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Heparin-induced thrombocytopenia among patients of a comprehensive cancer center

Weixin Wu[1,2], Kelly Merriman[1], Amr Nabaah[1], Nikhil Seval[1], Vahid Afshar-Kharghan[3] and Sai-Ching J Yeung[1,4]

Abstract

Most clinical studies of heparin-induced thrombocytopenia have not included cancer patients who have high risk of thromboembolism, frequent exposure to heparin, and many potential causes of thrombocytopenia other than heparin-induced thrombocytopenia. To estimate the incidence and prevalence of heparin-induced thrombocytopenia in cancer patients, we identified cases based on diagnostic codes, anti-heparin antibody testing, and clinical characteristics (4T score) at a comprehensive cancer center between 1 October 2008 and 31 December 2011. We estimated that the prevalence of heparin-induced thrombocytopenia to be 0.02% among all cancer patients and 0.24% among cancer patients exposed to heparin. The annual incidence of heparin-induced thrombocytopenia was 0.57 cases per 1000 cancer patients exposed to heparin. Of the 40 cancer patients with the International Classification of Diseases (Ninth Revision; ICD-9) code for heparin-induced thrombocytopenia, positive anti-heparin antibody, and 4T score ≥4, 5 (12.5%) died of related thromboembolic or hemorrhagic complications. In a multivariate logistic regression model, male gender was a significant ($p = 0.035$) factor, and non-hematological malignancy was a significant ($p = 0.017$) factor associated with anti-heparin antibody positivity. Future studies may further examine the risk factors associated with heparin-induced thrombocytopenia in larger cohorts.

Keywords

Heparin-induced thrombocytopenia, cancer, incidence, prevalence

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Introduction

Patients with active cancer are at high risk of thromboembolic events.[1] Classically, the association of pancreatic cancer with thromboembolism is called the Trousseau syndrome.[2] Hematologic malignancies, lung cancers, and gastrointestinal cancers appear to have higher risk of thromboembolism than others.[3] Anticoagulation therapy for thromboembolism usually starts with some form of heparin therapy. Moreover, heparin is used in many cancer patients for indications such as thromboembolism prevention and maintenance of patency of vascular access devices. With exposure to heparin, heparin-induced thrombocytopenia (HIT) may become an infrequent but potentially serious complication in cancer patients.

HIT type 2 is caused by immunoglobulin G autoantibodies against epitopes on platelet factor 4 (PF4) in a complex with heparin.[4,5] HIT can potentially result in death,[6] and recently, we reported a fatal case of HIT in a cancer patient.[7] There is a lack of information regarding HIT among cancer patients.[8] A retrospective study of 55 HIT patients in a Canadian tertiary care hospital reported 11 patients with malignancies and 44 patients without malignancies, and the odds for developing HIT was significantly higher in cancer patients than non-cancer patients in an inpatient setting.[9] Only two cohort studies examined HIT incidence in hospitalized cancer patients using unfractionated heparin[10] and low molecular weight (LMW) heparin.[11] Pooling the data from both studies, there were 5 HIT cases (1.5%) among 335 hospitalized cancer

[1]Department of Emergency Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[2]Zhongshan Hospital, Xiamen University, Xiamen, Fujian, People's Republic of China.
[3]Department of Benign Hematology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[4]Department of Endocrine Neoplasia & Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Corresponding author:
Sai-Ching J Yeung, Department of Emergency Medicine, The University of Texas MD Anderson Cancer Center, P.O. Box 301402, Unit 1468, Houston, TX 77230-1402, USA.
Email: syeung@mdanderson.org

patients.[12] The current literature simply does not contain much information about HIT in cancer patients, and improved knowledge of HIT in cancer patients may have important implications for the medical care of these patients.[8] Therefore, we reviewed consecutive cases of HIT diagnosed in our comprehensive cancer center from 1 October 2008 to 31 December 2011 to address this significant gap in knowledge.

