed by adverse events at similar frequencies in both HDCT and P1CT.

Conclusions: The differential effects on hepatotoxicity suggest that underlying hepatic function may affect susceptibility to and patterns of DILI. The incorporation of additional measures of hepatic function may help identify those at highest risk of hepatotoxicity in future trials because baseline liver tests did not. *Clin Cancer Res; 22(22); 5472–9. ©2016 AACR.*

Introduction

Standard phase 1 clinical trials (P1CT) are conducted in cancer subjects to elucidate the safety and tolerability, pharmacokinetic and pharmacodynamic properties, and MTD or recommended phase 2 dose (RP2D) of antineoplastic drugs as single agents or in combination. Subjects with impaired renal or hepatic function are often excluded from P1CT because their altered drug metabolism and excretion may affect MTD and R2PD determinations. Liver test abnormalities secondary to hepatic metastases, underlying liver disease, or lingering effects of prior therapies may also preclude eligibility for a P1CT (1, 2). Taken together, oncologists often have little guidance on how to dose medications in subjects with varying degrees of organ dysfunction.

The FDA and the European Medicines Agency (EMA) have developed guidance on the conduct of studies addressing the optimal dose in subjects with hepatic dysfunction (3, 4). When the majority of antineoplastic agents being developed were cytotoxic with a narrow therapeutic index, only subjects with cancer could be enrolled on these trials based on ethical concerns over short- and long-term toxicities of these agents. With the development of molecularly targeted therapeutics, volunteers without cancer have been utilized in lieu of subjects with cancer for a quick assessment of whether single-dose exposure is altered by varying degrees of hepatic impairment. These trials do not assess long-term tolerability which could be altered for reasons other than drug exposure. Therefore, the Cancer Therapy Evaluation Program (CTEP) at the NCI prioritized study of these special patient populations with hepatic dysfunction phase I clinical trials (HDCT) to determine safe administration parameters of antineoplastic agents for subjects with varying degrees of liver dysfunction. HDCT sponsored by CTEP and others have provided clinically useful information on the optimal dosing of antineoplastic agents in subjects with different degrees of liver test abnormalities that have provided administration guidance in the labels for patients with abnormal organ function (5–15).

During drug development, preclinical testing and observation of clinical events in P1CT identify hepatotoxic drugs that may cause drug-induced liver injury (DILI). Hepatotoxicity is primarily identified by alterations to liver tests during the conduct of the clinical trials. CTEP maintains a large database that includes P1CT and HDCT. We compared the patterns of DILI, number of cycles administered, and reasons for discontinuation between subjects on HDCT and P1CT in a subject-level meta-analysis to gain insight

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Translational Relevance

Hepatic dysfunction phase I clinical trials (HDCT) provide safe administration parameters of antineoplastic agents for subjects with varying degrees of liver dysfunction. We compared clinical outcomes and found differential patterns of drug-induced liver injury (DILI) between subjects on standard phase 1 clinical trials (P1CT) and HDCT; however, baseline liver tests did not identify those most likely to experience severe DILI as defined by Hy's law. Patients on HDCT received fewer cycles of therapy but discontinued for similar reasons as patients on P1CT. Hepatic function is a critical component of treatment individualization frequently requiring dose modifications. Our findings suggest that within the context of clinical trials, it is safe to treat subjects with liver test abnormalities. We suggest that it would be worthwhile to include additional scores of hepatic function, such as the Model for End-Stage Liver Disease or Child–Pugh, to understand how underlying hepatic function relates to severe DILI.

into the safety and outcomes of subjects with hepatic dysfunction on clinical trials.

Patients and Methods

The records of participants in NCI-sponsored P1CT and HDCT are prospectively maintained in the Clinical Trials Monitoring Service database which is owned by the NCI and maintained by Theradex Systems under contract with the NCI. Theradex provides data management and auditing practices of the database during the conduct of the trials. The database records were abstracted and reviewed at the individual subject level for 1,896 subjects on 42 P1CT and 9 HDCT; we included clinical trials for which serial liver tests were available for review in the database. Liver tests (as described below), the total number of cycles administered of antineoplastic agents, and reasons for discontinuation were reviewed. All NCI-sponsored clinical trials utilized for this analysis were approved by the institutional Review Board with written informed consent being obtained on all subjects.

For this study, the upper limits of normal for aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were defined as 50 U/L, the upper limit of normal for total bilirubin was defined as 1 mg/dL, and the upper limit of normal of alkaline phosphatase (ALK) was defined as 150 U/L. The upper limits of normal for these tests were made independent of local laboratory definitions. Liver toxicity was assessed in multiple ways given the complexities that an individual test is not sufficiently robust: (1) Alterations in liver tests were assessed utilizing the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 to grade liver test results, (2) The NCI Organ Dysfunction Working Group (ODWG) definitions for hepatic dysfunction were used to define baseline and peak categorizations (Table 1; ref. 15), (3) A modified version of the FDA R ratio [(ALT value/ALT ULN)/(ALK value/ALK ULN)] was used to classify the pattern of liver test abnormalities (Table 1; refs. 16, 17), and (4) Hy's law was also utilized as previously described (Table 1; ref. 18). For the definition of peak, we used the most severe of whichever test. In addition, the NCI ODWG score and FDA R ratio (Table 1) use concurrent labs for the categorizations, the worse of which was used for the definition of peak.

