THROMBOSIS IN CANCER:
A MEDICAL PROFESSIONAL'S GUIDE TO CANCER ASSOCIATED THROMBOSIS

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FOREWORD

I have been practicing academic clinical hematologist and oncologist for more than 20 years now. The author, Dr. Supratik Rayamajhi is my cherished colleague who I have known for the past decade. Most of the other authors are also my colleagues, and I have been an attending physician and mentor to some. I was thrilled to learn that the authors were busy writing a book on the topic of cancer-associated thrombosis. I anticipated the publication of this book and was rewarded with this opportunity to read it. The authors are all uniquely qualified to write on this important subject based on their experience, research, and insight into this topic. This is an area that I also have direct and almost daily medical experience with and can attest to this book's current relevance and accuracy.

Why should you read this book? Well, are you someone that wants to get right to the point? Do you dislike long and verbose writing, that goes on and on? Are you someone that wants to keep current with the ever-changing medical literature? If so, then you are the right person for this book.

Cancer-associated thrombosis is a broad area but can be parsed into "bite-size" pieces that are easily "digestible" for consumption for the learner. The day of the giant 1,000-page medical tome is over. This is a book that highlights an important subject in an easy and to-the-point quick read that will not bore you with endless unnecessary detail. This book will turn you into a knowledgeable physician in this field in the shortest amount of time.

I have shown this book to other practicing hematologists and oncologists who have praised it. We all appreciate its accuracy and brevity without leaving anything of relevance out. I highly recommend this book to all eager students and practitioners of medicine, especially to anyone that wants to learn this topic from scratch or to those who might need a brief review.

I am the Director of the Michigan State University/McLaren hematology and oncology fellowship program and have made this text required reading for our fellows. Read this book and you will not be disappointed. You will have a whole world of cancer associate thrombosis knowledge right at your fingertips!

Borys Hrinczenko, MD, PhD
Director
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PREFACE

Cancer and Thrombosis are interrelated. Their relationship adds complexity to the already challenging domain of cancer management. Thrombosis can at times be a lead to cancer diagnosis, while it often complicates the situation as a co-existing disorder.

This book is a result of generalists' endeavor to put together a rather simpler version of compilation, as it pertains to cancer-associated thrombosis (CAT). Our product is clinically oriented as compared to some in-depth basic science coverage of preexisting books on CAT. Our primary target audience naturally remains generalists and graduate-level trainees.

We have strived to stay current in terms of literature review. Specifically, we notice a paucity of evidence-based literature on thrombosis prophylaxis among cancer patients. We hope to infuse interest among our audience through an easy read of a complex entity that includes specific clinical situations and challenges, and hopefully, a palatable end-produce.

We do not have any conflict of interest to disclose during the preparation of this book.

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CHAPTER 1

Overview of Cancer-Associated Thrombosis

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Abstract: Ever since the association between cancer and thrombosis was reported in the early 19th century multiple studies have confirmed the relationship between cancer and thrombosis. Cancer patients, especially in the first few months after diagnosis and those with distant metastasis, have an elevated risk for VTE, and conversely, the risk of cancer diagnosis is high within the first 2 years of idiopathic VTE. VTE has an important impact on the prognosis of cancer patients. Thrombosis was the second leading cause of death (9.2%) after the cancer progression (70.9%) itself. The risks of recurrent VTE and bleeding are higher in patients with cancer-associated venous thrombosis than patients with venous thrombosis but without cancer.

Keywords: Anticoagulants, Cancer-associated thrombosis, Cancer costs, Cancer treatment, Coagulation in cancer, Hypercoagulability, Idiopathic VTE, Malignancy, Pulmonary embolism, Risks for VTE, Thrombosis, Trousseau syndrome, Venous thromboembolism, VTE prophylaxis, VTE treatment.

INTRODUCTION

Thromboembolism, both venous and arterial, have been described in patients with cancer. While venous thromboembolism (VTE) in cancer includes deep vein thrombosis (DVT), pulmonary embolism (PE), and visceral thrombosis, arterial thrombosis includes myocardial infarction and stroke.

Historically, the association between cancer and thrombosis was reported early in the 19th century by Jean-Baptiste Bouillaud [1]. Later, in 1865, Armand Trousseau reported venous thrombosis in a case of gastric cancer [2]. Known as *Trousseau's syndrome*, the term is nowadays used to describe VTE associated with any type of malignancy. Recent studies have confirmed those observations of the relationship between cancer and thrombosis from the 19th century. Cancer patients, especially

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in the first few months after diagnosis and those with distant metastasis, have an elevated risk for VTE [3] and conversely, the risk of cancer diagnosis is high within the first 2 years of idiopathic VTE [4].

Despite many studies done in recent times, the exact pathophysiology of cancer and VTE is still unknown. Considerable overlap in cancer growth and coagulation pathways has been described along with a complex interaction between tumor cells, the hemostatic system, and the characteristics of the patient [5]. Additionally, the factors identified to elevate the risk of VTE such as hospital admissions, surgery, immobilization, chemotherapy, presence of catheters, and other comorbidities are present equally or even more in cancer patients than those without cancer [5 - 7]. Type and stage of the tumor, anti-cancer therapies, and other malignancy-associated factors are also associated with an increased absolute risk of VTE [8]. New risk factors, such as platelet and leukocyte count and tissue factor, have also been described with high VTE risk in cancer patients [9].

Evidence shows that VTE in cancer patients is associated with increased morbidity and mortality [10]. Additionally, cancer-associated thrombosis leads to increased utilization of health care resources and increased cost of care [11]. Cancer-associated thrombosis incurred higher overall all-cause inpatient costs, outpatient costs, and total health costs, leading to an average increase of all-cause costs of VTE by $30,538/patient [11]. Moreover, VTE may potentially interrupt or delay the management of cancer in addition to reducing the quality of life of cancer patients [12].

Despite recent studies and the development of clinical guidelines in the last few years, a substantial gap still exists in the knowledge of various aspects of cancer-associated thrombosis. As mentioned previously, the pathophysiology is not clear. Many risk factors have been identified but their impact in prophylaxis and treatment of VTE in cancer patients in addition to overall prognosis is still being studied. Moreover, there are major therapeutic challenges associated with VTE in cancer patients, that are further complicated by multiple cancer-related risk factors and comorbidities. Low molecular weight heparin and warfarin are recommended anticoagulants for treatment but there are many unanswered questions regarding the overall management of cancer-associated thrombosis, including the use of direct oral anticoagulants.

EPIDEMIOLOGY

Recent studies estimate that 20-30% of total VTE cases are associated with cancer [13 - 16]. The risk of VTE is increased by at 4- to 7-fold in cancer patients [17], with the risk increased to 28-fold in a certain type of malignancies [3]. The annual incidence of VTE is 0.5% in cancer patients, compared to 0.1% in the general

population [18]. In a meta-analysis in 2012, Horsted *et al*. concluded that VTE occurred in greater than 1% of cancer patients each year, with wide variation dependent on the cancer type and time since diagnosis [19]. The overall risk of VTE was estimated to be 13 per 1,000 person-years (95% CI: 7-23) among average-risk patients. Patients with cancer of the pancreas, brain, and lungs had a higher risk of VTE than others, with brain cancer having the highest risk of VTE (200 per 1,000 person-years; 95% CI: 162-247). In patients with higher risk secondary to metastatic disease or receipt of high-risk treatments, the risk of VTE was 68 per 1,000 person-years (95% CI: 48-96) [19]. High risks of VTE have also been reported in lymphomas, myeloma, and kidney, stomach, ovarian, and bone cancer, with relatively low risks in patients with breast or prostate cancer [15]. The incidence of VTE increases from localized to regional to remote cancer in every cancer type [20]. Additionally, treatment modalities used for cancer substantially increase the VTE risk. The annual incidence rate of cancer patients treated with chemotherapy may range from 11-20% [21]. Similarly, surgery increases 90-day VTE risk by 2-fold in cancer patients in comparison to noncancer patients [22].

Over the years, the overall incidence of venous thrombosis in cancer patients has also increased gradually. The analysis of data from the US National Hospital Discharge Survey reported the increase in cumulative incidence of VTE from 1.5% in 1989 to 3.5% in 1999 [23]. In another study with linkage of four United Kingdom databases, the incidence of VTE in cancer patients was 19/1000 person-years in 2006 compared to 10.3/1000 person-years in 1997 [24]. Similarly, Khorana *et al*. reported a 36% increase in VTE among hospitalized neutropenic cancer patients between 1995 and 2002 [25].

