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

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Abstract

Introduction—Venous thromboembolic events (VTE) 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 VTE identified amongst 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

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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.

VTE were observed less frequently in patients who were enrolled in HDCT than those who were enrolled in PICT; 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.

Keywords

Clinical Trials, Phase 1; liver diseases; neoplasms; pulmonary embolism; venous thrombosis

Background

Standard phase 1 clinical trials (PICTs) 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 (VTE) are a common complication for patients with malignancies and as many as 20% of incident VTE are related to cancer [2]. VTE 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 their thrombotic likelihoods. In order to gain insight into the risk of thrombotic events in patients with hepatic impairment, we sought to compare the incidence of VTE between subjects enrolled into PICTs, 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.

Patients/Methods

The records of participants in PICTs 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 VTE 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 VTE 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 PICTs 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 $\leq$ 1 mg/dL, AST $\leq$ 50 U/L

Mild (Group 1): Total bilirubin $\leq$ ULN, AST $>$ ULN

Mild (Group 2): Total bilirubin $>1.0\times$ to $1.5\times$ ULN, any AST

Moderate: Total bilirubin $>1.5\times$ ULN to $3.0\times$ ULN, any AST

Severe: Total bilirubin $>3\times$ 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.

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 VTE identified amongst the 1896 subjects (2.3%). Based on an intention to treat analysis including all 1896 subjects, there were significantly more VTE 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 P1CTs, and 513 subjects treated on 9 HDCTs. Similar to the intention to treat analysis, 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, $p=0.015$; Figure 1). This finding remained statistically significant after controlling for age ($p=0.01$), gender ($p=0.01$), level of hepatic dysfunction severity by ODWG criteria ($p=0.003$) and number of treatment cycles received ($p=0.04$). The total duration of treatment was associated with VTE. Of the 43 observed VTE, 8 occurred in patients who received 1-2 cycles of therapy, 14 occurred in patients who received 3-4 cycles of therapy, and 21 occurred in patients receiving more than 4 cycles of therapy ($p=0.018$). We did not find differences in the incidences of VTE between specific trials ($p=0.09$).

Of the 42 P1CTs that were analyzed, subjects were diagnosed with VTE in 19 of them (45%). No patient had multiple episodes of VTE that were documented. Sixteen of these trials in which VTE were observed tested novel combinations of therapies, two tested vaccines and one tested virotherapy. For subjects on P1CTs, VTE usually occurred on the second cycle of treatment [interquartile range (IQR) 1-4], were grade 3 (IQR 3-4) in severity, and were associated with the final cycle of trial treatment 42% of the time. These VTE were thought to be probably related ($n=1$), possibly related ($n=17$), unlikely to be related ($n=10$), and unrelated ($n=10$) to the investigational study treatments. At baseline, 33 subjects who developed VTE in the P1CTs had normal liver tests, three patients had mild (group 1) hepatic dysfunction and two patients had mild (group 2) hepatic dysfunction. Of these five patients without normal liver tests, four had cholestatic patterns and one had a mixed pattern of baseline liver function test. At the time of diagnosis of VTE, 19 patients had normal liver tests, 13 patients had a cholestatic pattern, 5 patients had a mixed pattern and 1 patient had a hepatic pattern of liver abnormalities by the FDA R ratio.

Of the nine HDCTs, subjects were diagnosed with VTE in 3 of them (33%). All of these trials utilized escalating doses of single agents. For subjects on hepatic dysfunction studies, VTE usually occurred on the second cycle of treatment (IQR 1-5), were grade 3 (IQR 2-3) in severity, and were associated with the final cycle of trial treatment 60% of the time. These VTE were thought to be unrelated ($n=3$) or unlikely to be related ($n=2$) to the investigational

treatments. At baseline, all patients with VTE in the HDCTs had severe liver disease by the NCI ODWG definitions and cholestatic patterns of liver function abnormalities by the FDA R ratio definitions. At the time of diagnosis of VTE, these five patients still had a cholestatic pattern of liver abnormalities.

There were no differences in the incidences of VTE between patients with or without any liver tests abnormalities (RR 1.12, 95% CI 0.59-2.13, $p=0.9$). For patients on HDCTs, severe dysfunction by the NCI ODWG definition had a high incidence of VTE (RR 10.5 (1.12-93.6), $p=0.021$; Figure 2). In a multivariate logistic regression analysis, subjects recruited in HDCTs were less likely to develop VTE [OR 0.13 (0.017 - 0.52), $p=0.001$]; however, more than 2 cycles of chemotherapy [OR 2.24 (1.99 – 4.31), $p=0.01$] and severe liver disease by NCI ODWG at baseline [OR 9.305 (1.63 – 75.94), $p=0.01$] remained associated with VTE in the model.

