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Full Length Article

Severe hepatic dysfunction is associated with venous thromboembolic events in phase 1 clinical trials

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ABSTRACT

Introduction: Venous thromboembolic events (VTEs) are a significant cause of death in patients with cancer. The incidence of VTE is not well characterized in early phase clinical trials of novel antineoplastic agents, or in hepatic dysfunction studies designed for patients with varying degrees of liver test abnormalities. We compared the incidences of VTE in phase 1 clinical trials (P1CTs) and hepatic dysfunction trials (HDCTs) sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) of the United States.
Materials & methods: We reviewed individual patient records of 1841 subjects for symptomatic VTE diagnosed while on study: 1328 subjects on 42 P1CTs, and 513 subjects on 9 HDCTs. The NCI's Organ Dysfunction Working Group definitions were used to categorize patients. The incidences of VTEs between patients were compared by the Chi square test. Confounders were evaluated with the Cochran–Mantel–Haenszel method.
Results & conclusions: There were 43 VTEs identified among all subjects (2.3%). There were significantly more VTE observed in the subjects on P1CTs (n = 38, 2.9%) than in the subjects on HDCTs (n = 5, 1.0%; RR 0.341, 95% 0.13–0.86, p = 0.015). For patients on HDCTs, those with severe dysfunction had a high incidence of VTE (RR 10.5 (1.12–93.6), p = 0.021) that remained significant in a multivariate model.
VTEs were observed less frequently in patients who were enrolled in HDCT than those who were enrolled in P1CT; however, patients with severe hepatic dysfunction were more likely to experience VTE. Severe liver test abnormalities may not be protective against VTE in patients with malignancies receiving chemotherapy.

1. Background

Standard phase 1 clinical trials (P1CTs) are critical to identifying a safe dose or schedule of a novel therapy or combination of therapies to test in larger clinical trials; however, the eligibility criteria of most clinical trials limit participation to subjects with relatively normal organ function or a minor degree of organ impairment. Accordingly, physicians often have little guidance on how to dose antineoplastic medications in patients with varying degrees of organ dysfunction. Most antineoplastic agents have a narrow therapeutic index and undergo some degree of metabolism by the liver [1]. The National Cancer Institute's Organ Dysfunction Working Group (NCI ODWG) has conducted a series of phase 1 clinical trials for patients with liver impairment (HDCTs) in order to provide physicians with dosing recommendations for future subjects on clinical trials as well as for FDA drug labels. Typically in these trials escalating doses of a single agent are tested in patients with various degrees of hepatic dysfunction as defined by the NCI ODWG. Patients without liver test abnormalities are often included as a control group, and extensive pharmacokinetic testing is performed in HDCTs to define optimal dosing.

Venous thromboembolic events (VTEs) are a common complication for patients with malignancies and as many of 20% of incident VTE are related to cancer [2]. VTEs are one of the most common causes of death in patients with cancer and can worsen prognosis [3]. For example, a VTE within 3 months of diagnosis of any stage of lung cancer portends a worse prognosis compared to patients without an observed VTE, even after controlling for age, stage, performance status and co-morbidities [4]. Patients with underlying liver disease or impairment may experience fewer VTE. In the multivariate analysis of a population based study in Olmsted County, Minnesota, patients with liver disease had lower odds of developing a VTE (OR 0.1, 95% CI 0.01–0.7) [5]. Conversely, patients with hepatic dysfunction and cancer may be hypercoagulable given their underlying malignancies. As patients with underlying hepatic disease and malignancy likely have a complex coagulopathic environment, it is challenging for clinicians to anticipate

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their thrombotic likelihoods. In order to gain insight into the risk or thrombotic events in patients with hepatic impairment, we sought to compare the incidence of VTE between subjects enrolled into P1CTs, conducted by CTEP phase 1 investigators, and HDCTs, conducted by the NCI ODWG, with the null hypothesis that there is no difference in the incidence of VTE between these patient groups.

2. Patients/methods

The records of participants in P1CTs sponsored by the NCI's Cancer Therapy Evaluation Program (CTEP) and HDCTs sponsored by the NCI's ODWG are prospectively maintained. These records were abstracted and reviewed in May 2014 at the individual patient level for any VTE that was diagnosed and reported while on study. The severities of the VTE were scored using the NCI Common Terminology Criteria for Adverse Events (CTCAE) by the treating clinician at the time of the event. We recorded the cycle of antineoplastic therapy during which the VTEs were diagnosed, and the total number of cycles of administered. VTE included deep vein thromboses (DVTs), splanchnic vein thromboses, as well as pulmonary embolisms. Non lower extremity DVTs were also included in the definition. We were not able to assess how these events were identified, be it ultrasound duplex, ventilation perfusions scans, computed tomography, or autopsy. All VTEs occurred after screening for the trials and initiation of therapy. The upper limits of normal for AST and ALT were defined as 50 U/L, the upper limit of normal (ULN) for total bilirubin was defined as 1 mg/dL, and the upper limit of normal of alkaline phosphatase was defined as 150 U/L. Six subjects in P1CTs and one subject in a HDCT did not have AST values available at baseline, and their ALT was used instead for the NCI ODWG classifications. The NCI ODWG definitions for hepatic dysfunction were used at baseline as follows:

