Venous Thromboembolism among Cancer Patients: A Review

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Abstract. Venous thromboembolism is associated with adverse outcomes in patients with cancer. It has a multifactorial pathogenesis and a different expression pattern among various types of malignancies. Administration of anticoagulants forms the key therapeutic approach towards the management of venous thromboembolism. However, this is associated with increased risk of bleeding during the treatment. Chemotherapy, surgery, use of central venous catheters and radiotherapy represent major risk groups, which lead to increased venous thromboembolism and bleeding. Consequently, risk stratification can be an important tool, which can provide better thromboprophylaxis in a patient-based manner. The present review summarizes the epidemiology, pathogenesis and risk factors of venous thromboembolism in cancer patients. In addition, indications for different strategies towards challenging thromboprophylaxis and management of venous thromboembolism in cancer patients are also deliberated.

Keywords: Cancer, Thrombosis, Anticoagulant,
Thromboprophylaxis, Venous thromboembolism.

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Introduction

Venous thromboembolism (VTE) remains a source of considerable threat to patients with cancer which may lead to death. Cancer patients with VTE are also more likely to have recurrent VTE events requiring frequent readmissions and hospitalizations[1]. Bouillard, *et al.*[2] had described association of deep vein thrombosis (DVT) and cancer initially in 1823, even though it is generally attributed to Armand Trousseau only in 1865[3]. Anticoagulant treatment to combat DVT can lead to major consequences such as increased bleeding and a higher mortality rate[4-7]. Hence, identification of cancer-associated VTE risk factors is required in developing prophylactic measures, as well as for the better management of cancer patients. Moreover, a better perception of epidemiology and pathophysiology of VTE helps to develop proper guidelines for the prevention and management of such a serious condition challenging cancer patients.

Pathophysiology

Cancer-related venous thrombosis occurs as a result of tumor cells interfering with the normal vascular coagulation process and promoting angiogenesis[1,3,8]. Cancer represents a hyper-coagulable state through several complex biochemical events affecting procoagulants, and fibrinolytic system[1]. Most patients with cancer exhibit high levels of procoagulant factors as well as coagulation activation markers. Thrombin-antithrombin, prothrombin fragment 1+2(F1+2), fibrinopeptide and D-dimer have been reported to be involved in the malignant process[9,10]. Several other studies have reported a high expression of the transmembrane glycoprotein: tissue factor (TF) with various tumors[11]. Tissue factor normally expressed by bacterial lipopolysaccharides and inflammatory cytokines activates the coagulation cascade, carrying malignant and metastatic potential[12]. Kakkar *et al.*[13] reported an increased expression of TF, thrombin-antithrombin complex, coagulation factors VIIa and XIIa, and F1+2 denoting activation of the coagulation cascade[13]. Moreover, high TF expression was associated with angiogenesis in

