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Cancer-Associated Thrombosis: Risk Factors, Molecular Mechanisms, Future Management

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Abstract

Venous thromboembolism (VTE) is a major health problem in patients with cancer. Cancer augments thrombosis and causes cancer-associated thrombosis (CAT) and vice versa thrombosis amplifies cancer progression, termed thrombosis-associated cancer (TAC). Risk factors that lead to CAT and TAC include cancer type, chemotherapy, radiotherapy, hormonal therapy, anti-angiogenesis therapy, surgery, or supportive therapy with hematopoietic growth factors. There are some other factors that have an effect on CAT and TAC such as tissue factor, neutrophil extracellular traps (NETs) released in response to cancer, cancer procoagulant, and cytokines. Oncogenes, estrogen hormone, and thyroid hormone with its integrin αvβ3 receptor promote angiogenesis. Lastly, patient-related factors can play a role in development of thrombosis in cancer. Low-molecular-weight heparin and direct oral anticoagulants (DOACs) are used in VTE prophylaxis and treatment rather than vitamin K antagonist. Now, there are new directions for potential management of VTE in patients with cancer such as euthyroid, blockade of thyroid hormone receptor on integrin αvβ3, sulfated non-anticoagulant heparin, inhibition of NETs and stratifying low and high-risk patients with significant bleeding problems with DOACs.

Keywords

angiogenesis, anticoagulants, cancer, coagulation, heparins, inflammation, integrin αvβ3, non-anticoagulant heparin, oral anticoagulant, thrombosis, thyroid hormone

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Introduction

In 1865, a French physician named Armand Trousseau described the first association between thrombosis and cancer, which was later called the Trousseau syndrome. Several clinical trials have revealed the link between venous thrombosis and cancer and demonstrated an increase in the prevalence of venous thrombosis in patients with cancer. In 1977, Sack et al. discovered that the Trousseau syndrome was chronically disseminated vascular coagulation associated with non-bacterial thrombotic endocarditis and arterial thrombosis in malignant patients.[1] A vicious cycle between cancer and thrombosis is termed cancer-associated thrombosis (CAT) where cancer amplifies the risk of thrombosis. Vice versa, where thrombosis amplifies the cancer progression, this is termed thrombosis-associated cancer (TAC) (Figure 1). Venous thromboembolism (VTE) includes the conditions of deep vein thrombosis (DVT) and pulmonary embolism.[2] The most important VTE-related risk is cancer; 20%-30% of VTE occurrences are assumed to be associated with cancer.[3] The risk of developing arterial and venous thromboembolism is significantly increased in patients with cancer.[4] Mortality is increased in cancer patients with VTE compared to cancer patients without VTE.[5] It has been reported that the annual incidence of VTE in patients with cancer is 0.5% compared to 0.1% in the non-cancer population.[6] Survival of patients with VTE was poorer in CAT.[7]

This review focuses on the interplay between cancer and thrombosis and the impact on a cancer patient's management, with special emphasis on treatment of CAT.

Risk Factors for CAT

Cancer Type and Stage

Cancer is a heterogeneous illness because it has different types and stages, which may have effects on VTE.[8] CAT is common

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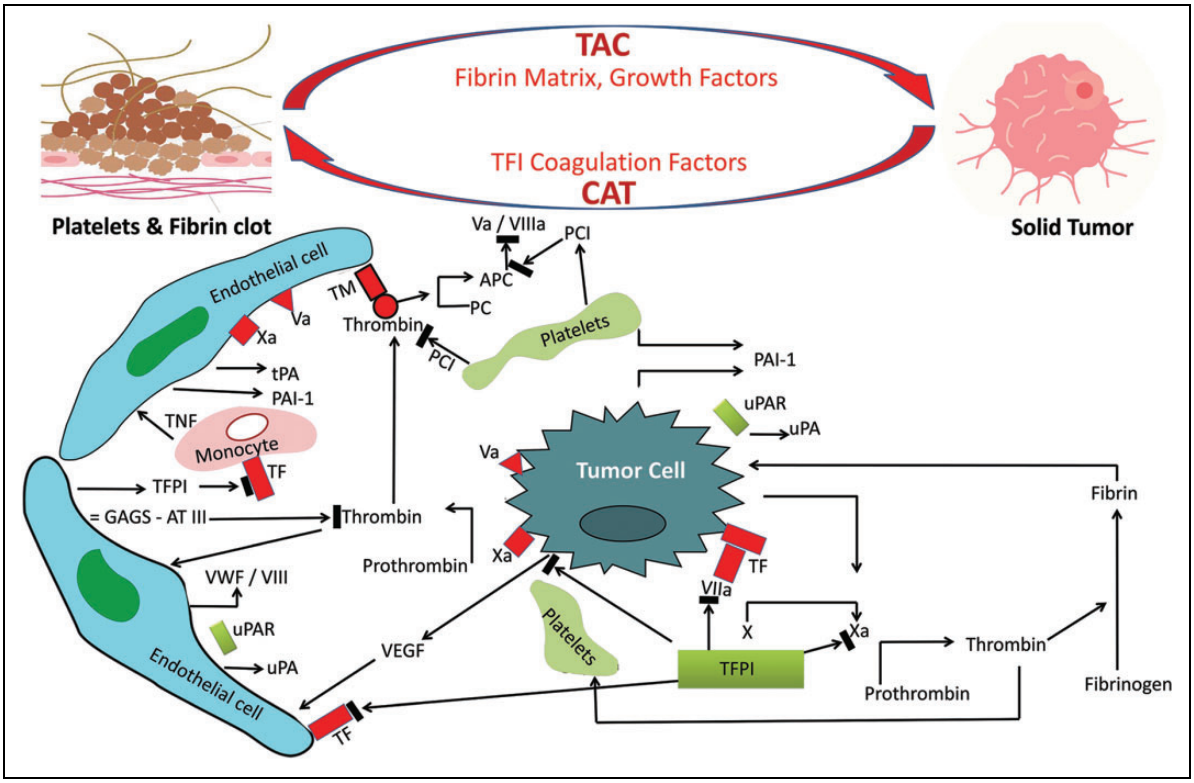