Drugs were categorized as hepatotoxic or not, based on review of LiverTox (http://livertox.nlm.nih.gov) and their package inserts (if approved by the FDA or EMA), or available clinical trial data (if

Table 1. Classifications of hepatic impairment and patterns of hepatotoxicity

	Categorization of hepatic impairment		
		NCI Organ Dysfunction Working Group	
	FDA or EMA CP	Total bilirubin	ALT or AST
Normal			
Mild	A (5–6 pt)	B1: $\leq$ ULN B2: >1–1.5x ULN	B1: > ULN B2: Any
Moderate	B (7–9 pt)	>1.5–3x ULN	Any
Severe	C (10–15 pt)	>3x ULN	Any
CP score	**1**	**2**	**3**
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	1.0–2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time (seconds prolonged)	1.0–4.0	4.0–6.0	>6.0
Encephalopathy grade	None	1 or 2	3 or 4
DILI			
Patterns of liver function test abnormalities		FDA R ratio	
No abnormality		All liver function tests below the ULN	
Hepatic		>5	
Cholestatic		<2	
Mixed		2–5	

$$\text{FDA R ratio} = \frac{(\text{ALT value}/\text{ALT ULN})}{(\text{ALK value}/\text{ALK ULN})}$$

Hy's law

A rule that is used for determining which drugs are high risk for causing a fatal DILI.

1. The drug causes hepatocellular injury, generally shown by a higher incidence of >3x ULN of ALT or AST than the control drug or placebo.
2. Elevated serum total bilirubin to >2x ULN in subjects showing aminotransferase (AT) elevations without initial findings of cholestasis (elevated serum ALP >2x ULN).
3. No other reason can be found to explain the combination of increased AT and Total bilirubin, such as:

- viral hepatitis.
- pre-existing or acute liver disease.
- another drug capable of causing the observed injury.

not approved by the FDA or EMA). Drugs that had black box warnings or precautions due to drug-related severe or fatal liver injury in the package inserts or labels were deemed to be hepatotoxic. If the investigational drug had not been approved by the FDA or EMA, drugs that were associated with dose-limiting toxicities or serious adverse events related to liver injury were deemed to be hepatotoxic. In the absence of data suggestive of hepatotoxicity, drugs were scored as nontoxic (Supplementary Table S1).

Descriptive statistics were used to summarize results. Data are displayed as medians with interquartile ranges unless specified otherwise. The χ^2 test was used to compare categorizations among groups, and the Kruskal–Wallis test was used to compare numeric data between groups. A t test was used in order to analyze the change in CTCAE grade (peak CTCAE category – baseline CTCAE category) by number of cycles received. JMP 11.2.1 (SAS Institute Inc.) was used for statistical analyses. Figures were created with Prism 6 for Mac OS X (GraphPad Software Inc.). Circos diagrams were made using an online interface (http://mkweb.bcgsc.ca/tableviewer; ref. 19) and modified with Adobe Photoshop CC 2014 for clarity.

Results

Demographic data

The NCI CTEP database included 51 P1CT ($n = 42$) and HDCT ($n = 9$) with subject-level information on 1,896 subjects. Due to late determination of ineligibility or complicating intercurrent illnesses, 1,841 subjects actually received at least one dose of study treatment on trial, and further analysis was restricted to these subjects (Table 2; Supplementary Table S2). There were 1,328 subjects treated on P1CT and 513 subjects treated on HDCT. The median ages were 59.0 years (range, 49–67) on PICT and 58.6 years (range, 51–66) on HDCT ($P = 0.88$). There were fewer females included in HDCT (44%) than P1CT (50%; $P = 0.03$).

Alterations in hepatic function on treatment by ODWG and CTCAE definitions

At baseline, 84% of subjects in P1CT were classified as normal by NCI ODWG criteria, but fewer subjects met this classification in HDCT (27%; Table 2; Fig. 1). Patients without hepatic dysfunction are included in HDCT for comparative pharmacokinetic analyses. Changes in subject categorization by NCI ODWG definitions between baseline and peak levels of liver tests are displayed with circos diagrams (Fig. 2). Whereas the liver tests of some subjects with mild group 1, mild group 2 or moderate classifications of liver dysfunction at baseline normalized, the liver tests of subjects with severe liver dysfunction did not (Fig. 2A). In addition, worsening categorizations or stabilization of liver dysfunction categorizations was more commonly observed than normalization in P1CT (Fig. 2B) and HDCT (Fig. 2C).