various malignancies[12]. Cysteine protease (CP) is yet another tumor related procoagulant factor that can act directly through factor X, even when factor VII is absent[14]. Higher levels of CP have been observed in malignantly transformed cells as compared to their normal counterparts[14]. TF and CP, along with tumor cells induce hypercoagulable state through down regulation of the fibrinolytic system[12,15]. The high levels of CP in cancer patients slowly decline which might justify the higher incidence of VTE in the early stages of the disease. Furthermore, tumor cells also release some soluble mediators of coagulation such as ADP, thrombin, and other proteases, which leads to platelet activation and aggregation (Fig. 1)[16].
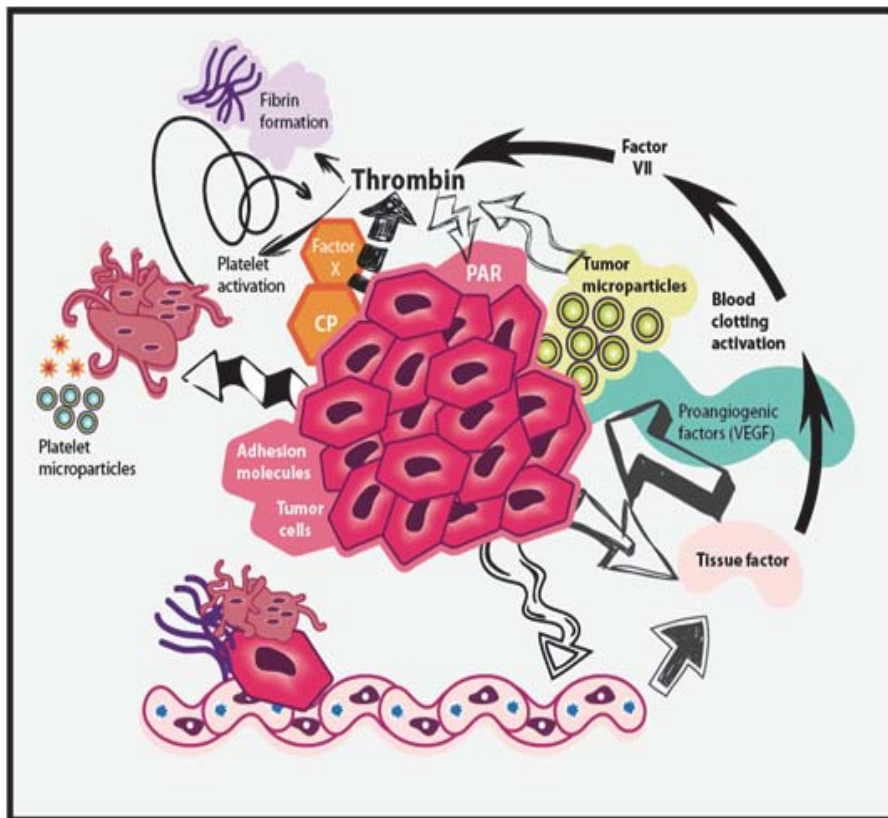
Fig. 1. **Mechanism of hemostatic activation by malignant cells involving different pathways: Tissue factor (TF), procoagulant cyteine protease (CP), platelets**

activation, vascular endothelial growth factor (VEGF) and protease activated receptor (PAR).

Epidemiology

Venous thrombosis has been observed in several association studies on cancer and VTE. These studies have inevitably concluded that VTE is considered a high risk factor especially during initial stages of cancer[16,17]. The annual incidence of VTE in the general population is 0.1%, increasing to about 0.5% in cancer patients. The incidence of VTE among cancer patients can vary due to patient diversity. In addition, the complexity of performing large epidemiological studies can cloud precise data[18-21]. Generally, the prevalence of thrombosis in cancer is underestimated[20]. Only autopsy studies can largely confirm the true incidence[20]. A large population-based epidemiological study reported that about 20% of new VTE cases are associated with cancer[21]. Others have indicated that patients with solid tumors of the pancreas, ovary and the brain carry an increased risk of VTE as compared to patients with hematological malignancies. However, more recent studies imply a similar incidence among the solid as well as hematological malignancies[22-24]. Blom *et al.*[25] reported the risk of developing the first attack of VTE in hematological malignancies with an odds ratio of 26[25].

Cancer associated VTE can occur at any stage of the disease process. This may be explained by patients-related factors, the disease itself and the various treatment protocols[3].

Patient-Related Risk Factors

Factors of cancer-related thrombosis include age, sex, obesity, previous thrombosis, chronic renal and hepatic disease, hypertension and heart failure. These co-morbidities have a significant effect on patient survival; as a stronger risk of VTE has been noted in malignancy of the ovary and brain[22,23]. Higher rates of VTE are reported among males in some reports, while others have suggested a higher incidence in females[3,17].

Cancer-Related Risk Factors

Cancer-related factors include tumor type, histological subtype, cancer stage, the disease aggressiveness and rate of metastatic spread. A retrospective study that included in-hospital cancer patients, noted the highest risk of VTE was observed in pancreatic, brain, endometrial and cervical malignancies (12.1%, 9.5% and 9%, respectively)[20].

Histological classification also predicts the risk for VTE in some malignant diseases. Lung adenocarcinoma subtype exhibited a 9.9% incidence of VTE while the incidence was lower with squamous cell carcinoma (7.7%)[24]. Patients diagnosed with localized malignancies have a comparatively lower incidence of VTE[19]. Furthermore, rapidly growing malignancies and patients with advanced disease has been associated with a higher rate of VTE[6,23].

Treatment-Related Risk Factors:

Patients with cancer are treated with different treatment modalities, such as chemotherapy, radiotherapy and surgical resection. Chemotherapy, by far, carries the highest risk for VTE. If the cancer subtype carries a four-fold risk of thrombosis, the risk for VTE is amplified to six folds with chemotherapy[26,27].

