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Venous Thromboembolism in Cancer Patients

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1. Introduction

Venous Thromboembolism (VTE) is a major complication of cancer and is one of the leading causes of death in patients with cancer. The risk for VTE in this group of patients is increased several folds in hospitalized cancer patient and in those on active therapy. The short and long term consequences of VTE diagnosis in cancer patients are many including increased in mortality rate, bleeding while on therapy for VTE. It has, therefore, become important to identify the risk factors for cancer-associated VTE, develop guidelines for prevention strategies for high-risk patients as well as management of VTE when it complicates the course of cancer disease or its treatment with chemotherapy immunomodulatory agents, antiangiogenesis or hormonal therapy. Proper understanding of the epidemiology and pathophysiology of VTE and its risk factors in cancer patients is central to adequate prevention and management of this serious complication in cancer patients.

2. The epidemiology and pathophysiology of venous thrombosis in cancer patients

2.1 Cancer cells and the haemostatic mechanisms

The haemostatic system is a complex, multifaceted mechanism that participates in maintaining the integrity of the vascular system and fluidity of blood. In coordination with the mechanisms of inflammation and repair, the haemostatic mechanism produces a coordinated response. Haemostatic systems are normally quiescent and are only activated after injury and results in the production of a platelet plug, fibrin-based clot, deposition of white cells at the site of injury, and activation of inflammatory and repair processes.

Tumor cells can activate blood coagulation through multiple mechanisms, including (a) production of procoagulant, fibrinolytic, and proaggregating activities; (b) release of proinflammatory and proangiogenic cytokines and (c) direct interaction with host vascular and blood cells through adhesion molecules.

Miller et al (1) studied the link between the haemostatic systems and cancer where the authors evaluated haemostatic status every year for 4 years in a population of approximately 3000 middle-aged men without cancer. Among patients with the activation

of the haemostatic system (defined as persistent elevation of fibrinopeptide A and prothrombin fragment 1+2 levels), total mortality was significantly higher in participants with persistent activation (17.1/1000 person-years) than in patients without activation (9.7/1000 person-years; p=0.015). This difference was attributed to an increased incidence of death from cancers (11.3/1000 vs. 5.1/1000 person-years).

The majority of patients with cancer has increased levels of procoagualnt factors V, VIII, IX, and XI, as well as increased levels of markers of coagulation activation (e.g., thrombin–antithrombin, prothrombin fragment 1+2, fibrinopeptide and D-dimer (2). In addition, patients with some disseminated malignancies seem to have a deficient activity of von Willebrand's factor-cleaving protease (ADAMTS-13), resulting in unusually large von Willebrand factor multimers leading to platelet thrombosis (3).

Many tumors have been shown to activate blood coagulation through an abnormal expression of high levels of the procoagulant molecule tissue factor (TF). In normal vascular cells, expression of TF is not expressed, except when induced by inflammatory cytokines such as interleukin 1β and tumor necrosis factor a (TNF-a) or by bacterial lipopolysaccharides. In tumor cells, TF is expressed and causes activation of the extrinsic pathway. In the elegant study conducted by Kakkar et al (4) plasma levels of TF, factor VIIa, factor XIIa, the thrombin–antithrombin complex, and prothrombin fragments were elevated in patients with cancer compared with healthy controls. Tissue factor and factor VIIa levels were both significantly higher, suggesting significant activation of the extrinsic pathway. On the other hand, levels of factor XIIa were only marginally elevated, indicating that the intrinsic pathway is not involved to a significant degree in the hypercoagulable state seen in patients with cancer (5).

Tumor cells express cancer procoagulant, a cysteine protease expressed only on malignant tissues. Cancer procoagulant directly activates factor X in the common pathway independent of factor VII (6). The activity of this protease seems to be driven by the stage of cancer. The onset of cancer is usually associated with high levels of protease slowly declines thereafter (7), partially explaining the tendency of thromboembolic events to occur during the first three month following the diagnosis of cancer.

In addition to the expression of TF and cancer procoagulant, tumor cells enhance coagulation in patients with cancer by expressing proteins that regulate the fibrinolytic system, including plasminogen activators, plasminogen activator inhibitors 1 and 2, and plasminogen-activator receptor, leading to an imbalance of fibrinolytic mechanism (8) Tumor cells may elicit platelet activation and aggregation through direct cell–cell interactions or through the release of soluble mediators, including ADP, thrombin, and other proteases. Furthermore, expression of certain cytokines by tumor cells, including TNF-a and interleukin 1β, induces expression of TF on endothelial cells and simultaneously downregulates the expression of thrombomodulin, resulting in a prothrombotic state at the vascular wall.Multiple studies have provided considerable evidence for a bidirectional clinical association between VTE and cancer, in that cancer elicits expression of procoagulant activities, contributing to the prothrombotic state in these patients, and the procoagulant activities themselves seem to elicit cancer growth, proliferation, and metastasis. Fibrin and platelet deposition around solid tumor cells promotes angiogenesis through platelet-derived proangiogenic factors, and may seal immature tumor vasculature

and provide a degree of protection to the cancer cells from the immune system. Fibrin has also been shown to increase expression of TF and induce expression of IL-8 and vascular endothelium growth factor (VEGF) and thereby, enhancing angiogenesis (9-10).

The TF–factor VIIa complex can signal through cleavage of protease-activated receptors, which, in turn, induce the mitogen-activated protein kinase (MAPK) signal transduction cascade (11). The MAPK pathway is involved in the induction of genes involved in angiogenesis, migration, and proliferation. In addition, phosphorylation of the cytoplasmic tail of the TF receptor has also been shown to indirectly activate transcription of VEGF, downregulate thrombospondin (an antiangiogenic protein), and induce cell migration. Expression of TF by malignant cells also seems to support metastatic process and is dependent on the formation of the TF-factor VIIa complex (11).

2.2 The incidence of venous thromboembolism in cancer patients

The first description of deep vein thrombosis (DVT) in patients with cancer was made by Bouillard in 1823(12) although this was popularly first credited to Armand Troussean, the French Physician, in 1865 (13-14). Since that time, hundreds of studies have provided solid data on the clinical association between VTE and cancer, and delineated the elevated risk for VTE particularly during the first few months following the diagnosis of cancer and in the presence of distant metastasis (15-18).

The incidence of DVT or PE in patients with cancer varies widely because of the heterogeneity of the patients' population and the difficulty of conducting large epidemiological studies. Based on a prospective medical database in the United States, the annual incidence of a first episode of DVT or PE in the general population is 0.1% (15), while the estimated annual incidence of VTE in the cancer population is 0.5%. (19-21) The prevalence of cancer-associated thrombosis may be underestimated by more than 10-fold as autopsy studies in cancer patients have demonstrated even higher rates of VTE (17-22). In a large population-based epidemiological study, approximately 20% of all new cases of VTE are associated with underlying cancer, whereas 26% of incident cases had idiopathic VTE (15).

The risk of VTE associated with different malignancies has more recently been quantified in NHL (23), colonic cancer (24) ovarian (25) lung (26) and breast cancer (27). It was generally thought that solid tumors, such as pancreatic, ovarian and brain cancer carry a much higher risk for VTE than haematological malignancies. However, recent studies suggest that the incidence of VTE in patients with haematological malignancies may be similar to that observed in patients with solid tumors (28). In a population based case-control study of patients with a first episode of VTE, Blom et al found that the odds ratio of developing VTE among patients with haematological malignancies was approximately 26 compared to the general population (18). Similar results were also reported by other authors (29-31).

Prospective studies has shown that VTE have inflicted a higher risk of several adverse complications on patients with cancer including recurrent VTE, bleeding complications while on anticoagulant treatment, increase in both short-term and long-term mortality (32-33) and increased mortality during first 3 month of therapy. The risk of VTE is markedly different for cancer patients throughout the course of the disease and this variable incidence of VTE comorbidity in cancer patients can be attributed to a combination risk factors related to the patient, the cancer itself and treatment (34).

2.3 Patient-related factors and risk of VTE

a. **Age:** Older age has been shown to be associated with VTE in hospitalized cancer patients, but not in ambulatory patients (35-37). The rate of VTE in patients older than 60 years of age undergoing surgery for various solid tumors was significantly higher than that in younger patients by multivariate analysis (OR 2.6) (36-38).
b. **Gender:** Among cancer patients, most studies have identified male gender as a significant predictor of VTE. (19-20) However, A recent pooled retrospective study of VTE rates in a large cohort of hospitalized cancer patients reported a higher rate in females (OR 1.1, $p < 0.0001$) (39)
c. **Race:** In the general population, the incidence of VTE varies by race. In the USA, it is highest among blacks and lowest among Asian-Pacific Islanders (40).
d. **Previous thrombotic episode:** Cancer patients with a past history of VTE have a 6–7 fold increased risk of developing VTE compared to those with no history of VTE (38).
e. **Obesity** has been confirmed to be an important risk factor in cancer-associated thrombosis. Body mass index ≥35 kg/m^2 was identified as one of five variables in a risk prediction model proposed by Khorana et al with an OR of 2.1 (38)
f. **Chronic co-morbid Medical Conditions:** The presence of chronic medical co-morbid conditions such as chronic renal disease, chronic liver disease, hypertension and chronic heart failure has a marked effect on the incidence of cancer-associated thrombosis and survival. The presence of three or more chronic medical conditions was the strongest risk factor for development of VTE among the patients with gliomas and ovarian cancer, and was the second strongest risk factor among patients with breast or colon cancer (39-40).