As expected, subjects on HDCT had higher baseline CTCAE grades for liver tests than subjects on P1CT (Fig. 3). There was a greater increase in peak ALT CTCAE grades for subjects on P1CT

Table 2. Subject characteristics

	Total	P1CT	HDCT
Number of trials	51	42	9
Number of patients	1,841	1,328	513
Age (years)	59.0 (50–67)	59.0 (49–67)	58.6 (51–66)
Gender			
Female	893 (49%)	665 (50%)	228 (44%)
Male	948 (51%)	663 (50%)	285 (56%)
Cycles of therapy			
	2 (1–4; 1–62)	2 (1–5; 1–52)	2 (1–3; 1–62)
Baseline NCI ODWG			
Normal	1251 (68%)	1112 (84%)	139 (27%)
Mild group 1	221 (12%)	120 (9%)	101 (20%)
Mild group 2	109 (6%)	74 (5.5%)	35 (7%)
Moderate	118 (6%)	21 (1.5%)	97 (19%)
Severe	142 (8%)	1 (0%)	141 (27%)
Peak NCI ODWG			
Normal	601 (33%)	534 (40%)	67 (13%)
Mild group 1	411 (22%)	326 (25%)	85 (17%)
Mild group 2	288 (16%)	239 (18%)	49 (10%)
Moderate	228 (12%)	145 (11%)	83 (16%)
Severe	313 (17%)	84 (6%)	229 (45%)
Modified peak FDA R ratio			
Normal	601 (33%)	534 (40%)	67 (13%)
Mixed	206 (11%)	179 (13%)	27 (5%)
Hepatic	67 (4%)	60 (5%)	7 (1%)
Cholestatic	967 (52%)	555 (42%)	412 (80%)
Hy's law			
Met	11 (0.6%)	11 (0.8%)	0 (0%)
Reason for discontinuation			
Disease progression on study	1084 (59%)	764 (58%)	320 (63%)
Toxicity/side effects	220 (12%)	173 (13%)	47 (9%)
Refused further treatment	114 (6%)	72 (5%)	42 (8%)
Other	108 (6%)	72 (5%)	36 (7%)
Death on study	67 (4%)	43 (3%)	24 (5%)
Complicating disease/intercurrent illness	45 (2%)	29 (2%)	16 (3%)

NOTE: The medians and interquartile ranges, or number and percentages are shown above. For "Cycles of Therapy," the interquartile range and total range are shown in order.

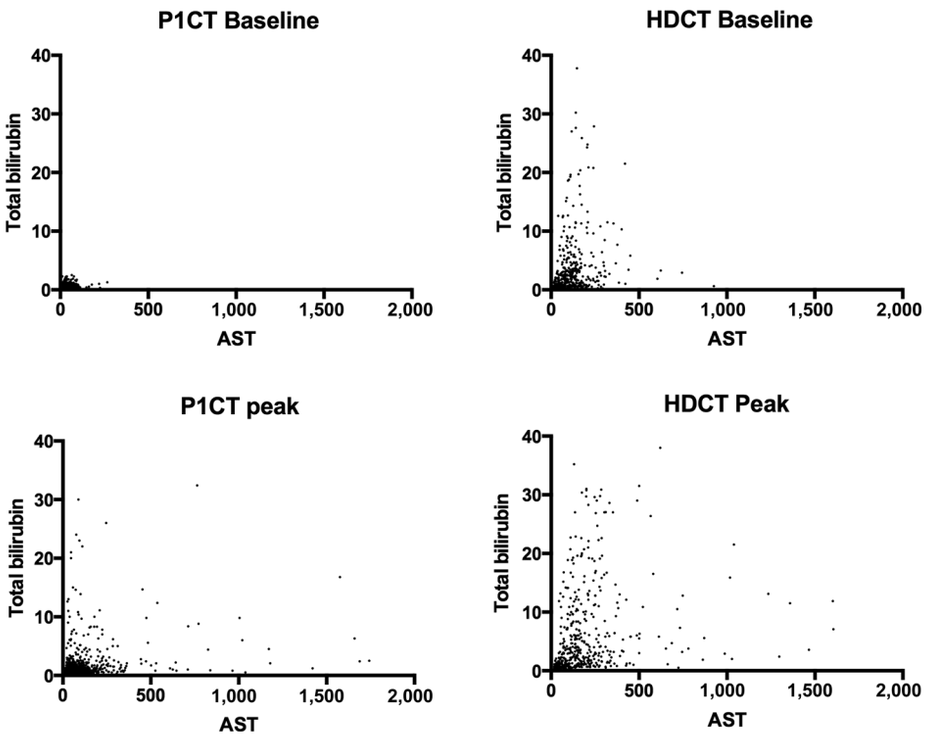


Figure 1.
Baseline and peak values of liver tests. The baseline and peak values for total bilirubin and AST are shown between P1CT and HDCT.

than HDCT ($P = 0.04$), and a greater increase in peak total bilirubin CTCAE levels for subjects on HDCT than P1CT ($P < 0.01$; Supplementary Table S3).

Alterations in hepatic function on treatment by hepatotoxic agents

Among all subjects, there were higher peak ALT CTCAE scores for subjects receiving hepatotoxic agents than nontoxic agents ($P < 0.01$; Fig. 4). Similarly, there was a significant worsening from baseline of ALT and total bilirubin CTCAE grades for those receiving hepatotoxic agents than nontoxic agents ($P < 0.01$ and $P = 0.04$, respectively; Supplementary Table S4). Among subjects enrolled on P1CT, there were higher peak ALT CTCAE grades for those receiving hepatotoxic agents than nontoxic agents ($P < 0.01$; Supplementary Fig. S1), whereas higher peak CTCAE grades for ALK ($P < 0.01$) and total bilirubin ($P = 0.01$) were seen in subjects on HDCT receiving hepatotoxic agents than nontoxic agents (Supplementary Fig. S2).