Prothrombotic states induced by chemotherapy are due to vascular endothelium injury, decreased levels of natural anticoagulants, increased levels of procoagulants, TF expression, platelets activation and up regulation of monocyte-macrophages TF expression[28,29]. Cisplatin, 5-Fluorouracil, L-asparaginase and thalidomide are associated with high risk for VTE[30-32]. Meta-analysis of the safety of lenalidomide for multiple myeloma patients revealed a relative risk of DVT of 2.5[33]. Surgery further compounds the risk by two-fold. In

addition, the longer duration of surgery and the need for surgical re-exploration, the higher is the risk[34].

Even though, isolated radiation therapy associated thrombosis has not been reported considerably, the compound effect of both chemotherapy and radiation results in a profound inflammatory response, which could lead to thrombosis along with other predisposing factors[35].

(i) Hormonal Therapy

Tamoxifen binds to estrogen receptors to produce anti-estrogenic effects. It also inhibits angiogenesis, and induces apoptosis, which explains its beneficial effect as adjuvant therapy for breast cancer[36]. Thrombosis was the most frequent side effect in patients treated with tamoxifen[37]. In a systematic review, 5 years of tamoxifen therapy in women with breast cancer had a dramatic increase in risk for VTE (1.5-7.1 fold increase); however, VTE risk becomes less problematic with the third generation oral aromatase inhibitors[37].

(ii) Hemopoetic Growth Factors

Anemia may induce a state of decreased oxygen in the tumor that can lead to resistance to chemotherapy and radiation therapy[38]. Guidelines suggest erythropoietin therapy to increase hemoglobin (Hb) levels in chemotherapy-associated anemia after a detailed patient history has ruled out other causes for anemia[39]. Recombinant human erythropoietin (rHuEpo) can maintain higher Hb levels in patients undergoing radiation therapy[35]. Initial studies reported VTE rate of 20% in patients with cervical carcinoma receiving rHuEpo with chemotherapy or radiotherapy[36]. This has been supported by the Cochrane meta-analysis that included 35 trials representing almost 7000 patients[40]. Prothombotic effect of rHuEpo in cancer patients is the result of increasing red cell mass, whole blood viscosity and increasing metabolically active reticulocytes, which augment platelet reactivity in vitro[41,42]. Recombinant human erythropoietin also has synergistic effect with thrombopoietin for platelet and endothelial activation[3].

The role of hematopoietic growth factors in increasing the risk of cancer-associated thrombosis is unclear[43].

(iii)   Central Venous Catheters (CVC)

The use of indwelling central lines has facilitated the easy intravenous administration of not only chemotherapy, but also, parental nutrition, and antibiotics as well as other supportive therapy. However, CVCs use increases the risk of catheter-associated thrombosis (CAT). The incidence of symptomatic CAT in patients with cancer varies between 0.3% to 28%; moreover, the rate of catheter-related VTE confirmed by venography has been reported to be higher[44]. Risk factors for the development CAT include; site of the catheter, synthetic material, number of lumens, nature of the infusion and the position of the catheter's tip. Non-invasive serial compression ultrasonography (CUS) is the standard test for the upper extremity thrombosis evaluation; however, patients with high-pretest probability and negative CUS require evaluation using contrast venography[3].

Use of Biomarkers for Risk Assessment of VTE in Cancer Patients

Presently, thromboprophylaxis improves the outcome among patients with cancer in limited number of clinical studies despite the well-documented increased risk of thrombosis in this population[45]. Moreover, the pharmacological thromboprophylaxis is considered a major therapeutic challenge in view of thrombocytopenia caused by chemotherapeutic agents. Therefore, identification of a high-risk group who would benefit from this mode of thromboprophylaxis is well justified.

Various biomarkers such as leukocyte count, platelet count, and levels of tissue factor, P-selectin, D-dimer and CRP have been associated with higher risk of cancer VTE[18]. Leukocytosis upon initial diagnosis has been found to be associated with risk for developing VTE[18]. Venous thrombosis occurred in 4.5% patients with baseline leukocytosis, WBC $\geq$ 11 x 109/L, compared to (1.8%) with normal WBC[18]. Thrombocytosis is often observed in patients

with cancer. A baseline platelet count ($\geq$ 350 x 109/L) before starting chemotherapy can activate coagulation resulting in a higher risk for developing VTE[18].