Figure 1. Representation of the reciprocal links between cancer and thrombosis. Tumor cells can express procoagulant factors, such as tissue factor (TF), that trigger the cascade of coagulation, which would be suppressed by mechanisms that induce endothelial tissue factor pathway inhibitors (TFPI). Tumor cells interact with endothelial cells, platelets, and leukocytes and these interactions induce inflammatory cytokines and pro-angiogenic factors such as vascular endothelial growth factor (VEGF). Neutrophil attraction contributes to the accumulation of neutrophil extracellular traps (NETs) and triggers adhesion, activation, and generation of thrombin. In general, the adherence of cancer to the endothelium causes the release of procoagulants and formation of thrombus, leading to CAT occurrence. TF also triggers the generation of factor VIIa, factor Xa, and thrombin (IIa), which activate platelets and induce protease-activated receptor-mediated signaling. The plasminogen activator (PA) system is expressed on platelets and it consists of plasminogen activators: urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA), cell membrane receptor for uPA (uPAR), and the plasminogen activator inhibitors plasminogen activator inhibitor I (PAI-I) and plasmin. The PA system has an effect on cell adhesion and migration, which is particularly important in cancer progression. Also, TF suppress vasculoprotective molecules, such as thrombomodulin (TM). Release of von willebrand factor (VWF) promotes recruitment, adhesion, and activation of platelets and leukocytes with formation of NETs. abbreviations: APC, activated protein C; GAGS, glycosaminoglycans heparin sulfate; PC, protein C; PCI, protein C inhibitor; TNF, tumor necrosis factor-alpha.

in many types of cancer such as pancreatic, brain, lung, and ovarian cancers.[9-11] Patients with prostate cancer usually have a relatively low risk,[12] and patients with breast cancer are reported to develop VTE 3 to 4 times more often than patients of equivalent age without breast cancer.[9] The aggressiveness of cancer, early metastatic development, and short survival were particularly associated with a high incidence of VTE.[13]

The risk of VTE occurrence is higher in advanced metastatic cancer than in localized cancer.[14] Previous studies confirmed that tumor grade and stage were significantly associated with risk of venous thrombosis.[9] Moreover, the risk of VTE was high in the first 3 months after the cancer diagnosis and then decreased gradually during the 10 years after the cancer diagnosis.[11] This may be because multiple cancer therapies (e.g., chemotherapy, radiotherapy) boost VTE risk. Also, a percentage of patients with cancer enter a remission phase, which reduces the danger of VTE. Another reason is that a large proportion of cancer patients will succumb to the disease over time. This contesting event (death) prevents the observation of thrombotic events.[8]

Cancer Treatment

Tumor pressure on blood vessels results in stasis and VTE. Some medications that are used in treatment of cancer are related to high risk of thrombosis. Examples of these medications are hormonal therapy such as tamoxifen, chemotherapy (e.g., paclitaxel, doxorubicin, thalidomide), molecular targeted therapy such as osimertinib, anti-angiogenesis therapy (e.g., bevacizumab, ramucirumab), immunotherapies and radiation therapies.[15]

Chemotherapy. Using combination therapy of chemotherapeutic drugs increases the risk of arterial thrombosis occurrence in patients with breast cancer, but the mechanism is not clear.[16] Also, chemotherapy increases the risk of VTE[17] and produces a

prothrombotic condition through a number of distinct mechanisms[18] that can harm the endothelium directly,[19] decrease endogenous anticoagulant substances, and/or boost the procoagulant protein.[20] Chemotherapy also can cause apoptosis and cytokine release, which can in turn lead to enhanced endothelial and monocyte tissue factor (TF) expression that is considered as the physiologic initiator of coagulation.[21] Chemotherapy can ultimately lead to platelet activation.[22]