2.4 Cancer-related factors to incidence of VTE

a. **Tumor type:** certain tumors are strongly associated with VTE. In the retrospective cohort study of hospitalized cancer patients. Khorana et al (38), reported that sites of cancer with the highest proportion of patients with VTE were pancreas, brain and endometrial or cervical were 12.1%, 9.5% and 9%, respectively (California Cancer Registry). The incidence of VTE in pancreatic cancer patients is at least 10-fold higher than the rate in patients with prostate cancer. Histological subtype also predicts the increased risk of VTE in some types of malignancy. The incidence of VTE in patients with non-small cell lung cancer was 9.9% in patients with adenocarcinoma subtype versus 7.7% in patients with squamous cell carcinoma (HR 1.9, CI 1.7–2.1) (27, 26). Although mucin production was once proposed as the common feature and the thrombogenic mechanism amongst these mucin-producing tumors, the exact pathogenesis of the prothrombotic state of mucin is still not fully understood.
b. **Initial cancer stage:** Patients diagnosed with local-stage cancer, in general, have a very low incidence of VTE, whereas the incidence is much higher in patients diagnosed with metastatic disease at time of diagnosis (24-27).
c. **Biological aggressiveness of cancer:** The observed differences in the incidence of VTE between different cancer types correlate with the biological behavior of the cancer. A very strong correlation was found between the 1- year fatality rate and the 1-year cumulative incidence of VTE (41). In addition, presence of metastatic disease at the time

of diagnosis is a strong independent risk factor for developing VTE within the first year of cancer diagnosis (42-43).

d. **Rate of metastatic spread:** The incidence of VTE has been reported to correlate with the rate of growth and spread of the cancer cells. Fast growing cancer such as colonic and ovarian, has been associated with a higher rate of VTE (24-25, 41-42) and patients with advanced and metastatic disease had a higher risk of VTE (OR 19.8, CI 2.6–149). The observed incidence of VTE in ovarian, colorectal, pancreatic, lung and breast cancer supports the finding that advanced stage increases the risk of cancer associated VTE (24-25, 44).

2.5 Cancer Treatment-related factors and risk of VTE

2.5.1

Chemotherapy is one of the most important treatment-related factors in the aetiology of cancer-associated VTE as cancer alone is associated with a four-fold risk of thrombosis, while chemotherapy increases the risk by six-fold (45-47)

Several different mechanisms have been reported to explain the prothrombotic states induced by chemotherapy including (a) damage to the vascular endothelium (48-49), (b) reduction of endogenous, physiological, anticoagulant factors (56-59), (c) increase of levels of procoagulants (54-57), (d) induction of tumor and endothelial level apoptosis and cytokine release that, in turn, lead to increased expression and hence activity of TF (56-57), (e) induction of platelet activation (58) and (f) direct induction of expression of monocyte-macrophages TF (59).

The following chemotherapeutic agents are associated with high risk for VTE:

- **Cisplatin based regimens**

Weiji et al (60), in a retrospective review of VTE in germ cell cancer patients treated with cisplatin and bleomycin-based chemotherapy reported an estimated risk of thrombosis of 8.4%. In a prospective study of VTE in non-small cell lung cancer patients treated with cisplatin and gemcitabine, Numico et al (61) reported VTE incidence of 17.6%.

The mechanisms by which cisplatin induces thrombosis is not well known but in vitro studies suggest increase in the level of TF (48), platelet activation (50) and increased levels of von Willebrand factor suggesting endothelial injury (58). The latter perhaps explain the cisplatin induced arterial thrombosis. Moore et al (62) conducted a large retrospective analysis to determine the incidence of venous and arterial thromboembolic events in patients treated with cisplatin-based chemotherapy and confirmed the unacceptable incidence of those events and recommend randomized studies to examine the question of prophylactic anticoagulation in patients with cancer treated with chemotherapy.

- **L-Asparaginase**

L-Asparaginase (ASNase) has been a mainstay in the treatment of paediatric patients with acute lymphoblastic leukemia since the 1960's and there are several reports of ASNase containing regimen used in the treatment of paediatric ALL achieving a higher survival rate than non-ASNase treatment regimens used for ALL in adults and adolescents (63-65).

L-Asparaginase converts L-Asparagine to L-aspartic acid and, thereby, reduces levels of L-Asparagine, an essential amino acid for protein synthesis and as a result, leukemic cell growth is inhibited. However, the production of multiple plasma proteins by the liver including haemostatic factors, is also reduced and hence causing marked disruption of the haemostatic mechanism: prolongation of PT and aPTT, reduced fibrinogen level, reduced levels of protein C and protein S, Antithrombin III (AT) , plasminogen, factor IX and factor XII. On the other hand, ASNase causes increased procoagulant factors V, VIII (54-56). In addition, to the profound effects of the drug on the pro- and anticoagulant molecules, ASNase has also been shown to increase levels of immunomodulin a marker of vascular injury (66).

The simultaneous effects of ASNase on both procoagulant and thrombolytic proteins increase the risk of both bleeding and thrombosis, the latter being the main challenge.

The incidence of ASNase – associated VTE complications is age-dependent, 3-5% in children (67, 31) whereas the incidence reported from Dana-Farber Cancer Institute (1991-2008) in adult patients (≥ 30 years) was 34% and 42% (68). Less intensive ASNase regimen in adult patients have reported lower rates of thrombotic complications (69). Limited reports and data on a small number of patients treated with pegASNase –related DVT may be less frequent than those treated with after E. Coli ASNase (70-74). In UKALL 2003, Children with DVT were routinely retreated with pegASNase and concurrent heparin prophylaxis without recurrence of thrombosis (75). The confounding factors for VTE during ASNase therapy are presence of indwelling catheter, oral contraception, prednisolone and inherited thrombophilia (76).

The majority of clinically important thrombotic events were those related to venous catheters and those in the central nervous system. The majority of catheter-associated thrombosis (CAT) are asymptomatic and the majority, in both children and adults, occur during induction (68).

In the randomized trial of native ASNase versus pegASNase (74), the incidence of cerebral venous sinus thrombosis (CVST) of 2-3% in children was reported. In children ≥ 10 years, initial WBC > $50x10^9$ /L at diagnosis may predict higher risk for CVST (77). The GIMEMA study on adult ALL patients protocol, including E. Coli ASNase in the induction phase, CNS thrombotic events was 3% (77).

Prevention and Management of ASNase induced thrombosis

Primary Prevention: In children and adolescents prophylaxis is rarely undertaken and there has been few reports that the use of AT concentrate may decrease the incidence of thrombosis (78-79)

In a historically controlled study of adult patients, Mitchell et al (78) reported that the incidence of VTE was lower in a cohort of patients who received prophylactic AT concentrate but the study did not establish efficacy. A retrospective comparison of cohort of patients at two centers in Canada who had prophylaxis against CNS thrombosis with fresh frozen plasma and cryoprecipitate did not develop CVST (80).

Most paediatric oncology centers do not perform the coagulation screening tests or perform AT levels routinely. If prophylaxis is deemed appropriate for a particular patient, it is best applied during induction phase of therapy when the majority of VTE events take place.

For intracranial thrombohemorrhagic complications, the use of AT concentrates and/or cryoprecipitates to replace both AT and fibrinogen, respectively, is a reasonable approach. In case of unavailability of AT, fresh frozen plasma (FFP) at a dose of 20 ml/kg can raise the AT level by approximately 20%. However, FFP may also replenish asparagine and, thereby, counteract the anti-leukemic effect of ASNase. There is no clear indication from the literature about whether further administration of ASNase should be stopped in adults after a thrombotic event while on therapy. In children, ASNase is continued under cover of low-molecular-weight heparin. Patients with thrombotic events after ASNase have been successfully re-challenged with ASNase without recurrence of thrombosis (75). In the Dana-Farber Cancer Institute review (63) confirms that, after venous thromboembolic events, asparaginase can be restarted after demonstrating clot stabilization or improvement by imaging with close monitoring of anticoagulation. Therefore, a history of venous thromboernbolic events does not seem to adversely impact prognosis.

The expert panel, Wendy Stock et al (81) in their excellent article published in Leukemia and Lymphoma, 2011 detailed the management of ASNase associated VTE and put down the recommendation which is being adapted/summarized hereunder:

1. In adults, activated partial thromboplastin time (APTT), international normalized ratio (INR), AT, and fibrinogen levels should be measured prior to ASNase therapy for baseline assessment.
2. Between doses of native ASNase and for 1 week after pegASNase therapy, these tests, as well as factor Xa, should be serially monitored as clinically indicated.
3. AT concentrates and cryoprecipitate infusions should be considered for treatment of thrombohemorrhagic events due to AT and fibrinogen deficiency, respectively.
4. For non-urgent thrombohemorrhagic episodes, fresh frozen plasma should be avoided since it contains asparagine and may counteract the anti-leukemic effect of ASNase. However, careful follow up is advised for possible evolution of the thrombohemorrhagic event into a major one.
5. For a clinically significant DVT, the patient should be anticoagulated with or without AT supplementation, and whether or not it is associated with a central venous line.
6. Early diagnostic imaging, CT scan and or MRI should be performed in patients with a suspected CNS event related to ASNase therapy and urgent consultation of the neurologist/ neurosurgeon should be secured and documented.
7. For CNS thrombosis, the patient should be anticoagulated with or without AT supplementation after careful evaluation.
8. Anti-epileptic medications in patients with thrombohemorrhagic complications should be administered prophylactically or therapeutically as appropriate at the discretion of the neurologist.
9. ASNase is discontinued for all clinically significant bleeding or thrombosis and whether it is resumed depends on the nature and resolution of the thrombohemorrhagic event and outcome of discussion of the case at the tumor board.

5-Fluorouracil

This synthetic pyrimidine analogue is an important chemotherapeutic agent for treatment of various solid tumors. The incidence of VTE in patients treated for colorectal cancer with this

drug has been reported at 15-17%. During 5-FU infusion, there is a reduction of protein C and an increase level of fibrinopeptide through the action of thrombin (83-84).