The incidence of VTE is highest in the first few months after cancer diagnosis and gradually decreases thereafter. In the MEGA study, the risk for VTE was 54-fold higher in the first 3 months after diagnosis, declining to 14-fold after 3-12 months and 3.6 at 1–3 years after diagnosis [3]. The risk for VTE was close to those with no cancer after 10 years of diagnosis. Alcalay *et al*., in a retrospective analysis of colorectal cancer patients from the California Cancer Registry, reported the decrease in VTE incidence from 5.0/100 person-years in the first 6 months after a cancer diagnosis, to 1.4/100 person-years 6-12 months after a cancer diagnosis, and to 0.6/100 person-years 12-24 months after cancer diagnosis [26].

PROGNOSIS AND IMPACT OF VTE IN CANCER PATIENTS

VTE has an important impact on the prognosis of cancer patients. Thrombosis is a leading cause of death in patients with cancer [27]. An observational study was conducted by Khorana *et al*., with 4466 cancer patients. Among them, 141

CHAPTER 2

Pathophysiology and Risk Factors for Cancer-Associated Thrombosis

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Abstract: Virchow's triad of venous stasis, vascular damage, and blood hypercoagulability is the hallmark of VTE formation. Despite many studies done in recent times, the exact pathophysiology of cancer and VTE is still unknown. Various Tumor related, treatment-related and patient-related risk factors (RF) have been identified. Tissue-factor (TF), microparticles (MPs), inflammatory cytokines, and cancer procoagulants (CP) are some of the tumor-related risk factors. Tumor cellderived TNFa, IL-1b, and VEGF also contribute to cancer-induced hypercoagulability by other mechanisms, firstly they induce TF expression on monocytes. Several tumorrelated characteristics such as tumor site, type, stage (especially metastasis), histological variance and duration, are considered risk factors for the development of cancer-associated VTE. Surgery is the most important treatment-related risk factor in VTE in cancer patients along with other risk factors like hospital admission, chemotherapy, hormonal therapy, radiation therapy. patient-related factors such as age, gender, race, performance status, comorbidities, prior thrombosis, and prothrombotic mutations, are associated with an increased VTE risk in cancer patients. Several biomarkers have been investigated to quantitate and to predict the risk of VTE in cancer patients most important being D dimer, RF. Elevated levels of D-dimers are predictive of a higher risk of recurrent VTE in patients with cancer. Pre-chemotherapy platelet count has been shown associated with increased VTE risks in at least one study.

Keywords: Biomarkers of thrombosis in cancer, Cancer procoagulant, Coagulation cascade, D dimer in cancer, Hypercoagulability in cancer, Malignancy, Microparticles (MPs), Oncogene, Pathophysiology of thrombosis in cancer, Prechemotherapy platelet count, Risk factors for cancer thrombosis, Thrombosis in cancer, Tissue factor, Tumor suppressor gene, VEGF in cancer, Virchow's Triad.

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PATHOPHYSIOLOGY

Venous thromboembolism (VTE) and cancer are two intermingled processes that are linked by several pathophysiologic mechanisms. Virchow's triad of venous stasis, vascular damage, and blood hypercoagulability is the hallmark of VTE formation. Many risk factors (RFs) have been identified in cancer patients which promote one or more elements of the triad. These RFs can be divided into tumor-related which may be biochemical or non-biochemical, treatment-related, and patient-related RFs (Table **1**). Tissue factor (TF), microparticles (MPs), inflammatory cytokines, and cancer procoagulants (CP) are some of the players in the field of biochemical tumor-related risk factors. Fig. (**1**) is a simplified depiction of pathophysiology and factors involved in thrombosis associated with malignancy (Fig. **1**).

Table 1. Risk factors for cancerassociated venous thromboembolism and candidate biomarkers.

Tumor related risk factors	Tumor site. Tumor type. Tumor stage (especially metastasis). Histological variance. Duration (initial period after diagnosis of cancer).
Treatment related risk factors	Surgery. Hospitalization. Chemotherapeutic agents: Cisplatin, Fluorouracil, Thalidomide, Lenalidomide. Anti-angiogenic agents: Bevacizumab. Hormonal therapy: Tamoxifen. Supportive therapy: Erythropoietin, Erythropoiesis stimulating agents, Granulocyte-Colony Stimulating Factor, Granulocyte Macrophage-Colony Stimulating Factor, Platelets and Red Blood Cells transfusion and Central venous catheters.
Patient related risk factors	Comorbid conditions. Prior thrombosis. Prothrombotic mutations. Age, sex, and race. Performance status and mobility.
Biomarkers	Platelets $\geq 350{,}000/mm^3$ Leukocytes $> 11{,}000/mm^3$ Elevated Tissue factor Elevated D-dimer, F1+2, and TAT. Elevated soluble P-selectin. Elevated C-reactive protein

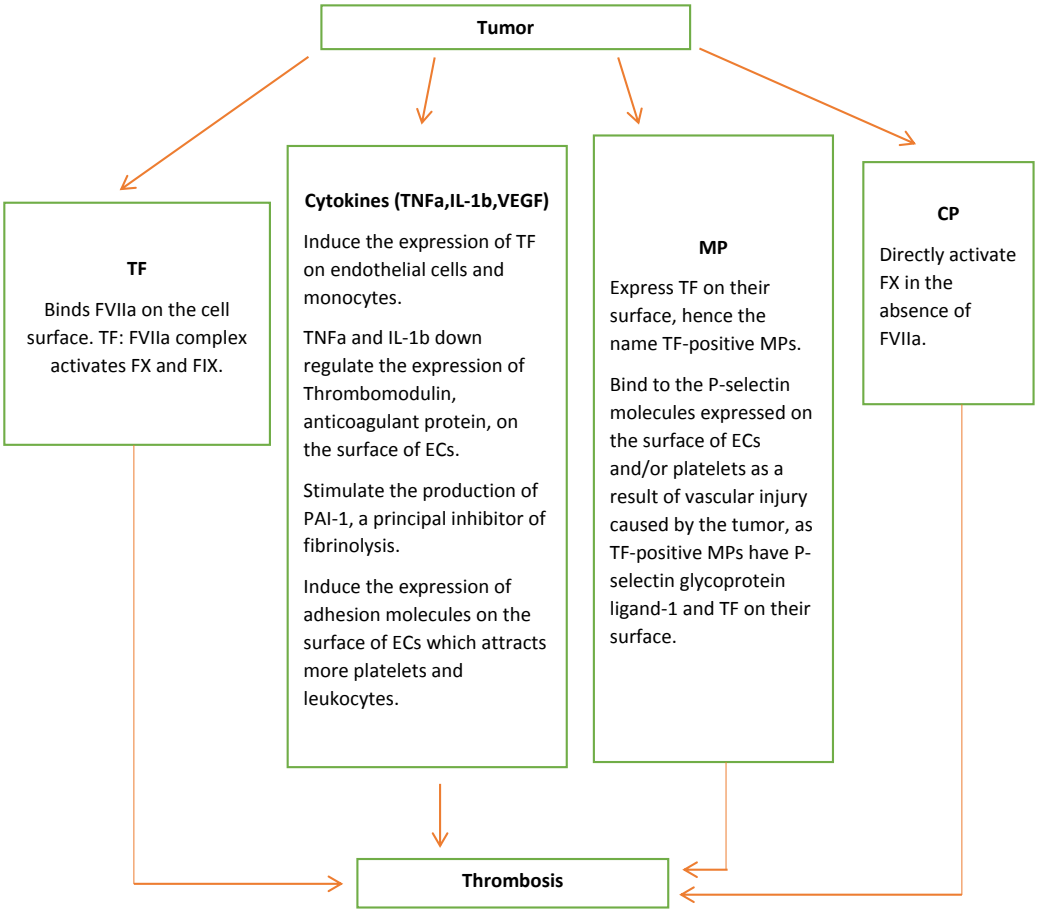

Fig. (1). Pathophysiology of thrombosis in malignancy.

TF plays a role in maintaining vascular integrity in the physiological response to injury [1, 2]. It is normally only expressed on subendothelial cells (such as pericytes, smooth muscle cells, and fibroblasts). This has no contact with blood or circulating FVII. TF interacts with blood only when the vascular integrity is compromised and subendothelial cells are exposed [3]. Only then will the activation of the extrinsic coagulation cascade commence. Two factors interplay to initiate this extrinsic coagulation cascade; these are factor VII (FVII) and TF [4, 5]. The focus of this discussion will be on the latter. TF, also known as coagulation factor III, thromboplastin, or CD142, is a protein that consists of three parts: a large extracellular domain; which contains the binding site for FVII, a short transmembrane domain; which helps anchor the TF/FVIIa complex and also expresses the pro-coagulant activity of TF, and a cytoplasmic tail [6].