Both cytotoxic and targeted chemotherapy are associated with VTE. For example, cisplatin induces endothelial cell apoptosis and results in the release of procoagulant endothelial microparticles.[23] L-asparaginase causes depletion of key proteins in the regulation of the coagulation pathway[24]—therefore VTE is a complication in patients with acute lymphoblastic leukemia receiving asparaginase inhibitor chemotherapy and these symptomatic VTEs can be reduced by low-molecular-weight heparin (LMWHs).[25] 5-Fluorouracil causes depletion of protein C, increases thrombin activity,[26] and damages endothelial cells to promote thrombus formation.[26] Another example is tamoxifen, an anti-estrogen drug. Its estrogenic activity might elevate the risk of VTE through depletion of protein C and protein S.[27,28]

Not only is chemotherapy associated with increased VTE risk but also cancer type is associated with further increase in VTE risk.[29] Patients with advanced pancreatic ductal adenocarcinoma have high risk of VTE, and chemotherapy can further increase that risk. Moreover, thromboprophylaxis with LMWH for 3 months decreased that risk, however, further anticoagulation expansion may be helpful to limit a future thromboembolic risk.[30] Because there are growing risks of CAT due to additional new antineoplastic drugs, immunotherapies, or chemotherapy combinations, a prospective registry named TESCO and promoted by the Spanish Society of Medical Oncology data highlight the evolution of CAT, with new agents and thrombotic risk factors.[31]

Radiotherapy. Radiotherapy can be used when VTE risk is high in early phases of cancer,[11] or as part of localized treatment, with or without chemotherapy for localized tumors.[32] As a result, there is increasing evidence that radiotherapy could affect the result of VTE anticoagulant therapy in cancer patients.[33] Ionizing radiation influences protein C pathway and its thrombomodulin interaction.[34] After radiation, procoagulant factors with activated factor VIII, pro-inflammatory nuclear factor kappa B, increased D-dimers and pro-thrombin fragments prompt pro-coagulant response.[35] Radiation also induces primary hemostasis through TF and von Willebrand activation[36] leading to endothelial dysfunction and thrombosis. Also, an in vitro study has shown that tumor irradiation activates cancer cell integrin $\alpha v\beta 3$,[37] which has a pivotal role in CAT, and that role will be discussed later in this review.

Hormonal therapy. Use of hormone therapy is a clear risk factor for the development of cancer[38] and it elevates VTE risk,[39] which can enhance the link between CAT and TAC.

Surgery. Major surgery is a well-known risk factor for VTE, and patients who develop VTE in the post-operative period have a higher mortality rate.[40] Additionally, the length of surgery has been associated with an increased risk of VTE.[41] A prothrombotic state may occur due to several processes including enhanced levels of fibrinogen, thrombin generation, activation of TF, decreased fibrinolysis and hemostasis.[42] Furthermore, patient immobility after an operation can lead to venous stasis and cancer procoagulants' overexpression that causes immediate damage to the vascular endothelium.[19] Other factors that may increase the risks from surgery on VTE formation are pelvic dissection, the patient's position during surgery, cancer, advanced age, heart or respiratory failure.[43]

Supportive therapy with hematopoietic growth factors. Previous studies showed that patients treated with erythropoiesis-stimulant agents in addition to red blood cell transfusions have a higher risk of VTE than do patients without additional erythropoiesis-stimulant agents.[44,45] Erythropoietin is found to be an activator to platelets and enhances factor VIII and thrombin generation and decreases protein C and protein S.[46] Erythropoietin also promotes signaling pathways in endothelial cells and enhances their thrombogenicity.[47]

Hormonal Risk Factors

Thyroid hormones. Thyroid hormones are key regulators of essential cellular processes including proliferation, differentiation, apoptosis, and metabolism.[48] A prospective study reported that subclinical hyperthyroidism was associated with enhanced risk of cancer, particularly in lung, prostate, ovarian, pancreatic, and renal carcinoma.[49]

Thyroid hormone has an effect on cancer cell proliferation and angiogenesis.[50,51] The intracellular metabolically active hormone in normal cells is 3,5,3′-triiodo-L-thyronine (T3) from prohormone L-thyroxine (T4). The thyroid hormone action is done by genomic and non-genomic actions. Genomic action is initiated when T3 binds to thyroid receptors that interact with specific responding elements. Non-genomic actions modulate gene transcription by activating pathways and other transcription factors.[52,53] The availability of T4 is the pivotal step for activation of the integrin and consequent transmembrane signaling into the cell. T3 and T4 bind to the plasma membrane protein integrin $\alpha v\beta 3$, which mediates the signal across the membrane. At physiological concentrations, T4 is the primary ligand at $\alpha v\beta 3$.[54]

Thyroid hormone also has a pro-angiogenic effect initiated by several thyroid hormone analogs affecting coagulation by acting on platelet integrin $\alpha v\beta 3$.[55] Thyroid hormone stimulates the aggregation of platelet and the release of platelets' adenosine triphosphate (ATP).[56] All of the above may explain the association between thyroid hormone, platelets, and CAT.[57] Concepts highlighted for future directions with regard to the role of thyroid hormone and integrin $\alpha v\beta$ in CAT warrant clinical investigations.