2.5.2 Angiogenic Inhibitors and immunomodulatory agents

a. Angiogenesis Inhibitors Associated with VTE:

Angiogenesis is a process involving the proliferation of new blood vessels and plays a central role in the growth and metastasis of cancer (85). The angiogenesis is driven mainly by the vascular endothelial growth factor (VEGF). The signaling pathway of VEGF has been a target of many angiogenesis inhibitors including bevacizumab, sorafenib and others (86-87). Bevacizumab (Avastin, Genentech Inc., South San Francisco California) is a recombinant humanized monoclonal neutralizing antibody against VEGF has shown efficacy in treatment of many solid tumors including colorectal cancer, non-small cell lung cancer and renal cell carcinoma.

Shobha R Nalluri et al (88) in their metanalysis of 15 randomized controlled trials (RCTs) demonstrated that bevacizumab is associated with significantly higher risk of VTE (RR, 1.33[95% CI 1.13-1.56]; P<0.001) in patients with a variety of metastatic solid tumors and this risk is observed for all grades of VTE.

The thrombogenic effect of bevacizumab may be related to (a) its exposure of the subendothelial procoagulant layer and inhibition of the VEGF induced endothelial cell regeneration (89), (b) reduction of production of nitric oxide and prostacyclin by bevacizumab (90), (c) release of procoagulant molecules from the tumor cells into the circulation (91) and (d) increasing the haematocrit and blood viscosity via over production of erythropoietin (92).

b. Thalidomide and its derivative Lenalidomide are immunomodulatory agents with antiangiogenic properties through blockade of basic fibroblastic growth factor and VEGF and are associated with increased risk of VTE in cancer patients. This topic has been well covered in chapter 5 of this book by Drs Gonzalez-Porras and Mateos.

2.5.3 Hemopoetic growth factors

Tumor hypoxia may contribute to the resistance of some tumors to both chemotherapy and radiation therapy (93-94). Many cancer patients are anemic. There are some data from the literature indicating that patients who received transfusions to maintain a higher hematocrit have improved outcomes with radiation therapy for cervical carcinoma. (95)

Studies on inducing and maintaining higher haemoglobin (Hb) levels in patients with malignant disease by administration of recombinant human erythropoietin (rHuEpo), the primary haematopoietic growth factor for erythropoiesis (96), have shown that rHuEpo is effective in increasing Hb levels in the majority of anaemic cancer patients (97-98) and that this increase is associated with an improvement in patient-reported quality of life. Because both fatigue and anemia are common complications of cancer, the use of rHuEpo in patients with cancer has increased significantly (99). Those studies typically have shown that a majority of patients will have an erythropoietic response to doses of rHuEpo between 150 IU/kg and 300 IU/kg given subcutaneously 3 times per week (98, 100).

Dusenbery et al (101) in a study of patients receiving rHuEpo along with chemotherapy and radiation therapy for cervical carcinoma, reported that 2 of 20 patients had DVT during therapy, and 2 other patients had DVT 9 days and 10 days after radiation therapy and rHuEpo were discontinued. Although it was a small sample, the rate of 20% in that study is similar to the rate found in by Ted Wun et al (102). The combination of chemotherapy and radiation may lead to a more vigorous inflammatory response that may predispose patients to thrombosis in the background of other predisposing factors.

In a recent Cochrane meta-analysis of 35 trials representing almost 7000 patients, epoetin or darbepoetin treatment was associated with a significantly increased risk for thromboembolic events (103).

Erythropoietin may contribute synergistically to thrombosis in cancer patients through several mechanisms. (a) Increasing red cell mass leading to increasing whole blood viscosity, (b) Erythropoietin therapy results in reticulocytosis, the metabolically active young red blood cells. Elegant studies have demonstrated that metabolically active red blood cells augment platelet reactivity in vitro (104-108) (c) rHuEpo is synergistic with the platelet growth factor, thrombopoietin, for platelet activation in vitro (109-110) at concentrations that can be achieved pharmacologically in vivo. (d) Erythropoietin has been associated with increased platelet reactivity and evidence of endothelial activation when administered to healthy male volunteers (111) (e) In vitro data have demonstrated receptor-mediated endothelial cell activation in response to rHuEpo and that extracellular matrix produced by the activated endothelial cells enhanced platelet aggregation and recent evidence suggests that platelet-red cell interactions can play a role in venous thrombosis (112).

The role of prophylactic myeloid growth factors: granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) in increasing risk of cancer-associated thrombosis is unclear (113-114).

2.5.4 Surgery

Is a well-known risk factor for development of VTE in patients without cancer. Underlying cancer increases the risk of surgery-related VTE by two-fold. Some studies have demonstrated that longer time in the operating room, longer time under anesthesia, and need for surgical re-exploration is associated with increased risk of VTE in cancer patients (37, 115-116). A study analyzing the effect of surgery in patients with glioma revealed that patients who underwent major neurosurgery or brain biopsy were 70% more likely to develop VTE within 3 months.

2.5.5 Indwelling central venous catheters (CVC)

The use of CVC has improved the management of patients with cancer as they simplified the administration of chemotherapy, parental nutrition, antibiotics and other supportive intravenous therapy. However, the CVCs are associated with complications including a significant risk of catheter-associated thrombosis (CAT). The risk of VTE associated with hospitalization has increased over the last decade a time associated with increased use of medical thromboprophylaxis. The incidence of symptomatic catheter-related DVT in adult

cancer patients ranges from 0.3% to 28% while the rate of catheter-related DVT assessed by venography is 27–66% (117).

Some of the factors that may influence the risk of thrombosis of the indwelling central lines are (a) site of the catheter: left subclavian lines are at higher risk than the right (b) synthetic material: polyvinyl chloride or polyethylene lines are more thrombogenic than are polyurethane or siliconized lines (c) number of lumen: triple lumen catheters may be more thrombogenic than double lumen (d) nature of the infusate: infusion of total parenteral nutrition fluids through the line have been found to be more thrombogenic than the infusion of crystalloid fluids (e) the position of the tip of the catheter located in the superior vena cava has almost a three-fold higher risk for thrombosis than that located in the right atrium and (f) insertion attempts of ≥2 carries higher risk for catheter related thrombosis.

Patient with CAT may present with pain, swelling, paresthesia, and prominent veins throughout the arm or shoulder. However, many patients may be asymptomatic.

Contrast venography is the gold standard for evaluation of patients suspected to have the upper extremity thrombosis. However, the non-invasive serial compression ultrasound is the standard test for UEDVT evaluation and if this is negative in a patient with high-pretest probability of UEDVT then the more expensive and invasive ultrasonography is resolved to.

In some centers, Color Doppler duplex ultrasound may be the modality of choice for the diagnosis of symptomatic CVC-R of UEDVT and for screening of suspected asymptomatic thrombosis in specific clinical situations (118)

Prevention: Despite the strong association between the CVCs and UEDVT, anticoagulant prophylaxis is not recommended. Studies evaluating the use of 1-mg (low dose) warfarin gave conflicting results **(**119-121).

On the basis of the available data from contemporary trials, it is difficult to recommend routine antithrombotic prophylaxis in cancer patients with central venous catheters. Institutions are encouraged to assess their rates of catheter-associated thrombosis and develop a protocol on how the catheters are inserted and maintained. This will be a useful tool to control the rate of complications associated with CVCs. When symptomatic thrombosis occurs in association with a catheter, it definitely complicates the clinical care of the patient because of the need for anticoagulant therapy and because often the catheter has to be removed.

Management of Catheter Associated Thrombosis

Treatment: ACCP guidelines recommend treating UEDVT patient with UH or LMWH and warfarin (INR 2-3) for at least 3-months (122).

- **Right Atrial Thrombus**

a. Surgical management

These thrombi may impede atrial or ventricular inflow and cause sudden death. For a symptomatic patient with a large mobile thrombus, surgical thrombectomy is strongly recommended (123-124) and the catheter should also be explanted (125, 126, 127). Early involvement of the cardiologist, the cardiac surgeon and intensivist is advisable for coordinated optimum management.

b. Medical management

A completely dissolved right atrial thrombus case without side effects was reported by Adamovich et al in a neonate after 5 days' with infusion of urokinase and heparin (128). Cesaro et al reported on a successful pediatric case that was treated with recombinant tissue plasminogen activator (rt-PA) and heparin for 6 days without significant side effects (129). Korones et al favoured conservative management for small-sized thrombus with no intervention but close follow up for evidence of growth in size is warranted. However, for a moderate-sized thrombus there is a need for anticoagulation rather than surgical thrombectomy (123). If medical treatment fails then surgical thrombectomy should be resolved to. In adults, medical treatment has been tried in only a few reported cases because it is believed that, even though antithrombotic agents may stabilize or regress catheter-related RA thrombi, anticoagulated patients remain at risk of pulmonary embolism and need to have surgical thrombectomy eventually (130-132).

