Assessing the Risk and Prognosis of Thrombotic Complications in Cancer Patients

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INTRODUCTION
The association between venous thromboembolism (VTE) and cancer has been described for more than 140 years, since Armand Trousseau reported that patients with idiopathic thrombosis frequently developed cancer in the following months. Since then, several studies have demonstrated the prothrombotic phenotype of neoplastic disease.

The annual incidence of VTE is 0.1% and globally affects 6.5 million people. The rate is higher in the cancer population. Despite the improved awareness and prompt treatment, such as those admitted to oncology centers and hospitalized neutropenic patients.

Cancer generates a prothrombotic state through the release of procoagulants, such as tissue factor (TF) and cancer procoagulant, with a further enhancement of the hypercoagulable state due to underlying clinical conditions. Risk factors can be related to cancer, patient characteristics, and treatment modalities. Prolonged bed rest and poor performance status, especially in the terminal stage of the disease, can lead to venous stasis. Moreover, localized stasis can be caused by pelvic tumors and external compression from leg edema. Surgical interventions, chemotherapy drugs, and local tumor infiltration can lead to endothelial damage, and subsequently to a prothrombotic state.

A wide range of thrombotic manifestations can be observed in the cancer population. About 50% of cancer patients and up to 90% of patients with metastatic disease have abnormal clotting tests, such as mild extension or shortening of prothrombin time or activated partial thromboplastin time; thrombocytosis, and increased levels of fibrinogen, fibrin degradation products, and D-dimers, without overt thrombosis. The most common thrombotic events are deep vein thrombosis (DVT) and pulmonary embolism (PE), whereas the incidence of arterial events, including stroke, myocardial infarction, and peripheral embolism, is lower.

The activation of the clotting system promotes tumor growth and angiogenesis, influencing the cancer prognosis. Venous thromboembolism is the second leading cause of cancer death and the most common cause of death in the postoperative period. Cancer patients have a greater risk of VTE recurrence compared with noncancer patients, even...
with full anticoagulation. Similarly, the bleeding rate in patients on anticoagulation is higher despite the appropriate and close monitoring. Cancer-related VTE is associated with a 21% annual risk of recurrent thrombosis and a 12% annual risk of bleeding.5

This review presents the available data regarding the risk factors, predictive biomarkers, and prognosis of VTE in an oncology setting. The understanding and interpretation of these factors may prove useful in identifying patients at high risk and implementing individualized practices of thromboprophylaxis, improving the survival and quality of life of cancer patients.

THROMBOSIS RATES

During the last decade several studies have evaluated VTE risk in the general population, hospitalized patients, and cancer outpatients receiving chemotherapy. However, VTE rates vary in the cancer population because of differences in patient characteristics, duration of follow-up, and diagnostic methods.3 Approximately 15% to 20% of cancer patients develop VTE during the course of the disease.1 In a study of 17 284 cancer patients and a matched control cohort, 12.6% of cancer patients and 1.4% of the control group developed VTE.3 The highest incidence of VTE has been reported in hospitalized neutropenic patients (6.4%) and in those admitted to oncology departments (7.8%).4 Additionally, cancer patients undergoing surgical operation have a 2-fold VTE risk compared with surgical patients without cancer.5

The Multiple Environmental and Genetic Assessment (MEGA) study6 indicated that cancer patients have a 7-fold elevated VTE risk, and in some cancer types the risk is 28-fold higher. In particular, the highest VTE risk has been reported in hematologic malignancies, lung cancer, gastrointestinal cancer, and metastatic disease. Levitan et al7 evaluated the incidence of DVT and PE in approximately 1.2 million cancer patients 65 years or older. Lymphomas, kidney, stomach, pancreas, brain, and ovarian malignancies were associated with the highest VTE incidence. Risk for VTE is higher soon after cancer diagnosis and gradually drops after the third month. However, the risk remains high and steady for the next 15 years after the diagnosis.6,8

Notably, VTE rates are higher in more contemporary studies. Venous thromboembolism incidence in hospitalized cancer patients increased significantly during the period 1979–1999. This increase was more prominent compared with the elevation reported in hospitalized noncancer patients.9 Similarly, Khorana et al4 reported a 36% increase of venous events in hospitalized neutropenic cancer patients between 1995 and 2002.

Arterial ischemic events are less common in oncology settings and include acute coronary episodes, ischemic strokes, and peripheral arterial thromboembolism. The prevalence of these events ranges from 1.5% to 3.1% according to few available data. During the period 1995–2002, there has been a 124% increase in reported arterial events.4

IDIOPATHIC THROMBOSIS AND CANCER

Thrombosis can represent the earliest manifestation of an occult malignancy. Approximately 18% to 20% of VTE cases are caused by an underlying malignancy, whereas 26% of them are characterized as idiopathic VTE.10 A study of 59 534 patients with VTE showed that the risk for cancer diagnosis remained high 2 years after the initial thrombotic event. For all cancer types, the risk of cancer diagnosis was 4.2-fold higher within 6 months following thrombosis. The most common underlying malignant diseases were ovarian cancer, Hodgkin lymphoma, and non-Hodgkin lymphoma.11 In a study of 192 patients with critical limb ischemia, the reported incidence of occult malignancy was 11.5%.12

