Venous Thromboembolic Disease and Cardio Oncology

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Abstract

Venous thromboembolism along with peripheral arterial thrombosis and cardio toxicity are some terms from the vocabulary of Oncologists that have been used increasingly in recent years. Several mechanisms have been related to the increased thrombotic complications observed in patients with cancer: 1) the expression of tissue factor by circulating tumor cells, 2) the shedding of pro coagulant micro particles by malignant cells, 3) the interaction of cancer cells with blood platelets, 4) the generation of neutrophil extracellular traps and 5) the secondary deleterious effects of anti-cancer therapies. Cancer patients with venous thrombosis experience 3fold higher rates of recurrences and 2fold major anticoagulation-associated bleeding complications than do patients without cancer. Anticoagulation treatment for venous thromboembolism differs in various groups of patients suffering from malignancies and demands a detailed knowledge of advantages and side effects of available medications. Low Molecular Weight Heparins are the first line choice, followed by vitamin K antagonists, which are widely used when treatment has to be prolonged. The new oral anticoagulants have been proven effective for venous thromboembolism (in general) and for atrial fibrillation embolic disease and thus are promising, though more studies are needed in order to investigate their detailed behavior in cancer populations. The emerging interplay between Oncologist and Cardiologists is a new provocation for the two specialties, which will probably impel them to specify a new subspecialty, the Cardio Oncology.

Keywords: Thormboembolism; Cancer; Anticoagulation Treatment; Prevention; Chemotherapy

Abbreviations: VTE: Venous Thromboembolic Event; TF: Tissue Factor; MPs: Microparticles; NETs: Neutrophil Extracellular Traps; VEGF: Vascular Endothelial Growth Factor; Ctcs: Circulating Tumor Cells; NK: Natural Killers; Cfdna: Cell Free DNA; LMWH: Low Molecular Weight Heparin; Noacs: New Oral Anticoagulants; VKA: Vitamin K Antagonists; P-Gp: P-Glycoprotein; VS: Versus; IV: Intravenous; SC: Subcutaneous; INR: International Normalization Ratio; PE: Pulmonary Embolism.

Introduction

Cancer is a complex multi-dimensional clinical entity, due to different types of neoplasms based on primary localization, histology, stage, chemotherapeutic options,

and due to a variety of complications that affect various systems as well.

Thromboembolism is one of the most intriguing complications, and it is the second leading cause of death in cancer patients in recent years [1]. The latest pharmacological advances of Cardiology in the area of prevention and treatment of thromboembolism, in general, have created a new field open for a distinctive cooperation between Cardiologists and Oncologists.

Thromboembolic Disease with Undiagnosed Cancer

The occurrence of a new unexpected venous thromboembolic event (VTE) in a patient without any previous comorbidity must raise the suspicion of a possible undiagnosed neoplasm. A significant percentage (10-20%) of patients presented with idiopathic VTE is subsequently diagnosed with cancer during the first year of follow-up [1,2].

There are 5 variables that may raise the suspicion of a

hidden cancer after an episode of VTE: a) no profound etiology (idiopathic), b) age 60–75 years, c) bilateral thrombosis, d) anemia [3] and e) recurrence of idiopathic venous thrombosis, despite antithrombotic treatment, especially during the first six months of follow-up (odds ratio: 4,3) or during the first year of follow up (odds ratio: 3,2) [4,5].

Patients with idiopathic VTE have a 2-4fold increased risk for a tumor diagnosis in pancreas, ovary, liver, brain, or for a lymphoma, especially during the first year while the majority of these patients will be presented with advanced disease stage (40 % with distant metastases, 25 % with regional spread of cancer, and 36 % with no spread) [5-8].

Cancer and Risk Factors to Develop Thromboembolic Disease

The risk factors associated with the development of thromboembolic complications can be divided into patient characteristics, comorbidities, plasma biomarkers, tumor factors, and types of treatment (Table 1) [1,6,9-12].