Assessment in DILI on treatment

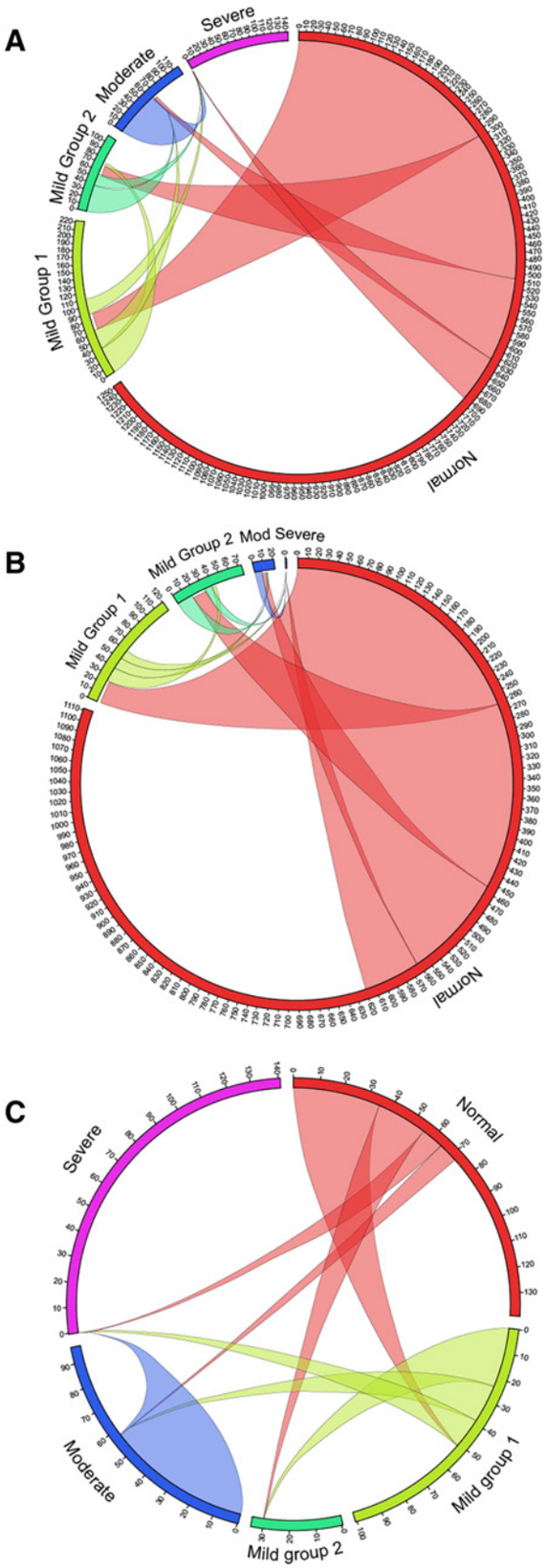
Cholestatic peak patterns of liver impairment by the FDA R ratio were more frequent in HDCT than P1CT ($P < 0.01$). Criteria for Hy's law (Table 1) were met by 11 subjects on P1CT (baseline NCI ODWG normal = 8, mild group 1 = 1, mild group 2 = 1, moderate = 1) but not by any subjects on HDCT. No difference in the baseline total bilirubin CTCAE grades was observed between subjects who did and did not meet Hy's law criteria ($P = 0.78$).

Hepatic function and outcomes

Subjects typically received fewer cycles of therapy on HDCT [median, 2; mean, 2.9; interquartile range (IQR), 1–3; full range, 1–62] than subjects on P1CT (median, 2; mean, 4.0; IQR, 1–5; full range, 1–52; $P < 0.01$). Subjects with severe liver test abnormalities on HDCT typically received one cycle of treatment (median, 1; mean, 1.7; IQR, 1–2; full range, 1–12). The reasons for treatment discontinuation were similar for subjects on HDCT and P1CT with disease progression being the most common reason followed by adverse events (Table 2). There was no significant difference in the rates of discontinuation for toxicity between those who received two or fewer cycles [12.2%; 95% confidence interval (CI), 10.4–14.3%; $n = 1{,}105$] and those who received more than two cycles of therapy (11.7%; 95% CI, 9.6–14.3%; $n = 726$). Subjects who received more than two cycles of therapy were more likely to experience an increase in CTCAE grade of ALT (mean, 0.53; 95% CI, 0.48–0.59) than those who received two or fewer cycles (mean, 0.43; 95% CI, 0.38–0.47; $P < 0.0001$). Conversely, subjects who received two or fewer cycles of therapy were more likely to experience an increase in CTCAE grade of alkaline phosphatase (mean, 0.35; 95% CI, 0.31–0.40) than those who received more than two cycles (mean, 0.27; 95% CI, 0.23–0.32; $P = 0.02$). There were no significant differences in CTCAE grade of AST or total bilirubin based on whether patients received two or more cycles.