Approximately half of occult malignancies can be detected with a limited workup based on medical history, clinical examination, and routine laboratory tests.13 Piccioli et al14 assessed the value of extensive screening for undiagnosed cancer in patients with a documented first episode of symptomatic idiopathic VTE. Extensive screening consisted of abdominal–pelvic ultrasonography, computerized tomography, gastroscopy or double-contrast barium swallowing, colonoscopy, or sigmoidoscopy, followed by barium enema, fecal occult blood test, sputum cytology, and tumor markers (carcinoembryonic antigen, α-fetoprotein, CA125); prostatic ultrasonography was performed and prostate-specific antigen levels obtained for men, and Papanicolaou test and mammography were performed for women. During the follow-up, 13 of the 14 underlying malignancies were diagnosed by extensive screening, yielding a sensitivity of 93%.14 Extensive screening compared with limited screening raised the proportion of asymptomatic cancer diagnosis from 49.4% to 69.7% in patients with idiopathic VTE.15

THROMBOTIC RISK FACTORS

Cancer patients constitute a heterogeneous population, including patients with local or metastatic disease, at an early or advanced stage, on intensive chemotherapy or palliative care, and with hospitalized or outpatient status. Therefore, thrombotic incidence varies among different groups and depends on various factors. The Table summarizes the clinical variables and biologic markers that increase the thrombotic risk in cancer.

Patient-Related Risk Factors

Different studies have shown that in hospitalized patients, older age (≥65 years) was associated with higher VTE incidence (odds ratio [OR], 1.1; 95% confidence interval [CI], 1.0–1.1).16 A retrospective study of neutropenic patients showed that the VTE rate was 6.18% among patients 65 years or older, whereas in younger patients the risk was 23% lower.4 Similarly, elderly (≥60 years) cancer patients undergoing surgery had an elevated VTE risk (OR, 2.6; 95% CI, 1.2–5.7).17 However, a study conducted in all hospitalized cancer patients showed that there was no relationship between age and VTE.9

The data regarding the relationship between sex and VTE risk in cancer are conflicting. Population-based studies have not revealed any significant difference in VTE incidence between the two sexes.18 However, a study of hospitalized oncology patients showed an overall increase of VTE risk in women (OR, 1.1; 95% CI, 1.1–1.2).19 Lifetime estrogen exposure may be related to high VTE risk in the female population.20

According to some studies,18,19 there is a correlation between race and cancer-related thrombosis. The incidence is higher in African American patients (OR, 1.2; 95% CI, 1.2–1.3) and lower in Asians/Pacific Islanders (OR, 0.7; 95% CI, 0.7–0.8). However, racial disparities in VTE incidence do not exist among hospitalized cancer patients.19

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Immobility causes venous stasis, which has been recognized as a thrombotic risk factor. In a prospective study, 31% of patients with lung cancer who were on chemotherapy and had a poor performance status were complicated by VTE, whereas only 15% of patients with a better performance status had a thrombotic event. Poor performance status is also associated with recurrent VTE episodes. In malignancies characterized by high incidence of metastasis, the presence of comorbid conditions is the strongest risk factor for VTE, compared with malignancies with a lower metastatic rate, for which metastatic disease itself is the most important risk factor. Thus, in patients with brain glioma or ovarian cancer, the presence of 3 or more chronic diseases was the strongest risk factor, whereas metastatic disease itself significantly increased the risk in breast and colon malignancies. The presence of underlying obstructive atherosclerotic disease in combination with prolonged immobility, mechanical compression, and septic shock can lead to arterial thrombosis.

Prior thrombotic events constitute a considerable risk factor. History of thrombosis has been implicated in thrombotic events in myeloma, hepatocellular carcinoma, and ovarian and prostate cancer. Prior thrombosis increased the risk 7-, 6-, and 2-fold in outpatients, surgical cancer patients, and those with central venous catheters, respectively. Moreover, prior arterial thrombotic events can be associated with venous events (OR, 1.5; 95% CI, 1.4–1.5).
Notably, in myeloproliferative disorders history of thrombosis and an age older than 60 years are used to divide patients into low- and high-risk groups and determine the treatment approach.\textsuperscript{25} Patent foramen ovale or atrial septal defect can lead to intracardiac right-to-left shunt, and subsequently to paradoxical embolization in patients with a history of venous thrombosis. Iguchi et al\textsuperscript{27} reported right-to-left shunt in 55% of cancer patients presenting with stroke, and more than 50% of those with right-to-left shunt had DVT or PE.