Patient Characteristics	Female Sex	Older Age	Black Ethnicity	Obesity
Comorbidities	Previous VTE	Inherited thrombophilia,	Diabetes Mellitus	Venous Insufficiency
Plasma Biomarkers	Pre-chemotherapy platelet count ≥350,000/mL	Pre-chemotherapy leukocyte count ≥11,000/mL	Elevated D-dimer & C-reactive protein	High Tissue Factor plasma levels
Tumor factors	gastrointestinal, brain, lung, gynecologic genitourinary cancer, lymphoma	extent of disease	duration of cancer	circulating tumor cells
Type of treatment	Major surgery, abdominal surgery	prolonged hospitalization, & immobilization	chemotherapeutic hormonal, antiangiogenic, & erythropoiesis agents	Central venous catheters

Table 1: Risk factors for the development of thromboembolic disease in patients with cancer.

Platelet's function is of major importance in cancer patients, as they contribute to cancer development, metastases and VTE complications. High platelet counts have been linked to increased metastasis and poorer outcomes in multiple types of cancer. Platelets can bind to tumor cells via P-selectin and glycoproteins and they release angiogenic and growth factors inducing tumor growth and metastasis [13,14]. Apoptotic cells and cells that have undergone oncogenesis release pro coagulant micro particles (MPs) which are small (0.1-1.0 μm) membrane vesicles charged with Tissue Factor (TF) on

their surface, which in turn activate more platelets [13,15,16].

Activated platelets which are adhered on tumor surface may shield tumor cells from Natural killer (NK) cells, hampering them from killing the tumor cells or/and may interact with neutrophils undergoing cell death which are able to release chromatin fibers composing neutrophil extracellular traps (NETs). Neutrophil extracellular traps attract more fibrin deposition locally thus increasing their size. Additionally, platelets are a primary source of

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vascular endothelial growth factor (VEGF), a growth factor which increases vascular permeability, promotes extravasation, and is critical for angiogenesis [13,16].

Tissue factor (TF) is considered as a thromboembolic risk factor, because it is a molecule which is expressed by vascular and tumor cells, resulting in potent and continuous activation of coagulation which consequently increases thrombin generation. Additionally, TF is linked to the production of the VEGF, which increases vascular permeability allowing exposure to coagulation factors [6]. Tissue factor-positive MPs enhance thrombosis in mouse models and are elevated in the plasma of pancreatic cancer patients [16].

Tissue factor is widely considered to be the major molecular driver of cancer-associated coagulopathy and thromboembolic disorders [17,18]. Cancer cells circulate in the bloodstream, referred to as circulating tumor cells (CTCs), adhere to the luminal wall of micro-vessels (arterioles and capillaries) and migrate into the surrounding tissues, to eventually form secondary colonies. It has been hypothesized that circulating tumor cells may escape from NK cells by inducing the formation of a platelet-fibrin rich micro-emboli. In addition, fibrin (which is induced by TF from cancer cells surface) was found to envelop cancer cells, preventing their recognition by NK cells [18].

Chemotherapy Associated Thrombosis

Chemotherapy associated vascular toxicity involves various pathophysiologic mechanisms like a) vasomotor factors causing vasoconstriction, b) vascular smooth muscle cells contraction, c) endothelial dysfunction (endothelin-1 over expression, nitric oxide and prostacyclin inhibition) promoting hypertension and ischemia, while oxidative stress and pro-inflammatory cytokines are produced, thus promoting platelet activation and thrombosis [19].

The concentration of cell-free DNA (cfDNA) circulating in the blood is increased as a result of chemotherapy and it has been shown to induce thrombin generation [18]. Different chemotherapeutic agents, including cyclophosphamide, methotrexate, 5-fluorouracil, cisplatin, gemcitabine, doxorubicin, epirubicin, daunorubicin, and antiangiogenic agents have been found to greatly potentiate the aberrant hemostatic response leading to an increased risk of VTE and associated mortality [18,20].

Treatment of VTE

Cancer patients experiencing VTE have a significantly worse clinical outcome than cancer patients without VTE. The Danish Cancer Registry indicated an increased risk of mortality in tumor patients with VTE compared to those without VTE. Possibly, patients with malignancies and VTE represent a cohort of more aggressive tumors accompanied with clotting system deregulation [4,21].

Various aspects in the treatment of cancer-associated VTE deserve special attention, because the clinician must answer to a variety of questions. Which is the recommended treatment and in what dosing? Which is the optimal duration of anticoagulation? How should we treat cancer patients undergoing surgery? How can we respond facing thrombocytopenia during anticoagulation treatment? What should be done when an asymptomatic and unexpected venous thrombosis is diagnosed in a patient with cancer?

