

Venous thromboembolism in cancer patients: Still looking for answers (Review)

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Abstract. Patients with cancer-associated venous thromboembolism (VTE) represent a real challenge in clinical practice. Patients with cancer have a greater risk both of VTE and bleeding. There are only a few studies regarding the therapeutic approach of VTE in patients with cancer, especially after cancer surgery, and on thromboprophylaxis during chemotherapy. Many of the anticoagulation therapy recommendations for cancer patients are extrapolated from trials that are not conducted in cancer cohorts. It is essential to assess the efficacy and safety of VTE prophylaxis in this particular subgroup, which bears higher risks both of VTE recurrence and major hemorrhagic events. The introduction of direct oral anticoagulants in everyday practice represented a major evolution of the anticoagulant treatment. Direct anticoagulants could represent a more appealing alternative to low-molecular-weight heparin in paraneoplastic venous thrombosis, due to the patient comfort, easy administration of the drug and emerging studies that prove similar efficacy and safety as the standard treatment. However, there is limited data on the treatment with direct oral anticoagulants in patients with paraneoplastic venous thromboembolism.

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1. Introduction

Venous thromboembolism (VTE) is a term describing deep vein thrombosis and/or pulmonary embolism (PE) and even superficial vein thrombosis and splanchnic vein thrombosis. Malignancy is well-known to be associated with venous thromboembolism, because of the hypercoagulable state induced by malignancy. VTE is the second leading cause of death in patients suffering from malignant tumors, after death from cancer itself.

Thrombotic events in cancer patients can manifest as migratory superficial thrombophlebitis, very well known as Trousseau's syndrome, deep venous thrombosis, nonbacterial thrombotic endocarditis (marantic endocarditis), disseminated intravascular coagulation, thrombotic microangiopathy, such as thrombotic thrombocytopenic purpura, and arterial thrombosis (1).

Many of anticoagulation therapy recommendations for cancer patients are extrapolated from trials that are not conducted in cancer cohorts. It is essential to assess the efficacy and safety of VTE prophylaxis in this particular subgroup, which bears higher risks of VTE recurrence and major hemorrhagic events (2).

2. Risk factors for venous thromboembolism

A cancer patient can have multiple well-known risk factors for a hypercoagulable state, such as prolonged immobilization,

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infections, surgery, chemotherapy, cancers with a high risk of VTE, and previous VTE or PE (3). Patient-related risk factors also include comorbidities such as chronic heart failure, acute infectious diseases, and obesity, especially in patients older than 75 years (4). A significant risk factor that creates the premise of thrombosis is the presence of central venous catheters (5).

Some of the medications used for treating cancer can also increase the risk of developing VTE, such as antiangiogenic therapies, erythropoiesis-stimulating agents, platinum-derived agents such as cisplatin, l-asparaginase, hormonal therapies and thalidomide (6).

Untreated deep vein thrombosis has a 50% risk to determine PE within three months from the onset, with a 25% mortality risk (3). Also, PE has a greater risk of recurrence in cancer patients than in non-cancer patients (7).

The relationship between the time of cancer diagnosis and VTE development was studied in a Danish retrospective study. A total of 44% of patients who had cancer at the time of VTE had distant metastasis, with a 1-year survival rate of 12%. Patients that had VTE one year before the cancer diagnosis had a slightly increased risk of distant metastasis at the time of diagnosis (8).

3. Epidemiology

The prevalence of clinical VTE in cancer patients is 15% and is associated with poor outcomes, with a six-fold decreased survival rate, compared with cancer patients without VTE (9), particularly in older patients, with a myeloproliferative type of cancer and patients with a late diagnosis, such as pancreatic cancer. This type of malignant tumor has a high risk of thrombosis, both arterial (3%) and venous (10%) (10-12). The annual incidence of VTE is 1-2/1,000 individuals in the general population, but in patients with cancer, it is 6.5-fold higher (13).