In the MEGA study,\textsuperscript{6} cancer patients with factor V Leiden or prothrombin 20210A mutation had a 12- to 17-fold increased risk compared with patients without cancer and prothrombotic mutations. Cancer patients with factor V Leiden\textsuperscript{6} (OR, 2.2; 95% CI, 0.3–17.8) and prothrombin gene mutation\textsuperscript{28} (OR, 1.2–6.7) had a higher VTE risk compared with noncarrier cancer patients. The risks of central venous catheter–related thrombosis were 13.1% and 4.5% in cancer patients with factor V Leiden and prothrombin mutation, respectively.\textsuperscript{29} In a small series of patients with lung cancer, methylenetetrahydrofolate reductase A1298C gene polymorphism differed significantly ($p = 0.04$) between patients with and without DVT.\textsuperscript{30} In myeloproliferative neoplasms, the presence of the JAK2V617F mutation is of special interest. In patients with polycythemia vera, there was no significant difference between those heterozygous and homozygous for the JAK2V617F mutation. In contrast, in essential thrombocytopenia, an increase in cardiovascular events and recurrence rate was observed in homozygous patients compared with heterozygous patients and those without the mutation.\textsuperscript{31,32}

**Cancer-Related Risk Factors**

The primary site and histologic type of cancer influence the risk of VTE. Kidney, stomach, pancreas, ovary, and lymphoma malignancies were associated with a 4.126-fold increased risk compared with lower-risk cancers, such as head/neck, bladder, breast, esophagus, uterus, and cervix. Hematologic malignancies had the highest risk (OR, 28; 95% CI, 4.0–199.7), followed by lung (OR, 22.2; 95% CI, 3.6–136.1) and gastrointestinal (OR, 20.3; 95% CI, 4.9–83) cancers. The VTE rates in advanced stages of pancreatic and stomach cancer were 20% and 10.7%, respectively, whereas in prostate and breast cancer they were 0.9% and 2.8%, respectively.\textsuperscript{6,7,18} Venous thromboembolism incidence varies according to the cancer histologic type. Thus, in non–small cell lung cancer VTE risk was higher in adenocarcinomas than in squamous cell carcinomas (hazard ratio [HR], 1.9–3.1).\textsuperscript{33}

Patients with localized disease have lower VTE rates compared with those with metastatic disease. In surgical cancer patients, advanced disease is associated with elevated VTE risk (OR, 2.7; 95% CI, 1.4–5.2).\textsuperscript{17} However, in ambulatory nonhospitalized patients with ovarian cancer there is no relationship between cancer stage and VTE.\textsuperscript{24} Malignancies characterized by early metastases and poor overall survival are associated with increased VTE risk. Metastatic disease presented at the time of cancer diagnosis is a strong independent risk factor in the first year after diagnosis.\textsuperscript{35} Interestingly, tumor growth capacity and proliferation rate have more essential roles in assessing VTE risk than the extent of metastatic disease itself, because they indicate the biologic behavior of cancer.\textsuperscript{36} The MEGA study\textsuperscript{6} indicated that the OR for developing cancer-related VTE was 53.5 in the first 3 months, and it dropped to 14.3 and 3.6 at 3 to 12 months and at 1 to 3 years after cancer diagnosis, respectively. For instance, in patients with diffuse large B-cell lymphoma, 82% of thrombotic events were reported 1 to 3 months after the initial diagnosis.\textsuperscript{4} Multiple myeloma patients had a 9.2-fold increase in VTE risk, and the greatest risk was observed during the first year following diagnosis.\textsuperscript{37} In a Swedish study including 18,627 myeloma patients and 70,991 matched controls, VTE rate was 7.5-fold after 1 year of follow-up and 4.1-fold after 10 years for myeloma patients compared with control group.\textsuperscript{38} In a study of women with metastatic ovarian cancer, 15% died within the first 3 months and another 15% died 4 to 12 months after diagnosis. Notably, in the first group the VTE incidence was 27%, whereas in the second group it was 10.7%, despite the spread of metastatic disease. Venous thromboembolism incidence is almost the same as that reported in noncancer patients 15 years after cancer diagnosis.\textsuperscript{39}

In the setting of arterial ischemic episodes, several tumor types, such as prostate, lung, and colon cancer, have been associated with thrombotic complications; however, there is no particular predominance.\textsuperscript{4} In contrast, there is a correlation with certain hematologic malignancies, namely, acute leukemia, primary amyloidosis, and myeloproliferative neoplasms. De Stefano et al\textsuperscript{40} showed that the incidence of thrombosis in acute promyelocytic and lymphoblastic leukemia is 9.6% and 1.4%, respectively, at the time of presentation. More than 50% of these events involved an arterial bed. Cardiovascular thrombotic events are found in 26% to 33% of patients with primary amyloidosis, despite preserved left ventricular ejection fraction and absence of cardiac arrhythmias.\textsuperscript{41} Feng et al\textsuperscript{41} reported a 26% mortality rate in instances of amyloidosis-related thrombosis. At the time of diagnosis, the prevalence of thrombosis is 34% to 39% and 10% to 29% in polycythemia vera and essential thrombocythemia patients, respectively,\textsuperscript{42} and 64% to 96.7% of these episodes have an arterial origin.\textsuperscript{33} During follow-up, the occurrence of thrombotic episodes ranges from 8% to 19% and from 8% to 31% for polycythemia vera and essential thrombocythemia patients, respectively.\textsuperscript{33} Studies have reported that thromboembolic tendency manifests 5 to 6 years before the diagnosis of myeloproliferative neoplasms.\textsuperscript{43}