CHAPTER 3

Impact of Venous Thromboembolism on Cancer Survival

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Abstract: Incidence of venous thromboembolism (VTE) is more common in cancer patients compared to non-cancer patients. Various factors that influence the incidence of VTE are patient population, duration of follow-up, patient-related factors, type and stage of tumor, chemotherapy agent or the treatment modality used, presence of central venous catheters, detection methods, and reporting. Mortality is increased by various factors such as delay or withdrawal of chemotherapy treatment, directly VTE-related complications like pulmonary embolism. Development of VTE within 2 years was found to be a significant risk factor for increased mortality and the rate was high among patients with localized disease. For the prevention of VTE in patients with cancer LMWH is given increased consideration, specifically Dalteparin [26, 27]. Further studies are necessary to determine the effectiveness of thromboprophylaxis in the reduction of mortality or thromboembolic complications in these high-risk populations.

Keywords: Cancer-associated thrombosis, Incidence of VTE in cancer, Mortality due to VTE, Recurrent VTE, Thrombosis in ALL, Thrombosis in malignancy, VTE prevention, VTE risks.

BACKGROUND

The incidence of venous thromboembolism (VTE) is four to six times more common in cancer patients compared to non-cancer patients [1, 2]. Cancer often tends to be in an advanced stage and is associated with a poor prognosis when VTE is present [3].

INCIDENCE

Patients with hematological malignancies are at increased risk for venous thrombosis. Various factors that influence the incidence of VTE are patient population, duration of follow-up, patient-related factors, type and stage of tumor, chemotherapy agent or the treatment modality used, presence of central venous

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catheters, detection methods, and reporting [4, 5]. In lymphomas and multiple myeloma, the use of immunomodulation with chemotherapy and corticosteroids significantly increases the risk of VTE [4]. All the hematological malignancies were associated with a 5-10 times higher incidence of VTE except for indolent lymphoma. The risk was noted to be the highest in aggressive non-Hodgkin lymphoma and lowest in Hodgkin lymphoma [6]. The incidence of VTE in leukemia varies from 1.1% to 36.7% [7]. The wide range in the reported incidence could be due to the variations in the stage of leukemia at which it was examined, subtypes of leukemia, and the treatment protocol [2]. However, a retrospective analysis by Mohren *et al*. showed that the rate of VTE in acute leukemia was 12.1% which is higher than solid tumors and lymphomas [8]. Incidence of VTE was higher among female sex, older age, presence of multiple comorbidities, presence of a central venous catheter, and patients undergoing stem cell transplantation [9]. Transplant recipients had the highest risk (IR: 8%, 95% CI: 4–13%) per one of the recent meta-analysis which also showed a VTE incidence of 6% (95%CI: 4–8%) in patients with acute myeloid leukemia (AML) [2]. In a population-based cohort study, the 2-year cumulative incidence in AML was 5.2%, out of which 3.6% had deep vein thrombosis and 1.6% had thrombophlebitis of the deep veins of the upper extremity or thorax [9]. During the first 3 months of follow-up after the diagnosis of ALL, the rate of VTE was 11.1 per 100 patient-years [9]. According to one of the studies, the incidence of VTE during the initial 2 years of ALL diagnosis is 4.5% [9]. In ALL, the cumulative incidence of VTE varies from 2% to 10.6% [10, 11]. Thrombotic events were highest during the initial 3 months of diagnosis and decreased to 2.0% in the next 21 months. Patients with acute leukemia are at increased risk of thrombosis due to thrombin generation, disseminated coagulation [12], and procoagulant activity of leukemic cells especially with treatment-induced cell lysis of leukemic cells [13]. Older age, central venous catheter, and chronic comorbidities are important risk factors for VTE in ALL. The incidence of VTE in patients with metastatic pancreatic cancer was the highest with 20.0 VTE cases per 100 patient-years, VTE rate was approximately 4.3 VTE cases per 100 patient-years in metastatic colorectal cancer [14]. In a population-based study among patients with colorectal cancer using California based registry, Asians/Pacific Islanders had decreased risk of VTE compared to Caucasians [14]. The above findings apply to patients with prostate, breast, lung, pancreas, and stomach cancer and non-Hodgkin lymphoma as well [15 - 17]. Patients with rectosigmoid cancer had a modestly lower incidence of VTE [14].

MORTALITY

Apart from death due to VTE mainly pulmonary embolism, mortality is increased by various factors such as delay or withdrawal of chemotherapy treatment [18]. In

a retrospective analysis by Chew *et al*. VTE caused a continued increase in mortality among patients in the California Cancer Registry [17, 19], the results were similar in a subsequent study on patients with breast cancer. During the initial months of chemotherapy, regardless of the cancer stage, VTE was found to be an independent risk factor for mortality [20]. Advancing age and the presence of chronic comorbidities were found to be significant predictors of death in AML [9]. The risk of death was increased by 40% for M1/2 subtypes of AML compared to 50% higher risk with M4/5 subtypes within the first year. There was a racial difference as well; mortality among Asians was lower with a 20% decreased risk of early death (HR = 0.8; CI: 0.7-0.9) [9]. Mortality during the first year of diagnosis was 50% lower among patients with central venous catheters [9]. The development of VTE itself increased the risk of mortality by 40% during the 1st year of diagnosis [9], with the risk of death significantly greater with older age.

VTE RECURRENCE

VTE recurrence rate in ALL was about 20% which is suggestive of the challenge associated with the treatment of cancer-related VTE [8]. One of the plausible explanations for VTE recurrence in ALL is the inability to achieve therapeutic anticoagulation due to risks of bleeding secondary to concurrent thrombocytopenia. Also, current anticoagulation guidelines recommend anticoagulant contraindication when the platelet count less than 500,000/μL 10*3/uL thereby increasing the risk of thrombosis [21, 22]. Among patients with VTE in colorectal cancer, one's with local- or regional-stage cancer had a significant reduction in survival [14]. The survival rate was higher among patients who undergo major abdominal surgery [14]. Development of VTE within 2 years was found to be a significant risk factor for increased mortality and the rate was high among patients with localized disease (HR 4.7, 95% CI: 2.3-9.5) [23].

EFFECT OF ANTICOAGULATION IN CANCER

A trial on patients with recurrent VTE found that the incidence of cancer was lower among subjects randomly assigned to 6 months of anticoagulation with warfarin than among those randomly assigned to only 6 weeks of anticoagulation [24]. Another trial on non-small cell lung cancer showed that the progression of cancer is delayed and also improves their survival [25]. Low molecular weight heparin (LMWH), specifically Dalteparin has been given increased consideration, for the prevention of VTE in patients with cancer [26, 27]. Further studies are necessary to determine the effectiveness of thromboprophylaxis in the reduction of mortality or thromboembolic complications in these high-risk populations [17].

CHAPTER 4

Occult Cancer Workup in Idiopathic Venous Thromboembolism

Manoj Rai[1,*]

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Abstract: Idiopathic VTE comprises about 40% of total VTE cases and may be an early sign of occult cancer. In patients with acute unprovoked VTE, the risk of having occult cancer is increased by four-folds compared to patients with provoking risk factors. Despite evidence that occult malignancy may be associated with unprovoked VTE cases, there is a paucity of data and no specific guideline regarding whether to perform occult cancer screening and what investigations to include. The National Institute for Health Care Excellence (NICE) guidelines suggest that idiopathic VTE cases should undergo extensive history taking, a comprehensive physical examination, a chest X-ray, basic laboratory investigations, and urinalysis. For now, only age-appropriate cancer screening along with complete history, and physical examination are advised in idiopathic VTE cases, with more focused evaluation depending on the initial findings. Further studies are required to assess the extent and benefits of extensive occult cancer screening in patients with idiopathic VTE.

Keywords: Cancer-associated thrombosis, Cancer screening, Idiopathic VTE, Occult cancer, Risks of VTE in cancer, Thrombosis, Thrombosis in malignancy, VTE in overt cancer, VTE Screening in cancer.

INTRODUCTION

Idiopathic or unprovoked venous thromboembolism (VTE), defined as VTE not associated with a transient risk factor (for example surgery, prolonged immobility, trauma, and pregnancy) or overt cancer, comprises about 40% of total VTE cases [1]. In some cases, idiopathic VTE may be an early sign of occult cancer [2, 3]. *Trousseau syndrome,* named after Professor Armand Trousseau, who was one of the first to describe the clinical association between idiopathic VTE and occult malignancy, is defined as migratory thrombophlebitis as a presenting manifestation of occult cancer [4].

