Malignancy-Associated Thrombosis

by Brandon McMahon, MD

Venous thromboembolism (VTE) is a well-known and common complication of many malignancies. VTE not only introduces a new morbid condition to patients with malignancy, but also complicates the treatment of the underlying disease and is associated with a poorer overall prognosis. The presence of VTE likely reflects a more aggressive malignancy. Both the one-year death rate and the percentage of cases initially diagnosed with metastatic disease for each type of cancer are directly proportional to the incident rates of VTE.[1] A lower survival has been shown in patients with malignancy with VTE than without thrombosis, even after adjusting for age, cancer stage, and comorbidities.[1,2]

Mechanisms of Malignancy-Associated VTE

The exact mechanisms involved in malignancy-associated thrombosis have yet to be clearly determined, and are likely related to a number of variables in each specific cancer. Increased expression of tissue factor (TF) explains, at least in part, the increased rates of VTE in malignancy along with the associated poorer prognosis. Tissue factor [a glycoprotein] is a well-known initiator of the coagulation cascade and precipitating thrombin [a coagulation protein] generation. In addition, TF has been shown to promote tumor growth, angiogenesis, and metastasis.[3-5] Evidence also exists that TF expression may play an important role in preventing apoptosis.[6,7]

Cancer procoagulant (CP) is a cysteine protease that can directly activate factor X [an enzyme in the coagulation cascade], and is therefore a procoagulant protein.[8] A number of malignant cell types have been shown to express CP, but what effect—if any—it has in malignancy-associated thrombosis remains unclear.

Cellular activation and/or apoptosis can lead to formation of microparticles, composed of small membrane vesicles that can activate thrombin generation. Microparticle formation is associated with hypercoaguability in a number of diseases, including heparin-induced thrombocytopenia [reduced platelet count], which has a very high rate of both arterial and venous thromboses. Tissue factor has been demonstrated on circulating microparticles, and likely plays a role in the thrombogenesis of malignancy-associated VTE. Increased TF expressing microparticles were found in patients with metastatic breast and pancreatic cancer compared with healthy controls in one study.[9] Higher TF microparticle expression was further associated with a reduced survival and with higher rates of VTE in this population.[9]

Treatment with cytotoxic chemotherapy, immunomodulatory agents, and antiangiogenic agents also appears to upregulate the coagulation system. Cytotoxic chemotherapy can damage the vascular endothelium, potentially leading to platelet activation and thrombus formation. The clinical manifestations of venous thrombosis have correlated with the findings of increased plasma concentrations of markers of thrombin generation, including thrombin-antithrombin (TAT) complexes and D-dimer, a small protein fragment. Zurborn and colleagues demonstrated significant elevations in TAT complexes and prothrombin F1+2 four hours after infusion of a multidrug regimen for treatment of non-Hodgkin's lymphoma.[10] This upregulation in proteins involved in hemostasis is believed to be related to further endothelial activation and increased expression of tissue factor beyond that already seen with the underlying malignancy itself.

PHOTOGRAPH/FOTOLIA

Risks for Development of Malignancy-Associated VTE

The presence of active malignancy is estimated to increase the risk of VTE at least five-fold, with the annual incidence being reported at 0.5 percent in those with cancer versus 0.1 percent in those without.[11] The risk of VTE varies with

type of underlying malignancy. Among the most common cancers, brain, pancreatic, gastric, acute myelogenous leukemia, and renal cell carcinoma have the highest rates of VTE, ranging from 3.5 to 6.9 percent in the first year of cancer diagnosis.[1] This risk increases dramatically in those patients with metastatic disease. Hematologic malignancies including multiple myeloma, myeloproliferative disorders, and lymphomas also have high rates of thrombosis, with reports ranging from 1.5 percent up to as high as 59.5 percent; the highest rates have been found in those with CNS lymphoma.[12] Higher grade lymphomas have an even greater risk of VTE, with rates of 10.6-12.8 percent, versus 5.8 percent in low grade non-Hodgkin lymphoma.[13,14]

The risk of thrombotic complications can be further exacerbated by a number of other variables that often accompany malignant disease, with hospitalization, use of erythroid stimulating agents, and presence of an indwelling central venous catheter (CVC) being among these.[15,16] As mentioned previously, treatment with a number of malignancy specific treatments adds to the underlying hypercoaguability seen with cancer. The odds ratio for VTE was 6.5 in patients with malignancy receiving chemotherapy versus 4.1 for patients with malignancy not receiving such treatment in a case control study.[17] A 1.93 percent symptomatic VTE incident rate was reported in another prospective study, with incidence varying depending on type of underlying malignancy.[18] Two separate studies have demonstrated a clear increase in the rate of VTE in lymphoma patients undergoing multiagent chemotherapy, with rates of 10-27 percent.[19,20]

