Cancer-Associated Thrombosis: Epidemiology, Pathophysiological Mechanisms, Treatment, and Risk Assessment

Clinical Medicine Insights: Oncology
Volume 17: 1–14
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DOI: 10.1177/11795549231220297

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ABSTRACT: Cancer patients represent a growing population with drastically difficult care and a lowered quality of life, especially due to the heightened risk of vast complications. Thus, it is well established so far that one of the most prominent complications in individuals with cancer is venous thromboembolism. Since there are various improved methods for screening and diagnosing cancer and its complications, the incidence of cancer-associated thrombosis has been on the rise in recent years. Therefore, the high mortality and morbidity rates among these patients are not a surprise. Consequently, there is an excruciating need for understanding the mechanisms behind this complex process, as well as the imperative for adequate analysis and application of the most suitable steps for cancer-associated thrombosis prevention. There are various and numerous mechanisms offering potential answers to cancer-associated thrombosis, some of which have already been elucidated in various preclinical and clinical scenarios, yet further and more elaborate studies are crucial to understanding and preventing this complex and harsh clinical entity. This article elaborates on the growing incidence, mortality, morbidity, and risk factors of cancer-associated thrombosis while emphasizing the pathophysiological mechanisms in the light of various types of cancer in patients and summarizes the most novel therapy and prevention guidelines recommendations.

KEYWORDS: Cancer-associated thrombosis, incidence, mortality, morbidity, risk factors, pathophysiological mechanisms

RECEIVED: July 13, 2023. **ACCEPTED:** November 28, 2023.

TYPE: Review

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Ministry of Education, Science, and Technological Development of the Republic of Serbia (agreement no. 451-03-47/2023-01/200111).

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Venous thromboembolism (VTE) is a medical condition that includes a state of excessive blood clotting, whereby various factors contribute to the development of a clot or thrombus within the blood vessels. This condition can manifest in different forms, including deep vein thrombosis (DVT), pulmonary embolism (PE), superficial vein thrombosis, and splanchnic vein thrombosis, which is a less common site of VTE.[1] Jean-Baptiste Bouillaud is credited with having made initial assessment regarding the link between cancer and VTE.[2] Armand Trousseau expounded on this correlation in greater depth in his section titled "Phlegmasia alba dolens" within the published compilations of his lectures.[3] In the last 2 decades, substantial progress has been made in comprehending the process of therapy and prevention of thrombosis associated with cancer.[4] Cancer-associated thrombosis (CAT) refers to VTE (comprised of DVT and PE), arterial thrombosis, and disseminated intravascular coagulation that manifests in individuals diagnosed with cancer. This category of VTE primarily encompasses DVT affecting the upper or lower extremities, as well as PE.[5] Considering the high incidence, morbidity, and mortality rate of VTE in cancer patients, there is a substantial need for understanding the pathophysiological mechanisms behind this clinical entity. In that manner, this article discusses the incidence and risk factors, elaborates on the pathophysiological mechanisms of CAT in a variety of cancer categories, and describes the current state of therapy and CAT prevention guidelines.

The Incidence, Morbidity and Mortality of Cancer-Associated Thrombosis

The occurrence of CAT varies according to the characteristics of the patient population, the length of the period of monitoring, and the technique used to identify and record thrombotic events. The presence of active cancer is associated with a 4- to 7-fold increase in the risk of developing CAT. Furthermore, cancer patients comprise between 20% and 30% of new cases of VTE in the overall population.[6] In total, 18% of patients in the Registro Informatizado de Enfermedad Trombo Embolica registry, a large prospective cohort of VTE patients, had active cancer.[7] The incidence of VTE within the initial 6 months of cancer treatment is significantly elevated, ranging from 12 to 23 times greater compared with the general population. This risk is particularly heightened in patients undergoing chemotherapy or targeted therapy.[8] Furthermore, from 1997 to 2017, the overall prevalence of CAT has increased from 1.0% to

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3.4%. This increase can be plausibly attributed to the improved prognosis among cancer patients and the heightened utilization of computed tomography scans, which has resulted in higher rates of incident PE diagnoses.[8] Also, VTE in cancer patients is associated with greater morbidity, which can lead to a decline in quality of life, treatment interruptions, and elevated mortality rates.[9-11] Thus, VTE represents the second most frequent cause of mortality in cancer patients, surpassed solely by the cancer itself.[12] A prospective cohort of 9754 participants in the Framingham Heart Study showed that CAT had a worse prognosis among VTE patients.[13] Similarly, findings from the Global Anticoagulant Registry in the Field (GARFIELD)-VTE registry indicated that among a group of 10 315 VTE patients from 419 centers and 28 countries, the total mortality rate was 9.7% within a 6-month period, with 54.3% of all fatalities being attributed to cancer.[14] In addition, the financial impact of VTE in individuals with cancer is significant, given that VTE is associated with elevated health care costs.[15,16] Furthermore, a quarter of individuals diagnosed with both cancer and VTE experience hospital readmission due to either bleeding or a relapse of VTE.[17]

