Heparin-Induced Thrombocytopenia in Cancer

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Abstract
Heparin-induced thrombocytopenia is a common and clinically important drug-induced complication that can cause life- and limb-threatening thrombosis. Epidemiologically, the disease has been studied in many different clinical settings, but little is known about it in cancer patients, a population at increased risk for thrombosis and thus exposure to heparin products. Additionally, thrombocytopenia is a common finding in cancer patients. The convergence of these variables highlights the importance of an increased understanding of the disease in cancer patients. (JNCCN 2011;9:781–787)

Heparin-induced thrombocytopenia (HIT) is a clinically important drug-induced complication. The rates of HIT vary significantly based on the clinical context, but estimates have ranged from 0.2% to 3%. Rates are higher among general medical, surgical, orthopedic, and cardiac patients, but lower in chronic hemodialysis, obstetric, and pediatric patients. The formulation of heparin also influences incidence, with markedly lower rates associated with low-molecular-weight heparin (LMWH; 0.2%) than with unfractionated heparin (UFH; ~3%). Other minor factors reported to impact HIT incidence include route of administration (e.g., intravenous, subcutaneous), gender, and heparin source (e.g., bovine, porcine).

Although a full discussion of the pathophysiology of HIT is beyond the scope of this review, several articles were recently published. Briefly, HIT is an immune-mediated response to UFH or LMWH. The immunologic targets are macromolecular complexes between platelet factor 4 (PF4), which is an abundant platelet protein, and heparin products, resulting in heparin-PF4 antibodies. These antibodies bind to the macromolecular heparin-PF4 complexes and can then bind to Fc receptors on the surface of platelets. The size of the macromolecular complexes often allows binding to multiple Fc receptors, leading to platelet activation, release of procoagulant microparticles, and significant thrombin generation. The massive thrombin generation leads to thrombosis, both arterial and venous, and is the basis for treatment with direct thrombin inhibitors. The heparin-PF4 antibodies are detectable in the laboratory using immunologic or functional assays, and are often used to support the clinical suspicion of HIT.

Patients with cancer represent a population of interest with respect to HIT, both because of the potential diagnostic complexity, given the number of potential confounders, and the relatively high risk for heparin exposure, which is driven through multiple mechanisms. For example, venous thromboembolism (VTE) is common in cancer patients. Approximately 15% of all cancer patients have clinically detectable VTE, and VTE is identified in 2% to 8% of hospitalized cancer patients. Hospitalization also results in heparin exposure, in many cases for thromboprophylaxis. Active treatment with chemotherapy increases the risk for VTE, and certain agents such as thalidomide, bevacizumab, and irinotecan increase the risk further. Additionally, routine care for venous access devices, commonly found in cancer patients, often involves heparin flushes.
Thrombocytopenia in Malignancy

Thrombocytopenia is not an uncommon finding among cancer patients. The most common causes of thrombocytopenia in malignancy are treatment-related, primarily from myelosuppressive chemotherapy, but radiation effects also contribute. The dynamics of treatment-related bone marrow toxicity depend on numerous variables. Risks of treatment-related thrombocytopenia vary significantly according to treatment regimen.9 Beyond the risk of thrombocytopenia, the timing of onset, severity, and duration of thrombocytopenia are dependent on treatment regimen (either chemotherapy or radiation). Among patients with solid tumor malignancies, cisplatin and carboplatin are strongly associated with significant thrombocytopenia.10 Additionally, the cumulative effects of prior therapies also impact treatment-related thrombocytopenia, and therefore patients with advanced disease often have more severe myelosuppression. Direct suppression of normal trilineage hematopoiesis through malignant infiltration of the bone marrow is another common cause of thrombocytopenia in this population. This occurs in malignancies of hematologic origin (leukemias and lymphomas), but also in solid tumors that metastasize to bone.9