Discussion

We reviewed the NCI CTEP experience sponsoring HDCT and P1CT and found expected differences in baseline liver test abnormalities at enrollment. Further review of the classifications of hepatic impairment revealed that subjects with severe impairment on HDCT typically do not experience improvement in their liver tests during the course of treatment, but many other subjects with less severe liver impairment do. In addition, different patterns of hepatotoxicity were observed between trial types. Higher ALT CTCAE grades were associated with hepatotoxic agents in P1CT, and higher alkaline phosphatase and total bilirubin CTCAE grades were associated with hepatotoxic agents in HDCT. This differential effect on hepatotoxicity suggests that underlying



hepatic function may affect susceptibility to and patterns of DILI. Even though there was a statistically significant difference in the number of cycles received by subjects on HDCT or P1CT, we believe that this result may be due to the large sample size of our study and is not clinically relevant as patients typically received up to two cycles of treatment on either type of study.

DILI is typically classified as hepatic (hepatocellular), cholestatic, or mixed based on the pattern of liver test abnormalities (17). The FDA R ratio is one means of defining these patterns based on ratios of ALT to ALK. Hy's law is an additional measure that identifies a population at high risk of death when DILI results in hepatocellular injury with jaundice. The use of liver tests to assess hepatic function is imperfect because the elevation of transaminases may be a better indicator of injury or inflammation than dysfunction. About 3% of subjects are expected to fall outside of two standard deviations of the Gaussian distribution for liver tests (20); however, a study of 6,000 healthy individuals that did not consume excessive amounts of alcohol and did not have hepatitis C identified that 8% of patients had elevations in transaminases, possibly due to nonalcoholic steatohepatitis or metabolic syndrome (21, 22). Standard liver tests also fail to identify liver damage as proven by histologic analysis from biopsies in subjects with chronic hepatitis C or nonalcoholic steatohepatitis 16% or 13% of the time respectively (23, 24). The situation for subjects on P1CT and HDCT is confounded further by potential liver metastases, lingering effects of previous treatments, and novel combinations. At baseline, we observed that 16% of subjects who enrolled onto P1CT had abnormal liver tests, but the reasons for the liver tests abnormalities were not always certain.

Other scores have been developed to assess prognosis in patients with chronic liver disease such as the Child–Pugh (CP) score and the Model for End-Stage Liver Disease (MELD). These scores incorporate additional measures such as creatinine (MELD), serum albumin (CP), prothrombin time (both), and clinical observations such as ascites and hepatic encephalopathy (CP). In our study, very few subjects had serial testing performed that provided information on hepatic synthetic function such as prothrombin time. Also, we were not able to retrospectively determine if patients had ascites. Thus, we were not able to retrospectively determine the traditional CP Score or MELD for the patients in this analysis. It is uncertain as to how baseline CP and MELD scores affect DILI in P1CT and HDCT.

Figure 2.
Baseline and peak categorizations of hepatic dysfunction. These circos diagrams display the baseline and peak categorizations of hepatic dysfunction by NCI ODWG definitions for all subjects (**A**), subjects in standard P1CT (**B**), and subjects in HDCT (**C**). Segments of the circles are color coded to represent groups of subjects as defined by the NCI ODWG based on their baseline categorization. Tick marks around the circles mark the number of subjects in each group at baseline. Ribbons that connect groups are shown in a ratio layout that visually estimates the ratio of subjects that transition from one NCI ODWG group at baseline to another at peak. For example, in **A,** the red ribbon that connects the Normal and mild group 1 groups tapers because 297 subjects who were normal at baseline were mild group 1 at peak, whereas 24 subjects who were mild group 1 at baseline were classified as normal for the rest of their participation on trial. Where ribbons transition to a point, no subjects from the pointed end of the ribbon transitioned to other group. For example, no subjects categorized as having severe dysfunction by NCI ODWG transitioned to another category, whereas many subjects developed severe dysfunction. Subjects not connected by ribbons had the same baseline and peak categorizations.