Anticoagulation Treatment

Treatment of VTE with anticoagulation serves several purposes. It helps prevent extension of existing clots, embolization, and thrombotic recurrence, and relieves symptoms of venous congestion. In the past, standard of care consisted of using unfractionated heparin as a continuous infusion with longer term replacement using an oral vitamin K antagonist, such as Coumadin. Although efficacious, unfractionated heparin introduces a number of complications to VTE treatment. Among these are the need for intravenous access, frequent laboratory monitoring for aPTT (Activated Partial Thromboplastin Time) adjustments, prolonged hospitalization, drug binding to plasma proteins, and relatively high rates of heparin-induced thrombocytopenia. The introduction of the low-molecular-weight heparins (LMWH) in the late 1990s alleviated a number of these negative features of unfractionated heparin, and have, therefore, been considered the standard of care in acute treatment of VTE in the appropriate patient populations. Until recently, LMWH have been used primarily as a bridge in VTE treatment until patients' INR levels on oral vitamin K antagonists are adequate.

Vitamin K antagonists have a number of drawbacks, particularly in patients with malignancy. Besides the inconvenience of frequent INR (international normalized ratio) monitoring, several potential barriers to therapeutic levels exist, including multiple drug interactions, liver dysfunction, and malnutrition, all common in cancer. The risk of bleeding is increased with many malignancies and supratherapeutic INR levels, owing to chemotherapy-induced thrombocytopenia and anatomical issues associated with the underlying malignancy itself (e.g., hemoptysis, or coughing up blood, in lung cancers). The rates of recurrent VTE and major bleeding with use of vitamin K antagonists have therefore, not surprisingly, been shown to be much higher in patients with cancers than those without.[21-24]

Due to the multiple potential complications associated with UFH (unfractionated heparin) and vitamin K antagonists, studies have been conducted looking at longer-term treatment of malignancy-associated VTE with LMWH. The CLOT (randomized comparison of low-molecular-weight heparin versus oral anticoagulant therapy for the prevention of recurrent VTE in patients with cancer) trial has made a large impact in this area, and has changed the standard of care with regard to treatment of cancer-associated thrombosis.[25] In this study, 676 patients with new VTE and various underlying malignancies, two-thirds of which were metastatic, were randomized to an oral vitamin K antagonist or longer term treatment with LMWH. The oral anticoagulant group received dalteparin 200 IU/kg subcutaneously (SC) once daily for 5-7 days followed by a vitamin K antagonist titrated to an INR 2.0-3.0. The LMWH group received dalteparin 200 IU/kg SC once daily for one month followed by approximately 150 IU/kg SC once daily. After 6 months of treatment, the dalteparin group had a 52 percent risk reduction in recurrent, symptomatic VTE (9 percent of patients in the dalteparin group, versus 17 percent in the vitamin K group). There was no difference in major bleeding events between the two groups. Of note, almost half of the recurrent clotting events in the vitamin K group occurred when the INR was above 2. These results have led to the recommendation that patients with malignancy-associated thrombosis be treated with LMWH over oral vitamin K antagonists for at least 6 months. There is currently no substantial evidence either for or against continuation of therapy beyond 6 months, and the risks and benefits of continuing anticoagulation should be evaluated on an individual patient basis until more data is available.

Treatment with New Anticoagulants

A number of new agents targeting VTE have been or are in the process of being developed. These agents may prove to be a vital component in the prevention and/or treatment of cancer-related thrombosis.

Fondaparinux is a small, synthetic pentasaccharide that rapidly binds to antithrombin III, thereby inhibiting factor Xa, a key component in thrombus formation. It is delivered as a weight-based subcutaneous injection once daily with a half life of 17 hours, with no routine monitoring required. Fondaparinux has been demonstrated in a number of studies to be safe and effective in treatment of VTE and acute coronary syndromes, but to date has not been formally studied in thrombosis related to malignancy.[26-29] Its long half life, renal metabolism, and increased incidence of catheter-associated thrombosis as seen in patients who underwent percutanous coronary intervention may limit its use in cancer-associated thrombosis.

