

Cancer and venous thromboembolism

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Summary

Clinical examples of coagulation abnormalities may occur from single or multiple abnormalities and include both inherited and acquired defects. Risk factors that further increase clotting include obesity, recent surgery, pregnancy and cancer. Venous thrombosis is a common complication in patients with malignant diseases. The estimates of the prevalence of cancer among patients with venous thrombosis vary from 3 to 18%. Since cancer is a common disorder in the aging population, it may be responsible for a considerable proportion of all cases of thrombosis. The pathogenic mechanisms of thrombosis in the cancer patient involve a complex interaction between the tumor cell, the patient, and the hemostatic system. These include activation of the coagulation system, platelet activation, endothelial damage, indwelling venous access devices, direct effects of chemotherapy/hormonal therapy, and host

inflammatory responses. Furthermore, local peritumoral activation of coagulation may have important effects on the biology of cancer. In recent years there have been many new developments in understanding basic mechanisms and optimizing clinical care of thrombosis in cancer patients. Subcutaneous low-molecular weight heparin (LMWH) has replaced intravenous unfractionated heparin (UFH) for the initial treatment of thrombosis. In the search for new agents matching the "ideal" anticoagulant profile, a number of different steps in the coagulation cascade have been targeted, including direct thrombin inhibition, and inhibition of factor Xa, factor IXa, the factor VIIa-tissue factor complex and the factor Va-factor VIIIa complex. Such agents could potentially improve thrombosis management in cancer patients.

Key words: cancer, prophylaxis, thrombosis, treatment

Introduction

More than a century ago, Rudolph Virchow identified a triad of factors responsible for vascular thrombosis: vessel injury, alteration in blood flow, and changes in the coagulability of the blood. Precipitating or anatomic factors for thromboembolic disease,

such as pregnancy, surgery, obesity and malignancy, are examples of the first two factors described by Virchow. The delineation of the clinical entity of "hypercoagulability" was designed to identify a syndrome of abnormalities of the third factor of Virchow, coagulability of blood. Consequently, the traditional diagnosis of "hypercoagulability" was created for thromboembolic disease that occurred in the absence of precipitating or anatomic (noncoagulant) factors. Traditional hypercoagulability generally excluded patients who were 45 years of age or older or who had identifiable noncoagulant risk factors [1].

Which are the causes of hypercoagulability? The best clue for the presence of hypercoagulability is a positive family history. The defects that are responsible for hypercoagulability can be divided into inherited defects and acquired forms (Table 1) [2].

Before 1993, the chance of discovering a coagulation abnormality in patients with "traditional"

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Table 1. Risk factors for venous thrombosis

<i>Acquired</i>	<i>Inherited</i>	<i>Mixed/unknown</i>
Age	Antithrombin deficiency	Hyperhomocysteinemia
Previous thrombosis	Protein C deficiency	High levels of factor VIII
Immobilisation	Protein S deficiency	APC-resistance in the absence of factor V
Major surgery	Factor V Leiden (FVL)	Leiden (FVL)
Orthopaedic surgery	Prothrombin 20210A	
Cancer	Dysfibrinogenemia	
Oral contraceptives		
Hormone replacement therapy		
Antiphospholipid syndrome		
Hematologic malignancies		

hypercoagulability was as low as 5-15% [3]. Since the descriptive details of the protein C pathway and activated protein C (APC) resistance have been identified, the frequency of finding underlying causes of hypercoagulability has increased significantly. Defects of the other proteins in this pathway, such as protein C and protein S, are discovered as etiologic factors but with a lesser frequency. The frequency of these abnormalities may be skewed by the geographic origin of the population being analyzed [4].