Estrogen hormone. Estrogen has been associated with an increased risk of thromboembolic events in patients using combined hormone replacement or estrogens.[38,58] Venous thromboembolism risk increases in patients with cancers such as breast cancer[59] and endometrial cancer, which are positively correlated with serum estrogen levels.[60] Estrogens have pleiotropic effects due to a large tissue distribution of their receptors[61] in many tissues such as platelets with different effects.[62] A high level of estrogen enhances the secretion of angiogenic cytokines such as VEGF that influence the expression of integrin αvβ3, which in turn contributes to angiogenesis. By influencing angiogenesis, these angiogenic factors affect the growth of cancer such as breast and ovarian.[63,64]

Molecular Risk Factors

Oncogenes. CAT may be activated directly or indirectly through an oncogenic process.[65] The indirect effect of oncogenes may happen through vascular invasion, metastasis, bleeding, vascular permeability, angiogenesis,[65] recruitment of inflammatory cells[66] and extracellular vesicles (EVs)[67] that may reprogram coagulant phenotypes of endothelial cells[68] or leukocytes.[67] The direct effect of oncogenes on CAT includes the negative effect of an epidermal growth factor receptor (EGFR) antagonist on the expression of TF in cancer cells.[65]

Examples for these oncogenes are K-RAS oncogene and p53 tumor suppressor gene.[69] A previous study reported a link between integrin αvβ3 and p53 activity in that blockade of αvβ3 suppresses the expression and/or activity of p53.[70] K-RAS alters the levels of crucial angiogenic mediators such as VEGF or thrombospondin[71] and affects multiple facets of the cancer,[72] recruitment of inflammatory cells,[66] immune responses,[73] and CAT.[74] Other oncogenes may regulate TF, such as MET proto-oncogene EGFR, and erb-b2 receptor tyrosine kinase 2 (ERBB2).[75]

Mechanisms Involved in CAT

Platelets. Cancer cells can activate platelets by direct and indirect mechanisms that lead to CAT.[76,77] Tumor-cell induced platelet aggregation (TCIPA) was also linked to greater metastatic potential.[76] A significant TCIPA mechanism is secretion of thrombin by cancer cell procoagulants that turn fibrinogen into fibrin. Another mechanism is the activation of coagulation factors V, VIII, XI, XIII, and protease-activated receptors (PAR receptors) that are highly expressed on platelets.[78] Tumor cells also express adenosine diphosphate (ADP) that activates platelets to release more ADP and thus activates more platelets.[79] Platelets also express TF on their membrane, contributing to CAT.[80] Platelets have many growth factors[81] that are also present in the tumor microenvironment[82] and cause development of the tumor and support angiogenesis.[83]

Coagulation. Together with cells and platelets, TF is important for normal hemostasis. Coagulation occurs in 3 overlapping phases: initiation, amplification, and propagation.[84] In the initiation phase, TF binds to factor VIIa to activate factor IX and factor X. Activation of factor IX works as the link between the extrinsic and intrinsic pathways. Factor Xa then binds to factor II to form thrombin. The amplification phase starts because the amount of thrombin generated is not enough to form a widespread clot, therefore positive feedback loops are present to bind thrombin with platelets. In the propagation phase, enzyme complexes (tenase complex and prothrombinase complex) on the platelet surface support high amounts of thrombin generation and platelet activation.[85] This occurs to ensure continuous generation of thrombin and subsequently fibrin generation and polymerization to form a stable clot.[86]

Tissue factor. The main cause of coagulation in patients with cancer is TF expression on the surface of cancer cells[87] as shown in Figure 2. The coagulation extrinsic pathway is initiated by TF because it binds to factor VII and promotes proteolysis and activation to factor VIIa.[88] The binary TF/factor VIIa complex activates factor IX and factor X, leading to the development of thrombin, culminating in the production of fibrin.[89] The existence of TF in the blood as a component of EVs from vascular cells, and subsequently from tumor cells, increases the prothrombotic status of patients with cancer.[90] Other cancer-related phenomena, such as the epithelial-mesenchymal transition, may also trigger the release of EVs containing TF.[68]

Microvesicles. A heterogeneous population of small membrane-enclosed structures, EVs are released into the extracellular space. They have been divided into 3 main categories according to their biogenesis; exosomes, microvesicles (MVs) and apoptotic bodies.[91] The diversity of MVs' origin is responsible for a variety of structures and composition in lipids, proteins and nucleic acids and thus MVs are involved in different pathophysiological processes such as coagulation, inflammation, angiogenesis or endothelial dysfunction.[92] MVs have to be integrated in their complex vascular environment with all partners (innate immune cells such as polymorphonuclear cells, monocytes, endothelial cells, platelets, and tumor cells) contributing to thrombus formation.[93]