Which Treatment and In What Dosing?

Treatment of choice is the group of Low Molecular Weight Heparins (LMWH) undoubtfully [22]. Long-term treatment with LMWH is considered safer and more efficacious than standard Vitamin K Antagonists (VKA) therapy, based on the results from the CLOT and CATCH [23,24]. Warfarin was inferior to Dalteparin in terms of risk for recurrent thromboembolism in the CLOT trial (17% versus 9%, p = 0.002) with the same bleeding frequency and with no difference in mortality, while the same inferiority has been proven in the CANTHANOX randomized clinical trial [25].

In the group of patients who experience a recurrence while receiving VKA therapy, LMWH is preferred over increasing the intensity of VKA therapy, due to the superior efficacy of LMWH and due to the bleeding risk when INR fluctuates around a higher target [6].

Although LMWH is generally accepted as the treatment of choice, this is not reflected in recent physicians' surveys. Anticoagulation with VKAs is the first choice of physicians in the FRONTLINE survey of 3891 physicians treating cancer patients, where oral Warfarin was favored for long-term treatment of VTE (66–80%) [26]. Similarly, the majority of patients with cancer-associated VTE were treated with long-term VKAs (81%) as opposed to LMWH monotherapy (19%) in a retrospective cohort study [27].

The reasons for the choice of VKAs included lack of coverage or inability to afford LMWH (49%), physician preference (32%), refusal of long-term injections (13%), heparin-induced thrombocytopenia (2%), and renal failure (2%) [6].

Treatment prolongation for over 6 months with LMWH may add certain problems to the clinician, such as treatment adherence, quality of life, medication costs and cutaneous complications from multiple injections usage. The recent 2012 ACCP guidelines downgraded the recommendation for LMWH in this setting from 1A to 2B, recognizing the burden (financial and lifestyle) that is imposed to patients from daily injectable LMWH treatment [28].

Rivaroxaban, apixaban and edoxaban as well as the direct thrombin inhibitor dabigatran, (NOACs) may offer a precious therapeutic alternative to LMWH in special subgroups of cancer patients, albeit until now no clinical trial has presented a head-to-head comparison of NOACs vs LMWH in cancer patients with acute VTE [21,22].

In a recent study of cancer patients with VTE treated with rivaroxaban(20 mg) for secondary prophylaxis, the rivaroxaban group showed noninferior efficacy vs enoxaparin, followed by VKA (2,1% vs 3% respectively), while rivaroxaban had superior efficacy [1.3%], vs. placebo [7.1% hazard ratio, 0.18] to prevent recurrent VTE [29].

NOACs is a therapeutic option in cancer patients with VTE when subcutaneous injections represent an everyday difficulty (as it is observed in patients with coexisting diabetes mellitus on insulin), when the treatment has to be continued beyond 6 months, or in those patients with heparin-induced thrombocytopenia. A diabetic patient will find difficulties to follow a plan with 3 and 4 subcutaneous injections per day, while the sites of injections must be carefully selected to avoid cutaneous complications.

However, Gastrointestinal Cancer, Liver metastases, hepatotoxicity or renal dysfunction from anticancer treatment along with vomiting, nausea, or diarrhea may limit the choice of NOACS or VKA as an antithrombotic treatment alternative. Especially for VKA, patient's quality of life under chemotherapy is further compromised by the need of frequent blood test assessments of INR, which is difficult to be standardized for longer intervals at the optimal level of 2 to 3 [30].

Another parameter that might influence the efficacy of rivaroxaban and apixaban in cancer patients is the co-administration of anticancer or other drugs, which are CYP3A4 cytochrome subunit inducers, or inhibitors of P-glycoprotein (P-gp). This parameter has not been controlled in the above mentioned trials [31].

In contrast, dabigatran is a regimen which presents no involvement to CYP450 enzymes and imposes limited drug interactions only to the P-gp inhibitors, but needs proper renal function. The most common adverse reactions of dabigatran treatment are dyspepsia and gastritis-like symptoms [31].