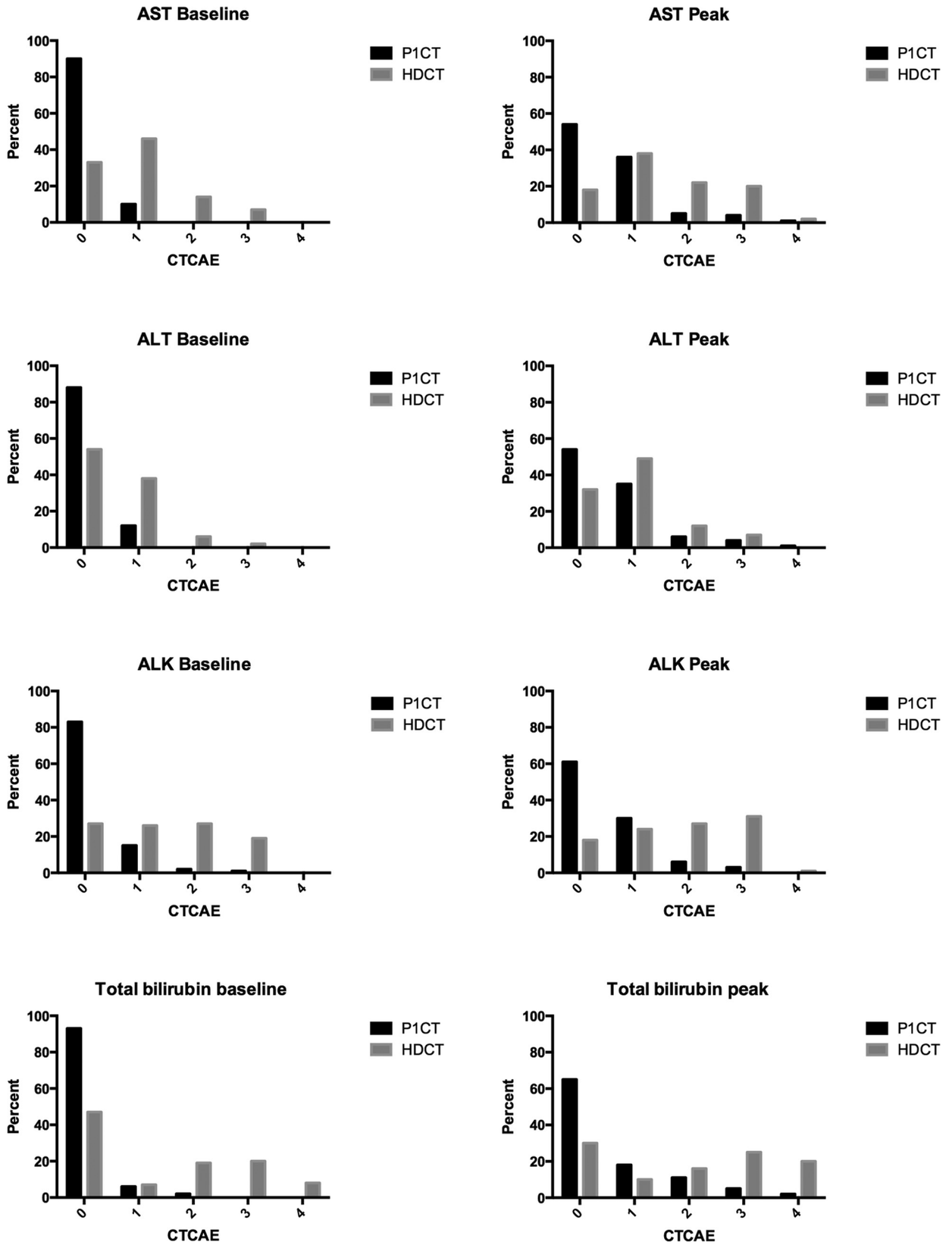


Figure 3.
Baseline and peak CTCAE grades. The baseline and peak CTCAE grades for AST, ALT, alkaline phosphatase, and total bilirubin are shown between P1CT and HDCT.