Endothelial. Although TF is widely expressed on subendothelial cells such as fibroblasts, pericytes, and vascular smooth muscle cells, it is not expressed in normal endothelium; malignant tissue involving endothelial and tumor cells express TF constitutively.[94] Platelets and endothelia cells have p-selectin on their surfaces.[95] P-selectin could increase VTE through leukocyte recruitment.[96]

Neutrophil extracellular traps. Cancer cells may release NETs[97] and they have been shown to endorse venous and arterial thrombosis.[98] NETs can activate endothelial cells and eventually increase the release of von Willebrand factor (a significant glycoprotein for platelet adherence and thrombosis aggregation)[98] and serve as a platform to adhere and aggregate platelets,[99] which is vital for thrombus formation.[100] Cancers create a systemic environment that prevents NETs from releasing

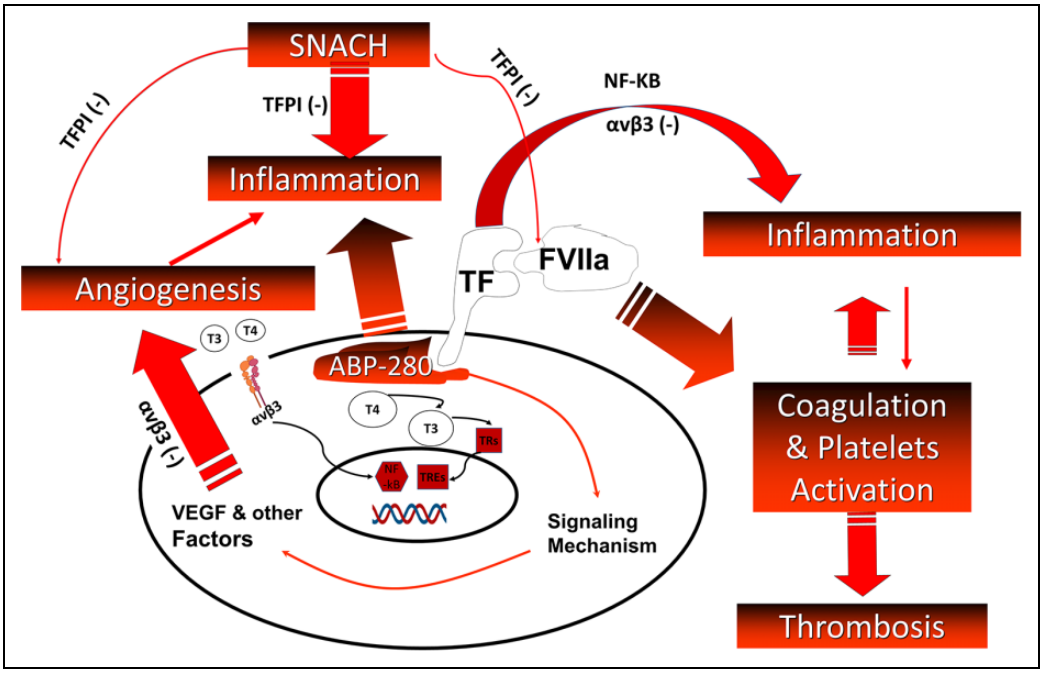

Figure 2. Relationship between integrin αvβ3, thyroid hormones, TF/FVIIa, angiogenesis, inflammation, and thrombus formation. When TF is released, it activates factor VII (VIIa) forming a complex that activates thrombus formation. TF is expressed on vascular endothelial cells, circulating monocyte and platelet where its activation upregulates VEGF that promotes angiogenesis. Non-genomic actions of thyroid hormones are initiated on integrin αvβ3. Thyroid hormones activate the NF-kB pathway, thus promoting the production of VEGF, cell proliferation and angiogenesis. Thrombus formation and angiogenesis stimulation affect inflammation pathway and vice versa. Either sulfated non-anticoagulant LMWH (SNACH) or integrin αvβ3 receptor blockade suppresses inflammation, angiogenesis, and indirectly the thrombosis processes. abbreviations: ABP-280, actin-binding protein 280; NF-KB, nuclear factor kappa B; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TREs, thyroid hormone response elements; TRs, thyroid hormone receptors. (Modified with permission from Mousa SA. Heparin and low-molecular weight heparins in thrombosis and beyond. Methods Mol Biol 2010;663:109-132.).

neutrophils that modulate different facets of the tumor biology, including metastasis.[101]

Cancer procoagulant. Cancer procoagulant (CP) is unlike TF in that it directly activates factor X independent of coagulation factor VII. It has been detected in different malignant cells such as leukemia and breast cancer and is present in solid and hematologic tumors but not in normal tissues.[102]

Monocytes. Monocytes and macrophages express TF in an inactive form and then specific inflammatory agonist pathways convert it to totally procoagulant TF. Activation of TF on monocytes or macrophages requires an exchange of thiol-disulfide and involves protein disulfide isomerase (PDI). While the PDI can be released during vessel wall injury,[103] in vitro research showed that PDI is present on the surface of intact cells[104] in complex with TF[105] and PDI-regulated TF activity on EVs.[106]

