Journal of Hematology & Thromboembolic Diseases

Mozaheb, J Hematol Thrombo Dis 2014, 2:6
DOI: 10.4172/2329-8790.1000176

Review Article Open Access

Cancer and Thrombosis

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Rec date: Nov 11, 2014, **Acc date:** Nov 26, 2014, **Pub date:** Dec 5, 2014

Abstract

Venous thromboembolism (VTE) is a common and life-threatening condition in patients with cancer. The incidence rate depends on the tumor type. Many of risk factors for development of VTE are common in patients with cancer, which include cancer related factors and treatment related factors. In this review we define VTA to include deep vein thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombisis (SVT), Splanchnic vein thromboses (SPVT), Involving the splenic, portal, mesenteric, or hepatic veins. Prophylactic anticoagulation therapy recommended for patients with active cancer who do not have a contraindication are Low molecular Wight heparins, fondaparinox, and subcutaneous Unfractionated Heparin, warfarin, and aspirin only for low risk multiple myeloma. In cancer patients low-molecular-weight heparin monotherapy has been identified as a simple and efficacious regimen compared with an initial parenteral anticoagulant followed by long-term therapy with a vitamin K antagonist.

Keywords Venous thromboembolism; Heparin monotherapy

Introduction

The close relationship between venous thromboembolism and cancer has been known since at least the 19th century by Armand Trousseau [1]. Thrombosis is a major cause of morbidity and mortality in patients with cancer [2]. One study showed that approximately 3-12% of adult cancer patients with neutropenia depending on the type of malignancy, experienced VTE during their first hospitalization [3]. The occurrence of VTE has been reported in 12.6% of ambulatory patients during 12 month from initiation of chemotherapy [4]. Increasing age, cancer prevalence, and greater thrombogenicity of chemotherapeutic regimens, enhanced detection of incidental thrombosis. Venous thromboemboly has been reported to increase the likelihood of death for cancer patients by 2-6 fold [5], and also has been reported VTE to be the most common cause of death at 30-days follow-up among cancer patients undergoing surgery [6]. A study showed increase in the incidence of cancer-associated thrombosis during the recent decades [3] that may be related to the cancer treatment.

Risk Factors

Several reasons induce thrombosis in cancer patients, which many of them are common in cancer patients [7]. Active cancer itself is often the underlying mechanism. The type of cancer is one of the most important risk factor for venous thromboembolism occurrence. The stage of cancer and the histological grade of a tumor have been found to be associated with the occurrence of cancer- related VTE, also the regional lymph node metastases are a strong risk factor for VTE. Patients with regional or distant metastasis have significantly higher levels of factor VIII, D dimer, p-selectin, platelets, and lower hemoglobin levels than those with local stage [8-10]. When monocyte or macrophage lineage cells interact with malignant cells, they release tumor necrosis factor, and interleukins (1 and 6), causing endothelial damage and converting to thrombogenic surface. The interaction between tumor cells and macrophages also activates platelets, factors X and XII, which leads to the thrombin generation. Procoagulant substances in tumor cells such as cysteine proteases and tissue factor can directly activate factor X and factor VII respectively. Aggressive chemotherapy with commonly used agents such as platinum compounds, high dose fluorouracil, mitomycin, and hormonal therapy with tamoxifen, angiogenetic agents, and growth factors increase the risk of thrombosis [11]. Central venous catheters inserted for chemotherapy and hyperalimentation, are also associated with a risk of thrombosis. The thrombogenic surface of these catheters induce platelets and serine proteases activation. Gram-negative organisms that infect central venous catheters can release endotoxin, and gram-positive organisms can release bacterial mucopolysaccharides, that can activate factor XII, induce a platelet-release reaction, and cause sloughing of endothelial cells; and increase the risk of thrombosis. Also endotoxin induces the release of tumor necrosis factor, tissue factor, and interleukin-1, which can incite thrombogenesis [12]. We can see other risk factors in Table 1.