The most common cancer sites diagnosed during a VTE episode were established by a large Danish retrospective study where in the first place was pulmonary cancer (17%), followed by pancreatic cancer (10%), colon and rectal cancer (8%), renal cancer (8%) and prostatic cancer (7%) (8). However, the VTE incidence in previously diagnosed patients was the highest in pancreatic cancer (8.1%), kidney (5.6%), ovary (5.6%), lung (5.1%) and stomach cancer (4.9%), the lowest being associated with bladder cancer (14,15). In clinical practice, it is more common to find patients with prostate, breast and lung cancer with VTE than patients with pancreatic cancer and VTE, due to the incidence of these types of cancers (16).

In a population-based cohort study, the incidence of paraneoplastic thromboembolism was the highest in older patients and in males. The study included 6,592 active cancer-associated VTEs, with a total of 112,738 cancer-associated person-years of observation. The incidence rate of first VTE in patients with active cancer was 5.8 (95% CI 5.7-6.0) per 100 person-years. A total of 591 patients presented first VTE recurrence, with an overall incidence rate for recurrence of 9.6 (95% CI 8.8-10.4) per 100 person-years. There was significant mortality (64.5% after one year and 88.1% after 10 years) (16).

4. Pathophysiology of VTE in cancer

Several mechanisms have been proposed for pathogenesis of the hypercoagulable state, such as tumor production of

tissue factor-like procoagulant and cancer procoagulant (a calcium-dependent cysteine protease), alongside with procoagulant activities expressed by host tissues (P-selectin found in platelet granules and in Weibel-Palade bodies of endothelial cells, tissue factor produced by monocytes, increased platelet activation secondary to amplified production of thrombin, neoplastic cell ADP production and high levels of von Willebrand factor, neutrophil extracellular traps) (17).

5. Treatment and secondary prevention options

Low molecular weight heparins (LMWH). The first-line treatment of venous thrombosis in cancer patients is represented by LMWH, while unfractionated heparin (UFH) is recommended for patients with renal dysfunction. Fondaparinux and direct oral anticoagulants (DOACs) for initial treatment of acute paraneoplastic VTE have insufficient data for the routine recommendation, some studies have revealed that fondaparinux was associated with higher rates of VTE recurrence (18). For initial and long-term treatment of VTE, LMWH represents the drug of choice, due to a large amount of data that support this recommendation, that highlights the good safety and efficacy profile. LMWH have rapid onset and offset, can be easily monitored, and extensive clinical experience have been gained. Also, few drug-drug interactions have been reported, given the fact that the cancer patient receives more medications than a non-cancer patient, such as chemotherapy for cancer and different drugs for comorbidities. Dalteparin is preferred, due to data support, and represents the first recommendation for cancer-associated VTE (19). The dalteparin dose is weight-adjusted for patients up to 90 kg. The maximum dose is 18000 IU/day, even if the patient weighs more than 90 kg.

For the initial treatment of VTE and PE in cancer patients, guidelines suggest LMWH over unfractionated heparin UFH, DOACs (grade 2C) and VKA therapy (grade 2B) (19), given the fact that data are insufficient to recommend the use of DOACs or fondaparinux (20).

Several guidelines, including those of the American College of Chest Physicians (ACCP), the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO), recommend LMWH as monotherapy for 3 to 6 months in patients with cancer-associated thrombosis. The NCCN guidelines also recommend that anticoagulation should be continued indefinitely in patients with active solid cancer and in those with risk factors (21,22).

One of the largest meta-analyses of 8 randomized trials including 2327 cancer patients described reduced rates of recurrent VTE with LMWH compared with warfarin (RR 0.58; 95% CI 0.43-0.77), a benefit that followed without significant survival improvement or major bleeding events (23).

The CLOT trial (on 672 cancer patients) revealed the superior efficacy of dalteparin treatment (200 IU/kg in the first month, followed by 125 IU/kg for 5 months) compared with vitamin K antagonists after initial treatment with LMWH, in cancer patients, with no increase in major bleeding events and a substantial reduction of recurrent VTE rate observed in the dalteparin-treated group (9 versus 17%; HR, 0.48, 95% CI 0.30-0.77) (24). Also, the CANTHANOX and ONCENOX trials, that compared enoxaparin with warfarin, showed the

same efficacy, but with fewer bleeding events in the enoxaparin arm (25) or no difference at all (26).