Cytokines. Tumor cells release cytokines into the bloodstream. Leukocytes and vascular cells are both cytokine sources and targets for them. Hemostatic balance depends on the complex interactions between endothelial cells, blood cells, the coagulation-fibrinolytic system, and cytokines.[107] Pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) induce TF in monocytes.[108,109] Such cytokines not only trigger procoagulant activity but also impede the anticoagulation pathway of thrombomodulin/protein C and affect fibrinolysis by upregulating urokinase type plasminogen activator and type I inhibitor of such activation.[107] Indeed, cytokine production is significantly increased in cancer patients by activating host cells, like monocytes and endothelial cells as well as by cytokine release itself through tumor cells.[110] Cytokines like IFN-α, IFN-γ and TNF can boost the activity of tumor cell procoagulants and consequently activate clotting in patients with cancer.[111]

Current Management of CAT

Low-molecular-weight heparin. LMWH inhibits coagulation by activating antithrombin III, which binds to and inhibits factor Xa and IIa.[112] In the absence of contra-indications, LMWH is preferred over vitamin K antagonists (VKA) for the treatment of VTE in patients with cancer based on 4 previous studies that showed the high efficacy and superiority of LMWHs compared to VKAs.[113-116] First, the Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) study compared dalteparin (LMWH) to warfarin and showed a 55% reduction in relative

Table 1. Comparison Between Low-Molecular-Weight Heparin (LMWH) Versus Other Anticoagulants for Treatment of VTE in Patients With Cancer.

Study	Months	No. of enrolled patients	Treatment arms	Outcome
CLOT[114]	6	672	Dalteparin versus warfarin	Dalteparin superior to warfarin in VTE recurrence ($P = 0.002$). No difference in major bleeding or mortality.
CATCH[116]	6	900	Tinzaparin versus warfarin	Statistical tendency of VTE recurrence reduction with tinzaparin. No difference in major bleeding or mortality.
CANTHANOX[113]	3	138	Enoxaparin versus warfarin	Warfarin associated with high bleeding rate in patients with VTE and cancer. Prolonged treatment with LMWHs may be as effective as oral anticoagulants and may be safer in these patients.
Hull et al.[115]	12	200	Tinzaparin versus warfarin	Long-term LMWHs more effective than vitamin K antagonist therapy for preventing recurrent VTE in patients with cancer and proximal venous thrombosis. Usual-care group had excess of recurrent VTE.
Hokusai Cancer VTE[118]	12	1046	Edoxaban versus dalteparin	Edoxaban was non-inferior to dalteparin. Statistical tendency of superiority of edoxaban in VTE recurrence reduction, more major bleeding with edoxaban.
SELECT-D[119]	6	406	Rivaroxaban versus dalteparin	Less VTE recurrence (HR 0.43, 95% CI 0.19–0.99) and statistical tendency of more bleeding (HR 1.83, 95% CI 0.68–4.96) with rivaroxaban.
ADAM-VTE[120]	6	300	Apixaban versus dalteparin	Primary efficacy outcome, recurrent symptomatic VTE or death related to VTE, occurred in 2.3% in apixaban group and 2.7% in conventional therapy group. From an efficacy standpoint, apixaban considered non-inferior to standard anticoagulant therapy. Major bleeding significantly lower for patients receiving apixaban.
Caravaggio Investigators[122]	6	1170	Apixaban versus dalteparin	Recurrent VTE occurred in 5.6% in apixaban group and 7.9% in the dalteparin group ($P < 0.001$) for non-inferiority). Major bleeding occurred in 3.8% in apixaban group and 4.0% in dalteparin group.

risk of recurrent VTE without increasing major bleeding.[114] Another study is the Comparison of Acute Treatments in Cancer Haemostasis (CATCH) trial that compared LMWH (tinzaparin) to warfarin and showed a trend toward reduction in VTE recurrence, but the difference was not statistically significant. Tinzaparin showed a safer profile in clinically relevant non-major bleeding than warfarin.[116] The other 2 studies confirmed that warfarin is associated with a high bleeding rate in patients with CAT.[113,115] Therefore, in CAT, LMWH is preferred in VTE prophylaxis and treatment.