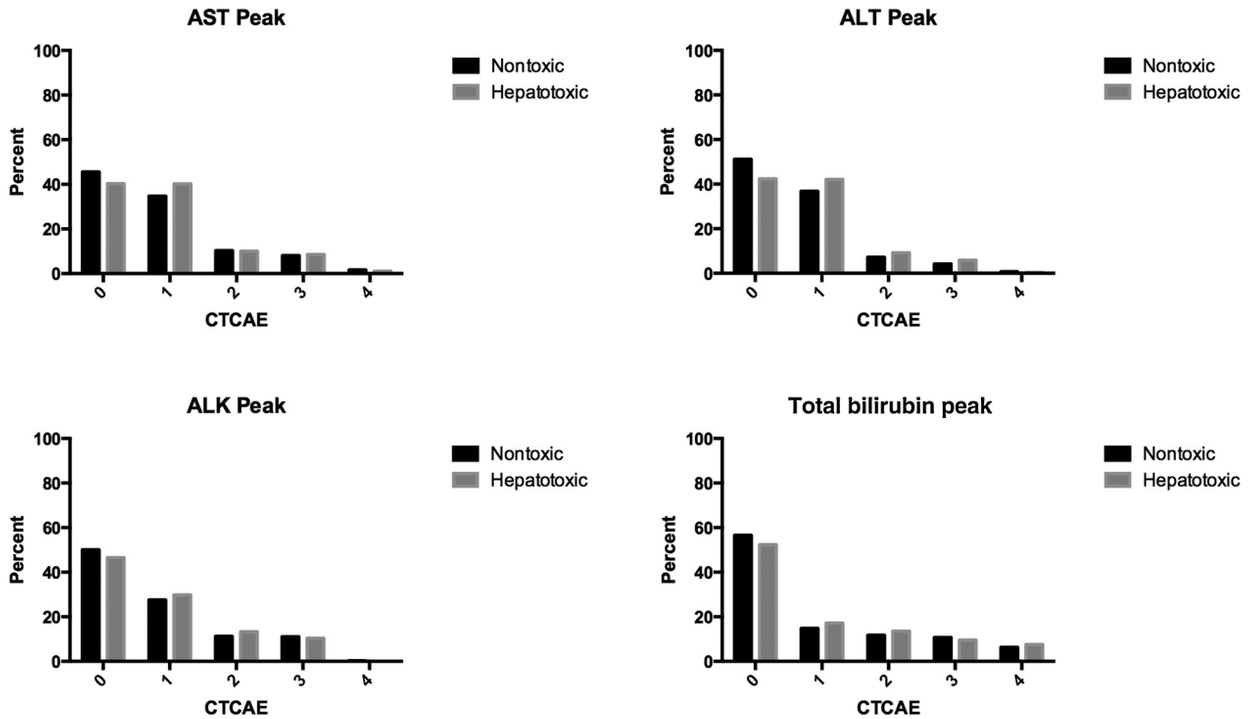


Figure 4.

CTCAE grades of liver tests by hepatotoxic agents for all subjects. The peak CTCAE of liver tests for all subjects are shown above, separated by whether the agents subjects received were hepatotoxic. There were higher ALT CTCAE grades for subjects receiving hepatotoxic agents than nontoxic agents ($P < 0.01$), but not for other liver tests (AST $P = 0.30$; ALK $P = 0.45$; total bilirubin $P = 0.08$).

Because the P1CT and HDCT included in this meta-analysis standardly obtained AST, ALT, alkaline phosphatase, and bilirubin, we were better able to assess cellular injury, cholestasis, or duct injury than liver function *per se*. In addition, the currently used attribution system did not allow us to distinguish whether baseline liver test abnormalities were related to liver metastases, underlying liver disease, or lingering treatment effects as the CTCAE attributions typically do not require further clarification if the adverse event is not thought to be related to the investigational agent(s). Previous work by NCI has shown that there is a correlation between CP categories and NCI ODWG classifications (25). As the MELD is a preferred predictor for liver-related outcomes compared with CP for patients with chronic liver disease, consideration should be given for its inclusion in HDCT, and even possibly P1CT, as it may provide additional useful information on hepatic function as it relates to safe drug dosing and DILI (26–28).

Hy's law is a prognostic marker in patients who experience DILI (17), and the observation of multiple subjects who meet Hy's law criteria in a clinical trial is concerning that an investigational agent(s) would result in severe DILI if administered to a larger population (29). We unexpectedly found more subjects who met Hy's law criteria in P1CT than HDCT. This is not surprising when one considers that "preexisting or acute liver disease" excludes qualification for Hy's law; therefore, subjects with the most severe abnormalities in HDCT did not qualify as meeting Hy's law based on the attributions of their liver test abnormalities. Previous work has shown pretreatment bilirubin to be the most important predictor of meeting the criteria in Hy's law (30), but most patients in our series who met Hy's law criteria had normal bilirubin values at baseline. The few cases in our series that met Hy's law criteria limit any meaningful conclusions, but the multifactorial nature of DILI makes it challenging to predict severe DILI with a single test. In terms of P1CT and HDCT, we are not certain what role Hy's law should have beyond its prognostic capabilities in subjects who experience severe DILI.

Overall, our findings suggest that within the context of organ dysfunction trials, it is safe to treat subjects with hepatic dysfunction. Subjects on HDCT discontinue trial participation for similar reasons and at similar frequencies to those on P1CT. The differential effects of hepatotoxic agents on hepatotoxicity between subjects on HDCT and P1CT suggest that underlying hepatic function may affect susceptibility to and patterns of DILI. We suggest that it would be worthwhile to include additional scores of hepatic function, such as MELD in P1CT and HDCT, to determine if underlying hepatic dysfunction is predictive of severe DILI.

Disclosure of Potential Conflicts of Interest

A.S. Mansfield is a consultant/advisory board member for Celegene, Genentech, Rockpointe, and Trovagene. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Development of methodology: A.S. Mansfield, M.A. Rudek, S.P. Ivy

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.S. Mansfield, G.L. Smith, S.P. Ivy
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.S. Mansfield, M.A. Rudek, S.P. Ivy
Writing, review, and/or revision of the manuscript: A.S. Mansfield, M.A. Rudek, G.L. Smith, P.J. Harris, S.P. Ivy
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.S. Mansfield, S.P. Ivy
Study supervision: A.S. Mansfield, M.A. Rudek
Other (management of data submitted by treating sites): D. Vulih