Cancer-Associated Thrombosis Risk Factors

Multiple risk factors, including patient-associated risk factors, cancer-associated risk factors, therapy-associated risk factors, and the presence of certain biomarkers, have been identified as contributing to the pathogenesis of CAT.[18,19] Patient-associated factors include older age,[20] ethnicity (eg, Hispanic and Asian cancer patients have a lower incidence of VTE complications during the first year compared with white and black patients),[21] history or family history of VTE,[22–25] functional status, smoking, parenteral nutrition requirements, concurrent conditions (eg, renal failure, respiratory disease, acute infection, and obesity),[26] and prolonged immobility.[27] In addition, concurrent prothrombotic genetic risk factors, including factor V Leiden and non-O blood types, are linked to CAT events, as well.[28] Cancer-associated risk factors include cancer site, stage, and duration since diagnosis.[27-32] Brain, pancreatic, gastric cancers, and adenocarcinoma are associated with the highest risk of VTE, followed by lung, ovarian, testicular, renal, and bladder malignancies.[33,34] Numerous investigations have shown that metastatic disease is a significant risk factor for CAT.[10,35] Thrombosis is also associated with hematological malignancies, particularly multiple myeloma, acute leukemia, and lymphoma.[24] The treatment outcomes of solid and hematological malignancies were compared in a study of cancer patients with VTE from the Registro Informatizado Enfermedad TromboEmbólica (RIETE) registry.[36] According to the authors' findings, individuals with hematological malignancies had a lower probability of developing PE in comparison with those with isolated DVT. In addition, they were more prone to experiencing upper extremity DVT, which was frequently associated with catheterization.[36] Compared with patients with solid tumors, those with hematological CAT had substantially lower rates of symptomatic recurrent VTE, major bleeding, and all-cause mortality. Treatment-associated risks encompass various medical interventions, including surgery, hormonal therapy, erythropoiesis-stimulating agents, blood transfusions, hospitalization, central venous catheters, chemotherapy, endocrine therapy, angiogenesis inhibitors, immunotherapy, protein kinase inhibitors, transfusions, and cell-line stimulating agents, targeted therapies, immune checkpoint inhibitors, which all have been linked to VTE.[18,23,24,37-40] An increased number of platelets are significantly and autonomously linked to VTE in cancer patients, particularly when considering hematologic indicators.[41-43] According to one study, people with a platelet count of $\geqslant 443 \times 109/L$ have a 3.5 times higher chance of developing VTE.[44] In addition, decreased hemoglobin concentrations and increased leukocyte counts are associated with an increased risk of VTE in cancer patients.[43,45,46] Additional biomarkers that are linked to the presence of VTE in cancer patients in the Cancer and Thrombosis Study (CATS) include elevated levels of soluble P-selectin (sP-selectin), prothrombin fragment 1 + 2 (F1 + 2), and D-dimer in the plasma, and the thrombin generation potential.[42,47-49] In addition, individuals who have faraway metastases have substantially higher levels of sP-selectin, F1 + 2, and D-dimer than patients with localized cancers.[50] C-reactive protein (CRP)[44] has been linked to a higher likelihood of cancer-associated VTE. Nevertheless, it ought to be noted that certain investigations have failed to reproduce the correlation between CRP and VTE that is linked to cancer.[51]

Pathophysiological Mechanisms of Cancer-Associated Thrombosis

To comprehend the complexity of CAT, the observed pathophysiological mechanisms of CAT in various cancer types will be discussed (Table 1). In addition, the pathophysiological mechanisms of CAT can be divided into 2 main categories: direct and indirect mechanisms, all of which elucidate the complexity of such a common and burdensome clinical entity.

Direct Mechanisms of Cancer-Associated Thrombosis

Tissue factor

The protein known as tissue factor (TF) is widely recognized as a procoagulant that originates from tumors, but it is expressed in large quantities on subendothelial cells, including fibroblasts, pericytes, and vascular smooth muscle cells.[88] Its primary function is to initiate a hemostatic response following vascular injury. Cancer-associated thrombosis is distinguished by the initiation of coagulation, disruption of fibrinolytic mechanisms, inflammation, and the generation of cytokines.[89,90] as illustrated in Figure 1. The role TF in inducing hypercoagulability in the context of CAT appears to be significant.[91] The TF is known to act as a procoagulant by triggering the extrinsic pathway of the coagulation cascade through its association

Table 1. Mechanisms of CAT in patients with various types of cancer.

	MECHANISM	TYPE OF CANCER	REFERENCE
TF	Initiate the extrinsic pathway of blood coagulation	PDAC, glioblastoma, colorectal cancer, NSCLC	Khorana et al,[52] Kasthuri et al,[53] Yu et al,[54] Regina et al,[55] and Regina et al[56]
EVsTF		Pancreatic cancer, multiple myeloma, adenocarcinoma, PDAC, ovarian cancer	Khorana et al,[57] Auwerda et al,[58] Thaler et al,[59] Woei-A-Jin et al,[60] Hisada et al,[61] Bharthuar et al,[62] Kasthuri et al,[63] Uno et al,[64] Sakurai et al,[65] and Abu Saadeh et al[66]
PDP	Interacts and activates platelets, leading to platelet aggregation and clot formation	Brain cancer, with pancreatic cancer, colorectal cancer, mesothelioma, seminoma, glioma, pulmonary squamous cell carcinoma	Riedl et al,[67] Mege et al,[68] Zwicker,[69] Kimura and Kimura,[70] Kato et al,[71] Wang et al[72]
PAI-1	Impairs fibrinolysis, leading to a prothrombotic state and an increased risk of thrombosis	Melanoma, colorectal, breast cancer, pancreatic cancer	Hanekom et al,[73] Herszènyi et al,[74] Ferroni et al,[75] Andrén-Sandberg et al,[76] Tipoe et al,[77] and Hisada et al[78]
CP	Activates the clotting cascade and inhibits natural anticoagulant mechanisms, thereby increasing the risk of clot formation	Brain cancer	Mandoj et al[79]
Tumor-derived platelet agonists	Release various substances that activate platelets, such as ADP, TXA2, and serotonin which enhance platelet activation, aggregation, and clot formation, contributing to thrombosis	Pancreatic cancer	Woei-A-Jin et al[60]
MPs	Provide a procoagulant surface that supports clot formation and activate platelets and the clotting cascade	Breast cancer, hepatocarcinoma, pancreatic cancer	Abdol Razak et al[80] and Stark et al[81]
NETs	Promote platelet activation and clot formation	Lung cancer, pancreatic cancer, breast cancer, hepatocellular carcinoma, MPN	Mauracher et al,[82] Seo et al[83] and Guy et al[84]
Coagulation gene defects	Involved in the coagulation pathway can lead to an imbalance in the clotting system and predispose individuals to thrombosis	Colorectal adenocarcinoma, gastrointestinal cancers, breast cancer	Rak,[85] Heraudeau[86] and Tinholt et al[87]