**Treatment-Related Risk Factors**

Anticancer drugs can provoke the release of procoagulants and cytokines from damaged tumor cells and direct alterations on vascular endothelium. Conventional chemotherapy increases the risk of VTE 2- to 6-fold. Agents with a strong correlation with thrombotic complications are platinum (8%–18%), asparaginase (4%–14%), fluorouracil (15%–17%), and antiangiogenic agents, such as thalidomide and lenalidomide.\textsuperscript{44} Cisplatin is correlated with a 12% to 17.6% risk of strokes, recurrent peripheral arterial events, and aortic thrombosis.\textsuperscript{21}

Pharmaceutical agents used in multiple myeloma have a clear implication in thrombotic complications. The incidence of VTE in myeloma patients treated with melphalan and prednisone is 2% to 6%, and in those receiving high-dose dexamethasone the incidence is 3%.\textsuperscript{46} Thrombotic risk in patients receiving thalidomide as monotherapy was 2%, whereas the risk increased to 12% to 26% for patients receiving thalidomide in combination with either dexamethasone or doxorubicin.\textsuperscript{37} Lenalidomide as a single-agent treatment does not increase the risk in relapsed or refractory
myeloma patients. The dose of dexamethasone has been shown to affect VTE risk. In a randomized clinical trial comparing lenalidomide plus low-dose dexamethasone versus high-dose dexamethasone, the incidence was 12% and 26%, respectively.48

Bevacizumab is a recombinant humanized monoclonal antibody that binds to and inhibits vascular endothelial growth factor A. In a meta-analysis of 7956 patients with advanced solid tumors, those treated with bevacizumab had a significantly increased risk, with an overall VTE incidence of 11.9% (relative risk, 1.33; 95% CI, 1.13–1.56; P < .001) compared with the control group.49 Scappaticci et al.50 showed that the rate of arterial thromboembolic events was 5.5 per person-year in patients receiving bevacizumab and chemotherapy. Both sunitinib and sorafenib are novel agents targeting the angiogenesis pathway and have been associated with an increased risk for arterial events (relative risk, 3.03; 95% CI, 1.25–7.37).51

Hormonal agents used in breast and prostate cancer have thrombogenic properties. Tamoxifen is a selective estrogen receptor modulator used in hormone receptor-positive breast cancer. In a randomized study of 1312 patients,52 those receiving adjuvant treatment with tamoxifen had a 2.5-fold higher thrombotic risk. Premenopausal women receiving chemotherapy and tamoxifen had significantly more thrombotic complications than those receiving only chemotherapy (2.8% versus 0.8%; P = .03). Similarly, postmenopausal women undergoing chemotherapy with tamoxifen had more VTE episodes compared with those receiving tamoxifen alone (8% versus 0.4%; P < .001). The incidence of arterial thrombosis was also significantly higher in women undergoing chemotherapy with tamoxifen compared with those receiving chemotherapy alone (1.6% versus 0%; P = .004).53 Aromatase inhibitors inhibit the synthesis of estrogens from androgens. The Arimidex, Tamoxifen Alone, or in Combination (ATAC) study64 of 9000 postmenopausal women showed that the VTE rate after 68-day follow-up was 4.5% in the tamoxifen group compared with 2.8% in the anastrozole group (P < .001). Diethylstilbestrol is a synthetic estrogen used in prostate cancer and associated with an increased risk of cardiovascular events, especially in combination with chemotherapy. In an Eastern Cooperative Oncology Group (ECOG) study,55 diethylstilbestrol plus doxorubicin increased 10-fold the rate of cardiovascular toxicity compared with the doxorubicin arm alone (6.75% versus 0.7%). Patients with prostate cancer on leuprolide,56 flutamide,57 and steroidal antiandrogens, such as megestrol acetate, cyproterone acetate, and medroxyprogesterone acetate, have a lower VTE risk compared with those receiving diethylstilbestrol.58

Cancer patients often receive erythropoiesis-stimulating agents for anemia treatment. These agents are associated with both arterial and venous events, especially in combination with chemotherapeutic agents. The reported thrombotic rates range between 13% and 27%, and they are particularly correlated with an approximately 67% increase in VTE risk.59 In a systemic review of randomized trials, 229 of 3728 patients on darbepoetin or epoetin were complicated by VTE, whereas only 118 of 3041 patients who did not receive erythropoiesis-stimulating agents had a thrombotic episode (relative risk, 1.7; 95% CI, 1.4–2.1).59 In a study of myeloma patients treated with lenalidomide and dexamethasone, the addition of epoetin increased the incidence from 5% to 23%.60 Similarly, white blood cell growth factors can provoke hemostatic alterations. In patients with higher-risk cancer types, such as upper gastrointestinal, lung, and lymphoma, VTE rate was 5.9% in those receiving white blood cell growth factors, whereas the rate was 1.52% in the cohort without growth factor use (OR, 4.0; 95% CI, 1.8–8.7; P < .001). Lower-risk cancer sites were not correlated with increased VTE risk with the use of white blood cell growth factors (1.31% versus 1.42%; P = .84).61 A retrospective study showed that packed red blood cell transfusion was an independent risk factor for VTE (OR, 1.6; 95% CI, 1.5–1.7), arterial thrombosis (OR, 1.5; 95% CI, 1.5–1.5), and inhospital mortality (OR, 1.34; 95% CI, 1.29–1.38).61 Similarly, platelet transfusion was found to increase the risk of both venous (OR, 1.20; 95% CI, 1.11–1.29) and arterial (OR, 1.55; 95% CI, 1.40–1.71) events.61