- **Central Venous Thrombosis**

a. Surgical management

The course of action for implantable venous access device (IVAD) after CVT is variable. Medical antithrombotic treatment was widely applied, but most of the devices were still explanted and some were removed before medical treatment is started (5,6) and some were explanted after fibrinolytic, antithrombotic or anticoagulant treatment failed (133-135). The reasons for explantation of IVAD are (a) prevention of thrombosis progression, especially in the case of SVC syndrome, (b) persistent pain, (c) combined with a documented infection and extravasation. However, Lokich et al (136) reported that the vascular occlusion rarely resolve after the explantation.

b. Medical management

For all CVT patients with or without IVAD explantation, antithrombotic treatment is necessary. Removal of the device should be decided by clinical necessity for venous access or by evidence of pulmonary embolism (134), especially in patients with very difficult venous access.

c. Unfractionated Heparin

Intravenous UFH is the initial treatment of choice for acute CVT. UFH can prevent clot propagation but does not dissolve it and, therefore, recanalization may not develop. UFH can be given by continuous intravenous infusion for 5–10 days, starting with a bolus of 5000 IU followed by 30,000–35,000 IU/day, with activated partial thromboplastin time of 1.5–2.5 times the control (137).

d. Low Molecular Weight Heparin

In view of the many advantages particularly the subcutaneous route q12 hours dosage, no need for laboratory and home treatment basis of the LMWH over the UFH, many experts favor its use for management of acute CVT

e. Fibrinolytic agents

Fibrinolytic agents, such as recombinant tissue plasminogen activator (rt-PA), streptokinase, and urokinase are usually effective for the lysis of fresh thrombi. Resolution of thrombi is

more significant in acute occlusions than in CVT, which is always detected after a period of time i.e. chronic organized thrombosis. Although some studies mentioned their usage, antithrombotic agents are still the first choice (134,138).

- **Intraluminal thrombotic occlusion**

a. Surgical management

Surgical explantation of the device should be considered after fibrinolytics have failed or therapy has been terminated because of its minor severity and the high success rate of medical treatment (134,139-140).

b. Medical treatment

Fibrinolytic agents, such as rt-PA, urokinase and streptokinase, have been used in recent decades to lyse intraluminal thrombi, to restore device patency and to avoid catheter removal. Intraluminal installation of fibrinolytic agents is still considered the safest and most effective therapy for the treatment of IVAD intraluminal thrombotic occlusions. These agents are associated with some complications e.g. bleeding, hypersensitivity reactions, arrhythmias, hypotension, fever, nausea or vomiting and the attending physician is advised to make note of this at the time when a decision is made.

c. Recombinant tissue-plasminogen activator (rt-PA)

Alteplase is the most popular and effective rt-PA used in the treatment of thrombotic occlusions. It is a serine protease that activates plasminogen to plasmin in the cleavage of thrombus-bound fibrin. In adult patients, 2 mg alteplase in 2 mL sterile water may be injected into the occluded catheter. Restoration of function is assessed 30–120 minutes later and if function is not restored, a second attempt with the same dose is performed (141-142). In 64-86% of patients successful treatment was achieved after a single dose, and two doses achieved 81–94% success. In addition, alteplase has the advantages of a low incidence of allergic reactions (< 0.02%) and no documented reports of sustained antibody formation after administration (134). Although small dose alteplase is so far not commercially available, large dose alteplase can be split into unit doses and cryopreserved at –20°C for 30 days (141). Reconstruction to small dose aliquots makes this a cost-effective treatment without compromising safety and efficacy (141-142). However, the production of a single-dose rt-PA vial is still needed, not only for small institutions but also as a convenient, economically sound and safe agent for oncologic patients.

d. Urokinase

In 1999, the FDA reported on microorganism contamination of urokinase and issued a warning about variations in quality control during manufacture, recommending that urokinase be restricted to specific patients in whom the physician has judged urokinase to be critical to the clinical situation (143).

e. Streptokinase

Although streptokinase can resolve occlusions without hemorrhagic side effects or coagulation changes. Its use is fraud with some difficulties: allergic reactions and the induction of antibody formation, fever and shivering in 1–4% and anaphylactic reactions 0.1% of patients these risks/issues led to the restriction of its usage (141,144). The producers

of streptokinase, AstraZeneca, released an Important Safety Information letter on streptokinase in December 1999 and warned that there is a risk of significant allergic reactions and that streptokinase is not indicated for restoration of IVAD patency (144).

2.5.6 Radiation

There are limited data on the effect of isolated radiation modality on risk of cancer-associated thrombosis. However, the combination of chemotherapy and radiation could lead to a more vigorous inflammatory response that may predispose patients to thrombosis in the setting of other predisposing factors. In a study of patients receiving rHuEpo along with chemotherapy and radiation therapy for cervical carcinoma, Dusenbery et al (101) reported that 2 of 20 patients had DVT during therapy, and 2 other patients had DVT 9 days and 10 days after radiation therapy and rHuEpo were discontinued. Although it was a small sample, the rate of 20% in that study is remarkably close to the rate found by other investigators. Large, randomized studies of combined chemotherapy and radiation therapy in patients with carcinoma of the cervix did not report on the rate of venous thrombosis (145-148).

2.5.7 Hormonal therapy: Tamoxifen and exemestane

Tamoxifen was discovered by pharmaceutical company Imperial Chemical Industries (now AstraZeneca) and is sold under the trade names Nolvadex, Istubal, and Valodex. However, the drug, even before its patent expiration, was and still widely referred to by its generic name "tamoxifen."

Tamoxifen binds to estrogen receptors but produces both estrogenic and antiestrogenic effects. It reduces circulating insulin-like growth factor-1, inhibits angiogenesis, and induces apoptosis (149)

Tamoxifen is highly beneficial as adjuvant therapy for breast cancer, and more recently, its effectiveness has been demonstrated for prevention of breast cancer in high-risk women. (150-151)

The most frequent side effect in patients treated with tamoxifen versus placebo was a doubling of the rate of DVT and PE: 118 versus 62 cases and a similar increase in superficial phlebitis (68 versus 30 cases) (152) A systematic review of adjuvant hormonal therapy for breast cancer estimated that women treated with 5 years of tamoxifen have a 1.5-7.1 fold increased risk of VTE compared to women treated with placebo or on observation only. (153)

As to the evaluation of women who are about to initiate tamoxifen to prevent the development of breast cancer, the question raised is cost: benefit ratio of tamoxifen therapy if the patient have risk factors for DVT or PE. On the basis of the solid data favoring tamoxifen, the prevention of breast cancer should take priority over the risk of venous thromboembolism. If the risk of developing DVT is high, it is reasonable to go for concomitant anticoagulation with Coumadin (INR 2-3) for the planned treatment period with tamoxifen.

However VTE risk may become less problematic in breast cancer patients as the third-generation oral aromatase inhibitors, such as the irreversible steroidal inactivator

exemestane, are being used in place of tamoxifen for long-term prophylaxis after initial therapy of breast cancer. Exemestane is the generic name for the brand-name drug Aromasin and works by binding irreversibly to the body's aromastase enzyme, which is responsible for producing estrogen. Many breast cancer cells depend on estrogen to grow and multiply quickly. Once the aromatase inhibitor binds to the aromastase enzyme, the bound aromatase enzyme can no longer produce estrogen. This drug caused lack of estrogen "starves" estrogen- dependent breast cancer cells, preventing them from multiplying. Coombes et al, in a trial in which 4742 breast cancer patients were randomized to continue tamoxifen or to switch to exemestane. Those receiving exemestane experienced improvement in disease-free survival (154-155) The adjusted hazard ratio was 0.67 (95% CI 0.56 to 0.82, P<0.001) and the rate of thromboembolic events was almost halved in those receiving exemestane as compared with tamoxifen (1.3% versus 2.4%, p=0.007).

3. VTE and occult cancer

Thrombosis can be the first manifestation of malignancy. Patients who present with idiopathic or unprovoked DVT are more likely to be diagnosed with cancer during follow-up than patients with secondary DVT. In pooled analyses of cohort studies, the odds ratio for subsequent cancer in patients presenting with idiopathic VTE compared with patients with secondary VTE is 4.8 (156). About 10% of patients with idiopathic VTE were diagnosed with subsequent cancers over the next 5–10 years. More than 75% of these cases were reported within the first year after the diagnosis of DVT (157).

Prins et al studied (158) the incidence of newly diagnosed malignancy in patients with unexplained venous thromboembolism during the first year after a thromboembolic event in comparison to controls (odds ratio, 3.9-36). The authors used extensive screening with computed tomography, endoscopy and tumor markers and stated that they identify most of these undetected malignancies. However, the authors continued, approximately half of these can also be identified based on a simple clinical evaluation.

Monreal et al (159) reported on retrospective analysis of our 5-year experience with a series of 674 consecutive otherwise healthy patients, and a more restricted battery of diagnostic tests including: abdominal CT-scan; carcinoembryonic levels, and prostate-specific antigen levels. The authors reported that cancer was more commonly found in patients with idiopathic VTE: 13/105 patients (12%) versus 10/569 patients (2%); p <0.01; O.R.: 7.9 (95% CI: 3.14-20.09). During the same period of time they diagnosed VTE in 147 patients with previously known cancer. When overall considered, VTE was the first sign of malignancy in most patients with prostatic and pancreatic carcinoma. However, most patients with breast, lung, uterine and brain cancers developed VTE as a terminal event of the disease (159).

Piccioli et al (160) also concurred with Monreal et al (159) that the diagnosis of venous thrombosis although may help to uncover previously occult carcinoma by prompting a complete physical examination, chest roentgenography, and mammography, extensive cancer screening with computed tomography to neck, chest, abdomen and pelvis or magnetic resonance imaging has not been shown to be cost effective for patients with venous thrombosis.

In another publication, Piccioli et al (161) reported that patients with symptomatic idiopathic venous thromboembolism and apparently cancer-free have an approximate 10% incidence of subsequent cancer. In their study, apparently cancer-free patients with acute idiopathic venous thromboembolism were randomized to either the strategy of extensive screening for occult cancer or to no further testing. Patients had a 2-year follow-up period. Of the 201 patients, 99 were allocated to the extensive screening group and 102 to the control group. In 13 (13.1%) patients, the extensive screening identified occult cancer. In the extensive screening group, a single (1.0%) malignancy became apparent during follow-up, whereas in the control group a total of 10 (9.8%) malignancies became symptomatic [relative risk, 9.7 (95% CI, 1.3–36.8; $P < 0.01$]. Overall, malignancies identified in the extensive screening group were at an earlier stage and the mean delay to diagnosis was reduced from 11.6 to 1.0 months ($P < 0.001$). Cancer-related mortality during the 2 years follow-up period occurred in two (2.0%) of the 99 patients of the extensive screening group vs. four (3.9%) of the 102 control patients [absolute difference, 1.9% (95% CI,) 5.5–10.9)].