Normal: Total bilirubin ≤ 1 mg/dL, AST ≤ 50 U/L.
Mild (Group 1): Total bilirubin ≤ ULN, AST > ULN.
Mild (Group 2): Total bilirubin > 1.0× to 1.5× ULN, any AST
Moderate: Total bilirubin > 1.5× ULN to 3.0× ULN, any AST
Severe: Total bilirubin > 3× ULN, any AST

Severe dysfunction, as defined by the NCI ODWG, correlates well with Child Pugh C classification, which is a defined score for functional liver disease severity [6]. A modified version of the Food and Drug Administration (FDA) R ratio [(ALT/ULN)/(ALK/ULN)] was used to classify the pattern of liver function abnormalities. Patients with normal liver function tests were categorized as normal. The other definitions are as follows:

Hepatic: R ratio ≥ 5
Cholestatic: R ratio ≤ 2
Mixed: R ratio between 2–5

Descriptive statistics were used to summarize results. Unless otherwise stated the median and interquartile range were reported. The incidences of VTE between patients treated on predictive variables were compared with Chi square or a two-sided Fisher's exact as appropriate. Continuous variables were categorized using the median as a dichotomous cutoff. We evaluated for potential confounder effects using the Cochran–Mantel–Haenszel (CMH) method; these variables included follow up time (extrapolated from number of cycles received), baseline liver disease severity, and age. Variables with a $p < 0.10$ were added to a multivariate logistic regression model in a backwards selection method where VTE was the dependent variable. All analyses were performed with JMP Pro 11.2 (SAS institute 2013). Circos diagrams were made using an online interface (http://mkweb.bcgsc.ca/tableviewer, accessed on June 1, 2015) [7] and modified for clarity with Adobe Photoshop CC 2014.

3. Results

The NCI CTEP database included 51 phase 1 or hepatic dysfunction trials, including patient level information on 1896 subjects. There were 1359 subjects enrolled on 42 P1CTs, and 537 subjects enrolled on 9 HDCTs. Patients enrolled on hepatic dysfunction trials were more commonly male (44.4% vs 57.3%, $p = 0.03$). There were 43 VTEs identified among the 1896 subjects (2.3%). Based on an intention to treat analysis including all 1896 subjects, there were significantly more VTEs in the subjects on P1CTs ($n = 38$, 2.8%) than in the subjects on HDCTs ($n = 5$, 0.9%; RR 0.333, 95% CI 0.13–0.84, $p = 0.015$). Due to late determination of ineligibility or complicating intercurrent illnesses, 1841 subjects actually received treatment on trial and further analysis was restricted to this group (Table 1). There were 1328 subjects treated on 42

Table 1
Patient characteristics and categorization by NCI ODWG and FDA R ratio.

	Total (n)		P1CTs (n)		HDCTs (n)	
Age (years)	59 (50–67)		59 (49–67)		59 (51–66)	
Gender						
Female	893 (49%)		665 (50%)		228 (44%)	
Male	948 (51%)		663 (50%)		285 (56%)	
	Total	VTE	Total	VTE	Total	VTE
Baseline NCI ODWG	1841	43 (2.3%)	1328	38 (2.9%)	513	5 (1%)
Normal	1251 (68%)	32 (2.6%)	1112 (84%)	32 (2.9%)	139 (27%)	0 (0%)
Mild group 1	221 (12%)	3 (1.4%)	120 (9%)	3 (2.5%)	101 (20%)	0 (0%)
Mild group 2	109 (6%)	3 (2.8%)	74 (5.5%)	3 (4.1%)	35 (7%)	0 (0%)
Moderate	118 (6%)	1 (1%)	21 (1.5%)	0 (0%)	97 (19%)	1 (1%)
Severe	142 (8%)	4 (2.8%)	1 (0%)	0 (0%)	141 (27%)	4 (2.8%)
Peak NCI ODWG						
Normal	601 (33%)	13 (2.2%)	534 (40%)	13 (2.4%)	67 (13%)	0 (0%)
Mild group 1	411 (22%)	7 (1.7%)	326 (25%)	7 (2.1%)	85 (17%)	0 (0%)
Mild group 2	288 (16%)	12 (4.2%)	239 (18%)	12 (5%)	49 (10%)	0 (0%)
Moderate	228 (12%)	5 (2.2%)	145 (11%)	5 (3.4%)	83 (16%)	0 (0%)
Severe	313 (17%)	6 (1.9%)	84 (6%)	1 (1%)	229 (45%)	5 (2.2%)
Modified peak FDA R ratio						
Normal	601 (33%)	13 (2.2%)	534 (40%)	13 (34%)	67 (13%)	0 (0%)
Mixed	206 (11%)	5 (2.4%)	179 (13%)	5 (13%)	27 (5%)	0 (0%)
Hepatic	67 (4%)	2 (3.0%)	60 (5%)	2 (5%)	7 (1%)	0 (0%)
Cholestatic	967 (52%)	23 (2.4%)	555 (42%)	18 (47%)	412 (80%)	5 (1.2%)

In the table above, P1CTs stand for standard phase 1 clinical trials, HDCTs stand for hepatic dysfunction clinical trials, NCI ODWG stands for National Cancer Institute Organ Dysfunction Working Group, FDA stands for Food and Drug Administration. The number and interquartile range or percent are displayed. The numbers of subjects diagnosed with VTE are displayed next to each categorization. The percents reported within categorization columns represent portions of total, whereas percents reported within VTE columns represent portions of their respective categories.