Surgical cancer patients have a 2- to 4-fold higher risk of postoperative VTE compared with noncancer patients.62 In the cancer population, a major neurosurgical operation or brain biopsy for glioma increased the VTE rate by 70% in the first 3 months compared with the procedure-free cohort. Interestingly, the rate of thrombotic events in patients who underwent a surgical procedure has remained stable in contrast to those on chemotherapy, possibly because of systemic thromboprophylaxis in the surgical setting.63 In a study of surgical cancer patients, thrombotic risk factors include age older than 60 years, past history of VTE, advanced disease, anesthesia period of more than 2 hours, and bed rest longer than 4 days. The VTE risk remained elevated even 30 days after surgery, with 40% of VTE events occurring 21 days after surgical intervention.17

Hospitalization significantly increases the risk of cancer-related VTE (OR, 2.3; 95% CI, 1.6–3.4).30 Hospitalized cancer patients had a 1.62-fold increased VTE risk compared with hospitalized patients without cancer.64 The risk was 4.1% per hospitalization and varied in different subgroups (12%–18%). Between 1995 and 2003, VTE incidence increased by 28% and the percentage of PE doubled, from 0.8% to 1.5%.19

Several venous implants are used in oncology settings, facilitating mainly chemotherapy infusion. In adult patients, the incidence of symptomatic central venous catheter-related DVT ranges between 0.3% and 28%, whereas the incidence of confirmed cases by phlebography varies widely, between 27% and 66%.66,67 Among patients with symptomatic central venous catheter–related DVT, 15% to 36% had a subsequent episode of PE.68 The wide range of incidence can be attributed to catheter type, catheter position, number of insertion attempts, previous catheter placement, duration of use, cancer type, and chemotherapy regime.69 Inferior vena cava filters have been associated with late thrombotic complications. In oncology patients, the reported VTE incidence is approximately 32% to 40%, due to either failure or contraindication of anticoagulation therapy. Significant risk factors for VTE recurrence are the presence of new metastasis (OR, 3.3), previous VTE history (OR, 10.6), and multiple neutropenic episodes (P = .04).66,67

The implication of radiotherapy in the prothrombotic state of cancer patients is not clear. The risk of coronary artery thrombosis was 2- to 5-fold higher in cancer patients with a history of atherosclerotic disease who received radiotherapy.68 Ionizing radiation causes atherosclerotic changes through oxidative stress, endothelial damage, and vascular fibrin deposition. The risk depends on radiation dose, technique, and extent of vascular exposure.69
**BIOLOGIC PREDICTIVE MARKERS**

Complex interactions between tumor cells and circulating platelets affect cancer growth and dissemination. Platelets provide a procoagulant surface for amplification of cancer-related coagulation. A prospective study of patients starting chemotherapy showed that high platelet count prior to chemotherapy was related to increased VTE risk. Venous thromboembolism was observed in 4% of patients with a prechemotherapy platelet count of 350,000/mm³ or higher, whereas only 1.25% of patients with a platelet count lower than 200,000/mm³ had VTE during the 2.5 months (P < .001) since the treatment initiation. Patients with VTE had a significantly higher prechemotherapy platelet count compared with those without thrombosis (P = .001). Similarly, a prechemotherapy white blood cell count above 11,000/mm³ was found to be significantly and independently associated with elevated thrombotic risk.

Interestingly, in myeloproliferative neoplasms, neither hemoglobin level nor platelet count is considered a thrombotic risk factor, in contrast to high white blood cell count (>15,000/mm³). Thrombocytosis is usually associated with an increase in hemorrhagic risk rather than thrombotic complications. In this setting, other factors, such as hypercholesterolemia, smoking, and diabetes mellitus, have been correlated with thrombotic risk.

TF, a transmembrane protein, enables clotting initiation. It is expressed in many cancer cells and tumor vasculature, and it has an important role in the pathophysiology of cancer-related thrombosis. TF expression can be assessed by immunohistochemical grading of tumor cells, measurement of TF antigen using enzyme-linked immunosorbent assay, and TF microparticle (MP) activity. The association between elevated TF expression and VTE risk has been reported in specific cancer types. In a small study of patients with pancreatic cancer and high TF expression in resected tumor samples, the incidence of VTE was 26.3%, whereas in those with lower TF expression it was 4.5% (P = .04). Similarly, in a prospective study of subgroups from the Vienna Cancer and Thrombosis (CAT) registry, TF was predictive of VTE in pancreatic but not in brain or colorectal cancers.