Abbreviations: CAT, cancer-associated thrombosis; CP, cancer procoagulant; EVs, extracellular vesicles; MPs, microparticles; NETs, neutrophil extracellular traps; NSCLC, nonsmall cell lung carcinoma; PAI-1, plasminogen activator inhibitor; PDAC, pancreatic ductal adenocarcinoma; PDP, podoplanin; TF, tissue factor; ADP, adenosine diphosphate; TXA2, thromboxane A2; MPN, myeloproliferative neoplasms.

with factor VII, thereby facilitating the activation of factor X and consequent generation of factor Xa. Tumorous cells have the ability to express TF in a constitutive manner and subsequently release extracellular vesicles (EVs) that express TF, ultimately resulting in the formation of thrombin and fibrin.[54,92,93]

Tissue factor is commonly identified in an extensive range of tumor subtypes, with an especially high prevalence in pancreatic ductal adenocarcinoma (PDAC) and glioblastoma.[52,53] Genetic mutations can lead to heightened expression of TF in specific variety of cancer. Mutations in the Kirsten rat sarcoma viral oncogene (*KRAS*) and tumor protein 53 (*TP53*) genes have been found to increase the expression of TF in human colorectal cancer cell lines.[54] In addition, it has been noted that aberrations in the *KRAS*, *TP53*, and Phospatase and tensin homolog (*PTEN*) genes have been linked with enhanced TF mRNA expression in nonsmall cell lung carcinoma (NSCLC) tumors of patients.[55,56] According to a recent investigation, the rearrangement of anaplastic lymphoma kinase (ALK) is correlated with heightened expression of TF protein in individuals diagnosed with NSCLC.[94] Moreover, a number of retrospective investigations[94-101] and clinical trials[102-105] have documented elevated incidences of VTE (ranging from 8% to 47% and 1.1% to 6.4%, respectively) among lung cancer patients exhibiting ALK rearrangement, as opposed to those without such rearrangement. Oncogenes have been demonstrated to enhance TF expression by cancer cells in animal studies; thus, it is probable that ALK rearrangement could also increase TF expression, thus raising the risk of VTE.[94] ALK-rearrangement-induced epithelial-mesenchymal transition (EMT) in NSCLC cells is one of the proposed pathways.[94] Epithelial-mesenchymal transition induces a procoagulant state via TF.

Extracellular vesicles are submicron vesicles secreted by cells, specifically cancer cells.[106] Extracellular vesicles are known to be a means by which active tumor-derived TF is released into the bloodstream. In-house assays that quantify

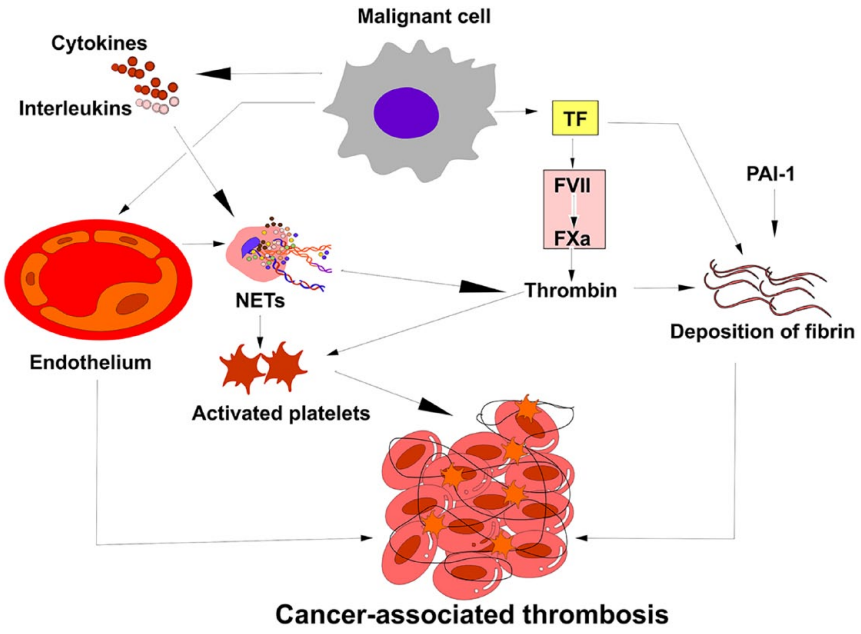

Figure 1. Mechanisms of CAT. CAT involves the activation of coagulation, dysregulation of fibrinolytic systems, inflammation, and cytokine production as its underlying mechanisms. FVII indicates factor VII; FXa, factor Xa; NETs, neutrophil extracellular traps; PAI-1, plasminogen activator inhibitor 1; TF, tissue factor; CAT, cancer-associated thrombosis.