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In patients with acute unprovoked VTE, the risk of having occult cancer is increased by four-folds compared to patients with provoking risk factors [5]. The incidence of occult cancer in unprovoked VTE varies widely and some studies estimated rates as high as 30% in the past [6 - 12]. However, Prandoni *et al.* reported a cumulative incidence of only 3.2% over a follow-up of 2.5 years [13]. Carrier *et al.* showed a 6% prevalence of occult cancer in unprovoked VTE which increased to 10% after one year of VTE diagnosis [5]. Usually, 60% of occult cancer are diagnosed shortly after VTE and the incidence of cancer diagnosis gradually declines to the rate in the general population after 6-12 months [3, 5, 13]. Male gender is at increased risk [14], and pancreatic, ovarian and hepatic cancers are frequently diagnosed in cases of idiopathic VTE [15].

Despite evidence that occult malignancy may be associated with unprovoked VTE cases, there is a paucity of data and no specific guideline regarding whether to perform occult cancer screening and what investigations to include. The National Institute for Health Care Excellence (NICE) guidelines suggest that idiopathic VTE cases should undergo extensive history taking, a comprehensive physical examination, a chest X-ray, basic laboratory investigations, and a urinalysis [16]. For patients over 40, a CT abdomen/pelvis and, mammography for women, are also suggested in addition to the abovementioned investigations. However, many studies have questioned the benefit of these additional imagings [17 - 20]. Multiple studies conducted to evaluate the utility and extent of occult cancer screening have shown mixed results. A prospective cohort study compared a limited occult cancer screening strategy to an extensive strategy also including mammography in women as well as thoracic and abdominal computed tomography (CT) [18]. No difference was seen in the number of cancer cases diagnosed (5.0 *vs.* 3.7%, respectively) or in overall mortality (8.3 *vs.* 7.6%, respectively). Carrier *et al.* reported no benefits with the use of imaging studies such as CT of chest, abdomen, and pelvis over the use of limited cancer screening in patients with unprovoked VTE [17]. A recent multicenter randomized trial including 195 cases concluded that CT-based strategy including thoracic, abdominal, and pelvic CT in combination with fecal occult blood test does not provide a significant benefit over more limited cancer screening for detection of occult cancer in patients with unprovoked VTE [19]. However, another randomized controlled trial reported increased detection of early-stage cancer (T1–2, N0) (64 *vs.* 20%, p =0.047) and reduction in cancer-related mortality (absolute risk reduction 1.9%) during 2-year follow-up with extensive screening methods [21]. Robin *et al.* compared screening with 1^{8}F-fluorodeoxyglucose positron emission tomography (1^{8}F-FDG PET) and low-dose CT to limited screening. No significant differences in cancer diagnosis were detected between the two groups. However, there was a lower risk of subsequent cancer diagnosis after the initial negative screening with 1^{8}F-FDG PET/CT than with negative

initial limited screening [22]. FDG-PET/CT was also shown to be feasible for the screening of occult cancer in patients with unprovoked VTE, with high sensitivity and negative predictive value [23]. In a systemic review and meta-analysis of five prospective trials, Klein *et al.* compared extensively with limited screening for occult malignancies in 2287 patients with idiopathic VTE [24]. Extensive screening yielded more diagnoses of cancer (Relative Risk, RR 2.17; 95% Confidence Interval, CI 1.42–3.32) but did not affect all-cause mortality at the end of follow-up (RR 0.86; 95% CI 0.58–1.27).

Thus, it is unclear whether extensive screening and earlier detection of occult cancer improve morbidity, mortality, and overall prognosis. Also, there is an increased economic burden and radiation exposure associated with extensive screening. On other hand, there have been concerns about whether the extensive screening was extensive enough or the limited screening was too limited [25]. Despite these concerns, until more data are available, it is advised that a complete history and physical examination along with age- and sex-appropriate cancer screening tests are adequate as a starting point [25 - 27]. Colonoscopy for patients older than 50 years, mammography in women older than 40-50 years of age, a Papanicolaou smear in women 21-65 years of age are advised (Table **1**) [28 - 33]. The United States Preventive Task Force advises against the use of prostate-specific antigen for prostate cancer screening in the general population [34] and the role of prostate cancer screening in VTE cases is unclear. Lung cancer screening is recommended only for high-risk patients [35].

Table 1. Summary of cancer screening guidelines in general population [29 - 36].

Cancer Type	Test	Population, Age in Years	Frequency of Test	USPSTF Recommendation
Breast*	Mammogram	Women, 40-49†	Annually	Uncertain
		Women, 50-74	Every 1-2 years	Recommended
Cervical	Pap smear only OR Pap smear with HPV test	Women, 21-65	Every 3 years with Pap smear only up to 30 years of age; After 30 years, every 5 years with Pap smear and HPV test (preferred) OR Pap smear only every 3 years (acceptable)	Strongly recommended
Colorectal	Colonoscopy	Men and women, 50-75 45-75§	Every 10 years	Strongly recommended
	Sigmoidoscopy‡		Every 5 years	Strongly recommended
	Fecal occult blood test‡		Annually	Strongly recommended

CHAPTER 5

Chemotherapy Induced Thrombosis

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Abstract: Chemotherapy is a known independent risk for the development of VTE which is also known to increase the risk of recurrence of VTE in malignancy by four-folds. Factors that influence the incidence of VTE in chemotherapy are the type, location of the tumor, type of chemotherapy, the presence of agents such as hormonal agents, targeted therapies. Chemotherapy can worsen the pro-thrombotic state by various mechanisms. Various scoring system such as Khorana's model and Ottawa score has been recommended to predict the risk of VTE with chemotherapy. Low molecular weight heparin (LMWH) has been shown be to effective in VTE prophylaxis in patients with active cancer undergoing chemotherapy. There is however limited evidence currently regarding the use of direct oral anticoagulants in the prophylaxis of cancer-associated thrombosis.

Keywords: Cancer-associated thrombosis, Cancer prophylaxis, Chemotherapy, Chemotherapy associated thrombosis, Direct oral anticoagulants, Khorana's Model, LMWH in VTE, Ottawa Score, Recurrent VTE with chemotherapy, Thrombosis in malignancy, VTE prophylaxis, Warfarin.

INTRODUCTION

Chemotherapy is a known independent risk for the development of venous thromboembolism (VTE). With an annual incidence of 10%, the risk of VTE is 2-6 times higher with chemotherapy compared to the general population [1]. Additionally, the risk of recurrence is increased by four-folds in patients with chemotherapy [2]. The recurrence rates are even higher in the male population and with older age. Various other factors that influence the incidence of VTE in chemotherapy are the type of tumor - hematological malignancy *versus* solid tumor malignancy, the location of the tumor, type of chemotherapy, the presence of additional agents such as hormonal agents, targeted therapies [3].

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PATHOPHYSIOLOGY

Chemotherapy can worsen the pro-thrombotic state by various mechanisms such as causing damage to the vascular endothelium, increasing endothelial cell apoptosis and cytokine release thus increasing the activity of TF. It can also increase platelet activation. According to one of the reports, the number of platelet-derived MPs in plasma was significantly lower compared to the baseline during the first 24 hours following the administration of cisplatin-based chemotherapy [4]. Thalidomide and thalidomide analogs such as lenalidomide and pomalidomide act by causing anti-angiogenic, immunomodulatory, and apoptotic effects [5]. The incidence of thromboembolism associated with thalidomide as induction or maintenance therapy in MM is below 5% [6]. The risk for thromboembolism increased significantly with the addition of dexamethasone with rates as high as 17% [7]. The risk of VTE during treatment with thalidomide–anthracycline combination regimens is highest in the first few months of treatment. Thalidomide-alkylating agent combination therapy increases the risk to a lesser extent compared to anthracyclines. Thalidomide analogs increase the risk for thrombosis by various mechanisms. The various hypotheses include a drop in anticoagulant pathway cofactor thrombomodulin [8], increase in expression of endothelial cell protease-activated receptor-1 (PAR-1) [9], acquiring resistance to activated protein C (APC) in the absence of factor V Leiden [10], increase in the levels of factor VIII and von Willebrand factor antigen [11], accumulation of promyelocytes, with high levels of cathepsin G contained in their azurophilic granules [12]. L-asparaginase causes a decline in the levels of anticoagulant proteins C, S, and antithrombin III and it decreases the synthesis of both procoagulant and anticoagulant proteins by the liver [13] increasing the risk of thrombosis. It also activates platelets and endothelial cells [14]. Fluorouracil increases the risk by causing depletion of protein C and increased thrombin activity [15, 16]. The use of a prolonged course of glucocorticoids itself increases the risk of thromboembolism [17] by increasing levels of coagulation factors particularly VII, VIII, XI, and vWF [18]. It also increases PAI-1 synthesis and enhances the activity of tissue plasminogen [19]. Its use of corticosteroids with thalidomide further increased the risk of thrombosis to up to 20-30% [20, 21]. Tamoxifen increases risk by decreasing antithrombin III and protein C levels in the blood [22]. Raloxifene which is a selective estrogen receptor modulator had a lower risk for thrombosis compared with Tamoxifen [23]. Among the progestins venous thromboembolism was seen with megestrol (5 of 81 patients), the other aromatase inhibitor formestane was not found to cause VTE [24]. Bevacizumab causes an increase in expression of PAI-1 *in vivo* by blocking the inhibitory effect of VEGF on PAI-1 expression by tumor cells [25]. Cisplatin has also been known to increase the risk for VTE however the mechanism is unclear [26, 27]. Gemtuzumab, a monoclonal antibody directed towards CD33, predisposes