Rickles et al (162) stated that while migratory thrombophlebitis is a clear indicator of an underlying neoplasm, the risk of cancer in patients with the more typical form of VTE has been the subject of intense debate over recent years. The authors concluded that, the cost-effectiveness of aggressive screening for cancer in patients with VTE remains questionable.

Nordström, M et al (163) conducted a prospective study of 366 patients in Malmo, Sweden, who had treatment after positive results on venography reported an overall incidence of deep venous thrombosis of 159 per 100 000 inhabitants per year. At the time of diagnosis of deep venous thrombosis, 71 patients (19%) had a known cancer and a further 19 (5%) developed cancer within the following year. Eight of the cancers were obvious at the time of diagnosis of the deep venous thrombosis and 11 were occult.

To date, there is very little evidence that routine cancer screening is indicated or cost-effective in patients with unprovoked thrombosis. Nonetheless, it is prudent to perform a comprehensive history and physical exam and check basic blood work with relevant tumor markers, as deemed appropriate, in patients with unprovoked thrombosis because about 90% of occult cancers can be detected using this conservative approach (164-165).

At our institutions, when performing pulmonary artery CTA and CTV for unprovoked VTE, our radiologist analyzes all information produced by the imaging examination. An attentive analysis of the entire thoracic and abdominal structures on all pulmonary artery CTA and CTV examinations is routine. Careful evaluation is also made in hospitalized patients in whom thromboembolic disease is discovered incidentally. In such patients, pulmonary artery CTA and CTV is considered a cancer screening procedure with an increased likelihood of finding an occult malignancy. When the CTV examination begins at the level of the diaphragm instead of below the level of the iliac crest, it permits the detection of venous thrombosis and serves as a simultaneous screening for possible underlying malignant disease.

4. The use of biomarkers for risk assessment for VTE in cancer patients

Despite the well documented association of cancer with increased risk of thrombosis, clinical studies have not consistently demonstrated improved outcomes with

thromboprophylaxis in all groups of cancer patients, and hence their risk for VTE in view of the heterogenity of cancer (166).

Moreover, treatment of VTE in patients with cancer or use of pharmacological agents for thromboprophylaxis is more difficult and is associated with considerable therapeutic challenges in view of thrombocytopenia caused by some chemotherapeutic agents and morbidity associated with VTE in often medically compromised cancer patients (32, 167)

Therefore, identification of a high-risk subgroup of cancer patients who will benefit from primary thromboprophylaxis is well justified. Recent data have identified multiple clinical risk factors as depicted under patient-, disease- and treatment-related risk factors above as well as biomarkers predictive of VTE in cancer patients. Biomarkers associated with increased risk of cancer associated VTE include leukocyte count, platelet count, and levels of tissue factor, P-selectin, D-dimer and CRP as discussed below.

a. **Leukocyte count:** Leukocytosis was identified as independent risk factor associated with increased risk of VTE in cancer patients before initiating chemotherapy (OR 2.0). VTE occurred in 4.5% patients with baseline leukocytosis, WBC ≥11x10^9/L, compared to (1.8%) without leukocytosis ($p < 0.0001$). In a prospective observational study of 3303 ambulatory cancer patients: "Awareness of Neutropenia in Chemotherapy" Study Group Registry, leukocyte count >11.0x10^9/L was also reported to be independently associated with an increased risk of subsequent VTE. Leukocytosis may be a marker of the aggressiveness of the cancer cells or represent a direct causative role in mediating cancer-associated thrombosis, through, as yet, unknown mechanisms (168-169).
b. **Platelet count:** Thrombocytosis is often observed in cancer patients and elevated platelet counts correlates with an activation of coagulation. In several studies of cancer patients, an elevated platelet count (≥350x10^9/l) prior to starting chemotherapy was found to be strongly associated with VTE (21, 19). The incidence of VTE was 4-7.9% in patients with a pre-chemotherapy platelet count ≥350x10^9/l compared to 1.25% in patients with lower platelet counts. The increased risk of VTE with higher platelet counts persisted while the patients were on chemotherapy and these patients had a 3-fold higher rate of VTE (32).
c. **D-Dimer** is a degradation product of cross-linked fibrin that is formed after thrombin-generated fibrin clots have been degraded by plasmin. Elevated fibrin D-dimer level (HR, 1.8) and elevated prothrombin split products (HR, 2.0) have recently been shown to be associated with increased risk of VTE in a large prospective study of cancer patients (170). D-dimer was also elevated in metastatic breast cancer patients compared to normal controls (171). These and other data suggest that D-dimer levels may be a predictor of VTE in cancer patients.
d. **Clotting factor VIII (VIII:C)** This factor plays an important role in the coagulation cascade. In non-cancer patients, a high FVIII: C activity has been established as a risk factor for primary and recurrent VTE (25-26, 51). In a prospective cohort study, a significant association was found between FVIII:C levels and the risk of symptomatic VTE in cancer patients (51). In an analysis of cancer patients including solid cancers and haematological malignancies, the cumulative probability of VTE after 6 months was 14% in patients with elevated FVIII (cut-off: 232%) as opposed to 4% in those with normal levels ($p = 0.001$). These results demonstrate that elevated FVIII:C levels in cancer patients proved to be a valuable, independent risk marker for VTE, predicting an

almost 3-fold increased VTE risk **(172).** Cumulative probability of VTE after 6 months was 14% in patients with elevated FVIII:C levels

e. **The prothrombin fragment** 1+2 (F1+2) is released when activated factor X cleaves prothrombin to thrombin and reflects the in-vivo thrombin generation. A systematic activation of coagulation has been observed in cancer patients which is reflected by elevated plasma levels of global coagulation markers, such as D-Dimer or prothrombin fragment 1+2 (F1+2) (49, 173).

f. **Tissue factor (TF)** is a transmembrane glycoprotein present on subendothelial tissue, platelets, and leukocytes that initiates coagulation and plays a critical role in regulating hemostasis and thrombosis (174-175). TF expression has been shown to be associated with increased angiogenesis in various solid neoplasms, including hepatocellular, colorectal and prostate cancers as well as in haematologic malignancies and play a role in cancer-associated thrombosis (176-177). TF induction was shown to be an early event in the development of pancreatic cancer and that the level of TF expression correlates with increased angiogenesis and with subsequent development of symptomatic VTE (176-179).

VTE was 4-fold more common (p = 0.04) among patients with high TF-expressing carcinomas (20%) than among those with low TF-expressing carcinomas (5.5%). There is a potential for circulating TF to be used as predictive biomarker for pancreatic cancer associated VTE. VTE was 4-fold more common (p = 0.04) among patients with high TF-expressing carcinomas (26.5%) than among those with low TF-expressing carcinomas (5.5%). In another study, TF expression correlated with subsequent VTE in a series of patients with ovarian cancer (173).

Furthermore, a retrospective analysis of cancer patients without VTE, revealed a 1-year cumulative incidence of VTE of 34.8% in patients with TF-bearing MPs versus 0% in those without detectable TF-bearing MPs (p= 0.002).

g. **Soluble P-selectin (sPS):** This is a cell adhesion molecule found in the membranes of platelets and endothelial cells (Weibel–Palade bodies) where it can function as a receptor and mediate cell adhesion via binding to several ligands. The interaction of sPS with PSGL-1 expressed on the majority of leukocytes results in the release of procoagulant, tissue factor-rich microparticles (MPs) from leukocytes, endothelial cells, platelets and cancer cells (179). In case-control studies of non-cancer patients with a history of VTE and healthy subjects without a history of venous or arterial thrombosis, high plasma levels of sPS have been demonstrated to be strongly associated with VTE (27, 35). In a multivariate analysis of the prospective observational Vienna Cancer and Thrombosis Study, elevated sPS (cutoff level, 53.1 mg/mL) was a statistically significant risk factor for VTE after adjustment for age, sex, surgery, chemotherapy and radiotherapy (HR = 2.6) and the cumulative probability of VTE after 6 months was 11.9% in patients with high sPS and 3.7% in those normal levels (p = .002) (180).

C- Reactive Protein

C-reactive protein (CRP) is an inflammatory marker produced by the liver and adipocytes. In a prospective study, CRP was significantly associated with increased risk of VTE by multivariate analysis (181-183)

		Factor
CLINICAL RISK FACTORS	Patient Related Factors	• Age - > 60 years • Gender • Race • Previous thrombotic episode • Obesity: BMI ≥ 35 kg/m^2 • Chronic co-morbid Medical Conditions
	Disease Related Factors	• Tumors type • Initial cancer stage • Biological aggressiveness of cancer • Rate of metastatic spread
	Treatment Related Factors	• Chemotherapy • Anti-angiogenic and immunomodulatory agents • Use of Hemopoetic growth factors • Surgery • Indwelling central venous catheters • Radiation • Hormonal therapy
BIOMARKERS	Biomarkers	• Leukocyte count ≥ 11x10^9 /L • Platelet count ≥ 350 x10^9 /L • D-Dimer • Clotting factor VIII • The prothrombin fragment • Tissue factor (TF) • Soluble P-selectin • C-Reactive protein

Table 1. Summary of the Risk Factors for VTE in Cancer Patients

5. VTE in haematological malignancies

Although the association between malignancy and thrombosis has been well recognized, less is known about the risk of thrombosis in patients with acute leukemia and the impact of VTE on survival. Certainly there is abundant biochemical evidence for thrombin generation and disseminated intravascular coagulation in patients with leukemia (184). The few single-center reports of the incidence of venous thrombosis in patients with leukaemia have focused primarily on children with acute lymphoblastic leukaemia. These studies have suggested the cumulative incidence varies between 2% and 10.6% (185-186).