extracellular vesicle tissue factor (EVTF) activity have been developed by other researchers.[57,107-110] Numerous researchers discovered that cancer patients have higher levels of EVTF activity in comparison with healthy participants.[57-61,107] Patients with adenocarcinoma exhibit significantly higher levels of EVTF activity in comparison with individuals who have different histological forms of tumor.[61] Enhanced EVTF activity has also been linked to an elevated likelihood of VTE among cancer patient populations afflicted with diverse malignancies.[107,111,112] In longitudinal and prospective investigations, an association was discovered between EVTF activity and VTE in PDAC patients.[57,60,62,63] In contrast, one study found no correlation between EVTF activity and VTE in patients with PDAC.[113] Even so, that research had a significantly longer (2 years) follow-up period than other studies. Collectively, these studies indicate that tumor-derived TF + EVs contribute to VTE in PDAC patients. Three studies have found that tumor TF expression is linked to VTE in ovarian cancer patients.[64-66] Unlike these studies, one study found no association between EVTF activity and VTE in ovarian cancer patients.[114] Other researchers have reported that there is no correlation between EVTF activity and VTE in patients with various types of cancer, including colorectal, stomach, small cell lung carcinoma, multiple myeloma, and acute myeloid leukemia.[58,63,113,115] Microparticles (MPs) are classified as small membrane vesicles with a diameter ranging from 0.1 to 1 µm. Typically, these vesicles are released by apoptotic or activated normal cells, as well as quiescent malignant cells.[80] When liberated from cancer cells, they have the ability to improve prothrombotic pathways in cancer in both direct and indirect ways. The coagulation protease cascade constituents are organized on their respective membrane surface. It has been reported that TF-expressing MPs in cancer patients originate from cancer cells; however, TF-positive MPs have also been detected to be released by activated endothelial cells and monocytes. The generation and release of various pro-inflammatory cytokines by cancer cells can trigger the activation of endothelial cells and monocytes, leading to the release of TF-positive MPs. The precise proportion of TF-positive MPs in cancer patients that can be attributed to either the tumor or host cells has yet to be definitively established.[80] In vitro and in vivo procoagulant activity associated with tumor-derived vesicles has been documented in breast and hepatocarcinoma cell lines, along with circulating MP that elevated in vivo coagulation in a number of additional cancer types.[80] The surface expression of active TF and the presence of phosphatidylserine are potential mechanisms for VTE induced by MPs. These factors facilitate the assembly of coagulation complexes on the negatively charged surface of phosphatidylserine.[116] The crucial role of cancer-associated DVT has been reported to involve the externalization of phosphatidylethanolamine from pancreatic cancer MPs.[81] The correlation between TF-positive MPs and VTE complications has solely been documented in pancreatic cancer patients.[117]

Platelets

The protein known as podoplanin (PDPN) has been identified as a potent activator and aggregator of platelets. This effect is mediated by the C-type lectin receptor 2 (CLEC-2) in response to tumor cell-induced platelet activation.[118] The production of PDP has been observed in pancreatic cancer cell lines, which is attributed to the cancer-associated fibroblasts.[119] C-type lectin receptor 2 depletion in platelets decreased venous thrombosis

in an inferior vena cava (IVC) stenosis model of DVT; this effect was reverted by infusion of wild-type platelets. This elevated level of circulating PDP in the IVC wall after stenosis was proportional to the severity of thrombosis.[120] The existence of tumor-related PDP has been identified as a risk factor for VTE in brain cancer patients.[67] Multiple hypotheses suggest that cancer cells secrete PDP into the bloodstream to control thrombosis at other locations. This is in line with the findings of additional research that identified tumor-derived MPs containing PDP in the peripheral circulation of patients with colorectal and pancreatic cancers.[68,69] Multiple varieties of cancer, including mesothelioma, seminoma, and glioma, express PDPN.[67,70,71] A recent study found a correlation between the expression of PDPN protein in tumors and VTE in pulmonary squamous cell carcinoma patients.[72] Similar to TF, PDPN is secreted from cells in the form of EVs. A research study employed flow cytometry to identify PDPN + EVs in the plasma of patients diagnosed with pancreatic and colorectal cancer.[68] Nevertheless, there was no correlation between the levels of PDPN + EVs and VTE in cancer patients. Gi et al[121] did research that assessed the expression of PDPN in venous thrombi obtained postmortem from cancer patients. According to the study, PDPN was expressed in 44% of cancer cells found in venous thrombi.[121]

Mucins are characterized by the presence of densely glycosylated O-linked sites, which serve as ligands for selectin molecules. Mucins use adhesion-dependent signaling to promote cell thrombosis. In vitro experiments have demonstrated that mucins are incapable of directly activating platelets. However, when incubated with whole blood, mucins were found to induce platelet activation, indicating a plausible association with the L-selectin. The administration of purified mucin in mice resulted in the formation of intravascular microthrombi that were rich in platelets. This finding is consistent with previous reports and provides additional mechanistic understanding of the role of mucin in the formation of microthrombi.[122] Numerous forms of cancer are characterized by abnormal expression and modified glycosylation of numerous mucins.[123] Cancer patients' prothrombotic potential is determined by the interaction between L-selectin and P-selectin glycoprotein ligand-1 on neutrophils and P-selectin on platelets to produce cathepsin G from neutrophils.[122] The activation of platelets and subsequent initiation of thrombosis in cancer patients may be facilitated by cancer cells. Several mechanisms contribute to platelet activation:[124,125]

1. Tumor Cell Release Procoagulant Factors: Many cancer cells release procoagulant factors such as TF and cancer procoagulant (CP). Such compounds have the potential to trigger the coagulation cascade and activate platelets.
2. Inflammation and Endothelial Damage: Cancer can cause inflammation and damage to endothelium. Injured endothelial cells expose collagen and TF, which activate platelets.
3. Platelet Interaction with Tumor Cells: Platelets can directly interact with tumor cells. This connection stimulates platelet activity, which subsequently boosts the viability and spread of tumor cells.
4. Platelet-Derived MPs: Platelets release MPs when activated. These MPs carry procoagulant molecules and contribute to thrombus formation.

Overall, CAT is a complex process involving the interaction of various factors, including cancer-related substances, inflammation, and the coagulation cascade. Platelet activation plays a critical role in the formation of blood clots in individuals with cancer, increasing their risk of thrombosis. It is important for health care providers to monitor and manage this risk in cancer patients to prevent potentially serious complications.