In recent years, D-Dimer gets attention due to its significant role in cancer associated VTE. Vormittag *et al.*[46] in a large prospective study of cancer patients, found that high levels of D-dimer were an important predictor of VTE occurrence. Coagulation activation markers such as prothrombin fragment 1+2 (F1+2), D-dimer and tissue factor (TF) have been elevated in cancer patients[18]. Tissue factor (TF) induction has been seen in various cancers, which up-regulates angiogenesis, initiating coagulation with subsequent VTE[11]. A four-fold occurrence of VTE has been reported in patients with high TF-expressing cancers. Hence, TF has been suggested to be used as a predictive biomarker of VTE seen in cancer patients[18].

Factor VIII, a vital part of the coagulation cascade, when elevated, can lead to VTE even among patients without cancer[3]. Among cancer patients, elevated FVIII levels carries a 5-fold risk for VTE and can carry a higher risk for developing recurrent VTE[47].

Soluble P-selectin (sPS) is an important cell adhesion molecule, which is expressed on endothelial cell membrane and in α granules of platelets. It interacts with leukocytes to release procoagulant, tissue factor-rich microparticles (MPs) seen in endothelial cells, platelets and cancer cells. Ay *et al.*[48] proposed the significant role of sPS in thrombotic events seen in cancer patients and their prospective observational study reported sPS as a significant risk factor of cancer associated VTE.

Scoring System of Risk Assessment for VTE in Cancer Patients

Developing a predictive risk assessment model in non-cancer patients has helped to stratify patients and tailor thromboprophylaxis accordingly (Table 1). A model-based approach that incorporates multiple risk factors would help to identify high-risk patients in this patient population. This model would allow a prophylactic strategy in an attempt to improve outcomes of management and sparing the low

risk patients from unnecessary potential complications of anticoagulant therapy.

Khorana *et al.*[18] developed and validated a simple predictive model of using initial clinical and laboratory data. In this study, five variables have been identified: namely cancer site, platelet count of $\geq$ 350 X 109/L, Hb < 100 g/L and /or use of erythropoiesis-stimulating agents, WBC $\geq$ 11 X 109/L, and BMI of $\geq$ 35 kg/m^2. Rates of VTE in the validation cohort were 0.3% in low-risk (score = 0), 2% in intermediate-risk (score = 1-2), and 6.7% in high-risk (score $\geq$ 3) category.

Table 1. Patient-related factors and biochemical markers as risk factors for venous thromboembolism.

		Cut–Off Value	**OR**
Patients Factors	Age	> 60	2.6
	Gender	Males Females	
	BMI	> 35 kg/m^2	2.1
	Previous thrombotic		6-7 folds
	Co-morbid Medical Conditions	Ø 3 conditions	
Biochemical Markers	Initial Leukocytosis	WBC $\geq$ 11x10^9/L	2.0
	Initial Thrombocytosis	Plt $\geq$ 350x10^9/L	3
	D-Dimer		1.8
	Factor VIII: C	> 232%	3

BMI = Body mass index; WBC = White blood cell; Plt = Platelets count

The advantage of the "Khorana-Score" is that all parameters of this risk model are routinely determined in patients with cancer at diagnosis. Further development of Khorana-Score to predict cancer associated VTE has been validated by Ay *et al.*[48]. Two additional markers were incorporated to Khorana's model: P-selectin level $\geq$ 53 mg/ml and D-Dimer $\geq$ 1.44 mg/ml. In their prospective observational study, the probability of VTE in the original risk model after 6

months reported as 17.7% in patients with highest risk score (≥ 3) and 1.5% in those with score 0[48].

Prevention of VTE

The clinical use of this scoring model assist in the decision for thromboprophylaxis in a patient-focused approach[18,48].   Anti-coagulant therapy in this clinical setting presents a major challenge, as the patients are at a very high risk of bleeding; secondary to concomitant thrombocytopenia. Thromboprophylaxis was found to be beneficial in certain high-risk populations such as during the perioperative period or during hospitalization; however, data in the ambulatory settings are inconsistent[49,50].

Prevention of VTE in the Perioperative Period

Postoperatively, VTE has been reported in literature to double or even quadruple in incidence. Venographic evidence of DVT ranges from 20% to 40% with a 1% mortality as a consequence of PE[49,50]. Therefore, postoperative thromboprophylaxis for significant reduction of VTE has been strongly recommended[51].