Patients with haematologic malignancies are at high risk of thrombotic or haemorrhagic complications. The incidence of VTE events varies considerably and is influenced by many factors, including the type of disease, chemotherapy used, and whether a central venous device is inserted. As in solid tumors, a number of clinical risk factors have been identified and contribute to the increasing thrombotic rate in haematologic malignancies. Biologic

properties of the tumor cells can influence the hypercoagulable state of patients with these malignancies by several mechanisms. Of interest, oncogenes responsible for haematological neoplastic transformation in leukemia also may be involved in haemostatic activation.

- **VTE in Central Nervous System Lymphoma**

Patients with brain tumors are at particularly high risk for VTE, and many studies found that the hazard for deep vein thrombosis in patients with malignant glioma may reach 28% (187-188) This high risk is maintained throughout the course of an active disease and during treatment, and not just in the immediate postoperative period (188). Risk factors for VTE in patients with glioma include the presence of paraparesis, a histologic diagnosis of glioblastoma multiforme, age ≥ 60 years, large tumor size, the use of chemotherapy, and length of surgery of > 4 hours. Because of the high incidence of VTE, patients who are treated for brain tumors are usually considered for long term prophylactic anticoagulation as deemed appropriate for a particular patient (189-190).

- **VTE in Non-Hodgkin Lymphoma**

The incidence of clinical VTE in patients with malignant lymphoma reportedly ranges between 6.6% and 13.3% (187, 190-194) In one study, 50% of patients had a bulky tumor compressing a vein, 25% of patients had a central catheter at the thrombosed vein, and, in the other patients, thrombosis was attributed to paraneoplasia or to chemotherapy (187)

Conlon SJ et al (194) reported the results of retrospective analysis of patients with a total of 18 653 cases on the NCI Working Formulation: there were 5496 low grade NHL, 12 251 aggressive NHL and 906 high-grade lymphoma cases. The cumulative incidence (CI) of VTE 24 months from diagnosis was 4.0%. The CI of VTE at 24 months were significantly different for the distinct lymphoma groups ($p < 0.001$, Chi-square and comparisons showed this difference to be significant only between the low grade and other histologies. Of 742 cases that had VTE, 454 died within 2 years (61%). For those without VTE, 7274 of 17911 (41%) died within 2 years. This difference was statistically significant ($p < 0.001$, Chi-square).

- **VTE In Patient with Acute Leukemia**

A population- based cohort study (1993-1999) to determine the incidence and risk factors associated with development of VTE among Californians diagnosed with acute leukemia (1993-1999) was reported in Blood 2009, by Ku GH et al (195). Among 5394 cases of AML, the 2-year cumulative incidence of VTE was 281 (5.2%) and 64% of VTE events occurred within 3 months of AML diagnosis. The authors reported that, in AML patients, female sex, older age, number of co-morbid conditions, presence of CVC were significant predictors for development of VTE within one year following diagnosis of acute leukemia but the event of VTE was not associated with poor survival in AML patients in the studied group. Among 2482 case of ALL, the 2-year incidence of VTE was 4.5% and risk factors in this group were presence of CVC, older age and number of chronic co-morbidities. In this study, development of VTE in ALL patients was associated with a 40% increase of dying within one year.

In the abstract #6595 published in JCO 2011 by Luong NV et al from MD Anderson Cancer Center, USA (196) of a retrospective chart review to determine the prevalence of VTE prior

to treatment and recurrence of VTE. Records of 299 ALL patients and 996 AML patients were included (Nov 1991-May 2005). The authors concluded that acute leukemia patients have a high prevalence of VTE but the occurrence of VTE prior to initiation of chemotherapy was not associated with poor prognosis similar finding to that reported by Ku GH et al.

Blast cells with their procoagulant properties, central venous catheters, chemotherapeutic agents (as discussed earlier in this chapter) concomitant infections, patient-and supportive treatment related factors are major determinants of haemostatic mechanism activation in acute leukemia. The clinical manifestations range from VTE to diffuse life-threatening hemorrhage. Anti-coagulant therapy in this clinical setting is fraud with major difficulties as the patients are at very high risk of haemorrhage because of thrombocytopenia. To date, no guidelines are available for prophylaxis or treatment of VTE in this group of patients (197)

- **VTE in Acute Promyelocytic Leukemia**

The use of the differentiating agent all-trans-retinoic acid (ATRA) in the treatment of APL allowed achievement of complete remission in more than 90% of the cases and improved dramatically the coagulopathy typical of this disease (198). The modifications induced by ATRA in the balance between procoagulant and fibrinolytic properties of the pathological promyelocytes before complete differentiation have been proposed to induce a prothrombotic effect (199).

- **VTE in Multiple Myeloma**

Multiple myeloma (MM) has been associated with increased risk of VTE events. Specific risk factors for VTE in MM are production of autoantibodies to haemostatic factors, high incidence of acquired protein C resistance, increased VIII:C levels and VWF and increase of production of inflammatory cytokines e.g. IL-6, TNF and C-reactive protein and paraprotein. These unique risk factors may operate along other common cancer VTE risk factors e.g. age, immobility, cancer procoagulant factors and chemotherapy.

Treatment regimens for MM include thalidomide, Lenalidomide combined with glucocorticoids and cytotoxic chemotherapy are associated with an increased risk of VTE particularly when the immunomodulatory agents are combined with anthracyclines. Combination chemotherapy including thalidomide plus dexamethasone and/or alkylating agents are associated with intermediate risk for VTE. The use of newer immunomodulator e.g. bortezomib seem to reduce the VTE risk **(200).** This topic has been well covered in chapter 5 of the book.

- **VTE in Monoclonal gammopathy of undetermined significance**

In 2004, Sallah S et al and Srkalovic G et al published in Ann Oncol and cancer respectively (201-202) two small hospital based studies on the association of monoclonal gammopathy of undetermined significance (MGUS) and subsequent risk of DVT and reported an elevated risk of DVT in MGUS. Kristinsson Y et al (203) conducted a retrospective study on 4,196,197 veterans hospitalized at least once. MM was identified in 2374 (0.06%) cases of MGUS 6192 (0.15%). A total of 31 and 151 DVTs occurred among MGUS and multiple myeloma, respectively (crude incidence 31 and 8.7 per 1000 person-years, respectively). The RR of DVT

after a diagnosis of MGUS and MM was 3.3 and 9.2 respectively with excess risk of DVT in the first year of diagnosis. Compared to the background population, patients with multiple myeloma have a 9-fold increased risk of developing DVT especially during the first year of diagnosis while the risk for DVT in MGUS was stable at 3-fold increased risk over time with no statistical association between DVT in MGUS and risk for progression into MM.

- **VTE in Myelodysplastic Syndrome**

Yang X et al (204), in 2009, reported a total of 7764 MDS patient who were prescribed Lenalidomide during the first two years of its commercial use in the USA. VTE was reported in 41 patients (rate of 0.53%) denoting a computed signal that did not exceed the statistical threshold for identification of a significant disproportional signal for VTE in MDS on Lenalidomide without erythropoietin. However, the authors found that a disproportional signal of VTE where erythropoietin was concurrently administered with Lenalidomide.

- **VTE in Myeloproliferative Neoplasms**

Life expectancy of patients with myeloproliferative neoplasms (MPNs) and particularly that of subjects with polycythemia vera (PV) and essential thrombocythemia (ET) has significantly increased over the last three decades, largely due to the use of cytoreductive treatments. Currently, PRV and ET are considered relatively benign diseases in which the main objective of treatment strategy is the prevention of thrombotic events. Widespread use of routine haematologic screening and novel diagnostic tools greatly facilitate disease recognition and treatment. This helps to prevent a significant number of early vascular events that still constitute the first disease manifestation in approximately one-third of patients (205). We can also expect that new therapeutic options and appropriate use of aspirin will result in a further reduction of morbidity and mortality. One of the unmet needs of PRV and ET is validated methods for vascular risk stratification. The evaluation of the thrombotic risk in the individual patients, as reported by Barbui et al. in their paper (206).

The pathogenesis of thrombosis in myeloproliferative neoplasms has been extensively investigated by focusing in particular on the possible contribution of disease related haemostatic abnormalities. However, the pathogenesis of thrombosis appears to be multifactorial. Red blood cell, platelet, and leukocyte abnormalities, both qualitative and quantitative, are likely to play a key-role in myeloproliferative neoplasm thrombophilia. High shear stress of the vessel wall, due to blood hyperviscosity, accounts for chronic endothelial dysfunction and platelet and leukocyte activation.

Platelets and endothelial cells play a pivotal role in regulating blood flow, both cells might contribute to determine a prothrombotic microenvironment in myeloproliferative neoplasm patients by producing more soluble selectins and less nitric oxide, likely as a consequence of inflammation (207).

According to the data of Barbui et al. (208) it is intriguing to consider the possibility that pentraxin 3 response to inflammation in subjects with high JAK2 burden might contribute to lower or enhance the thrombotic risk. More generally the association between JAK2 mutation, inflammation and thrombotic risk deserves scientific attention also for other speculative and practical purposes.