Discussion

In this patient-level meta-analysis of VTE in PICTs and HDCTs, 2.3% of the total subject population developed new VTE. Despite the relatively low incidence of VTE in our total subject population, we observed that there were almost three times as many VTE in PICTs than in HDCTs. This finding was independent of number of treatment cycles received. Our investigation is not an epidemiological study, thus it does not reflect the expected incidence of VTE in the population. In a large cohort that was prospectively observed for VTE in the Vienna Cancer and Thrombosis Study, among 1542 patients followed for a median of 24 months, 7.3% developed a VTE [8]. The limited follow-up of our population due to competing mortality likely limited our detection of VTE.

While it is plausible that the risk of VTE is lower among patients with liver tests abnormalities, further analysis of our data do not support that hypothesis. Patients with liver disease have decreased synthesis of factor II, V, VII, X, XI, XII and XIII [9]. The prolongation of prothrombin times among patients with liver disease is also well documented, but there are conflicting studies regarding a potential protective effect of liver coagulopathy in the incidence of VTE. The concurrent reduction in the synthesis of anticoagulation factors in patients with cirrhosis may place them in a delicate hemostatic balance that is challenging to manage clinically [9, 10]. Our findings do not support the concept [5] that liver disease is protective against cancer-associated VTE because patients with severe dysfunction had the highest risk of VTE amongst the NCI ODWG categories. It is plausible that these patients were more susceptible to medication toxicity; however, patients with severe liver disease were also more likely to have been poorly ambulatory which is also predictive of thrombosis. Cytotoxic chemotherapy is one of the known cancer-associated thrombosis risk factors [11-13]. Although it is possible that the dose-reduced treatments in HDCTs generated a lower VTE incidence, we did not observe this in the patients with severe hepatic dysfunction. Our results should be considered in light of observations of thrombotic events in patients with liver disease and cirrhosis. It has been reported that about 1% of patients with all categories of liver disease experience a thrombotic event during hospitalization, and as many as 2% of patients with cirrhosis [14-16]. This rate is lower than what we observed in our study, but our study had a longer

duration of observation. The Model for End-Stage Liver Disease score is a preferred predictor for liver related outcomes [17, 18] but the variables for such a construct were not available in all protocols, thus we cannot rule out that a functional hepatic dysfunction stratification would have discerned the possibility of functional liver disease as a negative predictor of VTE in patients with cancer.

There were several limitations to our study. The 51 clinical trials were designed to test the safety, maximum tolerated doses and potential efficacy of novel therapeutics, novel combinations of therapeutics, or escalating doses of therapeutics in patients with hepatic impairment. The included trials were not designed to prospectively identify VTE, and they did not mandate serial collection prothrombin times or albumin, nor other coagulation tests. Furthermore, there was no prospective adjudication for the development of VTE. The limited number of cycles administered and competing mortality from disease progression also limited detection of VTE. We did not have consistent time to event data, limiting our statistical analysis and interpretation[8]. Since one-third of VTE are fatal upon presentation, we may not have captured these fatal events in subjects who did not undergo autopsy. Also, it was challenging to extract information on exact location of each thrombotic event. These trials utilized various versions of the NCI's Common Terminology Criteria for Adverse Events (CTCAE). Whereas some investigators defined events vaguely (e.g. thromboembolic event), others utilized more specific criteria (e.g. portal vein thrombosis). Our study likely would have benefited from further standardization of VTE reporting systems for cancer clinical trials, as suggested by others [19]. Regardless, our findings underscore the importance of ongoing work to select patients with cancer who are most likely to experience VTE so that prophylaxis could be considered for these subjects. Despite these limitations, new symptoms of thromboembolism that develop on clinical trials are likely quickly addressed due to the potential causality with investigational therapies, so most VTE that occurred on study were likely identified. Additionally, we have a relatively large sample size on which to base our conclusions.

Conclusions

VTE were observed less frequently in patients who enrolled in HDCTs than those who were enrolled in PICTs; 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.

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Analysis and interpretation of data: all authors.

Critical writing and revisions: all authors.

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Highlights

- Venous thromboembolic events are a common complication and a frequent cause of death in patients with cancer.
- In this patient-level meta-analysis we observed that patients with severe hepatic dysfunction in phase 1 antitumor clinical trials were more likely to experience thrombotic events than those with less severe degrees of hepatic dysfunction.
- The addition of a measure of hepatic dysfunction to cancer-specific risk assessment models for thrombosis may improve risk stratification strategies.

Results by Trial Type

Figure 1.

Circos diagrams of VTE by trial type

The circos diagrams above represent each trial type. Each tick mark represents 10 subjects who received treatment. The blips in the centers represent the portion of subjects who experienced VTE while on study. Significantly more VTE were observed on P1CT than HDCT.

Figure 2.

Circos diagrams of VTE by trial type with hepatic dysfunction categorizations

The circos diagrams above represent each trial type. Segments of each circos diagram correspond to hepatic dysfunction categorizations. Each tick mark represents 10 subjects who received treatment. The blips in the centers represent the portion of subjects who experienced VTE while on study by hepatic dysfunction categorizations. Four of the five VTE observed in HDCT were experienced by subjects with severe hepatic dysfunction.

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 stands for standard phase 1 clinical trials, HDCTs stands 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.