In 1865 Armand Trousseau first reported the association between cancer and thrombosis [5]. Cancer, hematologic malignancies and dysproteinemias are recognized causes of hypercoagulability, but the mechanisms are unclear and may vary with each situation. With malignancy, excessive clotting is allegedly related to thromboplastin-like effects produced by tumor cells or their products. Mucin-producing malignancy has a high association of thrombosis. Excessive clotting with malignancy may also be caused by concomitant infections, effects of chemotherapy, malnutrition and possible folate deficiency with its consequences on homocysteine, and prolonged bed rest. Cancer patients also are relatively resistant to anticoagulation and have more episodes of recurrent thrombosis. Up to 20% of all cases of venous thromboembolism (VTE) occur in patients with cancer [6]. The patients with recurrent VTE will go on to have the diagnosis of a new cancer within 2 years [7]. This is reflective of the prevalence of cancer in the general population and that active malignancy, with or without chemotherapy, increases the risk for VTE. Cancer is also an independent risk factor for death within 7 days after thrombosis, and cancer patients with VTE have worse survival than cancer patients free of this complication [8]. The risk of VTE is highest in the first 3 months after the diagnosis of malignancy, decreases as the time progresses, but do not return to control rates until 15 years after cancer diagnosis. Patients with hematologic malignancies have

the highest risk of VTE (adjusted odds ratio=OR 28.0), followed by lung cancer (OR 22.2), gastrointestinal malignancies (OR 20.3) and breast cancer (OR 4.9) - 25% in women on hormonal therapy. The presence of metastatic disease in patients with solid tumors increases the adjusted OR to 19.8. Cancer patients carrying the factor V Leiden mutation have a two-fold increased risk of VTE compared with non-carriers cancer patients [6].

Treatment of cancer patients with VTE is difficult because these patients have an increased risk of both recurrent VTE and anticoagulant-induced bleeding compared with noncancer patients [9]. In addition, many cancer patients have a compromised quality of life that is further compromised by the occurrence of thrombosis. In some instances of end-stage cancer, the difficult decision exists of whether one should even treat the acute thrombotic event.

Pathogenesis

VTE is now viewed as a multifactorial disorder in which many susceptible individuals will have one or more genetic mutations and will manifest symptoms upon exposure to acquired prothrombotic stimuli. The pathogenic mechanisms of thrombosis in the cancer patient involve a complex interaction between the tumor cell, the patient, and the hemostatic system [10]. The laboratory tests for these thrombotic risk factors are defined as "the hypercoagulable workup" and their prevalence is [1]:

Prothrombin G20210A mutation (6-18%)

One of the newest detected causes of hypercoagulability is prothrombin 20210A allele, an abnormality described in 1996. The frequency of this abnormality varies from 0.7 to 6.0% among whites,

with rare appearances among Africans and Asians, suggesting that the defect may have also appeared after the divergent migrations of the populations. Combinations of prothrombin 20210A with other defects such as factor V Leiden, protein S deficiency, protein C deficiency, or antithrombin deficiency have been reported. The mechanism by which prothrombin 20210A allele is responsible for hypercoagulability is uncertain [4,11].

Deficiencies of antithrombin III, protein C, protein S (5-15%)

In the final phase of clot formation, thrombin converts fibrinogen to fibrin. Antithrombin (formerly referred to as antithrombin III), named for its action on thrombin, also inhibits the serine proteases of IXa, Xa, XIa, and XIIa. Antithrombin is inherited in autosomal dominant fashion with an estimated frequency of 1 in 2,000. Deficiency of antithrombin may be caused by decreased levels or by dysfunctional protein. The “anticoagulant” action of heparin requires the presence of antithrombin; thus, a clinical clue to diagnosis of antithrombin deficiency may be anticoagulation refractoriness to heparin [3,12,13].

Activated protein C resistance (factor V Leiden) (12-40%; Caucasians)

The pathophysiologic mechanism of the protein C pathway proteins is shown in Figure 1. On the surface of endothelial cells, thrombin (#1) binds to a receptor known as thrombomodulin. The thrombin-thrombomodulin complex is the site for interaction of protein C (#2). Once bound to this complex, protein C becomes activated (APC) (#3) and inactivates or destroys activated factor V (factor Va) and activated factor VIII (not illustrated). Protein S (#4) serves as a cofactor in this process. Uninhibited factor Va and factor VIIIa actively propagate coagulation; in the presence of Ca^{++} and Xa, factor Va converts prothrombin to thrombin (#5), and in turn, thrombin converts fibrinogen to fibrin. In addition, *in vitro* studies implicate a connection of the APC system to platelets and endothelial surfaces [1,6,14].