Cancer patients are at risk of opportunistic infections or fungal infections, thus they may receive P-gp inhibitors or inhibitors of CYP3A4. For this reason, administration of orally active NOACs in cancer patients should be particularly cautious. NOACs should not be used as first-line therapy for VTE in patients with advanced gastrointestinal cancers [30,31]. Some classes of chemotherapy appear to almost universally interact with CYP3A4, P-glycoprotein, or both. These include the antimitotic microtubule inhibitors (e.g., vinca alkaloids and taxanes), tyrosine kinase inhibitors (with the exception of erlotinib, gefitinib, and sorafenib), and the immune-modulating agents, including glucocorticoids and mammalian target of rapamycin (mTOR) inhibitors (with the exception of everolimus) [32].

Duration of Anticoagulation

To date, no study has specifically evaluated the optimal duration of anticoagulation in the setting of cancer-associated VTE in order to avoid recurrences [21]. The CANTHANOX and LITE studies presented their results with three months anticoagulation treatment, while in the CLOT, ONCENOX, and CATCH trials, anticoagulant treatment lasted six months [33,34]. Patients with persistent active cancer were followed for 12 months in the DALTECAN study. The patients in this study had an ongoing high risk of VTE recurrence, but this risk was significantly reduced from 5.7% during the first month to 3-4% per month over the 11 following months [35].

Optimally, at six months of anticoagulation, the presence of residual vein thrombosis must be reevaluated to assess any residual thrombus in order to decide the prolongation of the treatment. Low risk cases with resolution of thrombus are candidates for discontinuation of anticoagulation or for dosing reduction.

Cancer Patients Undergoing Surgery

Cancer surgery is an established risk factor for VTE, and LMWH is the treatment of choice for at least 10 days post discharge because LMWH significantly decreased the risk of VTE by nearly 40% with no excess risk of bleeding. Prophylaxis with LMWH for an extended period up to 4 weeks post discharge is safe but not very well documented so as to be applied for routine prescription [6].

The Problem of Thrombocytopenia

Systemic infections, bone marrow complications and myelotoxic anticancer treatments might lead to thrombocytopenia. The platelet level of 50x 10^9/L is the cut-off point which will affect the decision to stop anticoagulation, in a patient with a prior VTE, in order to avoid hemorrhagic complications. As the risk of recurrences is higher for the period 1-3 months post VTE diagnosis and diminishes thereafter to insignificant percentages, discontinuation of anticoagulation must be considered, if treatment has already been given for a 3 months period. The management of thrombocytopenic cancer patients with dose-adjusted LMWH is the only choice and recommendations should be based on experts' opinion and empirical knowledge [21].

Unexpected VTE without Symptoms in Cancer Patients

Routine imaging tests for cancer staging reveals a small percentage of asymptomatic VTEs (8% on cisplatin-based chemotherapy).If peripheral vessels are involved, there is a question, whether these patients would benefit from anticoagulation treatment, the same as in patients with symptomatic VTE. However guidelines recommend standard anticoagulant treatment for all cancer patients diagnosed with incidental VTE, for at least three months [21].

VTE Prevention in Cancer

All the above information leads us to a basic and reasonable question; "Can we predict, or prevent a VTE in cancer patients?" Indeed, prevention with LMWH is needed for 3-4 weeks in patients with major abdominal or pelvic surgery and a low risk of bleeding. Hospitalized cancer patients with reduced mobility are also candidates for thrombo prophylaxis with LMWH or fondaparinux [21].

However ambulatory cancer patients form quite a different group. The SAVE-ONCO trial [36]. Studied 3,212 unselected patients, receiving ambulatory systemic chemotherapy for locally advanced or metastatic lung (36.6 %), or colorectal (28.9 %) cancer and presented a benefit of 2 less VTE when you treat 100 patient with semuloparin (an ultra-LMWH, 20 mg daily) for 3,5 months versus placebo. Almost the same magnitude of prevention was published in the PROTECHT trial, where LMWH nadroparin was used versus placebo [37].