Markers of hemostatic activation, including D-dimers, thrombin–antithrombin complexes, and prothrombin fragments F1+2, are elevated in cancer patients compared with healthy controls and can be used as predictive factors for new or recurrent VTE. D-dimers are specific cross-linked fibrin derivatives produced when fibrin is degraded by plasmin. Concentrations are therefore raised by thrombolytic activity, making them a highly sensitive indicator for VTE. However, their use in cancer is limited because the levels are increased because of underlying malignancy. In a prospective study of 821 patients with newly diagnosed cancer or progressive disease who did not recently receive any treatment, D-dimers and F1+2 levels were significantly higher in patients with VTE than in those without any thrombotic event. A 2-fold increase of D-dimers was associated with a 1.3-fold increase in HR for VTE (95% CI, 1.1–1.5; P < .001), and this remained stable in multivariable analysis after adjustment for age, sex, surgery, chemotherapy, and radiotherapy (HR, 1.3; 95% CI, 1.2–1.6; P < .001). A 2-fold increase of F1+2 also was a statistically significant risk factor for VTE in both univariate (HR, 1.8; 95% CI, 1.3–2.6; P < .001) and multivariable (HR, 2.1; 95% CI, 1.5–2.9; P < .001) analysis. Moreover, a recent study showed that each doubling of D-dimers was associated with a 1.5-fold (95% CI, 1.4–1.6; P < .001) increase in mortality HR, and this remained independently increased in different subgroups after adjustment for age, sex, VTE, and tumor type.

Clotting factor VIII (FVIII) dissociates from von Willebrand factor and acts as a cofactor to FIXa in FX activation, resulting in accelerated thrombin generation. The data regarding the role of FVIII as a thrombotic risk factor are limited. A small retrospective study showed higher FVIII levels in patients with various cancers and thrombosis compared with a matched control group without thrombosis. A study of 840 cancer patients showed that the cumulative probability of VTE after 6 months was 14% in patients with elevated FVIII and 4% in those with normal levels (P = .001). The association was stronger in younger patients, whereas in 40-year-old patients a 2-fold VTE risk per FVIII increase of 20% was observed (HR, 2.0; 95% CI, 1.5–2.7; P < .001).

C-reactive protein is an inflammatory marker and can be predictive of cardiovascular events and mortality. In a prospective study of 507 cancer patients, the multivariate analysis showed that elevated levels of C-reactive protein (38096 nmol/L) were associated with VTE development.

Soluble P-selectin expression above the 75th percentile is associated with an 11.9% probability of VTE during 6 months, whereas in case of expression below the 75th percentile, the probability is 3.7%.

Thrombin formation has a key role in the hypercoagulable state of malignancies. The CAT study showed that patients with elevated peak thrombin levels (>611 nM) had an increased VTE risk (HR, 2.1; 95% CI, 1.3–3.3; P = .002) and higher cumulative probability of VTE after 6 months compared with those with low levels (11% versus 4%; P = .002). Thus, thrombin measurement may help identify cancer patients at high VTE risk.

Microparticles are small vesicles derived from activated or apoptotic cells, including platelets, monocytes, endothelial cells, and tumor cells, by proteolytic cleavage of cytoskeleton. The procoagulant properties of MPs are attributed to their coagulation components, such as phosphatidylserine and TF. Several studies have demonstrated that cancer patients with elevated TF-positive MPs or MP TF activity are at greater risk. For instance, Zwicker et al found a 7-fold higher thrombotic risk in cancer patients with increased TF-positive MPs compared with patients with TF-negative MPs during a 2-year follow-up. Other studies have shown an association between TF-positive MPs and mortality, especially in patients with breast and pancreatic cancer. However, the use of MPs as a predictive biomarker is hampered by the lack of standardization in testing methods.

**ASSESSING THE RISK OF CHEMOTHERAPY-RELATED THROMBOSIS**

The identification of thrombotic risk factors and the subsequent risk stratification of cancer patients can affect the decision of thromboprophylaxis because anticoagulant treatment in cancer is related to high rates of hemorrhagic events compared with the general population. Using the data from the Awareness of Neutropenia in Chemotherapy (ANC) Study Group Registry, Khorana et al described a
simple predictive model for VTE incidence in patients starting chemotherapy. The risk model includes cancer primary site (2 points for very high-risk cancers, ie, stomach and pancreas; and 1 point for high-risk cancers, ie, lung, lymphoma, gynecologic, bladder, and testicular); platelet count of 350 000/mm\(^3\) or higher (1 point); hemoglobin level below 10 g/dL and/or use of erythropoiesis-stimulating agents (1 point); white blood cell count above 11 000/mm\(^3\) (1 point); and body mass index of 35 kg/m\(^2\) or higher (1 point).\(^{71}\)