Direct oral anticoagulants (DOACs). Four DOACs, including dabigatran (direct thrombin inhibitor), rivaroxaban, apixaban, and edoxaban (direct factor Xa inhibitor), have been approved by the FDA for VTE therapy. They have benefits over VKAs including safety such as a lower incidence of major bleeding, more convenient to use, fewer drug and food interactions, a wide therapeutic index, and there is no periodic laboratory tracking required. Furthermore, unlike LMWHs, DOACs are taken orally and don't require long-term subcutaneous injections.[117]

Previous randomized clinical trials compared DOACs and LMWHs in the treatment of CAT, such as the Hokusai VTE Cancer,[118] SELECT-D,[119] and ADAM VTE[120] trials. They reported that DOACs are not inferior to LMWHs for preventing VTE recurrence in patients with cancer. The Hokusai VTE trial and SELECT-D trial revealed that DOACs were non-inferior to subcutaneous LMWH, and the rate of recurrent VTE was lower, but the rate of major bleeding was higher with edoxaban (DOAC) than with dalteparin (LMWH).[118,119] The SELECT-D study reported significant bleeding events as a side effect to DOACs.[119] In patients treated with rivaroxaban (DOACs), more clinically relevant non-major bleeding did happen. Most bleeds were gastrointestinal, and the distinction in bleeding risk was most apparent for gastrointestinal cancer patients.[118] Recently, a meta-analysis study reported that the risk of VTE recurrence in patients with cancer receiving DOACs as compared to LMWHs is reduced but with an increased number of episodes of major bleeding.[121] Recently the results of the Caravaggio Investigators' study showed that there was no difference between treatment with DOACs and LMWHs in the number of CAT relapses over a 6-month period. Moreover, it showed that in patients less than 65 years of age, apixaban prevented the recurrence of VTE more than dalteparin and the effect of apixaban was decreased in elderly patients. There were also no differences in the risk of major gastrointestinal bleeding and total mortality although the number of clinically relevant non-major bleeding episodes was higher after apixaban use.[122] Table 1 summarizes data with LMWH versus warfarin and DOAC in CAT.

Future Directions in the Management of CAT

Euthyroid. Several studies have reported an increased thrombophilic risk profile in patients with overt hyperthyroidism and sub-clinical hyperthyroidism,; this transforms the hemostatic balance through hypercoagulable and hypofibrinolytic state with elevated levels of factor VIII, factor IX, von Willebrand

factor antigen (VWF: Ag), fibrinogen, and plasminogen activator inhibitor.[123] The evidence suggests that hypothyroidism may have a biphasic effect on fibrinolysis, depending on disease severity.[124] A previous study found that T3 may directly or indirectly control transcription of hepatic and vessel walls' coagulation; this transcriptional modification resulted in a change in the plasma coagulation factors,[125] Moreover, spontaneous or medically induced hypothyroidism may alter the clinical behavior of cancers such as breast cancer,[126] glioblastoma[127] and renal cell carcinoma.[128] T3 reduces serum thyrotropin levels (TSH) and T4 level and also improves clinical and radiological conditions in cancer patients.[129] In fact, T3 cannot induce tumor cell proliferation at physiological concentrations.[130] When the T3 level increases, it can stimulate cancer cell proliferation at the receptor on integrin αvβ3.[131] Nevertheless, in patients with euthyroidism and cancer, euthyroidism alone with a normal T3 level does not seem to promote the growth of the tumor.[130] T4 has a significant action on tumor cells and coagulation when compared to T3. This may represent a novel, inexpensive and nontoxic approach for improving CAT and TAC. The paradigm should be tested in prospective controlled trials in a wider variety of patients with cancer. Thus future studies are needed to investigate the effect of euthyroid in CAT and TAC.

Blockade of thyroid hormone receptors on integrin αvβ3. The plasma membrane integrin αvβ3 acts as a membrane receptor for thyroid hormone. Integrin αvβ3 binding facilitates the hormone's proliferative action on cancer cells and blood vessel cells.[131] The primary thyroid hormone ligand of this receptor is T4, which activates β-catenin and induces metastasis.[132] The activation and deactivation of thyroid hormones may also stimulate angiogenesis associated with primary or metastatic tumors. As stated above, various mechanisms stimulate angiogenesis among the non-genomic actions of T4 and T3 at αvβ3, of tumor cell proliferation, and of anti-apoptotic tumor defenses.[133], These problems may be avoided by using an analog of T4, tetraiodothyroacetic acid (tetrac), which prevents binding of iodothyronines to integrin αvβ3.[134] In order to limit tetrac to the cell surface of thyroid hormone receptor, diamino propane tetraiodothyroacetic acid (DAT) is preferred. Tetrac and DAT as thyroid hormone derivatives influence gene expression after crossing cellular membranes. We conjugated tetrac to the polymeric nanoparticle poly (lactic-co-glycolic acid) (PLGA) resulting in nano-diamino-tetrac (NDAT).[135] Many studies have shown that the formulation of NDAT is restricted to the extracellular area and to the integrin, thus slowing tumor development and vascularity.[136] NDAT's antitumor efficacy includes pro-apoptotic activity and gene transcription disturbance that are crucial to a number of mechanisms for cancer cell survival.[137] Tetrac blocks the pro-angiogenic activity of VEGF and of basic fibroblast growth factor (bFGF; FGF2) in the chick chorioallantoic membrane and in an endothelial cell microtubule formation assay[138] and PDGF.[51] Moreover, tetrac prevents radioresistance of cancer cells resulting from the activation of integrin αvβ3.[139] Another drug that can block thyroid hormone on integrin αvβ3 is compound XT199, which is an integrin antagonist that can block aggregatory effects on platelets. It acts at the cell surface via interaction with integrin αvβ3 and thyroid hormone receptors.[140]