Use of Low-Molecular Weight Heparin (LMWH)

Low-molecular-weight heparin is the most frequently used anticoagulant for thromboprophylaxis in surgical patients[51]. A meta-analysis of randomized trials evaluating surgical thromboprophylaxis, found no significant difference between the LMWH and unfractionated heparin (UFH) in symptomatic VTE, major bleeding, transfusion and death[51]. Extended prophylaxis of 21 days duration resulted in a significant reduction in the incidence of VTE from 12% to 4.8% (p = 0.02)[52].

Hospitalized or Bedridden Patients

The risk for thrombosis is significantly high if cancer patients require hospitalization or chemotherapy, especially in patients with advanced disease. The American Society of Clinical Oncology VTE Guideline Panel, recommends thromboprophylaxis in the above-mentioned set of cancer patients[53].

Those patients should always be considered for primary thrombo-prophylaxis. No clinical study has evaluated a cancer-specific population. However, general agreements and guidelines unanimously support the use of prophylaxis in cancer patients during hospitalization, particularly in patients diagnosed with advanced stage cancer, those admitted with an acute illness, or undergoing surgery[3].

Hormonal Therapy

Patients at risk for developing breast cancer should be evaluated for the risk of VTE[54].

Central Venous Catheters (CVC)

Despite the strong association between the CVCs and upper limb deep venous thrombosis, routine anticoagulant prophylaxis is not recommended[55,56]. Studies evaluating the use of low dose OAC revealed conflicting results[57,58]. Institutions are encouraged to assess their local rates of CAT and develop a protocol of thromboprophylaxis.

Ambulatory Cancer Patients

Only 3% of symptomatic VTE is reported in ambulatory advanced cancer patients, or those who have metastatic disease[3]. Recently, multiple studies reported the potential of beneficial effect on thromboprophylaxis in ambulatory patients, but fail to identify proper patients who would benefit from such prophylaxis.

Clear exceptions are ambulatory patients with multiple myeloma on thalidomide/lenalidomide - containing regimens that are considered as an established high-risk group and should receive thromboprophylaxis[59]. Therefore, instead of considering routine thromboprophylaxis, ambulatory patients will need to be evaluated for actual benefit and duration of thromboprophylaxis as necessary.

Palliative Care Settings

McLean *et al.*[60] concluded that primary thromboprophylaxis in cancer patients receiving palliative care are under-utilized despite

being supported by level 1A evidence. This may reflect physician's concern regarding the negative impact on the quality of life.

The eighth edition of the American College of Chest Physicians (ACCP) guidelines recommend VTE prophylaxis in all hospitalized cancer patients who carry a high risk for bleeding[61]. However, the compliance of oncologists with the recommendations remain low, which could represent lack of awareness or unfounded fear of bleeding within the oncology community[3]. Institution-based VTE prophylaxis guidelines with risk for VTE stratification, followed by effective monitoring and auditing policy by the institution and sustained awareness campaigns should be adopted to avoid complications of treatment. For evidence-based guidelines, the reader is referred to the ACCP guidelines, the American Society of Clinical Oncology Guidelines (ASCO) and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Venous Thromboembolic Disease[53,62,63].

Management of VTE

Initial Treatment

The treatment for acute VTE in cancer patients is the same as patients without cancer. Initial therapy with subcutaneous (SC) LMWH is as effective and safe as intravenous unfractionated heparin (UFH)[53,62]. However, the longer half-life, the SC injection, and the weight-based dosing, obtrude the need for laboratory monitoring to make LMWH a preferred option. The advantage of LMWHs is to allow outpatient administration and reduce the need for hospitalization. Unfractionated heparin can be given initially for 5–10 days, starting with a bolus of 80 IU/kg, followed by 18 IU/kg/hr, and maintaining the activated partial thromboplastin time at 1.5–2.5 times the control[53,62].

Secondary Prophylaxis

Oral anticoagulant therapy (OAC) with vitamin K antagonist is an established treatment method of VTE in clinical practice. This

therapeutic strategy could be applied along with heparin therapy. The recurrence rate of VTE quadruples in patients with cancer receiving OAC[64].

The high failure rates in cancer patients reflect the greater difficulty in maintaining therapeutic INR levels due to multiple drug interactions, gastrointestinal upset, vitamin K deficiency, and concomitant liver disease. In addition, temporary discontinuation of OAC is often necessary during periods of thrombocytopenia and when invasive procedures are needed, which lead to long periods of inadequate anticoagulation. Moreover, more frequent events of VTE have been reported in cancer patients under OAC while maintaining therapeutic INR targets[64].