Hyperhomocysteinemia (10-20%)

Suggestive pathophysiologic mechanisms of the effect of homocysteine include increased peroxidation injury, proliferation of smooth vessel, promotion of monocyte chemotaxis, enhanced cytotoxicity and inflammation, promotion of clotting, inhibition of

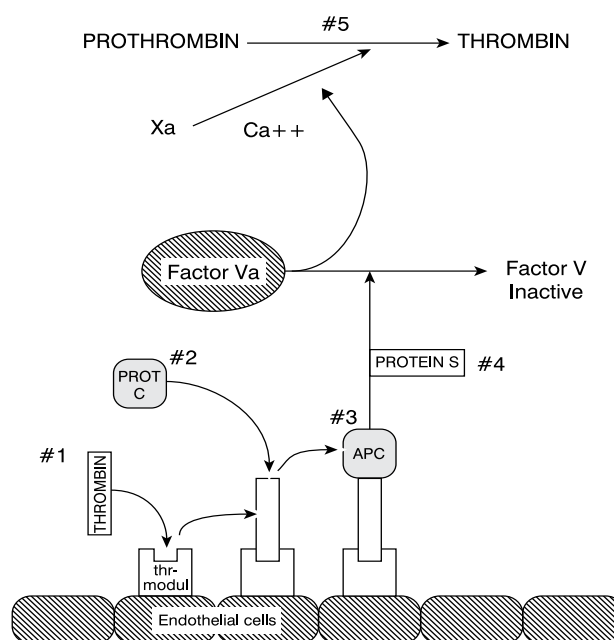


Figure 1. The pathophysiologic mechanism of the protein C pathway proteins. Detailed explanations in the text.

anticoagulation, direct effects on endothelial cells, and activation of platelet aggregation.

Levels of homocysteine are closely related to vitamins B; the conversion of homocysteine to methionine in the remethylation pathway requires folic acid and B12. The conversion of homocysteine to cystathionine and cysteine through transsulfation

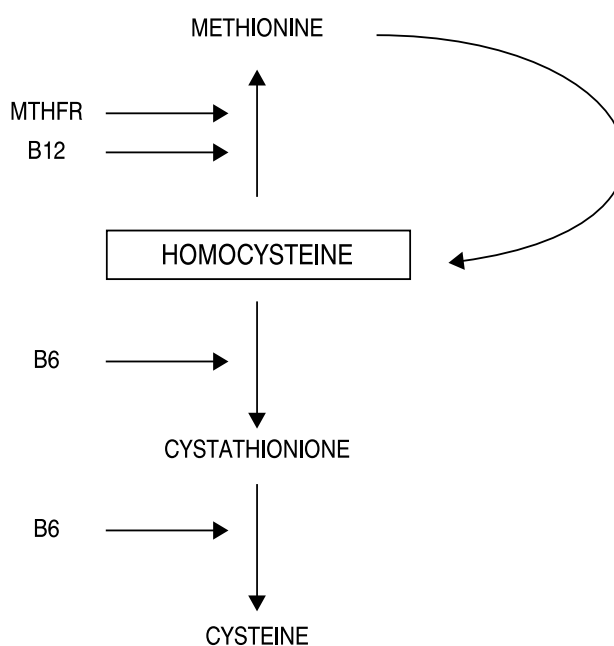


Figure 2. Metabolic cycle of homocysteine.

necessitates B6. Therefore, lowered levels of B12 or B6 can be associated with elevated homocysteine concentrations. Folic acid deficiency or methylenetetrahydrofolate reductase (MTHFR) deficiency are also causes of hyperhomocysteinemia. The recognition that homocysteine may play a role in hypercoagulability should raise consideration of nutritional replacement in patients with malignancy or pregnancy. Hyperhomocysteinemia can be obtained by quantitative blood tests; inborn errors in metabolism are assayed for MTHFR, methionine synthase, B12 mutants, or transport defects [2,3,15].