The CATCH study, that compared tinzaparin with warfarin, showed no differences in major bleeding, overall mortality and recurrence of VTE, but a significant reduction in clinically relevant non-major bleeding was observed with tinzaparin (27). Similar rates of bleeding and mortality, with reduced rates of recurrent VTE for tinzaparin, were demonstrated in the LITE trial (28).

Disadvantages of parenteral therapy are represented by the perceived treatment administration burden, training and handling the syringe, drug-induced thrombocytopenia, weight-adjusting dosage and the limited use in renal insufficiency (29).

Vitamin K antagonists (VKAs). Warfarin is not recommended for the treatment of acute VTE in patients with active cancer. Although there is extensive clinical experience and comfort of oral administration, as well as the rapid reversal of its overdose, a statistically significant amount of data pleads for limitation of VKA use in clinical practice. Also, chemotherapy, anorexia and vomiting contribute to the downfall of oral anticoagulants, especially warfarin (30).

DOACs. DOAC as single-agent (apixaban, dabigatran) for patients with active cancer are recommended by NCCN guidelines if LMWH cannot be administered or as a first option (edoxaban, rivaroxaban). Factors that could influence the efficacy of DOACs (advanced age, weight, gender, other medication, kidney or liver dysfunction, vomiting, proximal small bowel resection, urinary or gastrointestinal lesions) are stated as relative contraindications (22). The ASCO 2014 Guideline update did not include the use of DOACs, due to limited data (20). There is a current recommendation that DOACs (edoxaban and rivaroxaban) may be used for acute VTE in cancer patients with low risk of bleeding, with data to support their use (31).

Many of the large trials compared DOACs with warfarin in the general population and their results were extrapolated to cancer patients. In the EINSTEIN (32) and RECOVER (33) studies, that compared rivaroxaban versus warfarin, respectively dabigatran versus warfarin, there was no significant difference in recurrence events or bleeding events. However, these recurrence and bleeding events were higher in cancer patients than in non-cancer patients. Similar VTE recurrence rates were reported in a large meta-analysis of 6 studies (34). Apixaban reported a significant reduction in rates of recurrent VTE and hemorrhagic events versus enoxaparin followed by warfarin (35). However, there are emerging trials (36) that compare DOACs versus LMWH with or without warfarin, given the fact that practice guidelines have scarce recommendations on the optimal time to switch to DOACs [NCT02744092, CANVAS (37), NCT03240120 for dabigatran (38), NCT03045406 CARAVAGGIO - apixaban vs. dalteparin (39), NCT02581176 (40)].

Edoxaban was demonstrated to be non-inferior to dalteparin for the treatment of cancer-associated VTE in a phase III trial, now the superiority of this comparison is investigated. In this trial, the patients received 60 mg edoxaban daily, after 5-day treatment with LMWH, compared to 200 IU/kg dalteparin

administration in the first month, followed by 150 IU/kg daily (41).

The SELECT-D study, conducted on 406 patients, compared rivaroxaban (15 mg twice daily for three weeks, after that, reducing the dose to 20 mg daily for a total of six months) with dalteparin (200 IU/kg in the first month, then 150 IU/kg daily for 5 months) and reported a reduction of the VTE recurrence rate (4% versus 11%), with similar rate of major bleeding (6% versus 4%) (42). Bleeding events have also been assessed in phase II and III clinical trials, that compare safety and efficacy of rivaroxaban versus dalteparin [NCT03139487 PRORITY (43), NCT02746185 CASTA-DIVA (44)] and with other LMWH (NCT02583191 CONKO-011) (45).

UFH. A meta-analysis of 15 randomized controlled trials compared UFH with LMWH, the latter being associated with a reduction in mortality rate at three months (RR 0.66, 95% CI 0.40-1.1), without an increased risk of hemorrhagic events, as compared to UFH that showed a risk difference of 17 more cases per 1000 patients. Compared with fondaparinux, there was no significant difference regarding the mortality at three months, recurrent VTE or bleeding events (46).