As in the general medical population, infection and nonchemotherapeutic medications can cause thrombocytopenia in cancer patients. Additionally, thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura or hemolytic uremic syndrome, is associated with malignancy, specifically advanced breast and gastric adenocarcinoma, and with several chemotherapeutic agents (including mitomycin, bleomycin, cisplatin, and gemcitabine).11 Although HIT and thrombotic microangiopathy can often be distinguished based on the presence of microangiopathic hemolytic anemia and characteristic schistocytes on peripheral blood film in thrombotic microangiopathies, severe HIT can produce schistocytes, making the entities difficult to differentiate.11

Disseminated intravascular coagulation (DIC) is another cause for thrombocytopenia strongly associated with malignancy, and often mimics HIT. Although hematologic malignancies and adenocarcinomas are most strongly associated with DIC, up to 20% of cancer patients are affected by DIC.12 Compared with DIC associated with sepsis or trauma, DIC in malignancy is often insidious and chronic, with higher rates of VTE, and more subtle microvascular thrombosis.12

HIT in Cancer Patients

A paucity of data is available regarding incidence and prevalence of HIT in cancer patients. Many epidemiologic studies of HIT specifically excluded patients with malignancy or those who had received chemotherapy,13,17 or made no specific mention of patients with malignancy.14,16 An abnormally low baseline platelet count (< 150 × 10⁹/L) is another common exclusion criterion that potentially limits applicability of epidemiologic studies to oncology patients.13,16

Of the numerous cohort studies (both prospective and retrospective) evaluating HIT incidence, only 2 specifically consider cancer patients.16,17 These studies were similar in design. Both were prospective cohort studies evaluating the incidence of HIT in hospitalized medical patients. The first focused on patients treated using UFH,16 whereas the second study assessed those treated using LMWH.17 Combined, the studies included 335 patients with malignancy, among whom 5 (1.5%) developed HIT.18 In the rest of the combined cohort, 14 of 1998 (0.7%) developed HIT, resulting in a nonsignificant odds ratio (OR) of 2.13 (95% CI, 0.76–5.95).18 Thromboembolic events occurred in 2 of 5 patients with malignancy and HIT, and 5 of 14 without malignancy, resulting in an OR of 1.20 (95% CI, 0.15–9.77).18

In a single-institution retrospective analysis of patients with positive PF4 enzyme-linked immunosorbent assay (ELISA) tests, 55 evaluable patients were diagnosed with HIT based on the test results and an appropriate clinical setting.19 Among these, active biopsy-proven malignancy was present in 11, with 8 different tumor types represented. The risk of any thrombosis (arterial or venous) was higher in patients with malignancy, occurring in 8 of 11 patients with malignancy (73%) versus 13 of 44 patients without malignancy (30%), resulting in an OR of 6.4 (95% CI, 1.5–27.8), driven primarily by the risk of venous thrombosis, with an OR of 13.6 (95% CI, 2.9–63.8). Patients with malignancy were also at greater risk for limb amputation (OR, 16.1; 95% CI, 1.5–175.2). However, no increased all-cause mortality was seen among patients with malignancy and...
HIT compared with those without malignancy and HIT (OR, 2.0; 95% CI, 0.5–7.7).19

Other potential sources of epidemiologic data regarding HIT in malignancy are the numerous clinical trials evaluating various heparin products for VTE treatment or prophylaxis in patients with cancer. The safety focus in most of these studies, however, was on bleeding risk, and thrombocytopenia and HIT were not mentioned.20–23 In ENOXACAN I, one patient treated with LMWH experienced severe thrombocytopenia, defined as a platelet count less than 30,000 × 10^9/L,24 although no further follow-up information was provided. No cases of HIT were reported among 148 patients with advanced cancer who received LMWH for 6 weeks, although study protocol indicated that HIT testing would be triggered when platelets fell below 50,000 × 10^9/L.25 Comparing LMWH with warfarin for treatment of proximal vein thrombosis in cancer patients, Hull et al.26 found that 11 of 100 patients on LMWH and 7 of 100 on warfarin developed thrombocytopenia, with a platelet count of less than 150,000 × 10^9/L. Furthermore, 6 of 11 patients on LMWH and 4 of 7 on warfarin had platelet counts less than 100 × 10^9/L.26 Of those who developed thrombocytopenia, the origin of the thrombocytopenia for 10 of the patients on LMWH and 5 of those on warfarin was believed to be chemotherapy, although no specific mention is made of the origin of the thrombocytopenia for the remaining patients, nor is the determination of the origin discussed.26