Plasminogen activator inhibitor-1

The inhibition of fibrinolysis has been ascribed to plasminogen activator inhibitor (PAI-1), which has been discovered to be abundantly present in cancer cells. An increase in plasma PAI-1 concentration reduces fibrinolytic activity, thereby increasing the susceptibility of individuals to thrombotic events.[88,126] Patients with cancer exhibit alterations in the fibrinolytic system. Plasminogen activator inhibitor is a serine protease that inhibits the activity of tissue plasminogen activator and urokinase, thereby promoting fibrin formation and accumulation (Figure 1).[39] On administration of the anti-vascular endothelial growth factor (VEGF) drug bevacizumab, thrombus levels increase significantly, resulting in elevated levels of PAI-1 in both the tumor and plasma. The administration of a PAI-1 inhibitor reduced the thrombotic effect of bevacizumab significantly. This finding suggests that a PAI-1 inhibitor may have the potential to improve the resolution of VTE in CAT patients.[127] Elevated levels of circulating PAI-1 have been observed in other cancer types, such as melanoma, colorectal, breast, and mostly pancreatic cancer.[73-77] This occurs as a result of the suppression of plasminogen activator and consequent disruption of fibrinolysis, which leads to the development of disseminated intravascular coagulation, reduced blood flow, and dysfunction of organs in afflicted individuals.[77] The existing literature on the correlation between PAI-1 levels and VTE in cancer patients is scarce. It is hypothesized that the PAI-1 activity exceeds that of the PAI-1 antigen because the latter comprises both active and inactive forms of PAI-1. Indeed, a case-control research examining VTE biomarkers revealed that PAI-1 activity outperformed PAI-1 antigen in differentiating VTE patients from healthy individuals.[128] A correlation between PAI-1 activity degree and VTE among individuals with pancreatic cancer was identified. It appears that PAI-1 may contribute to the development of VTE in this patient population.[78] On the contrary, the other study did not find any correlation between PAI-1 antigen and VTE in individuals diagnosed with pancreatic cancer.[129] In addition, a lack

of correlation was observed between prior DVT and plasma concentrations of PAI-1 antigen and activity among individuals diagnosed with pancreatic cancer.[76] In total, 11 of 14 patients in this study, nevertheless, demonstrated intermittent maxima in both PAI-1 antigen and PAI-1 activity. This implies that such individuals might undergo temporary conditions of hypercoagulability.

Cancer procoagulant

Cancer procoagulant is a cysteine protease that can initiate the coagulation cascade by directly activating factor X, regardless of factor VII. Originally identified in malignant rabbit tissue, it was subsequently extracted from human carcinomas exhibiting procoagulant activity. Cancer procoagulant cleaves the FX heavy chain at a distinct location compared with all alternative factor X activators. [79] A study of women with breast cancer, nevertheless, found no correlation between CP and procoagulant markers, leading to doubts about the integrity of the CP preparations used in previous investigations and the possibility of TF/factor VIIa contamination.[130]

Tumor-derived platelet agonists

Cancer cells release adenosine diphosphate (ADP) to activate and aggregate platelets through the P2Y1 and P2Y12 receptors. Thrombin production has likewise been observed in pancreatic tumors, which was confirmed by elevated levels of thrombin in individuals with pancreatic cancer.[60] Thrombin and ADP are platelet aggregation agonists, which aid in the process of primary hemostasis. It might thus elucidate why these tumor-derived products in cancer patients improve platelet activation and coagulation, which is consistent with prior research on the impact of tumor-derived agonists on platelets.[80]

Indirect Mechanisms of Cancer-Associated Thrombosis

Cancer-derived factors and their associated mechanisms with the capacity to enhance interactions with host cells have been shown to induce thromboembolic complications in individuals with cancer.

Inflammatory cytokines

The c cells have the ability to produce and release a significant proportion of inflammatory cytokines that exhibit a procoagulant phenotype. These cytokines have the potential to augment thrombogenesis and cause damage to the endothelial cells of the host. The presence of a tumor induces a reactive response in the host's inflammatory tissues, leading to an excessive secretion of cytokines.[131] The production of cytokines by cancer cells (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, and IL-17), activated platelets, and leukocytes also contributes to endothelium injury and thrombus formation (Figure 1). All of these overlapping pathways may also result in the development of disseminated intravascular coagulation, which is a significant contributor to thromboembolic complications. Tumor necrosis factor-alpha and IL-1β are widely recognized as prominent pro-inflammatory cytokines. Studies have suggested that these cytokines may have prothrombotic effects and could potentially induce the expression of TF and von Willebrand factor on vascular endothelial cells.[132] Nonetheless, TNF-α and IL-1β exhibit a downregulating effect on thrombomodulin, which is a receptor present on endothelial cells. This receptor binds with thrombin and is responsible for activating protein C, thereby functioning as a regulator of antithrombotic activity. The inflammatory cytokines inhibit the production of nitric oxide and prostacyclin from endothelial cells while simultaneously increasing their prothrombotic activity. This is accomplished by stimulating the production of fibrinolysis inhibitor, PAI-1. The procoagulant phenotype observed in host cells is attributed to the secretion of growth and pro-angiogenic factors, such as granulocyte colony-stimulating factor (G-CSF), VEGF, and basic fibroblast growth factor (bFGF). Macrophages produce an excessive amount of TF, which is triggered and stimulated by the presence of VEGF produced by different types of tumor cells. The activation of hemostasis is facilitated by markers of endothelial activation, namely thrombomodulin and von Willebrand factor, as well as coagulation markers. The presence of G-CSF has been reported to induce hypercoagulation, as indicated by the elevated concentrations of these biomarkers. It has been established that bFGF exacerbates the upregulation of TF expression on endothelial cells.[133]