Patients and methods

Study population

The study was approved by The University of Texas MD Anderson Cancer Center (MDACC) Institutional Review Board in accordance with an assurance filed with and approved by the US Department of Health and Human Services. The Billing System Database of MDACC was searched for the International Classification of Diseases (Ninth Revision; ICD-9) code of 289.84 to identify consecutive patients with suspected HIT (i.e. patients who were evaluated at MDACC with laboratory testing for HIT). This patient list was crossed with the laboratory records of all patients tested for HIT at MDACC Clinical Laboratory, and all of these patients had laboratory testing for HIT. Thus, a total of 100 patients with suspected HIT who had anti-heparin antibody assay performed at MDACC were identified. The following exclusion criteria were applied to these 100 patients: (1) the absence of cancer as some of our patients present for cancer screening, diagnosis of a tumor, or management of a benign tumor and (2) incomplete records (including medication records).

The final study cohort consisted of 77 patients: 49 cancer patients with positive anti-heparin antibody assay and 28 cancer patients with negative anti-heparin antibody (comparison group). All patients had been referred to the hematology consult service for investigation of thrombocytopenia and were tested for HIT because of a clinical suspicion of the disorder by the consultant hematologist. The medical records of patients were evaluated for the presence of clinical criteria consistent with a diagnosis of HIT.[13] The 4T score[14] for the diagnosis of HIT was determined for each case based on the clinical information.

Anti-heparin antibody assay. The assay was performed by the clinical laboratory of MDACC. The patients' sera were tested using a PF4 enzyme-linked immunosorbent assay (ELISA) kit (Hologic Gen-Probe Incorporated, San Diego, CA) according to the manufacturer's instructions.

Data collection. Trained personnel reviewed online patient records to collect information on demographics, clinical characteristics, and known or suspected risk factors for HIT prognosis. Body mass index (BMI) for each patient was calculated using the recorded height and body weights closest to the date of anti-heparin antibody assay. Age was categorized as <65 and ≥65 years. Race was categorized as White and non-White. Obesity was categorized as obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2). The malignancy stage was categorized as advanced (stage 4 metastatic disease for solid tumors and relapsed or refractory disease for hematological malignancies) and non-advanced. The indication for the heparin dosage form was classified into three categories: flushes for cardiovascular access devices, prophylaxis of deep venous thrombosis, and treatment of thromboembolism. The exposure to the type of heparin was categorized as unfractionated heparin, LMW heparin, or exposure to both. Thromboembolic complications of HIT were defined as venous or arterial thromboembolic events that were diagnosed at the time of or within 2 weeks after the diagnosis of HIT and confirmed by vascular imaging studies: compression or Doppler ultrasound, venography/angiography, ventilation/perfusion lung scanning, spiral computed tomography (CT), or magnetic resonance angiogram. Other confirmatory tests include electrocardiography with myocardial enzyme measurements in case of myocardial infarction and cerebral CT scan or magnetic resonance imaging in case of stroke.

Statistical analysis

Baseline patient characteristics and risk factors of HIT were compared between groups by the chi-square test, Student's t-test, or Mann–Whitney rank sum test where appropriate. The relationships of risk factors to anti-heparin antibody positivity (e.g. age, race, BMI, malignancy stage at the time of HIT diagnosis, indication for heparin use) were analyzed using multivariate logistic regression analysis. These categorical variables were used in regression models to examine the association with specific clinical characteristics.

All statistical analyses were performed using SPSS version 18.0 (SPSS, Chicago, IL) and SigmaPlot version 11.0 (Systat, Chicago, IL) software with two-sided tests, with a p value of <0.05 considered statistically significant.

Results

Between 1 October 2008 and 31 December 2011, there were 263,460 unique cancer patients evaluated and treated at MDACC. During this same time period, 100 consecutive patients with suspected HIT were identified based on the ICD-9 code 289.84. Out of the 100 patients, 77 patients had their complete evaluation and diagnosis performed at MDACC, and their medical records were reviewed (Table 1). They were tested for anti-heparin antibody at MDACC, and 49 cancer patients with suspected HIT were tested positive by the anti-heparin antibody assay, whereas 28 cancer patients were negative. The optical density (OD) values of PF4 ELISA were plotted against the 4T scores of the patients (Figure 1). There were 40 anti-heparin antibody-positive patients with T score ≥4. For these patients, the median time

Table 1. Patient characteristics.