Data are also limited regarding development of heparin-PF4 antibodies in patients with cancer, without regard to clinical aspects of HIT, with ongoing heparin exposure for central venous catheter care. In one prospective case-control study, heparin-PF4 antibodies were measured serially using ELISA after insertion of a central venous catheter.27 Approximately one-third of patients (16/49) had intermediate or positive heparin-PF4 ELISA results at some point during evaluation, although 9 of 16 (62.5%) had elevated results at baseline. Furthermore, only 9 of 49 (18.3%) showed rising values, though in 7 of 9 cases, the values fell after an initial rise. However, only 2 of 20 normal volunteers had intermediate-level heparin-PF4 ELISA and none had a positive result, suggesting that patients exposed to heparin can become sensitized and that HIT is an important diagnosis to consider.27

Unfortunately, knowledge of the incidence of HIT in malignancy is limited to subgroup analyses in prospective cohort studies16,17 and a small (n = 55), single-institution, retrospective analysis.19 The generalizability of the prospective studies to a general oncologic population is limited in that both studies excluded patients with abnormal baseline platelet counts and hematologic malignancy, or those who were undergoing chemotherapy or radiotherapy.16,17 Furthermore, the prospective studies16,17 did not show an increased risk of thrombotic complications among cancer patients with HIT, whereas Opatrny and Warner19 showed a strong increased risk for thrombotic complications. Certainly, more insight into the phenotype of HIT in cancer patients, and the epidemiology, has important clinical implications.

Identifying HIT Risk

The diagnosis of HIT can be challenging, but an accurate and prompt diagnosis is important. Missed or delayed diagnosis increases risk for life- or limb-threatening thrombosis.28 Overdiagnosis and initiation of direct thrombin inhibitors for false-positive results expose patients with thrombocytopenia to significant hemorrhagic risk.29 Thus, appropriate identification of patients at risk for HIT (and therefore in need of further evaluation) is of great clinical significance.

The most recognized method of identifying risk for HIT in the clinical setting is the 4T’s scoring system,30 which uses 4 easily obtained factors: 1) timing of thrombocytopenia with respect to heparin exposure, 2) severity of platelet drop, 3) presence of thrombosis, and 4) presence of other factors causing thrombocytopenia. Each factor receives a score of 0 to 2, depending on the likelihood of the clinical variable being from HIT, with a cumulative score range of 0 to 8. Although a low score (< 4) essentially rules out HIT, the implications of intermediate (4–5) and high scores (≥6) are not entirely clear, and vary according to clinical scenario.30 More recent efforts at pretest assessment of HIT risk use a scoring system based on expert consensus.29 Conceptually, the risk factors identified in this study are similar to those used in the 4T’s system, although more factors are considered.

Although assessing HIT risk for a given patient in general medical or surgical populations is chal-
Challenging, the task is even more formidable in cancer patients. They receive treatments that induce thrombocytopenia, or have bone marrow involvement causing platelet production to be limited by direct malignant infiltration. Furthermore, they are exposed to heparin products at high rates because of a propensity toward thromboembolism and indwelling central venous catheters. The current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Venous Thromboembolic Disease recommend using the 4T’s scoring system to assess risk of HIT (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