Adhesion molecules

There have been reports indicating that cancer cells facilitate the adherence of blood vessel walls, stimulate interactions with blood cells, and activate the procoagulant capabilities of host leukocytes, platelets, and endothelial cells. Endothelial cell adhesion to tumor cells may induce regional coagulation and subsequent thrombus formation near the blood vessel wall. The attachment of various types of tumor cells to endothelial cells is facilitated by a myriad of adhesion molecules. Namely, E-selectin and vascular cell adhesion molecule-1 enable the attachment and rolling of human colorectal adenocarcinoma cell line (HT-29M) colon carcinoma cells and A375M cells on activated endothelial cells under shear stress. This occurrence results in heightened aggregate formation and facilitates thrombosis through the obstruction of vascular patency.[134] Moreover, the synthesis of P-selectin by endothelial cells and its activation by platelets promotes the adhesion of cancer cells. Nevertheless, the existence of the P-selectin ligand on cancer cells has yet to be verified. The interplay among cancer cells, platelets, and endothelial cells leads to the creation of cell-cell

aggregates, subsequently causing hindrance in blood circulation and encouraging coagulation and occlusion of vessels.[134]

Neutrophil extracellular traps

Neutrophil extracellular traps (NETs) are a type of mesh composed of DNA, histones, and neutrophil-derived proteases. Initially identified for their antimicrobial properties, these structures are noted to be generated in vitro in response to factors derived from pancreatic cancer. Neutrophil extracellular traps have been demonstrated to increase venous and arterial thrombosis in mice and act as a substrate for direct platelet adhesion and aggregation.[135,136] The presence of NETs associated with cancer may facilitate the stimulation of host cells, thereby promoting thromboembolic events. This may occur through the activation of endothelial cells by histones associated with NETs, which could result in an increase in the release of von Willebrand factor.[137–139] It has been observed that cytokines produced by tumors have the ability to stimulate the activation of endothelial cells (Figure 1). Neutrophil extracellular traps containing histones have the capability to activate platelets directly, thereby inducing additional thrombin generation,[140] but also, NETs have the capability to augment thrombosis by entrapping platelets and EVs, which comprise TF-positive (TF+) EVs.[141-144] Numerous agents such as cytokines, proteins, and other factors have been observed to induce the formation of NETs in cancer.[139,145-151] On the contrary, numerous biomarkers have been employed to evaluate the occurrence of NET formation[151-158] with citrullinated histone H3 (H3Cit) and H3Cit-DNA complexes, as well as Myeloperoxidase (MPO)-DNA complexes being the most optimal.[159] Multiple examinations have investigated the relationship between NET biomarkers and VTE and arterial thromboembolic events (ATEs) in cancer patients. Mauracher et al[82] conducted a study where they quantified the concentrations of cfDNA, nucleosomes, and H3Cit in the plasma of 984 individuals diagnosed with cancer; 9%, or 89, had a VTE during the 2-year follow-up. Significantly, H3Cit was linked to VTE. In addition, cfDNA and nucleosomes were only associated with VTE during the high-risk period (3-6 months after diagnosis). Although subanalyses were underpowered, Mauracher et al[82] identified significant correlations between plasma H3Cit levels and VTE in patients with lung and pancreatic cancer. They found a weak correlation in individuals with breast cancer, and no correlation in patients with brain or colon/rectal cancer. In a limited investigation involving 27 cancer patients, it was observed that there is no correlation between cfDNA or nucleosomes and VTE in cancer patients.[154] A research conducted on a sample of 177 patients diagnosed with hepatocellular carcinoma revealed that 43% of them had portal VT. The study found that cfDNA, neutrophil elastase, and DNA-histone complexes were significantly linked to thrombosis.[83] In a research conducted on a cohort of 52 individuals diagnosed with myeloproliferative neoplasms (MPN), half of whom had a prior previous medical record of thrombosis, the presence of MPO-DNA complexes was found to be significantly correlated with thrombotic events.[84] In addition, a recent study discovered that there was no discernible disparity in the amounts of H3Cit within thrombi from cancer patients and those from noncancer patients.[121] In a study conducted by Grilz et al,[160] the plasma levels of cfDNA, nucleosomes, and H3Cit were measured in a cohort of 957 cancer patients. Among these patients, 22 individuals (2%) experienced an ATE over the course of the 2-year monitoring period. No correlation was identified between any of the NET biomarkers and ATE. However, it was found that H3Cit and cfDNA were significantly linked to increased mortality. A smaller-scale investigation was conducted to evaluate cfDNA and nucleosomes in a group of 138 cancer patients, of whom 38 (27%) had experienced a stroke. The study revealed a significant correlation between cfDNA and stroke occurrence.[161]

Hypoxia

The hypoxic microenvironment created by tumors promotes endothelial dysfunction. During hypoxia, endothelial cells exhibit an increased release of phospholipase A2, resulting in excessive production of prostaglandins and synthesis of platelet-activating factor (PAF). In addition to its platelet-activating properties, PAF also stimulates neutrophils, thereby facilitating their adhesion to endothelial cells in hypoxic environments. The decrease in neutrophil adhesion to hypoxic endothelial cells was observed following the inhibition of PAF release.[162] The condition of hypoxia results in the exocytosis of Weibel-Palade bodies from the endothelial cells. Consequently, this results in the liberation of von Willebrand factor and P-selectin overexpression, which in turn increases the indirect procoagulant response. Increased ADP synthesis amidst hypoxia in cancer patients may also result in increased platelet activation.[163]

Damage-Associated Molecular Patterns

Damage-associated molecular patterns (DAMPs) are a group of molecules that consist of histones, high mobility group box 1 (HMGB1), S100 proteins, and heat shock proteins. These molecules are primarily located within the cell and are generated by senescent tumor cells either on cell death or due to cell stress. On their release, they activate innate immune pattern recognition receptors and trigger defensive reactions, thereby propagating a host response. Nevertheless, DAMPs can further induce chronic inflammation and immune cell activation in the host, leading to thrombotic events and facilitating the proliferation and viability of tumors. In contrast to a sample of healthy controls, plasma circulating nucleosomes were reportedly higher in cancer patients.[164] Histones and HMGB1 are DAMPs that exhibit significant procoagulant activity. The identification of these molecules in the peripheral circulation of individuals diagnosed with cancer signifies heightened

neutrophil activation and platelet aggregation Consequently, this results in the liberation of NETs and an increased potential for thrombosis.[165] Elevated levels of extracellular DNA have been documented in individuals diagnosed with PE, indicating a potential correlation between extracellular DNA and thromboembolic complications.[166] Nevertheless, the extent of their involvement in both cancer and noncancer patients remains to be comprehensively elucidated.