Antiphospholipid antibody syndrome (5-10%)

The “lupus anticoagulant” is an acquired biologic abnormality characterized as an “anticoagulant” *in vitro* but associated with excessive clotting *in vivo*. This abnormality, also referred to as the antiphospholipid syndrome, should be suspected in young persons with arterial disease (myocardial infarctions, cerebrovascular accidents and transient ischemic attacks), in women with recurrent pregnancy loss or in patients with increased thrombosis, especially in unusual locations (retinal veins, cerebral vessels, and hepatic venous channels=Budd-Chiari syndrome). Patients with antiphospholipid syndrome may have mild thrombocytopenia as well. This disorder is sometimes suspected when an unexplained prolongation of the partial thromboplastin time is found. The testing for antiphospholipid syndrome requires both inhibitor assays (Russell’s venom screening tests) and a search for antibodies against phospholipids and cardiolipins [1,3,4,16].

Laboratory testing undertaken at the time of acute thrombosis is often inaccurate or difficult to interpret. Multiple and interdependent mechanisms are responsible for the hypercoagulable state in patients with cancer [10,17]. These include:

- Tumor procoagulant activity: cancer cells activate intrinsic (endothelial damage) and extrinsic (cytokines – monocytes - tissue factor – VII - VIIa) pathways
 - Platelet activation
 - Host inflammatory responses
 - Direct effects of chemotherapy/hormonal therapy
 - Extrinsic factors, which are frequently iatrogenic

Furthermore, recent evidence has shown that tumor-induced coagulation activation is intrinsically involved with tumor cell growth, angiogenesis and metastasis [7,8].

Prophylaxis of VTE

The most important recent major advances in the use of anticoagulant prophylaxis and treatment for VTE are summarized below [7,8,17-21]:

- *Initial treatment with heparin is necessary.* In 1992, Brandjes et al. confirmed the value of a longstanding clinical practice by demonstrating that an initial course of heparin is required for the optimal management of VTE. In that study, patients with proximal deep VTE were randomly assigned to receive either heparin or placebo, followed by coumarin. Those assigned to receive coumarin had a significantly higher incidence of recurrence [18].

- *Reduction in duration of initial treatment with heparin from 10 days to 5 days.* The optimal duration of heparin treatment has been evaluated in 2 randomized trials; both demonstrated that a 4- to 5-day course of heparin was as effective as a 9- to 10-day course of heparin. With the shorter regimen, oral anticoagulants were started within 24 h of the heparin treatment and overlapped with heparin for 4-5 days. Reducing the treatment duration with heparin is important because it allows patients to be discharged from the hospital earlier and because it reduces the risk of heparin-induced thrombocytopenia [19].

- *Importance of continuing adequate anticoagulant treatment after hospital discharge.*

- *Introduction of LMWH.* LMWHs are fragments of UFH produced by either chemical or enzymatic depolymerization processes that yield glycosaminoglycan chains with a mean molecular mass of approximately 5000 daltons. Because of their reduced size, LMWHs have a longer elimination half-life and a more predictable dose-response when compared with UFH. As a consequence, LMWHs can be given subcutaneously once or twice daily in weight-adjusted doses without laboratory monitoring. Recent trials have shown that unmonitored subcutaneous LMWH is at least as safe and effective as intravenous UFH for the treatment of VTE [20,21].

- *Elucidation of optimal therapeutic range with coumarins.*
- *Elucidation of optimal duration of anticoagulant therapy.*

General surgery and chemotherapy

Anticoagulant prophylaxis is recommended routinely for patients undergoing major surgery because the risk of postoperative thrombosis is substantial. Many trials have been done to compare UFH and subcutaneous LMWH in this setting but few have

studied prophylaxis specifically. The ENOXACAN investigators conducted the first randomized trial that compared LMWH with UFH in patients undergoing general surgery for colorectal cancer [22]. No difference in efficacy was detected between enoxaparin 40 mg injected once a day and UFH 5000 U commenced 2 h prior to operation and continued 3 times daily in the postoperative period (5-10 days) [23].