patients to VTE by causing glutathione deficiency and inflammatory cytokine-induced endothelial activation [28, 29]. Following stem cell transplantation, thrombosis risk increases up to 19% with Gemtuzumab [30]. The prothrombotic activity of G-CSF is secondary to activation of prothrombin fragment 1.2 (F1+2), TAT, and D-dimer leading to increased formation of thrombin and fibrin [31]. It is also known to stimulate the release of PAI-1 from human umbilical vein endothelial cells similar to erythropoietin [32]. The incidence with GM CSF was noted to be 4.2% and 1.2% for G-CSF [33]. Erythropoietin or darbepoetin which are used in chemotherapy-induced anemia is known to cause VTE in 7.5% of patients compared to 4.9% in the control group [34]. By activating platelets and increasing vWF, factor VIII as well as thrombin generation, erythropoietin decreases protein C, protein S and triggers signaling pathways in endothelial cells [35].

PROPHYLAXIS DURING CHEMOTHERAPY

Various scoring system has been recommended to predict the risk of VTE with chemotherapy such as Khorana's model and Ottawa score [36, 37]. Khorana's model is based on clinical evaluation and laboratory values [38, 39]. The capacity to predict risk for VTE increased with the inclusion of soluble P-selectin and D-Dimer in the risk assessment model [40 - 42].

Low molecular weight heparin (LMWH) has been shown be to effective in VTE prophylaxis in patients with active cancer undergoing chemotherapy. LMWH has been reported to cause a significant reduction of risk of VTE in cancer patients receiving chemotherapy, compared to placebo. In one review, LMWH significantly reduced the risk of VTE compared to placebo (RR 0.53, 95% CI 0.38 to 0.75) without significantly increasing the risk of major bleeding (RR 1.30, 95% CI 0.75 to 2.23) [43]. In another randomized trial, the risk of symptomatic VTE within the first three months was significantly lower with LMWH without any increase in bleeding risk [44]. Low-dose warfarin was also found to be effective for patients receiving outpatient chemotherapy in a clinical trial on patients with stage IV breast cancer [45]. In the above study rate of thrombosis was lower in the low-dose warfarin group compared to the placebo group (0.7% *vs*. 4.4%) [45]. The optimal dose, duration of thromboprophylaxis, and specific patient populations have not been clearly defined yet. However, if LMWH is not used for any reason such as cost, patient preference, or aversion to injectables, warfarin can be used as an alternative. Regarding the use of direct oral anticoagulants in such patients, there is limited evidence currently.

CHAPTER 6

Catheter-Related Thrombosis in Cancer

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Abstract: Central venous catheters (CVC) are important for the infusion of chemotherapy, intravenous medications, and blood products. Catheter-related thrombosis (CRT) is common among cancer patients. The lower rates of CRT under-reported as many are asymptomatic. Many patient-related factors such as age, venous anatomy, tumor characteristics (histology, size, and location, and catheter-specific features) have been attributed to CRT. Also, limitations of the diagnostic criteria exist. Doppler ultrasound is the common initial test but can be non-diagnostic. Contrast venography is the 'gold standard' and considered once Doppler negative but with strong clinical suspicion. Newer diagnostic tools such as contrast CT or MRI has emerged as promising alternatives but with occasional use. Anticoagulation is the treatment of choice once DVT is confirmed but there are no established standard guidelines. The catheter should be preserved with low molecular weight heparin for a minimum of three months. No anticoagulants are advised for routine prophylaxis but can be considered in high-risk groups.

Keywords: Cancer-associated thrombosis, Catheter-directed local thrombolysis, Catheter-related thrombosis (CRT), Chemotherapy, Contrast venography, CRT, CVC-related infection, DVT treatment, Intraluminal clot, LMWH in catheter-related thrombosis, Mural thrombus, Port associated thrombosis, Thrombosis in malignancy, WARP study.

INTRODUCTION

Central venous catheters (CVC) play an important role in the management of cancer, especially with the infusion of chemotherapy, intravenous medications, and blood products. Catheter-related thrombosis (CRT), by interrupting the therapy, may lead to complications and increased morbidity in cancer patients [1].

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EPIDEMIOLOGY AND RISK FACTORS

The incidence of CRT has been reported from 5 to 35% in cancer patients [2]. Recent studies have reported lower rates although many CRT are asymptomatic, and the incidence of thrombosis is thought to be underestimated [3]. In one review, symptomatic catheter-related deep vein thrombosis (DVT) in adult patients ranged from 0.3% to 28%, whereas the rate of catheter-related DVT assessed by venography was 27% to 66% [4]. In a prospective study, the incidence of symptomatic CRT was 4.3% (19 of 444 patients; 95% CI, 2.6% to 6.6%) or 0.3 per 1,000 catheter-days (95% CI, 0.2 to 0.5 per 1,000 catheter-days) [1]. The median time to CRT in the study was 30 days (range 6-162) and the median catheter lifespan was 88 days (range 2-376).

The large variation in the incidence of CRT may be attributed to patient-related factors such as age and venous anatomy, characteristics of the tumor such as histology, size, and location, and catheter specific features as well as the limitations of the diagnostic criteria (Table **1**) [5 - 7]. Most of these factors relate to Virchow's triad of endothelial damage, stasis, and hypercoagulability [8]. Increased risk with CRT has been associated with multiple catheter insertion attempts (OR, 5.5; 95% CI, 1.2 to 24.6), placement on the left side (OR, 3.5; 95% CI, 1.6 to 7.5), catheter tip in superior vena cava compared to the right atrium (OR, 2.7; 95% CI, 1.1 to 6.6), use of arm port compared with chest port (OR, 8.1; 95% CI, 3.5 to 19.1), and previous CVC insertion (OR, 3.8; 95% CI, 1.4 to 10.4) [1, 4, 9]. In one meta-analysis of clinical trials and prospective studies with patient level-data, factors such as the use of subclavian venipuncture insertion technique, improper positioning of the catheter tip, and previous history of DVT increased the risk of CRT [10]. Tesselar *et al.* reported thrombosis with elevated homocysteine levels (OR=3.8, 95% CI 1.3-11.3), but not with factor V Leiden or prothrombin 20210A gene mutations, or high concentration of factor VIII, IX, or XI [9]. Few studies have studied DVT associated with implanted ports. In one study, symptomatic DVT was diagnosed in 4.5% of 400 cancer patients with a newly implanted port who were followed for a median of 1 year without any thromboprophylaxis [11]. Peripherally inserted central catheters (PICC), which are increasingly being used in recent times, have been associated with greater CRT risk than central venous catheters [10, 12]. Thus, CRT risk is thought is increase gradually from the use of ports to central venous catheters to PICCs [11 - 14].

PATHOPHYSIOLOGY AND TYPES OF CRT

Factors such as injury caused by catheter CVC insertion, venous stasis caused by the indwelling CVC, and cancer-related hypercoagulability play a role in the

development of CRTs. There are different types of thrombi associated with CVC insertion, namely peri-catheter sheath (fibrin sleeve), intraluminal blood clot, and mural thrombus- either superficial or deep (Fig. **1**) [6, 7, 15]. Each type of thrombus has its own mechanism of development.

Table 1. Risk factors associated with catheter-related thrombosis in cancer [1, 6, 7, 10].