Cancer-associated treatments

There are numerous cancer treatments, but currently, chemotherapy is the most prevalent and widely accessible. There are reports indicating that cisplatin-based treatment increases the occurrence of thromboembolic events in individuals with cancer. Nonetheless, the precise mechanism responsible for the development of cisplatin-induced thrombosis remains unclear. Two human endothelial cell lines were subjected to cisplatin treatment, which induced apoptosis. In addition, procoagulant endothelium MPs were produced, leading to the generation of thrombin. Notably, this thrombin formation occurred independently of TF.[167] Multiple separate mechanisms contribute to this prothrombotic activity, including the direct damage to the endothelium caused by the medication and the increased expression of TF procoagulant activity in monocytes and macrophages, which triggers a procoagulant response from the host cells. The direct hepatotoxicity of chemotherapy can contribute significantly to the promotion of hypercoagulation by blocking natural anticoagulant proteins, including protein S, protein C, and antithrombin.[168] In addition, chemotherapy triggers apoptosis in both cancerous and host endothelium cells, leading to the secretion of cytokines and an elevation in TF expression and function.[168]

Coagulation gene defects

There have been reports indicating that hemostatic genes in cancer cells can be deregulated by oncogenic mutations and certain coagulant effectors.[169] The occurrence of CAT has been linked to oncogenic mutations in cancer cells, irrespective of the tumor types, in certain individuals with cancer. Several mutations, including *STK11, KRAS, CTNNB1, KEAP1, CDKN2B*, and *MET*, have been identified as potential predictors of a substantial rise in the occurrence of colorectal adenocarcinoma in patients up to 1 year prior to their primary diagnosis.[85] Furthermore, it has been reported that the presence of elevated factor V Leiden and prothrombin gene G20210A mutation increases the likelihood of thromboembolic complications in individuals with gastrointestinal cancers.[86] The susceptibility to hypercoagulability in breast cancer patients was found to have a novel association with single nucleotide polymorphisms of factors V and X, and the endothelial protein C receptor (EPCR).[87] The presence of 2 identical copies of the fibrinogen gamma gene (FGG) rs2066865 has been linked to a higher likelihood of developing VTE in individuals with active cancer, specifically an elevated risk of PE in cancer patients.[170]

Treatment of Cancer-Associated Thrombosis

Various anticoagulant protocols, such as vitamin K antagonists, low-molecular-weight heparins (LMWHs), and direct oral anticoagulants (DOACs), have been assessed for the treatment of CAT. Low-molecular-weight heparin as a sole therapeutic agent has been the established method for treating CAT for a considerable period of time.[171,172] According to a meta-analysis, the use of LMWH in comparison with vitamin K antagonists was linked to a noteworthy mitigation of the risk of recurring incidents, while not posing an enormous escalation in the likelihood of severe bleeding.[173] Although LMWHs offer various benefits over vitamin K antagonists such as reliable pharmacokinetics, shorter half-life, and fewer drug-drug interactions, their requirement for injections administered once or twice as a day and at higher expenses may lead to reduced adherence and persistence among patients.[173] When it comes to the treatment of acute VTE in the general populace, DOACs have emerged as a genuine, a safer, more convenient, more and efficient option. As their risk-to-benefit ratio is superior to that of vitamin K antagonists, DOACs are currently the treatment of choice in this context.[174,175] In light of the abovementioned results and their favorable characteristics, DOACs—particularly the Direct Factor Xa Inhibitors Apixaban, Edoxaban, and Rivaroxaban—have been evaluated in comparison with LMWH for the treatment of CAT.[176-179] In comparison with LMWH, patients who received DOACs had a significantly reduced risk of recurrent VTE events, although there was no significant increase in major bleeding events. However, there was a significant rise in clinically significant nonmajor bleeding, according to a meta-analysis that compiled the results of all randomized controlled trials.[180] Studies using randomized controlled trials have indicated that patients who receive DOACs, specifically edoxaban and rivaroxaban, in comparison with LMWH, are at a greater risk for experiencing major bleeding episodes.[177,179]The observed results appear to be attributed to a surplus of gastrointestinal hemorrhages that predominantly manifest in patients diagnosed with gastrointestinal malignancies.[181] Due to the absence of comparative studies and substantial variability among the clinical trials, it is not feasible to endorse a particular DOAC over another. The present suggestions, which are grounded in the prior findings, suggest that the favored therapeutic alternatives for CAT are apixaban, edoxaban, rivaroxaban, or LMWH.[182-186] The optimal duration of anticoagulant therapy should be between 3 and 6 months, or longer if the malignancy is active or the patient has ongoing risk factors.[187] On the contrary, important

question is posted—specifically, does a 3% to 5% absolute gain in VTE incidence justify the treatment of >90% of patients who will not benefit but will be required to self-administer a daily injection, possibly for the remainder of their lives, with no improvement in progression free survival (PFS) or overall survival (OS)?[187] The customization of anticoagulation therapy should be contingent on the patient's individual characteristics and inclinations. Furthermore, it is imperative that the therapy be adjusted and evaluated periodically in response to changes in the patient's cancer status and treatment regimen.[188] Finally, it is noteworthy to mention that vitamin K agonist (VKA) is discouraged in cancer patients in many places due to difficulty in regulating international normalised ratio (INR)/less time in therapeutic range and thus higher bleeding risk, which can be due to many interactions with antineoplastic treatment, difficulties in securing consistent nutrient and fluid intake, and so on.