6. The scoring system for risk assessment for VTE in cancer patients

The development of predictive risk assessment model in non-cancer patients has helped to stratify patients according to their VTE risk and tailor thromboprophylaxis accordingly. Some models in surgical patients stratified patients according to the type of operation (major or minor), age and the presence of additional risk factors eg. cancer, prior VTE, obesity, co-morbid medical conditions.

In cancer patients, risk stratification is a dynamic process depending on the type and stage of cancer, performance status, and supportive and specific cancer therapy. A model-based approach that incorporates multiple risk factors for VTE can help identify the high-risk subgroups in the cancer population and would allow for a directed prophylactic strategy to improve outcomes of management and sparing the low risk patients from unnecessary anticoagulation therapy with its complications, social and financial burden. The ideal score model has to be simple, sensitive, specific and well validated.

Khorana AA et al (209) developed a simple model for predicting chemotherapy-associated VTE using baseline clinical and laboratory variables. The association of VTE with multiple variables was characterized in a derivation cohort of 2701 cancer outpatients from a prospective observational study. A risk model was derived and validated in an independent cohort of 1365 patients from the same study. Five (2 clinical and 3 laboratory) predictive variables were identified in a multivariate model: site of cancer (2 points for very high-risk site, 1 point for high-risk site), platelet count of ≥350 × 10^9/L, Hb <100 g/L (10 g/dL) and/or use of erythropoiesis-stimulating agents, WBC ≥11 × 10^9/L, and BMI of ≥35 kg/m2 or more (1 point each). Rates of VTE in the derivation and validation cohorts, respectively, were 0.8% and 0.3% in low-risk (score = 0), 1.8% and 2% in intermediate-risk (score = 1-2), and 7.1% and 6.7% in high-risk (score ≥ 3) category over a median of 2.5 months (C-statistic = 0.7 for both cohorts). Khorana AA et al stated that their model can identify patients with a nearly 7% short-term risk of symptomatic VTE.

Patients characteristics	Risk score
Site of Cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥ 350x10/L	1
Hemoglobin level ≤ 10g/dl or use or erythropoietin	1
Prechemotherapy leukocyte count more than 11000/mm^3	1
Body mass index 35 kg/m^2 or more	1

Table 2. Predictive model for chemotherapy-associated VTE
Adapted from Khorana et al. (209) with permission

To improve prediction of VTE in cancer patients, Ay C et al (210) performed a prospective and observational cohort study of patients with newly diagnosed cancer or progression of disease after remission. Khorana's risk scoring model for prediction of VTE that included clinical (tumor entity and body mass index) and laboratory (Hb, platelet and WBC count) parameters was expanded by incorporating 2 biomarkers, soluble P-selectin, and D-Dimer.

Of 819 patients 61 (7.4%) experienced VTE during a median follow-up of 656 days. The cumulative VTE probability in the original risk model after 6 months was 17.7% in patients with the highest risk score (≥ 3, n = 93), 9.6% in those with score 2 (n = 221), 3.8% in those with score 1 (n = 229) and 1.5% in those with score 0 (n = 276). In the expanded risk model, the cumulative VTE probability after 6 months in patients with the highest score (≥ 5, n = 30) was 35.0% and 10.3% in those with an intermediate score (score 3, n = 130) as opposed to only 1.0% in patients with score 0 (n = 200); the hazard ratio of patients with the highest compared with those with the lowest score was 25.9 (8.0-84.6). The authors demonstrated that clinical and standard laboratory parameters with addition of biomarkers enable prediction of VTE and allow identification of cancer patients at high or low risk of VTE.

Ay C et al concluded that with expanded risk model, which included sP-selectin ≥53.1 mg/ml and D-Dimer ≥1.44 mg/ml, (2 biomarkers) the risk prediction can be considerably improved. In patients with the highest compared with patients with the lowest risk, the probability for VTE was 26-fold higher.

The advantage of the "Khorana-Score" is that all parameters of this risk model are routinely determined in cancer patients at diagnosis.

7. Prevention of venous thromboembolism in cancer patients

Using Khorana risk scoring model or Ay Cihan et al expanded scoring model, it is within the reach of the attending hematologist/oncologist to stratify his/her cancer patient into one of the VTE risk groups: very high, high, intermediate or low and consider the patient for thromboprophylaxis in a patient-focused approach.

It also well understood that prophylaxis with antithrombotic agents can be problematic in cancer patients because they are at increased risk for anticoagulant induced bleeding. However, prophylaxis has been shown to be beneficial in certain high-risk populations such as post-surgical or hospitalized cancer patients but data in the ambulatory settings are conflicting.

7.1 Prophylaxis in surgical cancer patients

In general, surgery for cancer increases the risk of VTE and adequate prophylaxis has been shown to reduce VTE rates significantly [99,100]. A number of studies have shown that patients with cancer who undergo a specific type of major surgery have a 2-4 fold higher incidence of postoperative VTE compared with patients without cancer. The risk of venographically proven DVT varies from 20% to 40% and the risk of fatal PE is approximately 1%. Therefore, routine prophylaxis with anticoagulant therapy is strongly recommended, both in the immediate post-operative setting and in the extended period following major surgery.

The agents used most widely for prophylaxis in surgical patients are unfractionated heparin (UFH) and low-molecular- weight heparin (LMWH). Meta-analysis of randomized trials evaluating anticoagulant prophylaxis in general surgery, Mismetti et al. (211), found no significant difference between LMWH and UFH in symptomatic VTE, major bleeding, transfusion and death. This finding is supported by the ENOXACAN study (212). The

ENOXACAN II study was conducted to examine the effect extended prophylaxis i.e. 21 days, significantly reduced the incidence of DVT from 12% to 4.8% (p= 0.02).

7.2 Thromboprophylaxis in hospitalized or bedridden cancer patients

As the incidence of VTE in cancer patients who require hospitalization is very high, therefore they would benefit from primary anticoagulant prophylaxis. However, it is likely that the absolute and relative benefit of primary thromboprophylaxis will vary greatly amongst different patient groups because of the heterogeneity of cancer patient. It appears that the greatest potential impact of primary prophylaxis would be in patients initially diagnosed with advanced disease particularly those who are candidates for chemotherapy. Another subgroup of patients who may warrant primary thromboprophylaxis are patients initially diagnosed with local, or regional-stage cancer who progress and develop metastatic cancer or when they are admitted to hospital with an acute illness. Those patients should always be considered for primary pharmacological as well as mechanical thromboprophylaxis. Although none of the clinical studies evaluated a cancer-specific population, consensus statements and guidelines unanimously support the use of prophylaxis in cancer patients admitted to hospitals.

7.3 Thromboprophylaxis in ambulatory cancer patients

Much less is known about prevention of VTE in ambulatory cancer patients. The incidence of symptomatic VTE observed in ambulatory patients with advanced or metastatic malignancies in a recent clinical trial of 3% is considered low (26). Multiple recent studies have evaluated the potential benefit of thromboprophylaxis in ambulatory patients selected on the basis of one or two risk factors but have been unable to definitively identify patients who would benefit from prophylaxis

In the double-blind study by Levine et al (213) evaluated the anticoagulant effect of very low-dose warfarin (INR1.3-1.9) in Stage IV breast cancer while they were receiving chemotherapy. However, more recent trials have failed to confirm the benefit of primary prophylaxis in the ambulatory setting.

In summary, routine anticoagulant prophylaxis in medical oncology patients is not practiced because (a) the incidence of symptomatic VTE observed in ambulatory patients with advanced or metastatic malignancies is considered low. (b), the risk of bleeding remains a significant concern in most patients with cancer. (c) extended periods of primary prevention with an anticoagulant can be unattractive to most patients with cancer and (d) the optimal period of prophylaxis has not been identified.

One established high-risk group in the ambulatory setting is multiple myeloma patients receiving combination therapy. All newly diagnosed patients treated with thalidomide/lenalidomide- containing regimens should receive thromboprophylaxis as detailed in chapter 5.

7.4 Primary VTE prophylaxis in palliative care settings

Sarah Mclean and James S O'Donnell (214) published a qualitative systemic review that covered the period (1960-2010) on this important aspect of management of cancer patients

(Palliative Medicine June 2010). The authors pointed that primary thromboprophylaxis with LMWH is under utilized in the palliative setting although it is supported by level 1A evidence. The authors stated that studies examined practice in specialist patient care units and attitude held by a total of 32 palliative care physicians and 198 patients for thromboprophylaxis revealed that patient perception of LMWH is based on physician's concern regarding the negative impact on quality life and lack of evidence to support such practice. The authors concluded that LMWH prophylaxis in palliative patients with previous good performance status needs further studies.

7.5 Guidelines for VTE prophylaxis in cancer patients

The recommendation of the American College of Chest Physicians (ACCP) guidelines on prevention of VTE recommends prophylaxis for acutely ill hospitalized medical/surgical patients with cancer (215). However, the compliance of oncologists with the recommendations remains low (216) and this may be due to lack of awareness or unfounded fear of bleeding within the oncology community. Institution-based VTE prophylaxis guidelines with risk for VTE stratification followed by effective monitoring and auditing policy by the institution and sustained awareness campaigns could have a significant positive impact.