The 4T’s scoring system and the HIT Expert Probability (HEP) prediction model for assessing HIT risk were not designed for cancer patients. When considering the cardinal features of HIT, thrombocytopenia, and thrombosis, which both figure prominently in both the 4T’s and HEP models, myriad confounding factors exist for cancer patients (Table 1). Causes for thrombocytopenia are multiple, with the most obvious being chemotherapy-induced myelosuppression. Incorporating this into the 4T’s scoring system, the maximum score for many cancer patients is 6 (instead of 8), creating a bias toward underdiagnosis. Thrombosis rates in cancer patients, both incident and recurrent, contribute to difficulties in diagnosis, especially because recurrent VTE is often attributed to the potent hypercoagulable state induced by malignancy. However, whether a subset of patients exists in whom recurrent VTE while on therapeutic doses of LMWH represents HIT, rather than “LMWH failure,” is important to consider. Incorporating this into HIT scoring systems again biases toward undertreatment.

HIT is largely a clinical diagnosis that is increasingly supported by laboratory evaluations. Two types of assays are available: immunologic and functional. Immunoassays detect circulating heparin-PF4 antibodies using an immobilized antigen on a microtiter plate (ELISAs, enzyme immunoassays) or agglutination assays of antigen-coated particles (particle gel immunoassay [PaGIA]). Functional assays measure platelet-activating effects of HIT antibodies using several different end point measures of platelet activation: light transmission (via platelet aggregometry), platelet-activation markers detected by flow cytometry, or platelet granule release of ATP or radiolabeled 14 C-serotonin.

Most institutions offer immunoassays for heparin-PF4 antibodies for logistical reasons, including rapid turnaround time and ease of performance. In general, these tests are highly sensitive (> 99%), but specificity is modest (40%–70%) given frequent asymptomatic seroconversion, with asymptomatic heparin-PF4 antibodies detected in up to 17% of general medical and surgical patients treated with UHF, up to 8% of those treated with LMWH, and up to 2% of those treated with fondaparinux.

Functional assays of HIT dramatically improve the specificity of the diagnosis of HIT. When performed in experienced laboratories, sensitivity and specificity of functional assays exceed 95%, leading to positive predictive values greater than 87%. Unfortunately, functional assays are poorly standardized and technically complex to set up and perform, and are therefore only offered in a limited number of laboratories nationally. One recommended approach to integrating these 2 types of assays into practice focuses on patients with intermediate clinical risk for HIT (4T’s score, 4–5); if the immunologic assay is positive among this group, further investigation with a functional assay is reasonable to confirm or refute the diagnosis of HIT. No specific recommendations exist for using these laboratory tests in cancer patients.

### Table 1 Confounders of the 4T Score in Patients With Cancer

<table>
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<tr>
<th>4T Rule</th>
<th>Potential Confounder</th>
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<tr>
<td>Thrombocytopenia</td>
<td>Common finding in cancer patients, associated with marrow infiltration, myelosuppression secondary to chemotherapy, consumptive processes</td>
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<tr>
<td>Timing of platelet count drop</td>
<td>Timing also needs to be compared to chemotherapy administration</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Occurs in 15% of cancer patients, frequently recurrent, even while receiving anticoagulant therapy</td>
</tr>
<tr>
<td>Other causes of thrombocytopenia</td>
<td>Cancer and chemotherapy are common causes</td>
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Management of Suspected HIT

Initial management of suspected HIT is guided by the degree of clinical suspicion, as determined using criteria discussed earlier. If suspicion is sufficiently high and the 4T’s score is 4 or more, the NCCN Guidelines recommend stopping heparin products (including flushes), ordering heparin-PF4 antibodies, obtaining venous Doppler examinations of all 4 extremities, and considering initiation of a direct thrombin inhibitor.31 Direct thrombin inhibitors are the preferred therapy for HIT because of the need to avoid cross-reaction with circulating heparin-PF4 antibodies. No reversal agents exist for the available direct thrombin inhibitors, and bleeding complications are common, emphasizing the importance of accurate HIT risk assessment and appropriate patient selection. Three direct thrombin inhibitors are currently available for patients with HIT: lepirudin, bivalirudin, and argatroban,3,7 and this article provides a brief discussion of each.