The pre-mentioned results underline the need for a better risk stratification and this was firstly developed and validated by Khorana and colleagues [11]. They published a risk model based on the following parameters, 1) Site of cancer; Stomach, pancreas = 2 points, Lung, lymphoma, gynecologic, genitourinary excluding prostate= 1 point, 2) Pre-chemotherapy platelet count ≥ 350 x 109/L = 1 point, 3) Pre chemotherapy leukocyte count >11 x 109/L = 1 point, 4) Hemoglobin level < 10 g/dL or use of red cell growth factors =1 point, 5) Body mass index ≥ 35 kg/m^2 = 1 point. Patients with a total score of ≥ 3 are at high risk for venous thromboembolism.

Three more studies have proposed slightly different prevention models, trying to improve the performance of Khorana score. All three were based on the main body of Khorana score. The CATS score added the biomarkers D-dimer≥ 1.44 µg/mL and soluble P-selectin ≥ 53.1 ng/mL counting 1 point each. The PROTECHT score included carboplatin/cisplatin-based chemotherapy for 1 point and Gemcitabine-based chemotherapy for 1 point while the CONKO score replaced the BMI with the Karnofsky performance status [38-40].

All four scores were directly evaluated in a cohort of 876 cancer patients, with advanced malignancies, for 6 months where 6% of patients presented a new VTE diagnosis, but their performance was moderate [41]. These results emphasize that the predisposition of cancer patients to thrombosis is not only multidimensional, but complex as well and these scores reflect a part of the total "thromboembolic picture".

In contrast patients with pancreatic cancer and metastases, multiple myeloma under thalidomide treatment, or small-cell lung cancer need no risk stratification, as these malignancies independently impose high risk for thrombotic events.

A recent Cochrane systematic review of nine randomized controlled trials (including PROTECHT) addressed the efficacy and safety of anticoagulants in ambulatory cancer patients receiving chemotherapy

without VTE [42]. LMWH, but not warfarin, reduced symptomatic VTE with a non-significant increase in major bleeding (RR 1.57; 95% CI 0.69–3.60), as compared with inactive control.

Currently, international guidelines do not recommend routine thrombo-prophylaxis in ambulatory cancer patient's undergoing treatment with chemotherapy, except for those with multiple myeloma receiving thalidomide or lenalidomide in addition to chemotherapy or dexamethasone.

Clinical Question	Duration	Treatment	Additional Measures &Precautions
1st episode of acute DVT			
Initial Treatment	5 - 10 days (1C)	LMWH (SC) or Fondaparinux or UFH (IV or SC) (1A)	Against the use of non-steroidal anti-inflammatory agents (2B);
			Against Immobilization (1B)
Prolonged Treatment	3-6 months according to risk factors (1A) >6 months if high risk	LMWH (SC) or Fondaparinux (2B)	Thrombocytopenia; Bleeding risk
	>6 months if high risk	VKA, if SC injections are not tolerated, INR 2-3	Monitor INR; Bleeding risk
	until the cancer is resolved (1C)	VKA target INR 2-3 (2A)	Altered INR from other medications
	Indefinitely in active cancer (metastatic disease, continuing chemotherapy)	VKA target INR 2-3 (2A)	Elderly patients; Intracranial malignancy
Recurrent VTE	Indefinite treatment (2A)	If INR <2 ▶increase target INR 2-3 (2A)	Periodic reassessment of risk/benefit ratio (1C); Frequent INR
		If INR ≥2 ▶Change to LMWH or Ultra-LMWH	Repeat Ultrasonography & plasma D-dimer (2C)
		if on LMWH ▶ increase dosing	Elastic stockings (1A), Rutosides (2B)
		Vena Cava filter	if anticoagulation is contraindicated, or VTE/PE is present despite adequate long-term LMWH (consensus)
VTE Prophylaxis in patients with cancer			
Hospitalized patients	during immobilization and /or chemotherapy	UFH, LMWH, or Fondaparinux (1A)	Thrombocytopenia
Patients undergoing Surgery	preoperatively, or early postoperatively, continue for at least 7-10 days post discharge	UFH, LMWH, or Fondaparinux (1A)	Bleeding risk
	major abdominal or pelvic surgery for up to 4 weeks post-operatively	UFH, LMWH, or Fondaparinux (1A)	Bleeding risk
Ambulatory patients on chemotherapy without VTE	not recommended		Consider Pancreatic cancer with metastases, Small-Cell Lung cancer, Risk models (Khorana, CATS, PROTECHT, CONKO)
	myeloma patients during thalidomide therapy, chemotherapy or dexamethasone	LMWH or VKE adjusted-dose INR ~1,5	

Table 2: This table summarizes, in a simplified way, the main issues regarding treatment of VTE in cancer patients, including recommendations from the 9th edition of American College of Chest Physicians Guidelines (ACCP 2012), [28] recommendations from the American Society of Clinical Oncology Guidelines (ASCO 2007) [43] and data from the most recent studies, as quoted above.