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References

1. Field KM, Michael M. Part II: Liver function in oncology: Towards safer chemotherapy use. Lancet Oncol 2008;9:1181–90.
2. Field KM, Dow C, Michael M. Part I: Liver function in oncology: Biochemistry and beyond. Lancet Oncol 2008;9:1092–101.
3. EMA (European Medicines Agency). Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic function. London, UK. 2005 [cited 2012 Oct 18]. Available from: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003122.pdf
4. US Food and Drug Administration. Pharmacokinetics in patients with impaired hepatic function: Study design, data analysis, and impact on dosing and labeling. Rockville, MD. 2003 [cited 2012 Oct 18]. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf
5. Dobbs NA, Twelves CJ, Gregory W, Cruickshanka C, Richards MA, Rubens RD. Epirubicin in patients with liver dysfunction: Development and evaluation of a novel dose modification scheme. Eur J Cancer 2003;39:580–6.
6. Doroshow JH, Synold TW, Gandara D, Mani S, Remick SC, Mulkerin D, et al. Pharmacology of oxaliplatin in solid tumor patients with hepatic dysfunction: A preliminary report of the National Cancer Institute Organ Dysfunction Working Group. Semin Oncol 2003;30:14–9.
7. Gibbons J, Egorin MJ, Ramanathan RK, Fu P, Mulkerin DL, Shibata S, et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of renal dysfunction: A study by the National Cancer Institute Organ Dysfunction Working Group. J Clin Oncol 2008;26:570–6.
8. LoRusso PM, Venkatakrishnan K, Ramanathan RK, Sarantopoulos J, Mulkerin D, Shibata SI, et al. Pharmacokinetics and safety of bortezomib in patients with advanced malignancies and varying degrees of liver dysfunction: Phase I NCI Organ Dysfunction Working Group Study NCI-6432. Clin Cancer Res 2012;18:2954–63.
9. Ramalingam SS, Kummar S, Sarantopoulos J, Shibata S, LoRusso P, Yerk M, et al. Phase I study of vorinostat in patients with advanced solid tumors and hepatic dysfunction: A National Cancer Institute Organ Dysfunction Working Group study. J Clin Oncol 2010;28:4507–12.
10. Ramanathan RK, Egorin MJ, Takimoto CH, Remick SC, Doroshow JH, LoRusso PA, et al. Phase I and pharmacokinetic study of imatinib mesylate in patients with advanced malignancies and varying degrees of liver dysfunction: A study by the National Cancer Institute Organ Dysfunction Working Group. J Clin Oncol 2008;26:563–9.
11. Raymond E, Boige V, Faivre S, Sanderink GJ, Rixe O, Vernillet L, et al. Dosage adjustment and pharmacokinetic profile of irinotecan in cancer patients with hepatic dysfunction. J Clin Oncol 2002;20:4303–12.
12. Synold TW, Takimoto CH, Doroshow JH, Gandara D, Mani S, Remick SC, et al. Dose-escalating and pharmacologic study of oxaliplatin in adult cancer patients with impaired hepatic function: A National Cancer Institute Organ Dysfunction Working Group study. Clin Cancer Res 2007;13:3660–6.
13. Venook AP, Egorin MJ, Rosner GL, Brown TD, Jahan TM, Batist G, et al. Phase I and pharmacokinetic trial of paclitaxel in patients with hepatic dysfunction: Cancer and Leukemia Group B 9264. J Clin Oncol 1998;16:1811–9.
14. Venook AP, Egorin MJ, Rosner GL, Hollis D, Mani S, Hawkins M, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. J Clin Oncol 2000;18:2780–7.
15. Shibata SI, Chung V, Synold TW, Longmate JA, Suttle AB, Ottesen LH, et al. Phase I study of pazopanib in patients with advanced solid tumors and hepatic dysfunction: A National Cancer Institute Organ Dysfunction Working Group study. Clin Cancer Res 2013;19:3631–9.
16. Danan G, Benichou C. Causality assessment of adverse reactions to drugs–I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993;46:1323–30.
17. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc 2014;89:95–106.
18. US Food and Drug Administration. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Rockville, MD. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf.
19. Krzywinski M, Schein J, Birol I, Connors J, Gascoyne R, Horsman D, et al. Circos: An information aesthetic for comparative genomics. Genome Res 2009;19:1639–45.
20. Giannini EG, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. CMAJ 2005;172:367–79.
21. Ioannou GN, Boyko EJ, Lee SP. The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999–2002. Am J Gastroenterol 2006;101:76–82.
22. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137:1–10.
23. Gholson CF, Morgan K, Catinis G, Favrot D, Taylor B, Gonzalez E, et al. Chronic hepatitis C with normal aminotransferase levels: A clinical histologic study. Am J Gastroenterol 1997;92:1788–92.
24. Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology 2003;37:1286–92.
25. Patel H, Egorin MJ, Remick SC, Mulkerin D, Takimoto CHM, Doroshow JH, et al. Comparison of Child-Pugh (CP) criteria and NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD): Implications for chemotherapy dosing. J Clin Oncol 2004;22:no 14_suppl 6051.
26. Darwish Murad S, Kim WR, de Groen PC, Kamath PS, Malinchoc M, Valla DC, et al. Can the model for end-stage liver disease be used to predict the prognosis in patients with Budd-Chiari syndrome? Liver Transpl 2007;13:867–74.
27. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology 2007;45:797–805.
28. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–70.
29. US Food and Drug Administration. Guidance for industry drug-induced liver injury: Premarketing clinical evaluation. Rockville, MD. 2009 [cited 2015 Nov 23]. Available from: http://www.fda.gov/downloads/Drugs/Guidance/UCM174090.pdf
30. Cai Z, Bresell A, Steinberg MH, Silberg DG, Furlong ST. Pretreatment data is highly predictive of liver chemistry signals in clinical trials. Drug Des Devel Ther 2012;6:359–69.