The rates of symptomatic VTE in low-risk (score 0), intermediate-risk (score 1–2), and high-risk (score ≥3) subgroups were 0.3%, 2%, and 6.7%, respectively, during a median follow-up period of 2.5 months. This predictive model can successfully identify both low-risk patients for whom thromboprophylaxis may not give any benefit and high-risk patients for whom thromboprophylaxis is necessary.\(^{23}\) In a study of 1356 patients, the model had a negative predictive value of 98.5%, positive predictive value of 6.7%, sensitivity of 35.7%, and specificity of 89.6%.\(^{71}\) Several retrospective and prospective studies have further validated this risk score. In the Vienna CAT study,\(^{84}\) the 6-month cumulative probabilities of developing VTE were 1.5% (score 0), 3.8% (score 1), 9.4% (score 2), and 17.7% (score ≥3). Moreover, the inclusion of D-dimers and P-selectin in the original risk score raised the cumulative VTE risk. In particular, in patients with high (score ≥5), intermediate (score 3), and low (score 0) scores, the risks were 35.0%, 10.3%, and 1%, respectively, after 6 months.\(^{84}\)

**POSTTHROMBOTIC COMPLICATIONS**

Thrombosis in cancer is associated with a nearly doubled risk of death. Both PE and arterial events can be direct causes of death; however, the increased mortality in cancer patients with VTE cannot always be directly attributed to thrombosis. In a study of 4458 patients with solid tumors and lymphomas initiating chemotherapy, the multivariate analysis showed that VTE was a significant independent predictor of early (less than 4 months) all-cause mortality (HR, 6.98; 95% CI, 2.83–17.21; P < .001).\(^{85}\) Hospitalized cancer patients with VTE have a significantly higher mortality rate compared with those without VTE history (OR, 2.1; P < .001), and mortality is slightly increased in patients with metastatic disease (OR, 2.06; P < .001).\(^{4}\) Mortality rate is higher in patients with PE compared with those without such a history (24.8% versus 6.5%; P < .001).\(^{14}\) The @RISTOS study,\(^{13}\) was a prospective observational study of 2373 cancer patients undergoing general, urologic, or gynecologic surgery. The overall death rate was 1.72%, and in 46.3% of these cases death was caused by VTE, which was also the most common risk factor for death at 30 days after surgery.\(^{17}\) In a prospective observational study of 4466 patients on chemotherapy, the annualized death rates for VTE and arterial episodes were 448 and 716 per 100 000 patients, respectively, representing a 47-fold and 2.7-fold elevation, respectively, over the general population.\(^{86}\)

The risk score according to the predictive model for chemotherapy-related VTE and VTE occurrence were both significant independent predictors for reduced progression-free survival. Venous thromboembolism association with both disease progression and mortality suggests a strong correlation with underlying tumor behavior.\(^{2}\) Venous thromboembolism development worsens the prospects for long-term survival in cancer patients. Studies have failed to explain whether the poor prognosis can be attributed to adverse tumor biology and underlying comorbidities, or whether VTE is a direct cause of death. In a study of 100 000 breast cancer patients, VTE was a significant predictor of decreased 2-year survival (HR, 2.3; 95% CI, 2.1–2.6).\(^{83}\) Similar results have been reported in lung and colorectal cancer after adjustment for stage and other variables.\(^{33,36}\) The impact of thrombosis on overall survival is more prominent in localized disease. For instance, among patients with colorectal cancer, VTE was a significant predictor of death within 1 year after cancer diagnosis in the cohort with limited disease (HR, 1.8; 95% CI, 1.4–2.3), but not among those with metastatic disease (HR, 1.1; 95% CI, 1.0–1.2).\(^{36}\)

Cancer patients have a higher risk of VTE recurrence compared with those without cancer. Prandoni et al reported that the 12-month cumulative incidence of recurrent thromboembolism in cancer patients was 20.7% (95% CI, 15.6%–25.8%) versus 6.8% (95% CI, 3.9%–9.7%) in noncancer patients. The cumulative probability of hospital readmission with VTE within 183 days was highest in patients with prior VTE and malignant disease (0.22), followed by those with malignant disease (0.14), those with nonmalignant disease (0.08), and those with prior VTE alone (0.06).\(^{28}\)

Anticoagulants increased 2.2-fold (95% CI, 1.2–4.1) the risk of hemorrhage in the cancer population compared with noncancer patients. The 12-month cumulative incidence of major bleeding was 12.4% (95% CI, 6.5%–18.2%) in patients with cancer and 4.9% (95% CI, 2.5%–7.4%) in patients without cancer.\(^{87}\) Hutten et al reported that oncology patients on vitamin K antagonists for documented VTE had a 3- to 6-fold higher risk for both recurrence and major bleeding compared with noncancer patients. According to the Computerized Registry of Patients with Venous Thromboembolism (RIETE),\(^{89}\) patients younger than 65 years (OR, 3.0; 95% CI, 1.9–4.9), those with a PE diagnosis (OR, 1.9; 95% CI, 1.2–3.1), or those who developed VTE within 3 months after cancer diagnosis (OR, 2.0; 95% CI, 1.2–3.2) had an increased incidence of recurrent PE. Those younger than 65 years (OR, 1.6; 95% CI, 1.0–2.4) or less than 3 months from cancer diagnosis (OR, 2.4; 95% CI, 1.5–3.6) had an increased incidence of recurrent DVT. Finally, patients with immobility (OR, 1.8; 95% CI, 1.2–2.7), metastases (OR, 1.6; 95% CI, 1.1–2.3), recent bleeding (OR, 2.4; 95% CI, 1.1–5.1), or creatinine clearance below 0.50 ml/s/m\(^2\) (OR, 2.2; 95% CI, 1.5–3.4) had an increased incidence of major bleeding.\(^{89}\) Both VTE recurrence and bleeding events are related to cancer severity and are usually observed during the first month of anticoagulant treatment. Interestingly, they cannot be completely explained by either overtreatment or undertreatment, and therefore patients must be closely monitored during this period.\(^{8}\)