Trials evaluating LMWH for prophylaxis of VTE in ambulatory cancer patients receiving chemotherapy out of hospital continue.

The only agent that has been evaluated for the prevention is low-dose warfarin, dosed to achieve an INR of between 1.3 and 1.9 compared to placebo [24].

The “anticoagulant” action of heparin requires the presence of antithrombin; thus, a clinical clue to diagnosis of antithrombin deficiency may be anticoagulation refractoriness to heparin.

Heparin is an important adjunct in oncology practice, where it is used to treat and prevent thrombosis, to preserve venous access for catheter devices, and to treat disseminated intravascular coagulation. In addition to these traditional uses, however, heparin may also have anti-tumorigenesis properties. The heparin molecule is a polysaccharide glycosaminoglycan molecule that can exist with very heterogeneous chain lengths, with variations in the position and the degree to which the chain is sulfated. Although glycosaminoglycans superficially resemble one another, they each have fundamentally different properties. Glycosaminoglycans are put together as a hexadecimal code, in which 6 different disaccharide couplets can be linked side-by-side to create long-chain molecules with very different properties. The physiologic roles include hemostasis, inflammation, cell growth and organogenesis, embryogenesis, angiogenesis, wound healing and neoplasia. It is therefore believed that heparin, as a glycosaminoglycan, may have direct effects on tumorigenesis. The preclinical evidence for the effect of heparin on malignancy was first published by Alfred Goerner [25].

Catheter-related thrombosis

Long-term indwelling central venous catheters are commonly used in cancer patients. Early studies indicated that the risk of thrombosis was as high as 60%, or 1 event per 1000 device days. Treatment of central venous catheter-related thrombosis remains a controversial and poorly studied area. Currently, cancer patients with symptomatic thrombosis are treated with anticoagulant therapy – low-dose warfarin or LMWH. Routine removal of the catheter when there is a thrombosis is a controversial subject. Low-dose

warfarin can produce supratherapeutic anticoagulant levels in patients receiving fluorouracil-based chemotherapy. Recent studies suggest that prophylaxis with low-dose LMWH or low-dose warfarin is not effective in reducing symptomatic events [23, 26].

Treatment of VTE

Anticoagulants are the mainstay therapy for the treatment of acute VTE. Although these agents are highly efficacious and have an acceptable safety profile in most patients, cancer patients have a higher risk of recurrent VTE and anticoagulant-related bleeding compared with those without cancer [6, 26].

Initial therapy

Which are the benefits and limitations of established anticoagulants? [27]. Warfarin exerts its anticoagulant effect by interfering with the metabolism of vitamin K, inhibiting the synthesis of several coagulation proteins (factors II, VII, IX and X; proteins C and S). The benefits of warfarin therapy in a wide spectrum of patients with thromboembolic disorders are well established. However, warfarin’s use is hampered by numerous limitations, such as its narrow therapeutic window, its need for frequent coagulation monitoring and dose adjustments, dietary restrictions, bleeding risk and its delayed on- and off-set of action. UFH and the LMWHs are indirect coagulation inhibitors, too. UFH enhances the activity of the plasma cofactor antithrombin that in turn inhibits thrombin and factor Xa. While efficacious, UFH, like warfarin, has a number of limitations which restrict its clinical use, including its parenteral route of administration, frequent laboratory monitoring and the development of potentially life-threatening heparin-induced thrombocytopenia type II. LMWHs have an enhanced affinity for antithrombin-mediated inhibition of factor Xa relative to thrombin inhibition. LMWHs have overcome several of the limitations of UFH, including a more predictable anticoagulant effect resulting in no requirement for routine coagulation monitoring, but their use is still associated with a risk of heparin-induced thrombocytopenia – though to a lesser extent than that seen with UFH, while the need for parenteral administration limits their use in the outpatient setting [6,23,26].