Lepirudin irreversibly binds the catalytic site on thrombin and the anion-binding exosite. A summary analysis of prospective trials of patients with HIT treated with lepirudin showed a decreased rate of the composite outcome of death, amputation, and thrombosis among patients treated with lepirudin compared with historical controls (20.3% vs. 43%; P < .001), although with a markedly increased risk of bleeding (17.6% with lepirudin vs. 5.8% in controls).37 Therefore, the American College of Chest Physicians guidelines on heparin-induced thrombocytopenia recommend lower doses of lepirudin than were used in the initial prospective studies.3 Furthermore, lepirudin is renally excreted and doses are further reduced in patients with renal insufficiency. Finally, antibodies to lepirudin develop in approximately 30% of patients on first exposure and up to 70% on second exposure, with fatal anaphylaxis events reported. Accordingly, patients should not be treated with this agent on multiple occasions.38

Bivalirudin reversibly binds to the catalytic site and the anion-binding exosite of thrombin. Currently, bivalirudin is only indicated for patients who either have HIT or are at risk for developing HIT in the setting of percutaneous coronary intervention. Information regarding dosing and use in other settings is limited, but renal insufficiency should prompt dose reduction.7

Argatroban binds to the catalytic site of thrombin reversibly. As with lepirudin, prospective trials (combined n = 373) evaluating for the composite end point of death, amputation, and thrombosis showed lower rates among patients receiving argatroban (34%–35%) compared with controls (43%).30,40 Argatroban is hepatically metabolized and half-life is markedly prolonged in patients with hepatic insufficiency. Consequently, dose reduction, or an alternative direct thrombin inhibitor (preferred), is necessary in patients with liver failure. Additionally, at therapeutic doses, argatroban significantly prolongs the prothrombin time, which can complicate conversion of patients from argatroban to warfarin therapy.7

The duration of anticoagulant therapy in patients with HIT is determined by the presence or absence of thrombosis. Among patients without thrombosis, direct thrombin inhibitors are recommended until platelet counts normalize, and then additional anticoagulant therapy (warfarin) is recommended for an additional 4 to 6 weeks because of a persistent prothrombotic state.41 For patients with HIT who experience thrombosis, duration of anticoagulation (beyond direct thrombin inhibitor therapy) is determined by the specific thrombotic event.3 Regardless, warfarin is not initiated until after the platelet count has recovered to normal levels because of the potential for warfarin skin necrosis secondary to depletion of functional protein C.3

Because treatment of HIT pertains specifically to patients with malignancy, few data are available. The NCCN Guidelines for VTE (in this issue; to view the most recent version, visit www.NCCN.org) recommend considering direct thrombin inhibitors if the 4T’s score is 4 or greater.31 Although no differences in risk associated with direct thrombin inhibitors persist are seen in cancer patients, they may have an increased propensity towards multiorgan insufficiency (specifically hepatic and renal), whether because of disease involvement (hepatic metastases) or treatment effects (chemotherapy-related nephropathy or volume depletion), potentially making treatment of HIT in these patients more tenuous.

Conclusions

HIT is an immune-mediated reaction to heparin products that is associated with significant morbidity
and mortality. The diagnosis is primarily clinical but is often supported by laboratory evaluation for the presence of heparin-PF4 antibodies. HIT presents a diagnostic challenge in many cases, and perhaps even more so in patients with cancer. Unfortunately, current understanding of HIT in patients with cancer is incomplete and current clinical prediction models for HIT risk are inherently biased toward underdiagnosis in these patients.

Future efforts should focus on not only characterizing the epidemiology of HIT in cancer patients but also determining whether the phenotype of HIT differs in patients with cancer (i.e., is even more prothrombotic). These efforts eventually will allow development of prediction models that are tailored to the oncologic population. Specifically, models must account for baseline platelet counts; concomitant use of chemotherapy or radiation, with attention paid to regimen-specific risks of thrombocytopenia; and increased thrombotic events in the oncologic population.

References