Several studies have compared the safety and efficacy of LMWHs to that of OAC[61]. A Cochrane systematic review concluded that LMWH, when compared to OACs, reduces the risk of recurrent VTE in cancer patients when used for extended periods of time[65]. However, the duration of anticoagulant treatment has not been fully defined in patients with cancer. Generally, it is recommended that patients with metastases continue with ''indefinite'' therapy. For those with localized disease, anticoagulant treatment is recommended for as long as the cancer is ''active'' and the patient is receiving treatment[62,63].

Management of Catheter Associated Thrombosis (CAT)

Patients with CAT should receive antithrombotic treatment; however removal of the implantable venous device should be decided by clinical necessity for venous access or by evidence of pulmonary embolism[3]. Implantable venous access devices should be removed before medical treatment is started or after failure of fibrinolytic, or anticoagulant treatment thrombus progression and limits the risk of secondary infections[3]. Alteplase is the most popular and effective recombinant tissue-plasminogen activator (rt-PA) used in the treatment of thrombotic occlusions, rarely exhibiting hypersensitivity[66].

Implications of Cancer-Associated Thrombosis

Diagnosis of VTE in a patient with cancer influences the short and long term mortality and morbidity[18]. The one–year mortality in cancer patients increases as soon as VTE is diagnosed. In addition, the recurrence rate of VTE is tripled compared to patients without cancer[64]. Furthermore, the risk of dying from PE in cancer patients undergoing surgery is tripled compared to non-cancer surgical patients. The risk of bleeding complications from anticoagulants therapy in cancer patients with VTE are two-fold greater than patients with no cancer.

Post-Thrombotic Syndrome is characterized by devastating leg pain, swelling, and fibrosis, which may result in debilitating leg ulcer, mobilization problems, and the need for long-term nursing care[67]. Even though, little amount of data available on the incidence of cancer associated post-thrombotic syndrome; around 30% of patients with deep venous thrombosis develop this condition within 5 years where 8.1% will be severe[3]. It is expected that post-phlebitic syndrome in cancer patients has a higher incidence in view of patient and treatment related factors[67].

Tumour progression

Accumulating evidence confirms that VTE and cancer mutually coexist. Cancers spread through angiogenesis through a complexity of mechanisms involving procoagulant activity[12].

VTE and Occult Cancer

Patients can present initially with VTE can be investigated subsequently malignancy[68]. In a pooled analysis, the odds ratio for subsequent cancer in patients with idiopathic VTE was 4.8[69]. Moreover, about 10% of patients with idiopathic VTE were diagnosed with subsequent cancers in the following 5–10 years, the majority of which were reported in the first year of the initial presentation[70]. Piccioli *et al.*[71] found that extensive investigations for a period of up to two years in patients with idiopathic VTE led to an early detection

of cancer.   However, the cost-effectiveness of such a system is debatable.

In conclusion, despite available evidence, many questions remain to be answered about the association between VTE and cancer. The risk of VTE among patients with cancer continues to increase and is clearly linked to patient's disease staging and treatment-related factors. However, this risk, as well as the associated morbidity and mortality pose important challenges for hematologists, oncologists, and other healthcare providers.

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التجلطات الوريدية عند مرضى السرطان: مراجعة نقدية

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جدة　– المملكة العربية السعودية

المستخلص. تعتبر التجلطات الوريدية من الأعراض المرضية الهامة لمرضى السرطان كما تعتبر من أهم أسباب الوفيات في هذا المرض. وبالرغم من شيوع التجلطات الوريدية في جميع أنواع السرطانات إلا أن نسبة حدوثها تختلف طبقاً للأسباب العديدة للتجلطات الوريدية. ويعتبر استخدام أدوية منع التجلط للوقاية من التجلطات الوردية من التحديات الشديدة للطبيب المعالج بسبب مضاعفات النزيف أثناء العلاج. ومن أسباب زيادة التجلطات الوردية عند مرضى السرطان: العلاج الجراحي، استخدام العلاج الكيميائي، العلاج بالاشعةً واستخدام القسطرة الوريدية لإعطاء الأدوية، و من ثم يجب إعطاء الجرعة الوقائية من أدوية منع التجلط وفقاً لخطورة احتمالية حدوث هذه المضاعفات. في المقال التالي نناقش المسببات واحتمالية حدوث التجلطات الوريدية وبالتالي طرق الوقاية منها عند مرضى السرطان.