Anti-heparin antibody status	Positive (N = 49)			Negative (N = 28)			*p* value
	Mean	SD	Median	Mean	SD	Median	
Age	62.094	10.98		62.44	11.73		0.897
BMI			23.82			26.06	0.522
Male		28			11		
Female		21			17		0.204
White		35			19		
Non-White		14			9		0.944
Solid tumors		40			18		
Hematological		9			10		0.155
Advanced malignancy		23			14		
Not advanced		26			14		0.983
Drug allergy		25			13		
NKDA		24			15		0.880
No thromboembolism		24			13		
Thromboembolism		25			15		0.983

SD: standard deviation; NKDA: no known drug allergies; BMI: body mass index.

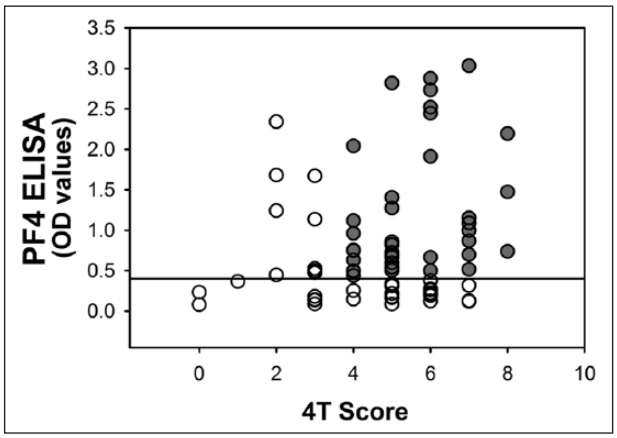

Figure 1. Scatter plot of the optical density (OD) values of the anti-heparin antibody assay (PF4 ELISA) against the 4T score of the cancer patients. OD above the reference line was considered positive. The patients with both positive anti-heparin antibody test and 4T score ≥4 were colored gray.

from the date of the first heparin dispensing record to the date of the anti-heparin antibody test was 28 days. To identify the number of cancer patients at risk of developing HIT during this 39-month time period, we queried our institution's pharmacy dispensing records for the number of unique patients who had received any dosage forms of heparin, and 21,618 unique cancer patients received some dosage forms of unfractionated heparin (including heparin flushes) or LMW heparin (enoxaparin or dalteparin). Therefore, we estimated the incidence of HIT in cancer patients to be (40/21,618)(1000)/(0.3077 years) = 0.57 cases per 1000 cancer patients exposed to heparin per year. Since 40 out of 77 reviewed patients were highly probably to have HIT, we estimated that the prevalence of HIT among cancer patients (heparin-exposed or heparin-unexposed, all included) to be (40/77)(100/263,460) = 0.02%, and the prevalence among heparin-exposed cancer patients to be (40/77)(100/21,618) = 0.24%.

Of the 49 cancer patients with positive anti-heparin antibody test (or 12.5% of the 40 cancer patients with 4T score ≥4 and positive anti-heparin antibody test) at MDACC, 5 (10.2%) died of causes directly related to HIT: one had intracranial thrombosis followed by intracranial hemorrhage; one had intracranial hemorrhage; one had extensive pulmonary embolism; one had gastrointestinal hemorrhage; and one had cerebrovascular accident with hemorrhagic transformation. None of the 28 cancer patients with negative anti-heparin antibody died of thromboembolic or hemorrhagic complications, but this rate is not statistically significantly different from the anti-heparin antibody-positive group (Fisher exact test, $p = 0.152$).

The odds of being positive for anti-heparin antibody were analyzed using a multivariate logistic regression model. The independent variables for the model are listed in Table 2. Male gender was a significant ($p = 0.035$) factor associated with positive anti-heparin antibody. The other significant ($p = 0.017$) factor was the type of malignancy; hematological malignancies are associated with a lower probability of positive anti-heparin antibody than patients with solid tumors.

Discussion

Very limited data exist concerning HIT in cancer patients. To our knowledge, this detailed study of 49 cancer patients with positive anti-heparin antibody is the largest study of such patients. The prevalence of HIT was estimated to be

Table 2. Multivariate logistic regression model for risk factors of positive anti-heparin antibody test.