The Guidelines

The reader is referred to the following rich evidence-based guidelines:

1. ACCP guidelines is an evidence-based on antithrombotic and thrombolytic therapy covering both prevention and treatment with selected issues related to cancer patients (http://www.chestnet.org/accp/)
2. National Comprehensive Cancer Network (NCCN), a non-profit, alliance of 20 leading National Cancer Institute-designated Cancer Centers. The NCCN develops and disseminates clinical practice guidelines in oncology. The latest version of recommendations on VTE management can be found on-line at nccn.org/professionals/physicians_gls/PDF/vte.pdf.
3. Italian Guidelines on Management of VTE in patients with cancer published on-line by the Italian Association of Medical Oncologists for Italian oncologists. The guideline covers different aspects of VTE and cancer (a) VTE associated with occult malignancies (b) prophylaxis in cancer surgery, during chemotherapy, during hormonal therapy (c) VTE prophylaxis of VTE associated central venous catheters (d) treatment of VTE in cancer patients (e) anticoagulation and prognosis of cancer. The Italian recommendations are updated annually.
4. The American Society of Clinical Oncology Guidelines published its latest recommendations for VTE prophylaxis and treatment in patients with cancer in Dec 2007, JCD volume 25, No. 34 (5490-5505). Our reader is encouraged to refer to this informative and comprehensive document. The ASCO recommendations are depicted in a user-friendly practical approach in a format of practical questions.
    1. Should hospitalized patients with cancer receive anticoagulation for VTE prophylaxis?
    2. Should ambulatory patients with cancer receive anticoagulation for VTE during systematic chemotherapy?

3. Should patients with cancer undergoing surgery receive preoperative VTE prophylaxis?
4. What is the best treatment for patients with cancer with established VTE to prevent recurrent VTE?
5. Should patients with cancer receive anticoagulants in the absence of established VTE to improve survival?

8. Consequences of cancer-associated thrombosis

As depicted above in this chapter, the implications of diagnosis of VTE in a patient with cancer are many:

a. Mortality: cancer diagnosed at the same as or within a year of an episode of VTE is associated with 3-fold increase in mortality at one year. Moreover, the mortality rate in hospitalized cancer patients is higher when they develop VTE. For ambulatory cancer patients, initiating treatment with chemotherapy, VTE and arterial thrombosis has been reported to account for 9% of death. The risk of dying from fatal PE in cancer patient undergoing surgery is 3-fold higher than similar surgery in non-cancer patients.
b. Bleeding complications: cancer patients with VTE and treated with anticoagulants are at two-fold greater risk of bleeding complications than patients with VTE but no cancer.
c. Negative impact on healthcare resources: in a retrospective study Etting LS et al (Arch Int Med 2008) reported that the average cost of hospitalization for the index DVT episode in cancer patients in USA was $20065 in 2002 and the attributable hospital stay was 11 days.
d. Recurrence rate of VTE in a patient with cancer is 3-fold more frequently than in patients without cancer. Prandoni et al (32) performed a prospective cohort study of consecutive patients with incident VTE and compared the incidence of recurrence and bleeding for those with and without cancer at the time of VTE. Patients were given heparin followed by warfarin. The 12-month cumulative incidence of recurrent VTE in the group with cancer was 20.7% (95% CI 15.6–25.8%) vs. 6.8% (95% CI 3.9–9.7%) in those without malignancy. The rate of recurrence was directly associated with tumor burden as prospectively assessed by the investigators. This study also confirmed that the risk of major bleeding was also higher for patients with extensive cancer on warfarin anticoagulation. Compared to patients without cancer, patients with cancer have a higher risk of thrombosis and recurrent thrombosis. Recent evidence from well-conducted clinical trials shows that cancer patients may benefit from a longer duration of prophylaxis after surgery and that treatment with long-term LMWH is more effective than conventional oral anticoagulant therapy. Randomized studies have shown that prolonged (6 months) treatment with LMWH results in both lower VTE recurrence rates and less bleeding. Thus, LMWH is the therapy of choice for treatment of VTE in patients with cancer. However, the optimal duration of therapy for patients with active cancer has not been determined.
e. Post-Thrombotic Syndrome

Available data on the incidence of post-thrombotic syndrome in patients with cancer is scarce. However, approximately 30% of patients with DVT subsequently develop this chronic, frequently disabling condition within 5 years of the event. Of those, 8.1% will have severe post-thrombotic manifestations (Prandoni et al, 1997b) (8). It is expected that the incidence of the syndrome in cancer patients would be higher in view of adverse patient and

treatment related factors. Symptoms of post-thrombotic syndrome include debilitating leg pain, swelling, and fibrosis. Severe manifestations may result in debilitating leg ulceration, mobility problems, and the need for long-term nursing care.

f. Pulmonary Hypertension

Pulmonary hypertension is a life-threatening condition associated with fatigue, chest pain, peripheral swelling, and increased mortality. Recent studies suggest that 4–5% of patients develop pulmonary hypertension within years after symptomatic PE, Pengo et al, 2004 (216).

9. Treatment of VTE

Several studies have addressed treatment of VTE in patients with cancer:

a. The CLOT (Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer, N Engl J Med. 2003) study, which compared dalteparin with vitamin K antagonist (VKA) therapy, is the largest randomized trial of VTE treatment in patients with cancer (n = 672) (183). This study reported a 52% RRR in the incidence of recurrent VTE in favor of dalteparin during the 6-month study period.
b. Three additional studies assessed the use of LMWH for extended VTE treatment in patients with cancer. The CANTHANOX (Secondary Prevention Trial of Venous Thrombosis with Enoxaparin) study compared 3 months of warfarin therapy with 3 months of enoxaparin therapy in patients with malignancy and proximal DVT or PE (218). Because of slow recruitment, the study was terminated prematurely. At 3 months, seven patients in the enoxaparin group had recurrent VTE or major bleeding (the combined primary end point) versus 15 patients in the warfarin group (P = 0.09). Most of the primary outcomes were due to major bleeding (five patients in the enoxaparin group versus 12 in the warfarin group). In the warfarin group, six of the patients died of major bleeding, and at the 6-month follow-up, 31% of patients in the enoxaparin group had died, compared with 38.7% of patients in the warfarin group (P = 0.25). The findings of this limited study suggest that warfarin may be associated with a higher risk of bleeding than LMWH when used as long-term VTE treatment in patients with cancer (218).
c. The three-arm ONCENOX (Secondary Prevention Trial of Venous Thrombosis with Enoxaparin) study included 101 patients with cancer and VTE. Because of the small number of patients enrolled, no differences between the enoxaparin and warfarin groups were observed with regard to the incidence of recurrent VTE, major bleeding, or death (219).
d. The LITE (Long-Term Innohep Treatment Evaluation) study found tinzaparin to be more efficacious than warfarin in 200 patients with cancer (220). Tinzaparin treatment reduced the rate of recurrent VTE by ~50%; however, the difference was not statistically significant at the end of the 3-month treatment period. There were no differences in bleeding rates between the two groups.

Compared with warfarin, LMWHs generally reduce the overall risk of recurrent VTE when used for the extended treatment of VTE, a finding confirmed by a recently published Cochrane systematic review (221). Furthermore, LMWHs do not increase major bleeding

rates and appear to be as safe as VKAs. These findings, like those seen in the prevention trials, appear to be related to the dose and the duration of therapy.

The standard treatment for acute VTE is anticoagulant therapy. For initial therapy, subcutaneous (SC) LMWH is as effective and safe as intravenous UFH (28, 29). LMWHs are administered once or twice daily by SC injection, have weight-adjusted dosing and do not usually require laboratory monitoring. These advantages over UFH allow LMWHs to be given on an outpatient basis and reduce the need for hospitalization.

Duration of therapy: Duration of anticoagulant therapy has not been addressed in cancer patients. Based on the accepted concept that the risk of recurrent thrombosis is increased in the presence of any ongoing risk factor, it is generally recommended that patients with metastases continue with ''indefinite'' therapy because metastatic malignancy is a persistent risk factor. In those without metastases, anticoagulant treatment is recommended for as long as the cancer is ''active'' and while the patient is receiving antitumor therapy.

Secondary prophylaxis: Oral anticoagulant therapy with a vitamin K antagonist can be started on the same day as heparin therapy to begin secondary prophylaxis. To effectively reduce recurrent VTE without excessive bleeding, the dose of oral anticoagulants must be adjusted to maintain the INR within a therapeutic range of 2.0 to 3.0. This usually requires twice weekly blood work for the first 1 to 2 weeks until a stable dose is identified. Using this regimen, the annual incidence of recurrent VTE in patients without cancer is approximately 8%, whereas the risk of recurrence is two- to threefold higher in patients with cancer.

The higher failure rate in cancer patients may reflect the greater difficulty in maintaining therapeutic INR levels because of multiple drug interactions, gastrointestinal upset, vitamin K deficiency, liver dysfunction and poor venous access. Also, temporary discontinuation of anticoagulant therapy is often necessary during periods of thrombocytopenia and to accommodate invasive procedures. Such interruptions can cause lengthy periods of inadequate anticoagulation because vitamin K antagonists have a delayed onset of action and a prolonged period of clearance. Furthermore, warfarin failure, i.e. recurrent VTE despite maintaining therapeutic INR levels, is not uncommonly reported in cancer patients on oral anticoagulant therapy.

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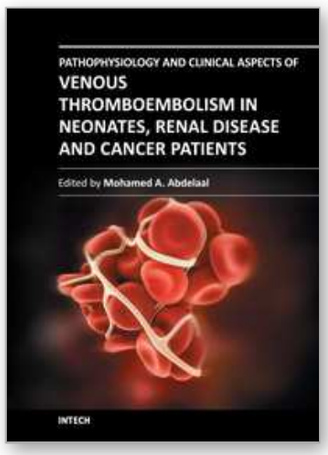

Pathophysiology and Clinical Aspects of Venous Thromboembolism in Neonates, Renal Disease and Cancer Patients

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Venous Thromboembolism remains a major health challenge in many countries because of the morbidity and mortality it inflicts, mainly in hospitalized patients. This book, with contributions from distinguished experts in the field, depicts some hot aspects on aetilogics of VTE, the disease burden in neonates, renal disease and cancer patients as well as issues relevant to prophylaxis and the concept of VTE as patient injury content.

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