Patient related factors
• Hypercoagulable states - inherited such as thrombophilia or acquired with comorbidities such as critical illness, catheter related or systemic infection, congestive heart failure, renal failure, *etc.*
• Previous history of deep vein thrombosis
• Drugs such as hormones, erythropoietin stimulating agents, thalidomide
Malignancy related factors
• Type, location, histology and stage of cancer (especially metastatic cancer)
• Chemotherapy
• Radiotherapy to thorax
Catheter related factors
• Peripherally inserted central catheter (PICC)
• Use of catheter with increased lumen size, multiple lumens
• Tip located in superior vena cava
• Insertion from left side
• Insertion through subclavian vein
• Insertion through femoral vein
• Multiple insertion attempts

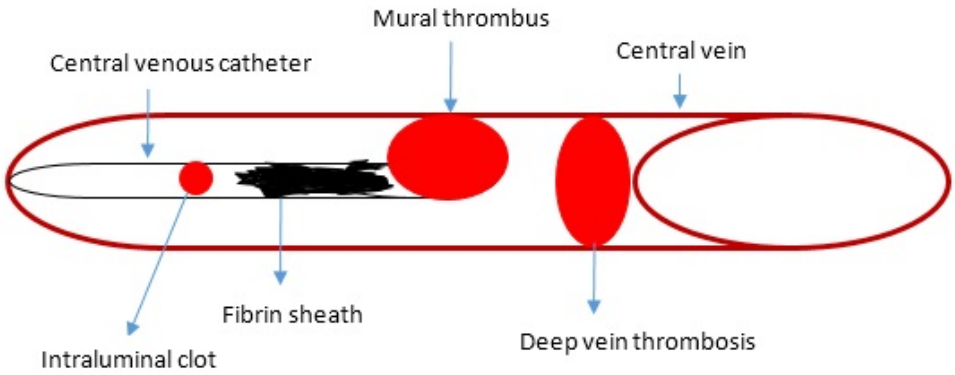

Fig. (1). Types of catheter-related thrombosis [6, 15].

Pericatheter Sheath or Fibrin Sleeve

Pericatheter sheath is one of the most common causes of catheter obstruction. Fibrin deposition and subsequent ingrowth of smooth muscle as well as endothelial cells begin within hours of insertion [16]. Slowly from days to weeks, a peri-catheter sheath is made up of a smooth muscle cell and collagen layer with overlying endothelial cells. The presence of these sheaths does not predict

CHAPTER 7

Management of Cancer-Associated Thrombosis

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Abstract: Anticoagulation options remain the same in those with or without cancer. It is used for the prevention and/or treatment of thrombus in those with low bleeding risk. No anticoagulation is recommended in active bleeding, recent surgery, pre-existing bleeding disorders, coagulopathy, or platelet count <50,000/microL. The immediate treatment options include low molecular weight heparin (LMWH) or unfractionated heparin (UFH) plus long-term management with LMWH, vitamin K antagonists, or direct oral anticoagulants. The acute VTE with malignancy requires initial anticoagulation therapy for 5-10 days, LMWH is the medication of choice unless contraindicated. The patient characteristics such as renal function, compliance, diet adherence determine drug selection. Fondaparinux and direct oral anticoagulants can also be initial treatment choices. UFH is preferred if a rapid anticoagulation reversal is required in circumstances such as renal disease, high bleeding risk, and for patients undergoing procedures. The factor Xa inhibitors are currently approved for initial DVT and acute PE treatment. They eliminate the need to monitor anticoagulation effectiveness. For those who are poor candidates for long-term LMWH, indirect oral anticoagulant (warfarin) is acceptable for chronic management. DOACs can be an alternative for those unable to use LMWH for reasons such as renal impairment (creatinine clearance less than 30mL/min), cost, non-compliance, or fear of needles. The duration of anticoagulation treatment is a minimum of 3 months. For those with malignancy and VTE with contraindications to anticoagulants, the only therapeutic option can sometimes be mechanical devices such as inferior vena cava filter (IVCF).

Keywords: Acute VTE, Cancer-associated thrombosis, Chronic anticoagulant malignancy, IVC filter, LMWH in malignancy, Management of VTE in malignancy, Oral anticoagulants, Rivaroxaban, Thrombosis in malignancy.

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INTRODUCTION

Anticoagulation treatment options are the same when it comes to the treatment of patients with or without cancer. The primary goal of anticoagulation use is prevention and/or treatment of progression of an already existing thrombus or embolization, all the while keeping the risk of bleeding to a minimum. The benefits and risks of anticoagulation therapy should always be considered, particularly in patients with limited life expectancy or with a high risk of bleeding.

Patients who have active bleeding, have had recent surgery, have pre-existing bleeding disorders, coagulopathy, or platelet count less than 50,000/microL should not be placed on anticoagulation therapy [1]. An alternative option for treatment would be an inferior vena cava filter discussed in the later section of this chapter.

Immediate treatment options for anticoagulation are low molecular weight heparin (LMWH) and unfractionated heparin (UFH) and, with subsequent long-term management with LMWH, vitamin K antagonists, or direct oral anticoagulants (DOACs) such as rivaroxaban, apixaban, edoxaban, dabigatran, betrixaban. However, fondaparinux and several other DOACs may be started from day one without LMWH or UFH. The choice of therapy depends on the patient's characteristics, such as renal function, compliance, willingness to adhere to a certain diet. LMWH is the preferred mode of therapy over UFH in initial treatment as well as over VKAs or direct oral anticoagulation for long-term therapy, given that a patient's creatinine clearance is >30mL/min [2 - 4]. LMWH is cleared *via* the kidneys and accumulates in patients with impaired renal function, defined as creatinine clearance <30mL/min. In such cases, UFH or LMWH with anti-Xa activity monitoring is possible or the use of direct oral anticoagulants is also an option [5]. However, agent selection should be based on the patient's renal function, inpatient/outpatient status, cost, ease of administration, monitoring, and the necessity to reverse anticoagulation effects.

INITIAL TREATMENT

Anticoagulants

Low Molecular Weight Heparin

In a patient with malignancy presenting with an acute VTE, immediate anticoagulation is the initial therapy for up to 5 to 10 days. As stated above, LMWH is the medication of choice, unless contraindications exist [5]. In comparison to UFH used in patients with or without malignancy, LMWH is as

effective and safe as UFH, (odds ratio, OR - 0.85 [CI, 0.63 to 1.14]; P > 0.2) [6]. Additionally, LMWH were shown to significantly reduce mortality, (OR - 0.71 [95% CI, 0.53 to 0.94]; P = 0.02) [6]. In the event of renal disease or the possible need for anticoagulation reversal might arise, UFH is preferred over LMWH [2, 4].

LMWH has been shown to have several advantages to UFH, such as longer half-life, superior subcutaneous bioavailability, and more stability [2]. Due to these reasons, the therapeutic effect can be easily achieved when administered subcutaneously once or twice daily. The dosage can be adjusted to body weight and no laboratory monitoring is required [2]. Essentially, this simplifies the treatment, making it easy for outpatient settings in patients with malignancy, thus improving quality of life and decreasing hospital stay [7 - 9]. However, patients taking LMWH are required to check the platelet level to monitor and prevent heparin-induced thrombocytopenia [10].

The best-studied agents amongst the LMWH group are enoxaparin, dalteparin, and tinzaparin. No study compares these agents amongst each other and all three are considered clinically equivalent. Enoxaparin is currently approved for prophylaxis and acute treatment of VTE [11]. Dalteparin is approved for acute VTE treatment and chronic treatment of symptomatic VTE in patients with malignancy [12]. However, it is important to note that tinzaparin is no longer approved for use in the USA. Moreover, the agents do indeed differ in their molecular weight, half-life, and their binding affinity with thrombin and factor Xa.

The dosing for LMWH in acute VTE treatment is based on the 2017 National Comprehensive Cancer Network (NCCN) guidelines and is listed in Table **1** below.

Despite some of the limitations of LMWH, it remains more desirable for use as it has no chemotherapy or dietary interactions, is not dependent on oral intake nor gastrointestinal absorption, and is easily adjustable to weight and in cases of thrombocytopenia [13].

Table 1. Anticoagulants for venous thromboembolism in patients with malignancy [19].

Drug		Dosage
LMWH	Enoxaparin	1mg/kg SC every 12 hours
	Dalteparin	200 units/kg SC daily
UFH		IV- 80 units/kg bolus with subsequent 18 units/kg/hr SC- 333 units/kg loading dose, then 250 units/kg every 12 hours

CHAPTER 8

Special Cases in Cancer-Associated Thrombosis

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Abstract: Thrombosis and thrombocytopenia are common in malignancy due to microangiopathic disorders (thrombocytopenic purpura, immune disorder, immune thrombocytopenic purpura, and heparin-induced thrombocytopenia), chemotherapy side effect, or direct cancer effect. Recurrent VTE (while on anticoagulation) is also common, risk factors include metastasis, young age, and short interval between cancer diagnosis and VTE. VTE remains a major challenge among those with renal impairment. Incidental VTE is an unexpected thrombosis detected in a patient undergoing imaging study for other indications. Incidental VTE has been attributed to malignancy or chemotherapy side effects. Philadelphia chromosome-negative Myeloproliferative Disorders (Polycythemia Vera (PV), Essential thrombocytosis (ET), and Primary Myelofibrosis (PMF) has been implicated with high risk for both venous and arterial thromboembolism. Venous thromboembolism (VTE) has been increasingly associated with hematological malignancy as well.