Conclusion

Cancer-associated VTE remains a challenge in daily practice, because cancer patients with VTE not only have a higher risk of VTE recurrence, but also a substantially increased risk of major bleeding during anticoagulant therapy. Therefore prediction of a VTE is crucial, and it is a continuing area of research. Bearing in mind, that apart from VTE there is a considerable percentage of cancer patients with arterial and ischemic complications, the clinicians must be ready to face multiple and difficult scenarios, beyond guidelines. Therefore, treatment for these patients is not a straightforward prescription routine and necessitates a closer and detailed cooperation between Oncologists and Cardiologists.

References

1. Elyamany G, Alzahrani AM, Bukhary E (2014) Cancer-Associated Thrombosis: An Overview. Clin Med Insights Oncol 8: 129-137.

2. Nordström M, Lindblad B, Anderson H, Bergqvist D, Kjellström T (1994) Deep venous thrombosis and occult malignancy: an epidemiological study. BMJ 308(6933): 891-894.

3. Trujillo-Santos J, Prandoni P, Rivron-Guillot K, Román P, Sánchez R, et al. (2009) Clinical outcome in patients with venous thromboembolism and hidden cancer: findings from the RIETE Registry. Journal of Thrombosis and Haemostasis 6: 251-255.

4. Prandoni P, Lensing AW, Büller HR, Cogo A, Prins MH, et al. (1992) Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. N Engl J Med 327: 1128-1133.

5. Sørensen HT, Mellemkjaer L, Steffensen FH, Olsen JH, Nielsen GL (1998) The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. N Engl J Med 338(17): 1169-1173.

6. Siegal DM, Garcia D (2012) Anticoagulants in cancer. J Thromb Haemost 10 (11): 2230-2241.

7. Sorensen HT, Svaerke C, Farkas DK, Christiansen CF, Pedersen L, et al. (2012) Superficial and deep venous thrombosis, pulmonary embolism and subsequent risk of cancer. Eur J Cancer 48(4): 586-593.

8. Hettiarachchi RJ, Lok J, Prins MH, Buller HR, Prandoni P (1998) Undiagnosed malignancy in patients with deep vein thrombosis: incidence, risk indicators, and diagnosis. Cancer 83(1): 180-185.

9. PabingerI, Thaler J, Ay C (2013) Biomarkers for prediction of venous thromboembolism in cancer. Blood 122(12): 2011-2018.

10. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, et al. (2000) Predictors of recurrence after deep vein thrombosis and pulmonary embolism. Arch Intern Med 160(6): 761-768.

11. Khorana AA, Kuderer NM, Culakova E (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111(10): 4902-4907.

12. Hoffman R, Haim N, Brenner B (2001) Cancer and thrombosis revisited. Blood Rev 15(2): 61-67.

13. Meikle CK, Kelly CA, Garg P, Wuescher LM, Ali RA, et al. (2016) Cancer and Thrombosis: The Platelet Perspective. Front Cell Dev Biol 4: 147.

14. Voutsadakis IA (2014) Review: Thrombocytosis as a prognostic marker in gastrointestinal cancers. World J Gastrointest Oncol 6(2): 34-40.

15. Owens AP, Mackman N (2011) Microparticles in hemostasis and thrombosis. Circ Res 108(10): 1284-1297.

16. Geddings JE, Mackman N (2014) Recently Identified Factors that Regulate Hemostasis and Thrombosis. Thromb Haemost 111(4): 570-574.

17. Ruf W, Mueller BM (1999) Tissue factor signaling. Thromb Haemost 82(2): 175-182.

18. Mitrugno A, Tormoen GW, Kuhn P, Mc Carty OJ (2016) The prothrombotic activity of cancer cells in the circulation. Blood Rev 30(1): 11-19.