Several oral anticoagulant agents have been developed. Ximelagatran is an oral direct thrombin inhibitor that showed efficacy in prevention and treatment of VTE without the need for routine drug monitoring. Unfortunately, a significant percentage of patients developed hepatotoxicity, and ximelagatran was not approved for use by the FDA. Dabigatran is another oral direct thrombin inhibitor that is currently being evaluated for treatment of VTE, and to date has not shown significant hepatotoxicity. It is renally excreted and has a long half life (14-17 hours). Other agents in development include the oral direct factor Xa inhibitors rivaroxaban, apixaban, and betrixaban. All of these agents show promise in the treatment of venous thromboembolism, and some are being investigated for their efficacy and safety in cancer-associated clotting events.

Treatment with IVC Filters

Data are lacking on the use of inferior vena caval (IVC) filters in VTE treatment related to underlying malignancy. The majority of reports published on IVC filters are relegated to case series and retrospective reviews, often from single institutions, with a large amount of bias. The only prospective, randomized controlled trial looking at IVC filters showed an increased risk of recurrent deep venous thrombosis (DVT) and post-phlebitic syndrome compared to those without a filter.[30] A more recently published retrospective review of outcomes of VTE in cancer patients showed that having an IVC filter in place was associated with a statistically significant increased risk of recurrent DVT, with almost one-third of patients with an IVC filter having a subsequent event.[31] Due to the lack of convincing evidence, routine use of an IVC filter in patients with malignancy-associated VTE is not recommended; consideration could be given in the event that a contraindication to anticoagulation exists, or the patient has a recurrent event despite adequate anticoagulation.

Treatment with Central Venous Catheters

Indwelling vascular devices, whose use is common in patients with malignancy receiving chemotherapy, increase the risk for development of VTE. The incidence of symptomatic VTE related to a central venous catheter is approximately 5 percent.[32,33] As many catheter-associated thromboses are non-occlusive, the incidence of asymptomatic VTE is likely much higher than this number. Despite the relatively high rate of catheter-associated thromboses, studies have failed to show a benefit of prophylactic anticoagulation in preventing VTE in these patients with warfarin, enoxaparin, or dalteparin.[32,34,35] Anticoagulation is recommended for treatment of catheter-associated clots, with or without device removal. Given the results of the CLOT trial discussed previously, long-term use of LMWH is probably the most appropriate intervention.

Anticoagulation and Survival in Patients with Malignancy

A number of studies have demonstrated a survival benefit in cancer patients receiving anticoagulation therapy, particularly LMWH. For example, a post-hoc analysis of the CLOT trial showed a survival benefit in those patients with limited disease treated with dalteparin versus a vitamin K antagonist (80 percent versus 64 percent) at one year.[36] There was no benefit for the overall population, however. The study was also not originally designed nor powered to look at a mortality benefit. These findings are nonetheless interesting, and there have been randomized controlled trials to evaluate whether LMWH improves cancer survival. The FAMOUS trial was the largest, and randomized 385 patients with various advanced malignancies to dalteparin 5,000 units daily or placebo.[37] Although there was no statistically significant increase in survival, it is of note that the study was powered to detect a 15 percent difference between the groups. A smaller benefit is therefore possible. Sub-group analysis did show those with a good prognosis seemed to benefit from dalteparin. A small but statistically significant survival advantage (8 versus 6.6 months) was found in another study of patients with locally advanced or metastatic solid tumors when treated for six weeks with the LMWH nadroparin.[38] Criticisms of these studies include heterogeneity of cancers enrolled and lack of uniformity of treatment for the underlying malignancy. These issues were addressed in a small study of patients with small cell lung cancer, who were randomized to standard chemotherapy alone or in combination with prophylactic-dose dalteparin.[39] Use of LMWH was found to have a greater overall survival, and those with limited disease had the most benefit.

A recently published meta-analysis pooled the data on five randomized controlled trials and found that use of heparin (either unfractionated or LMWH) conferred a survival benefit in cancer (hazard ratio, 0.77), particularly in patients with limited stage small cell lung cancer.[40] Use of anticoagulation did not translate into an increased bleeding risk in this study. More data are clearly needed prior to recommending the use of anticoagulation in cancer without a documented thrombotic event, for the purpose of improving overall survival.

The exact mechanism via which LMWH may improve survival in cancer is unclear. It does not appear to be solely due to decreased rates of VTE. Alterations in tumor phenotype, inhibition of angiogenesis, and induction of apoptosis are all potential pathways LMWH can help in treatment of underlying malignancies, in addition to their antithrombotic effects.

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