Keywords: Bone marrow transplant and VTE, Cancer-associated thrombosis, Chemotherapy, Incidental VTE in cancer, Recurrent VTE, Thrombocytopenia, Thrombosis, Thrombosis in malignancy, VTE and thrombocytopenia, VTE in myeloproliferative disorder, VTE in renal impairment.

INTRODUCTION

VTE and Thrombocytopenia

Thrombosis and thrombocytopenia are commonly encountered complications of malignancy [1], which can be caused by microangiopathic disorders (thrombocytopenic purpura [2, 3], immune disorder (immune thrombocytopenic purpura and heparin-induced thrombocytopenia) [4], chemotherapy side effect or direct cancer effect [5].

It is critical to assess for the severity, the possibility of reversing thrombocytopenia, the expecting duration of thrombocytopenia, and to evaluate

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for other risk factors like the risk of bleeding, advanced age, and evaluation of kidney function before considering a management plan [6, 7].

The risk of thrombosis is high in the acute phase of thrombosis. The decision to anti-coagulate a patient with VTE and thrombocytopenia should be applied on an individual basis after assessing the risk of thrombosis recurrence and serious bleeding [8].

During the acute phase, treatment of cancer-associated thrombosis depends on the platelet count. If the platelet count is > 50 x109/L treating with full anticoagulation dose without the need for platelet transfusion is appropriate. If the platelet count is less than 50 x 109 /L, then platelet transfusion to maintain platelet > 50 x109/L is recommended before treatment with full anticoagulation [1].

Evaluating the need for hospitalization is important, as a patient who is not able to get adequate and timely support for outpatient treatment, should be hospitalized. On the other hand, if a platelet transfusion is not possible or contraindicated one should consider the insertion of a retractable IVC filter and this should be removed when anticoagulation can be started or resumed [6, 7].

In the subacute and chronic periods, treatment depends on the risk of recurrence and platelet count. If the risk of recurrence is low and platelet counts are between 25 – 50 x109, this group can be treated with a 50% dose reduction of LMWH or using prophylactic dose without the need for platelet transfusion [8 - 10]. Anticoagulation should be held if the platelet count is less than 25,000/L until count recovery [11].

RECURRENT VTE

Recurrent VTE despite anticoagulation is common in cancer patients, seen in approximately 10-17% of patients treated with VKA and 6-9% treated with LMWH [12]. Studies have suggested that the presence of metastasis, young age, and short interval between cancer diagnosis and VTE diagnoses are high-risk factors and predictors for recurrent VTE [13].

Although there is a lack of randomized controlled trial data, observational studies and clinical experience suggests the use of LMWH. In a patient who developed recurrent VTE while anti-coagulated with VKA, observational studies showed switching to LMWH is safe and effective [14, 15].

In patients who developed recurrent VTE while on LMWH, it is important to exclude heparin-induced thrombocytopenia and to confirm patient compliance. If the above has been rolled out, the LMWH dose should be increased by 25% or

increased to a weight-adjusted therapeutic dose in-patient receiving a lower dose. Patients should be assessed in 5-7 days to evaluate for symptomatic improvement [16].

In patients, without symptomatic improvement anti-factor Xa level (FXa) should be checked and estimate dose-escalation, for daily dose LMWH, the dose should be increased to aim for anti-FXa level 1.6-2 U/ml and for a twice-daily dose to increase the dose and aim for 0.8 – 1.0 U/ml [13, 17].

Other therapeutic option that has been proposed including IVC filter placement in addition to anticoagulation showed additional survival benefit [18].

VTE IN RENAL IMPAIRMENT

Renal impairment is a major challenge in a cancer patient with VTE as the incidence of both cancer and renal impairment increase with age. Some cancer therapy is known to cause renal impairment [19].

Also, cancer patients with renal impairment that are being treated for VTE have an additional risk for bleeding and VTE recurrence [20].

The kidneys play an important role in anticoagulant metabolism by affecting renal clearance, non-renal clearance, and volume of distribution of many drugs and can lead to toxic effects and increased risk of bleeding. Mainly the liver metabolizes Vitamin K antagonist, but it is also affected by renal impairment by downregulation of hepatic enzyme [21].

On the other hand, LMWH is renally execrated and in renal impairment, this might lead to the accumulation of the drug and increased risk of bleeding [22]. Unlike Enoxaparin, dalteparin and tinzaparin do not appear to accumulate in renal impairment due to their molecular weight distribution [21, 23]. And in the CLOT trial; a sub-analysis of a large controlled trial compared LMWH (Dalteparin) to warfarin in-patient with moderate renal impairment (CrCl 30- 60 mL/minute) and severe renal impairment (CrCl < 30 mL/minute).

INCIDENTAL VTE IN CANCER

Incidental VTE is defined as unexpected thrombosis detected in a patient undergoing imaging study for other indications [7]. Although incidental VTE may be asymptomatic, some patient may report non-specific symptoms like difficulty in breathing and fatigue that can be attributed to malignancy or chemotherapy side effect, therefore careful history and examination is important before excluding symptomatic VTE [24].

CHAPTER 9

Antitumor Effects of Heparin

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Abstract: Heparin was isolated from the liver and heart in 1916. Heparin was demonstrated as an anticoagulant in the presence of heparin-cofactor, a plasma component. Over years many heparin molecules have been manufactured due to their anti-tumor properties. Heparin sulfate, an essential component of the extracellular matrix when degraded by heparanase secreted by tumor cells has shown to increase tumor invasiveness. The anti-angiogenic properties of heparin are due to its effect on decreasing fibrin level and inhibition of thrombin formation. Natural killer (NK) cells destroy circulating tumor cells. The anti-tumor properties of heparin have been demonstrated in various studies. Among various forms of heparin, butanoylated heparin has the lowest anticoagulation strength but much stronger anti-tumor activity compared with UFH at higher doses. The anti-tumor effects between LMWH and butanoylated heparin are yet to be compared.

Keywords: Antitumor effect of Heparin, Antiangiogenesis, Antitumor, Anticoagulation, Heparin, LMWH, Unfractionated Heparin.

INTRODUCTION

Heparin was isolated heparin from the liver and heart by Jay Mclean in 1916 [1]. Later Brinkhous *et al*. demonstrated that it could act as an anticoagulant only in the presence of a plasma component named heparin-cofactor [2]. Heparin acts as a cofactor that binds to inactive antithrombin and causes conformational change leading to its activation. Factor Xa then binds to antithrombin and gets inactivated thus conversion of prothrombin to thrombin does not occur, and fibrin does not form, and therefore blood does not clot [3]. Heparin acts as a cofactor that binds to antithrombin and increases the inactivation of Xa and blocks thrombin formation by 1000 folds [1,3].

Over the years many preparations of heparin molecules have been manufactured to target specifically its anti-tumor properties. Many animal studies to target this anti-tumor effect of heparin have been performed; almost all the experiments

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demonstrated its anti-tumor effects whether heparin was injected intravenously, subcutaneously or intraperitoneally with a wide range of doses [4]. Heparin sulfate is an essential component of the extracellular matrix. Degradation of this heparin sulfate of extracellular matrix (ECM) by heparanase by tumor cells has shown increased invasiveness by tumors [5]. Experiments showed that the expression of heparanase mRNA is directly correlated with tumor invasion. Another study showed increased expression of heparanase in human breast, colon, and liver cancers. Clonal DNA prepared with increased expression of gene translating heparanase activity showed its role in tumor invasion. Non-anticoagulant heparins inhibit heparanase-mediated degradation of extracellular matrix heparan sulfate thus arresting tumor invasion [6 - 8].

TYPES OF HEPARIN

Unfractionated Heparin

Unfractionated heparin (UFH) has >18 disaccharide units and can directly affect both factor Xa and factor IIa [9]. UFH is the go-to anticoagulant in patients with acute renal failure, acute coronary syndromes due to its superior hepatic clearance and it is reversible with protamine sulfate. Unfractionated heparin has been shown to inhibit experimental lung metastasis. However, it has potent anticoagulant properties which increase the risk of hemorrhage. Although UFH inhibited endothelial cell proliferation, it did not have any effect on endothelial tube formation.