Independent variable	Coefficient	Standard error	Wald statistic	Odds ratio	95% lower confidence limit	95% upper confidence limit	*p* value
Constant	1.478	1.169	1.598	4.385	0.443	43.387	0.206
Age >65 years	−0.402	0.562	0.511	0.669	0.222	2.013	0.475
Male versus female	1.216	0.578	4.425	3.374	1.087	10.478	0.035
White race versus non-White	−0.387	0.617	0.395	0.679	0.203	2.273	0.53
BMI ≥ 30 kg/m^2	0.119	0.639	0.0349	1.127	0.322	3.939	0.852
Hematological malignancies versus solid tumors	−1.765	0.742	5.66	0.171	0.04	0.733	0.017
Advanced malignancy	−0.61	0.638	0.913	0.544	0.156	1.898	0.339
Allergic to other drugs versus no drug allergy	0.486	0.557	0.761	1.626	0.546	4.845	0.383
Indications for heparin: 1 = therapeutic; 2 = prophylactic; 3 = vascular device patency	<0.001	<0.001	0.0496	1	1	1	0.824
Type of heparin exposure: 1 = unfractionated heparin; 2 = LMW heparin; 3 = both	−0.52	0.342	2.307	0.595	0.304	1.163	0.129
4T score ≥4	0.704	0.647	1.181	2.021	0.568	7.189	0.277

BMI: body mass index; LMW: low molecular weight.

approximately 3% in patients after cardiac and orthopedic surgery[15,16] and about 0.5%–1% in medical patients.[17,18] Our institution is a comprehensive cancer center that functions as a tertiary referral center for cancer care. Our estimation of the prevalence of HIT in patients with malignancies (all inpatients and outpatients with active cancer or history of cancer) was about 0.02% and was based on ICD-9 code data, the proportion of cases reviewed that have positive anti-heparin antibody and 4T score ≥4, and the number of unique patients served at our institution between 1 October 2008 and 31 December 2011. Since the anti-heparin antibody test may have false-positive results, adding the criterion of 4T score ≥4 to anti-heparin antibody positivity would improve the estimation of number of true HIT cases.

A previous estimate of the incidence of HIT among hospitalized cancer patients was 1.5% (i.e. 5 out of 335).[12] Based on the number of patients with any heparin dosage form dispensed from our institution during 39 months and the number of new cases of HIT diagnosed at our institution during that time, we estimated that the incidence of HIT in our cancer patient population to be 0.57 cases per 1000 cancer patients exposed to heparin per year. Our estimate of HIT incidence takes into account all of the non-hospitalized and hospitalized cancer patients exposed to heparin. HIT due to heparin exposure from flushes for vascular access devices is uncommon,[19] but it can occur with fatal consequences.[7] Another possible reason for our lower incidence rate compared with previous estimates is the inclusion of outpatients and patients with heparin exposure from flushes for vascular access devices in the denominator.

As mentioned above, having hematological malignancies, compared with solid tumors, is associated with a decreased risk of being positive for anti-heparin antibody in multivariate logistic regression. A higher risk of HIT has been reported in females than in males,[20] and this gender-associated difference in risk of HIT is greater in surgical patients than in medical patients.[20] Surprisingly, in our study of cancer patients, male gender was a significant factor associated with higher odds of positive anti-heparin antibody than female. This apparently opposite association with the male gender in cancer patients is intriguing and should be reexamined in future larger studies.

It is plausible that defects in the immune system in hematological malignancies or immunosuppression by cytotoxic chemotherapy can decrease the incidence of HIT among cancer patients compared with surgical patients or medical patients in general. This notion is supported by our finding that the odds of having positive anti-heparin antibody tests were higher among patients with solid tumors than patients with hematological malignancies. The size of our data set is rather limited and cannot support statistical analysis by the specific types of tumors. Future large studies may explore potential association of HIT with specific tumor types or tumor burden.

In HIT patients with cancer, there was no significant increase in all-cause mortality compared with those without cancer.[9] In this study, there were five deaths associated with thromboembolic events shortly after the diagnosis of HIT; in contrast, no deaths associated with thromboembolic events in cancer patients with suspected HIT but resulting in a negative anti-heparin antibody test. Although there is no statistically significant difference, this trend of higher mortality in cancer patients with HIT than in those with suspected but proven later not to be a HIT may be monitored in future larger studies.

Declaration of conflicting interests

The authors have declared no conflicts of interest.

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