SNACH (Sulfated non-anticoagulant heparin). It was shown that the effect of SNACH in inhibiting cancer metastasis is not related to the heparin anticoagulant property.[136] SNACH is a LMWH that has no effect on the systemic coagulation factors yet releases TF pathway inhibitor protein (TFPI), a key endogenous inhibitor of the TF/VIIa complex from the endothelium[141] (Figure 2). Release of TFPI may be responsible for the anti-angiogenic and antimetastatic activity. Like most of the non-antithrombin-mediated effects, TFPI release from the vascular endothelium is associated with N-sulfated regions of heparin and non-anticoagulant heparins.[141] The additional finding that SNACH exhibits anti-angiogenesis activity suggests another mechanism that could contribute to its role in tumor suppression.[141] As shown in Figure 2, it can be concluded that SNACH releases TFPI that affects inflammation and angiogenesis, and it has an inhibitory effect on TF/VIIa complex that affects activation of coagulation and platelets and consequently affects CAT.

Inhibition of NETs. In cancer, NETs circulate at high levels in blood,[142] activate the occlusion of small vessels,[143] activate the contact pathway of coagulation,[144] and help in digesting the major coagulation inhibitors such as antithrombin III and TFPI.[145] Dissolving NETs with DNase I restores normal perfusion of microvasculature in animal models.[143] Also, DNase I proved its significance in inhibiting tumorigenicity of some cancer cell lines.[146] There are many drugs that can be used as NET inhibitors by reducing NETs' formation such as peptidyl arginine deiminase type 4 inhibitors,[147] cyclooxygenase-2[148] and vitamin C.[149] Based on the above findings, targeting intravascular NETs may similarly reduce thrombosis in patients with cancer.

Risk stratification strategies. Prevention and treatment of CAT can be achieved by a variety of risk stratification strategies. Risk factors are either patient-related factors, cancer-related factors, or treatment-related factors.[150] The use of single clinical risk factors as a risk stratification failed. Therefore, the new American Society of Clinical Oncology (ASCO) guidelines recommend the use of a risk score that includes multiple variables to identify high-risk patients[151,152] such as elevated platelet and leukocyte counts, decreased hemoglobin, elevated D-dimer, elevated prothrombin activation products, elevated soluble P-selectin, peak thrombin generation, and elevated levels of TF-bearing microparticles.[153] Potential applications of risk factors stratification include educating patients about the warning signs and symptoms of VTE, which could lead to early detection and treatment[154] and targeted prophylaxis that supports the "precision medicine" approach that is the hallmark of anticancer therapy.[155]

The Link between CAT and TAC

The strong link between cancer and thrombosis is illustrated in Figure 1 along with CAT and TAC. Tumor cells may activate the coagulation system and lead to thrombosis through the production of procoagulant, fibrinolytic, and pro-inflammatory and pro-angiogenic cytokines, leading to the pro-thrombotic state and tumor metastasis in patients with cancer.[156]

On the other hand, coagulation factors also affect the progression of cancer leading to TAC. Previous studies suggested that hemostatic abnormalities in patients with cancer can contribute to inflammatory cell recruitment, tumor stroma production, and angiogenesis.[157] We know that TF is expressed on cancer cells and vasculature[158] as well as on endothelial cells and platelets, and TF-bearing EVs contribute to the thrombotic phenotype in cancer patients.[159] The TF/factor VIIa complex has an effect on processes of blood coagulation and has an effect on inflammation and angiogenesis.[160] Higher TFPI-1 levels may be due to the TF uptake in tumor cells or to damaged endothelial cells in ongoing coagulation activation in patients with cancer and DVT or metastases.[161] TF also regulates αvβ3 integrin, which as stated earlier, is expressed on platelets, cancer cells, and endothelium. Integrin αvβ3 activation facilitates tumor angiogenesis and tumor progression.[162] In summary, TF isoforms, factor VII, PAR2, and αvβ3 integrin affect cell process and cell interaction with their environment, including angiogenic events.[163]

Conclusion

There is a two-way clinical relationship between cancer and VTE. Thrombotic events, especially idiopathic thrombosis, can sometimes be a cause of cancer. At the same time, VTE is a serious complication of cancer and the second most frequent cause of death in patients with cancer. Moreover, the prevention and treatment of VTE in cancer patients is challenging because the risk-benefit profile when using anticoagulants must be considered. Further data are needed to confirm future directions in the management of CAT or TAC by either euthyroid, blockade of thyroid hormone on integrin αvβ3 by NDAT or other agents, by sulfated non-anticoagulant heparin (SNACH), inhibition of NETs, stratifying low and high risk patients with significant bleeding problems with DOACs, or other appropriate therapies.

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