19. Cameron AC, Touyz RM, Lang NN (2016) Vascular Complications of Cancer Chemotherapy. Canadian Journal of Cardiology 32(7): 852-862.

20. Oppelt P, Betbadal A, Nayak L (2015) Approach to Chemotherapy-associated Thrombosis. Vasc Med 20(2): 153-161.

21. Voigtlaender M, Langer F (2018) Management of cancer-associated venous thromboembolism –a case-based practical approach. Vasa 47 (2): 77-89.

22. Smrke A, Gross PL (2017) Cancer-Associated venous Thromboembolism: A Practical Review Beyond Low-Molecular-weight Heparins. Front Med 4: 142.

23. Lee AY, Kamphuisen PW, Meyer G (2015) Tinzaparinvs Warfarinfor Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial. JAMA 314(7): 677-686.

24. Deitcher SR, Kessler CM, Merli G (2006) Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost 12(4): 389-396.

25. Meyer G, Marjanovic Z, Valcke J (2002) Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med 162(15): 1729-35.

26. Kakkar AK, Levine M, Pinedo HM, Wolff R, Wong J (2003) Venous thrombosis in cancer patients: insights from the FRONTLINE survey Oncologist 8(4): 381-388.

27. Wittkowsky AK (2006) Barriers to the long-term use of low-molecular weight heparins for treatment of cancer-associated thrombosis. J Thromb Haemost 4: 2090-2091.

28. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, et al. (2012) Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141: e419S-494S.

29. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, et al. (2010) Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 363(26): 2499-2510.

30. Martin LK, Bekaii-Saab T (2012) Management of Venous Thromboembolism in Patients with Advanced Gastrointestinal Cancers: What Is the Role of Novel Oral Anticoagulants? Thrombosis 758385.

31. Gerotziafas GT, Mahé I, Elalamy I (2014) New orally active anticoagulant agents for the prevention and treatment of venous thromboembolism in cancer patients. Ther Clin Risk Manag 10: 423-436.

32. Short NJ, Connors JM (2014) New Oral Anticoagulants and the Cancer Patient. The Oncologist 19(1): 82-93.

33. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, et al. (2006) Long-term low-molecular weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med 119(12): 1062-1072.

34. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, et al. (2003) Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 349(2): 146-153.

35. Francis CW, Kessler CM, Goldhaber SZ, Kovacs MJ, Monreal M, et al. (2015) Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. J Thromb Haemost 13(6): 1028-1035.

36. Agnelli G, George DJ, Kakkar AK, Fisher W, Lassen MR, et al. (2012) Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. N Engl J Med 366(7): 601-609.

37. Agnelli G, Gussoni G, Bianchini C, Verso M, Mandalà M, et al. (2009) Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomized, placebo-controlled, double-blind study. Lancet Oncol 10(10): 943-949.

38. Pelzer U, Sinn M, Stieler J, Riess H (2013) Primary pharmacological prevention of thromboembolic events in ambulatory patients with advanced pancreatic cancer treated with chemotherapy?. Dtsch Med Wochenschr 138(41): 2084-2088.

39. Ay C, Dunkler D, Marosi C, Chiriac AL, Vormittag R, et al. (2010) Prediction of venous thromboembolism in cancer patients. Blood 116(24): 5377-5382.

40. Verso M, Agnelli G, Barni S, Gasparini G, La Bianca R (2012) A modified Khorana risk assessment score for venous thromboembolism in cancer patients receiving chemotherapy: the Protecht score. Intern Emerg Med 7(3): 291-292.

41. Van Es N, Di Nisio M, Cesarman G, Kleinjan A, Otten HM, et al. (2017) Comparison of risk prediction scores for venous thromboembolism in cancer

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patients: a prospective cohort study. Haematologica 102(9): 1494-1501.

42. Di Nisio M, Porreca E, Ferrante N, Otten HM, Cuccurullo F, et al. (2016) Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. Cochrane Database Syst Rev 12: CD008500.

43. Lyman G, Khorana A, Falanga A, Clarke-Pearson D, Flowers C, et al. (2007) American Society of Clinical Oncology Guideline: Recommendations for Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer. J Clin Oncol 25(34): 5490-5505.