General risk factor	Treatment related risk factor
Active cancer	Major surgery
Advance stage of cancer	Central venous catheter
Cancer type at higher risk	Chemotherapy such as:
Brain	Thalidomide,Lenalidomide,
Pancreas	High dose dexamethason
Stomach	Exogenoushormonaltherapysuch as:
Bladder	Hormone replacement
Gynecologic	Contraceptives
Lung	Tamoxifen/roloxifen
Lymphoma	Diethylstilbestrol

Myeloproliferative neoplasm	Modifiable risk factor
Kidney	Smoking, tobacco
Metastatic cancer	Obesity
Regional bulky lymphadenopathy with extrinsic vascular compression	Activity level
Acquired hypercoaglability	
Medical comorbidity	
Poor performance status	
Older age	
High Risk outpatients on chemotherapy	
Active cancer with high incidence VTE: stomach, pancreas, lung,lymphoma, gynecoloyic, bladder, and testicular	
Prechemotherapy Platelet count>300000/mcl	
Prechemotherapy WBC>11000/mcl	
Hemoglobin<10 g/dl	
Prior VTE	

Table 1: VTE Risk factor in cancer patients (The NCCN guidelines 2014).

Risk-assessment models may offer improved outcomes for oncology patients. Estimating an individual patient's risk for VTE is clinically more relevant because it allows physicians to target thromboprophylaxis in those who are most at risk for venous thromboembolism. Five independent risk factors were identified for symptomatic VTE during the first four cycles of chemotherapy: site of cancer, platelet count and leukocyte count (pre-chemotherapy), hemoglobin level or the use of red cell growth factors, and body mass index (BMI), that predicted VTE. Risk score model containing these five clinical and laboratory items was developed (Table 1) and based on these total risk score patients are classified into three categories: low-risk (score 0; VTE risk 0.3-0.8%), intermediate-risk (score 1 or 2; VTE risk 1.8-2.0%), or high-risk (score 3 or higher; VTE risk 6.7-7.1%). There are some limitation in this model scoring, the model may not be predictive of VTE development based on age and in some tumor types or in those who have advanced disease and a poor performance status. Also such new drugs (e.g., bevacizumab or thalidomide) cannot be considered as a risk factor in this model (Table 2) [10].

Patient characteristic	**Risk score**
Site of primary cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Platelet count prechemotherapy more than 350000/µl	1
Leukocyte count prechemotherapy more than 11000/µl	1
Hemoglobin less than 10 g/dl or using red cell growth factor	1
Body Mass Index 35 kg/m^2 or higher	1

Total score	**Risk category**	**Risk of symptomatic VTE**
0	Low	0.8-3%
1, 2	Intermediate	1.8-8.4%
3 or higher	High	7.1-41%

Table 2: Khorana predictive model for chemotherapy associated VTE [13].

Prevention of VTE in cancer: Hospitalized cancer patients are at high risk for venous thromboembolism, and ambulation in this patients is inadequate to reduce VTE risk [14]. The recommended prophylactic anticoagulation therapy for inpatients/ outpatients with active cancer who do not have a contraindication are Low molecular Wight heparins (LMWHs) (dalteparin 5000 units subcutaneous daily or enoxaparin40 mg subcutaneous daily), fondaparinox (factor Xa inhibitor) (2.5 mg subcutaneous daily), and subcutaneous Unfractionated Heparin (UFH) (5000 units 3 times/day), aspirin 81-325 mg daily (only for low risk multiple myeloma outpatients, warfarin (adjusted to INR 2-3). A meta-analysis of comparisons of a variety of low molecular-weight heparins with unfractionated heparin for deep-vein thrombosis showed that dalteparin was associated with fewer major bleeding episodes and a lower mortality rate than unfractionated heparin [15]. And also a study showed that the incidence of recurrent thromboembolism in the dalteparin group was half that in the warfarin group. An additional benefit is that dalteparin, has been deemed safe for use in the elderly (those older than 65 years of age) by the Food and Drug Administration. The multicenter trial reported by Lee et al. suggested that low-molecular-weight heparin should become the therapeutic and prophylactic agent of choice in cancer-associated thromboembolic disease [12].

All inpatients adult with cancer prior to the initiation of thromboprophylaxis should be undergo the following evaluation: comprehensive medical history and physical examination, complete blood count with platelet count, prothrombin time, activated partial thromboplastin time, and liver and kidney function tests.