Guidelines for Cancer-Associated Thrombosis Prevention in Cancer Patients

Taking into account the aforementioned factors, risk scores have been created to predict VTE events in cancer patients. Risk scores facilitate patient education, enhance awareness of VTE and its associated morbidity in individuals with cancer, enable VTE screening in asymptomatic cancer patients at high risk, and, in certain instances, permit the implementation of primary VTE prophylaxis in cancer outpatients.[189] The Khorana score is a commonly used metric.[43] The Khorana score helps assess the risk of VTE in cancer patients receiving chemotherapy. It includes the following parameters:

1. Site of cancer: Certain types of cancer, such as pancreatic, lung, stomach, and hematological malignancies, carry a higher risk of thrombosis.
2. Body mass index (BMI): Obesity is associated with an increased risk of thrombosis.
3. Hemoglobin level: Low levels of hemoglobin may indicate anemia, which is a risk factor for thrombosis.
4. Prechemotherapy platelet count: Elevated platelet counts may increase the risk of thrombosis.
5. Prechemotherapy leukocyte count: Elevated leukocyte counts may indicate an inflammatory state, which can contribute to thrombosis.

The mentioned system bestows points based on the distinct attributes of the patient and the tumor. Furthermore, it has the capability to categorize the risk of CAT into 3 distinct groups: high risk, intermediate risk, and low risk, with corresponding VTE event rates of 7%, 2%, and approximately 0.5%, respectively, over a period of 2.5 months. The Vienna score is an additional CAT risk score that has been validated for use.[190] The Vienna CATS score is designed to predict the risk of recurrent VTE in cancer patients. It includes the following parameters:

1. Site of cancer: Certain cancer types, such as pancreatic, lung, and gynecological cancers, are associated with a higher risk of recurrent VTE.
2. Previous VTE history: A history of previous VTE increases the risk of recurrence.
3. Platelet count: Elevated platelet counts may be indicative of a prothrombotic state.
4. Hemoglobin level: Low hemoglobin levels may contribute to thrombosis risk.
5. Leukocyte count: Elevated leukocyte counts may indicate an inflammatory state, increasing the risk of recurrence.

Both the Khorana score and the Vienna CATS score have been widely studied and have shown utility in risk stratification for CAT.[191] However, it is important to note that the success and applicability of these scores may differ contingent on the particular patient population and the context in which they are used. It is important to note that while these scoring systems can provide valuable risk assessment information, they are not infallible and should be used in conjunction with clinical judgment. Furthermore, continuous research and enhancements to these scoring systems have the potential to enhance their effectiveness and suitability in clinical settings. It should be emphasized that scores in cancer patients have only been evaluated in ambulatory outpatients, while studies for thromboprophylaxis have been conducted in ambulatory cancer patients receiving chemotherapy or in postsurgical cancer patients, while no specific studies are available in medical inpatients as cancer per se is a risk factor for VTE.

Also, several scores have been proposed for predicting the risk of cancer based on type of cancer and patient characteristics but they have a limited predictive value. In addition, only some of them incorporate biomarkers such as D-dimer or P-Selectin and but they do not include any cancer cytogenetic data.[192] The rationale behind the establishment of guidelines is attributed to the heightened susceptibility of cancer patients to VTE, with most of the occurrences transpiring in the outpatient milieu. The frequency of VTE among individuals with cancer is on the rise, in tandem with the growing population of cancer patients.[193] Guidelines have the advantage of aiding the integration of evidence into practice. However, the extent of these advantages varies across various medical fields, thereby necessitating the emergence of implementation research.[194] The latest data indicate that patient adoption of VTE prophylaxis is relatively high (>90%), but information regarding patient adherence at home, co-pay/out-of-pocket costs, and prescription refill is unavailable. Provider factors, external factors, and guideline content are additional areas that mirror the standard implementation obstacles seen in all medical fields. Several major oncology and hematology organizations have published guidelines[182,183,185,195,196] for the prevention of VTE in cancer outpatients. The implementation of VTE prophylaxis guidelines is influenced by external factors, primarily financial constraints and time limitations that

affect productivity and clinic flow. According to recent publications, prophylaxis has been found to be cost-effective in various health care systems. However, this is only applicable to patient populations with a higher risk and when lower-cost agents are used.[197-200] The limitations imposed by time include restricted opportunities for direct interaction with patients, a heavily burdened oncology workforce, and the requirement for substantial initial and continuous education in hematology. In this regard, there is a substantial obstacle for small or rural oncology practices that have restricted resources for information technology infrastructure and the execution of practice flow modifications. The literature describes the best VTE prophylactic approaches for outpatient cancer patients. These methods are based on limited studies.[201-204] In the aftermath, there is pressing need for novel interventions that can reduce the risk of hemorrhage, improve the education of both health care providers and patients, and facilitate the development of streamlined and effective risk assessment instruments.

Conclusions

Growing incidence, morbidity, and mortality rates from VTE in cancer patients pose a serious threat to an already complicated and harsh disease such as cancer. Cancer-associated thrombosis as a perplexing and dangerous adverse event is explained by numerous pathophysiological mechanisms, most of which are observed in clinical scenarios of various cancer types. Unfortunately, there is no consensus regarding prevention and prophylactic guidelines, especially for outpatients. Hence, further and more thorough research is necessary to define pathophysiological targets that can be aimed for adequate prevention and diagnosis of CAT.

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