Acute limb ischemia in cancer patients carries a high mortality rate. Sakka et al showed that 50% of patients with malignancy and critical limb ischemia died within 6 months compared with 20.6% of those without cancer. Antiplatlet therapy, namely, aspirin and clopidogrel, and management of traditional atherosclerotic risk factors, such as obesity and smoking, can improve the prognosis in myeloproliferative disorders and radiation-related arterial disease. Conversely, critical limb ischemia associated with solid tumors has a poor prognosis despite the available treatment approaches.\(^{24}\)
Few data are available regarding the long-term consequences of thrombosis in the oncology setting. Approximately 30% of patients with VTE develop postthrombotic syndrome, which can cause disability, within 5 years after the first VTE episode. The symptoms include debilitating leg pain, painful swelling, and fibrosis; and approximately 8.1% of patients have severe manifestations, such as leg ulcers and mobility limitation, and they need long-term nursing care. However, data suggest that malignancy does not influence the risk of postthrombotic syndrome. In addition, up to 50% of patients with documented DVT have pulmonary emboli, as detected by perfusion lung scanning. Inversely, asymptomatic venous thrombosis is observed in 79% of patients with clinically confirmed symptomatic PE. Pulmonary emboli result in increased right ventricular afterload, leading to right ventricular dysfunction and failure. Pulmonary hypertension is a life-threatening consequence, and recent studies report that 4% to 5% of patients develop pulmonary hypertension in less than 2 years after asymptomatic PE.

CONCLUSION

Cancer patients are exposed to a high risk of thromboembolic complications, especially during the first 3 months after cancer diagnosis. The prothrombotic properties of tumor cells, surgical interventions, and aggressive chemotherapy may contribute to the high incidence of thrombosis during the initial period. The frequency and risk factors vary widely because of differences in study design, patient selection, follow-up period, and diagnostic methods. Arterial events are less frequent in the cancer population, and besides the traditional risk factors, such as smoking, hypercholesterolemia, and diabetes mellitus, factors related to venous thrombosis are also valid. Recent studies show increased rates of thrombotic events that can be attributed to improved awareness of thrombogenic phenotype of cancer, prompt testing for VTE diagnosis, increased use of implanted venous devices, and intensive treatment modalities, even in elderly patients or in those with comorbidities. Inversely, thrombosis can indicate the presence of occult malignancy, because 20% of venous and 11% of arterial events are caused by an undiagnosed cancer. Although the extensive screening is useful in the diagnosis of occult malignancy, it is not recommended in daily clinical practice. The procedure-related complications, cost-effectiveness, and limited number of studies that support this strategy should be taken into account.

The alterations in the clotting system are directly correlated with progression of malignancy, influencing prognosis and survival. Thrombosis is the second leading cause of death in the cancer population, although it is not clear whether VTE is a direct cause of mortality. Nowadays, guidelines and consensus statements for anticoagulant treatment are available. Despite the fact that anticoagulants reduce the risk of thrombosis, the risk of VTE recurrence remains high in cancer. In addition, anticoagulants are often associated with bleeding events and adverse interactions with concomitant medications that may affect the overall treatment approach. The restriction of complications requires an accurate determination of patients at high risk.

During the last decade, relevant studies have facilitated the better understanding of thrombotic factors that can be related to patient, cancer, or treatment, and allowed the risk stratification of patients. A recently developed predictive score estimates the chemotherapy-related thrombotic risk using parameters that are easily available in clinical and laboratory practice, namely, platelet and leukocyte count, hemoglobin level, body mass index, and primary cancer site. The expansion of this model with markers measuring the overall thrombophilic tendency, such as D-dimers, TF, and P-selectin, could increase both the sensitivity and specificity of the risk calculator, but the testing methods either are not widely available or lack standardization.

The individualization of anticoagulant treatment in terms of dosage, duration, and intensity could offer a survival benefit, eliminating the episodes of recurrence and bleeding. This demands an individual stratification of cancer patients according to VTE risk. Further work based on studies with the appropriate methodology is needed to elucidate the pathophysiology of cloting abnormalities in cancer and investigate the prognostic and treatment implications of quantifying indices in routine practice.

References