Different studies showed that a high proportion of VTE occurs in the cancer outpatients setting [16]. Cancer patients with high risk for VTE could be consider for outpatients VTE prophylaxis on an individual basis (based on Khorana risk assessment score 3 or higher) (NCCN guideline 2014). Cancer patients undergoing abdominal or pelvic surgery have higher risk of VTE and should be considered for outpatients prophylaxis [6,17].

Mechanical prophylaxis: In patients with contraindication to pharmacologic agents in patients at very high risk of VTE, intermittent pneumatic compression devices and graduated compression stockings are mechanical prophylaxis option [18].

VTE Treatment

Options for the initial treatment of cancer-associated thrombosis include LMWH, unfractionated heparin (UFH), or, in some cases, fondaparinux in patients without contraindications to anticoagulantion. In a meta-analysis of trial comparing outcomes with UFH, LMWH, and fondaparinox as initial treatment of VTE in cancer patients, LMWH was associated with no significant reduction was found in mortality rate at 3-month follow up compared with UFH, but

without significant difference in recurrence of VTE, or bleeding. Therefore LMWHs are preferred for acute management of VTE in cancer patients because they do not require hospitalization or monitoring, and also are preferred option for long term therapy [19,20].

Several studies comparing the efficacy and safety of oral warfarin and LMWH in chronic VTE treatment. In comparing of enoxaparin and warfarin, major bleeding and VTE recurrence within 3-month in the enoxaparin using was significantly lower than the warfarin [21]. In another study, no significant differences were observed within 6-month threament with warfarin and enoxaparin [22]. Kaplan-meier study showed VTE recurrence risk within 6-month study significantly decreased with dalteparin compared with oral anticoagulant and no significant difference in bleeding risk was seen for two groups [23]. Vitamin K antagonists are less effective in patients with cancer, with rates of recurrent VTE threefold higher than in patients without cancer, despite maintenance of the international normalized ratio (INR) within the therapeutic range [24]. LMWH also offers other advantages including: no need for laboratory monitoring of its anticoagulant activity; a shorter half-life that facilitates temporary interruption for procedures or thrombocytopenia; limited drug interactions; and no food interactions. As a result, LMWH is recommended for both initial and long-term anticoagulant therapy in cancer-associated thrombosis by major consensus guidelines [25]. The use of oral factor Xa inhibitors has also been evaluated for extended anticoagulation therapy in patients who had VTE, but using of them in cancer patient remains to be investigated in future prospective trials [26].

Superficial venous thrombosis(SVT): Anticoagulation therapy with intravenous UFH or LMWH at least for 6 weeks is a recommendation with a non-peripheral catheter SVT in close proximity to the deep venous thrombosis, and 12 weeks treatment if SVT in close to the femoral vain. catheter removal, anti-inflammatory medications, warm compresses, and limb elevation in peripheral catheter related SVT is recomended.

Splanchnic vein thromboses (SPVT), Involving the splenic, portal, mesenteric, or hepatic veins, are uncommon in the general population, but significant rates have been reported in patients with intra-abdominal malignancies [27]. In a single-institution study, incidental splanchnic vein thrombosis was present in 23% [28]. A retrospective study showed that, the presence of malignancy was significantly associated with decreased survival for patients with SPVT, both in univariate and multivariate analysis [29]. Management of the patients with SPVT depends on the duration, location and extent of the thrombosis. In acute SPVT, which is associated with presenting sign and symptoms ≤8 weeks duration, without portal cavernoma and portal hypertension, anticoagulation with UFH or low molecular weight heparin (preferred) should be initiated, followed by oral agents for at least 6 months [29,30]. Anticoagulant therapy appears to lower the risk for recurrent thrombosis in patients with SPVT without increasing the risk for severe bleeding [31,32]. NCCN guideline recommends lifelong anticoagulation for SPVT in patients with active cancer, underlying thrombophilia, and idiopathic thrombosis. Thrombolytic therapy may be most useful when administered locally in patients with acute thrombosis; but should be used with caution because of major bleeding complications [33]. In chronic SPVT, the presence of portal hypertention may increase the risk of bleeding from esophageal varices and splenomegaly may decreased platelet counts, that increase the risk of bleeding in patients treated with anticoagulation [34]. An important management of patients with chronic mesenteric or portal thrombosis is risk reduction for and prevention of bleeding [35].

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