Low-Molecular-Weight Heparin

Low molecular weight heparin (LMWH) and fondaparinux [10] target only antithrombin binding and factor Xa inactivation. Low-molecular-weight heparin is the product of enzymatic hydrolysis of unfractionated heparin (UFH). Apart from its use for anticoagulation it has potential anticancer effects and may improve survival in cancer patients [11 - 14]. However, an updated meta-analysis in 2014 [15] and Cochrane review and meta-analysis did not show any survival benefits of LMWH in solid tumors [16, 17]. Nadroparin showed synergistic effects with radiotherapy on lung adenocarcinoma in one of the experimental studies by Xibing Z *et al*. [18]. It is believed that the above effects are due to the promotion of cell apoptosis, downregulation of CD147, MMP-2, and survivin, reduction of the TGF-beta1 level, inhibition of cell invasion, and metastasis [18].

Butanoylated Heparin

Because of its strong anticoagulant effect, antitumor effects of heparin can sometimes be hard to achieve as it increases the risk for hemorrhagic complications. Butanoylated heparin is a form of heparin that has a more potent antiproliferative agent and weak anticoagulant effects [19]. A study performed at Harvard medical school found butanoylated heparin to cause a significant decrease in lung tumor proliferation and growth *in-vitro*, reduction in the expression of CXCL12/CXCR4 cell proliferation pathway. Increased apoptosis of tumor cells especially at higher doses without increased risk of bleeding or increased toxicity to other tissues of the body. Tumor with A549 NCSLC cells and DMS 79 SCLC cells were significantly inhibited by butanoylated heparin as compared to UFH [19]. Mice treated with UFH died within 2 weeks due to bleeding. All mice treated with butanoylated heparin survived as it has a low anticoagulant effect. Butanoylated heparin showed no toxicity to the heart, lungs, liver, kidney. Apoptotic profiles of butanoylated heparin and UFH were tested to check apoptosis in mice by inhibiting p53/Rb/E2F pathway. Even though the apoptotic profile of butanoylated heparin was like UFH at low doses of 10 mg/kg, its effects on apoptosis were superior to UFH at doses of 100 mg/kg or 200 mg/kg. CXCL12 is a gene expressed in many tissues, and its signaling pathway is seen in many cancers. It binds to the CXCR4 receptor, and this pathway is involved cell proliferation, increased survival, and chemotaxis thus leading to angiogenesis and tumor progression. It was found BPH significantly reduced expression of CXCL12/CXCR4, thus inhibiting tumor proliferation and progression [20].

EFFECTS OF HEPARIN ON TUMOR

Anti-Angiogenesis Effects

The antiangiogenic properties of heparin [21 - 28] are secondary to its effect on decreasing fibrin level, and inhibition of thrombin formation and its downstream effects [29 - 32]. Angiogenesis is inhibited by heparin and certain steroids synergistically [23]. Heparin can inhibit monocyte TF, PAI-2 protein synthesis as well as mRNA transcription. Thus, it interferes with and inhibits cell-mediated thrombotic effects [33]. MicroRNA-10b (miR-10b) overexpression is known to induce angiogenesis. Heparin inhibits miR-10b and induces HoxD10 expression causing arrest in angiogenesis [34]. LMWH demonstrates its antiangiogenic effect by inhibiting VEGF and basic fibroblast growth factor (bFGF) which further

CHAPTER 10

VTE Prophylaxis

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Abstract: Cancer patients have an increased risk of VTE and its complications. It has been of utmost importance to identify high-risk patients. The Khorana score, which stratifies cancer patients into low and high risk, includes cancer type, chemotherapy regimen, hematological factors, and combinations of clinical and lab factors. In hospitalized cancer patients with limited mobility, pharmacologic prophylaxis with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is recommended. In those with contraindications to anticoagulation, mechanical prophylaxis can be used. In cancer patients undergoing surgery, perioperative VTE prophylaxis using pharmacologic anticoagulation is recommended, unless a minor procedure or an anticoagulant contraindication exists. In outpatients, the American Society of Clinical Oncology (ASCO) did not recommend routine anticoagulation in cancer patients except in high risk (*e.g.*, Khorana score ≥2, or multiple myeloma, receiving thalidomide or lenalidomide). Those patients should be offered VTE prophylaxis with apixaban, rivaroxaban, or LMWH. Also, ASCO recommended periodic assessment of cancer patients for VTE risk and educating them about VTE's signs and symptoms.

Keywords: Apixaban, Cancer-associated thrombosis, Contraindication to anticoagulation, Khorana Score, LMWH, Malignancy in cancer, Mechanical VTE prophylaxis, Pharmacological anticoagulation, Rivaroxaban, Thromboprophylaxis in cancer, VTE, VTE prophylaxis.

INTRODUCTION

Patients with cancer have an increased risk of VTE and its accompanying complications, compared to non-cancer patients [1, 2]. The American society of clinical oncology (ASCO) and the American society of hematology (ASH), recently updated their guidelines on VTE prophylaxis and treatment. The following chapter will discuss prophylactic anticoagulation for cancer patients based on their risk stratification.

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RISK STRATIFICATION

Several strategies have been proposed to identify patients that are at high risk for VTE [3]. The most important factors used to stratify patients into low and high risk are cancer type, chemotherapy regimen, hematological factors, and combinations of clinical and lab factors [3]. The Khorana score (Table **1**) is a risk assessment algorithm that combines several factors to give a score of 0-6; the higher the score, the higher risk is to develop VTE [2]. Khorana score was derived from an analysis of a cohort of 2701 cancer patients and validated in an independent cohort of 1365 patients [4]. It is the most widely used scoring system, as it has been validated in multiple studies [5, 6]. However, the Khorana score has been shown to perform poorly in some types of cancer, such as lung and pancreatic [7], and does not take into consideration each patient's chemotherapy regimen.

Table 1. Khorana score.

Characteristic	Score
Cancer type Stomach, Pancreas Lung, Lymphoma, Gynecologic, Bladder, Testicular Other	**2** **1** **0**
Pre-chemotherapy platelet count ≥350 x 10^9/L Yes No	**1** **0**
Hb level <10 g/dL or using red blood cell growth factors Yes No	**1** **0**
Pre-chemotherapy leukocyte count >11x10^9/L Yes No	**1** **0**
Body Mass Index ≥35 kg/m^2 Yes No	**1** **0**
Total score: 0= low risk, 1-2= intermediate risk, ≥3= high risk	

PROTECHT is a modification of the Khorana risk assessment model [8], other newer VTE risk assessment models include Vienna, CONKO-004, ONKOTEV, COMPASS-CAT, and Tic-Onco. Van Es *et al.* performed a multinational prospective study to compare the performance of Khorana, Vienna, PROTECHT, and CONKO-004 scores. The study showed poor VTE predictive ability of these scoring systems even though Vienna CATS, and PROTECHT could discriminate low risk from high-risk VTE patients [7].

INPATIENT VTE PROPHYLAXIS

Hospitalized patients carry an increased risk of developing VTE due to their complex acute medical illness, which is further augmented by the presence of cancer [9]. The rates of VTE in hospitalized cancer patients range between 0.6% to 7.8% [10 - 14].

To date, no clinical trials are evaluating VTE prophylaxis in hospitalized cancer patients. The current recommendations are merely an extrapolation of evidence from clinical trials on patients without cancer. Guidelines from the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) [10, 15, 16] have been published for VTE prophylaxis in hospitalized patients with cancer. A general approach can be summarized as follows:

In hospitalized cancer patients with reduced mobility, pharmacologic prophylaxis is recommended as their risk of VTE is considered high due to acute illness and cancer.

In hospitalized patients with active cancer, without additional risk factors, pharmacological thromboprophylaxis can be offered.

In patients where anticoagulation is contraindicated due to bleeding or other reasons, mechanical prophylaxis can be used.

For hospitalized cancer patients who require thromboprophylaxis, low molecular weight heparin (LMWH) or unfractionated heparin (UFH) is preferred over direct oral anticoagulants (DOACs) due to the lower risk of bleeding. In MAGELLAN trial [17], Rivaroxaban (at a prophylactic dose of 10mg daily) was compared with the LMWH (Enoxaparin) for 35 days in hospitalized patients with acute medical illness (592 patients had cancer), the risk of bleeding was twofold higher with rivaroxaban (2.8% *versus* 1.2%). The ADOPT trial [18] compared Apixaban (2.5mg twice daily) with Enoxaparin for 30 days in the same subset of patients (3% had cancer), and found a higher risk of bleeding with Apixaban, although the incidence of bleeding for both groups was <0.5%.

OUTPATIENT VTE PROPHYLAXIS

Two randomized, placebo-controlled, clinical trials (PROTECHT and SAVE-ONCO) [19, 20], and a comprehensive meta-analysis [21] showed that ambulatory cancer patients of any type had a 50% lesser chance of developing symptomatic VTE when treated with low molecular weight heparin (Nadroparin and Semuloparin) than placebo [3]. Two clinical trials published in 2019 assessed the use of direct oral anticoagulants apixaban (AVERT trial) [2] and rivaroxaban

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