To date, multiple randomized trials and meta-analyses of these trials have confirmed that for initial therapy LMWHs are at least as efficacious as UFH in reducing recurrent thrombosis and are likely to be associated with a lower risk of major bleeding. How-

ever, whether LMWHs and UFH perform comparably in patients with cancer and acute VTE has not been formally investigated [27,28].

Long-term therapy

Despite their pharmacological and practical limitations, clinical trials have shown that longer-duration oral anticoagulant therapy is associated with longer rates of recurrent VTE compared with shorter-duration treatment [29]. There is evolving consensus that the duration of antithrombotic treatment should be tailored to the patient's risk or recurrent thrombosis and bleeding. Moderate intensity anticoagulation (international normalized ratio=INR of 2.0 to 3.0) is as effective in preventing recurrent VTE and produces less bleeding than an INR of 3.0 to 4.5. Results of a number of studies indicate that patients with VTE complicating surgery, or limited medical illness have a relatively low risk of recurrence and should be treated for 6 weeks to 3 months, or until the precipitating factor resolves. In contrast, those in whom VTE develops in the absence of obvious risk factors are at higher risk for recurrence once anticoagulant therapy is discontinued, and should be treated for 6 months or longer. Long-term therapy is indicated for patients with recurrent VTE and those with continuing risk factors for recurrence such as metastatic cancer and certain hypercoagulable states (protein C deficiency, protein S deficiency, antithrombin deficiency, presence of an antiphospholipid antibody, homozygous factor V Leiden mutation).

Patients with active malignant disease have an ongoing thrombotic stimulus, and recurrent VTE has a major impact on a patient's quality of life. Hence, anticoagulant therapy should be continued for as long as cancer is active. In patients with metastatic disease, this therapy should be continued indefinitely or until a contraindication to therapy develops. In patients with nonmetastatic disease, treatment should be for at least 6 months or for as long as the patient is on chemotherapy or hormonal therapy [26,28,29].

How can anticoagulation therapy be improved?

By considering the shortcomings of the current anticoagulation agents we can determine the characteristics required for the "ideal anticoagulant"[27]:

- oral and parenteral administration
- no requirement for close coagulation monitoring and individual dose adjustments
- a wide therapeutic window
- an appropriate elimination half-life

- rapid onset of action
- rapid offset of action
- minimal interactions with food or other drugs
- low, non-specific plasma protein binding
- ability to inhibit free and clot-bound coagulation factors

Conclusion

Thrombosis is a common complication in patients with malignant disease. There is a growing recognition that appropriate prevention and management can have important implications not only for cancer outcome, but for their quality of life. Subcutaneous LMWHs have replaced intravenous UFH for the initial treatment of thrombosis. Beyond their use for prevention and treating VTE exciting observations from a variety of clinical trials suggest that they may prolong survival. The potential mechanistic explanation for such a survival advantage may include either the prevention of silent, but fatal thromboembolic episodes, and inhibition of the coagulation proteases that are activated in cancer patients. Additionally, the benefits of LMWH therapy may be explained by some direct antitumor effect of heparin-like molecules including inhibition of angiogenesis and induction of apoptosis. Prospective randomized studies in cancer patients using LMWHs rather than UFH should be undertaken in light of the more predictable pharmacokinetics, relative ease of administration, and relative safety of LMWHs. For this to occur, however, a change in thinking must take place.

For nearly the last half century, cancer treatment has been dominated by the "search and destroy" paradigm involving cytotoxic chemotherapy, immunotherapy (monoclonal antibodies, vaccines), and radiation therapy. While this approach has produced undoubted benefits, the possibility remains that growth modulation may also work as a therapeutic approach. Testing this hypothesis will require targeting various tumor growth factors, angiogenesis, cell-cell interactions, the integrity of the tumor cell matrix, and various tumor cell proteases as well as oncogene expression in an attempt to alter, in a favorable direction, the outcome of malignancy.

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