6. Thromboprophylaxis

Primary thromboprophylaxis. Regarding ambulatory patients with cancer, the ASCO Guideline recommends that only high-risk patients should receive prophylactic therapy with LMWH. Hospitalized patients with active cancer should receive anticoagulation therapy, especially during chemotherapy, either with LMWH or low-dose aspirin. For minor procedures, there is no eloquent data (20). The ACCP Guideline suggests a prophylactic dose of LMWH or UHF in outpatients with solid tumors and risk factors such as chemotherapy and immobilization (19).

For the DOACs efficacy in primary thromboprophylaxis in hospitalized patients plead the results of MAGELLAN trial, that demonstrated the superiority of rivaroxaban for 35 days over enoxaparin for 10 days, followed by placebo (47).

Secondary thromboprophylaxis - extended therapy. Anticoagulant treatment beyond the conventional 3 to 6 months is frequently used, given the fact that active malignancy represents a risk factor for VTE and VTE recurrence of 10 to 20% per year, while also taking into consideration the type and activity of cancer, burden of disease, oncologic treatment, patient choice, immobility and life expectancy (19).

However, the bleeding risk must be evaluated in the extended anticoagulant therapy, considering the fact that there are scarce data supporting the treatment with LMWH beyond 6 months, such as the DALTECAN trial (21). If necessary, ASCO guideline recommends secondary prophylaxis for long-term (beyond six months) (20). The NCCN Guideline recommends LMWH as the preferred agents for the first 6 months (dalteparin or enoxaparin), but also includes DOACs (rivaroxaban) if patients refuse or are poor candidates for LMWH (22).

A systematic review on 5 relevant randomized clinical trials with moderate quality of evidence for survival suggested a survival benefit of heparin treatment (UFH or LMWH) in cancer

patients and, in particular, in patients with limited small cell lung carcinoma (48). Still, a randomized trial of fraxiparin/nadroparin administration failed to show a survival benefit in patients with advanced prostate, lung or pancreatic cancer (49).

Rivaroxaban demonstrated its effectiveness and safety for the treatment of VTE and recurrence prophylaxis in patients with active cancer, in a prospective multicenter trial (50). There are large observational studies in progress, to follow-up the recurrence of VTE in extended therapy with rivaroxaban [NCT03214172 (51), NCT02742623-COSIMO (52), NCT01989845 (53)] and apixaban for the prevention of recurrent VTE in patients with active breast, prostate or colorectal cancer [NCT03692065 API-CAT STUDY (54), NCT02585713 ADAM-VTE (55)].

A Canadian systematic review of randomized trials that compared the benefit of using anticoagulation (LMWH or fondaparinux) with no anticoagulation in VTE prophylaxis concluded that there are still unknown risks and benefits of primary anticoagulant therapy for thromboprophylaxis in cancer patients (2).

7. Special categories

Management of recurrent thrombosis. Additional risk factors for recurrent thrombosis were cited in the RIETE Registry of 3805 patients, as being PE at debut (OR, 1.9; 95% CI 1.2-3.1) and a recently diagnosed cancer, less than 3 months (OR, 2.0; 95% CI 1.5-3.6). Also, the tumor site influenced the recurrence and bleeding risk, with similar rates of these events in breast cancer (5.6 and 4.1%, respectively) and colorectal cancer (10 and 12%, respectively). Lung cancer presented a two-fold higher risk of recurrence than the rate of bleeding (27 and 11%, respectively) whereas, prostate cancer showed recurrence half of the rate of bleeding (7 versus 13%, respectively) (56).

Despite adequate anticoagulation, VTE events have a three-fold increased risk of recurrence (57) and can indicate drug failure or resistance. Predictive factors for the recurrence are the presence of high concentrations of plasmatic tissue factor (3 fold increased risk), venous compression by the tumor or ganglia and hepatobiliary cancer (5.5 fold increased risk) (15). The recommendations include switching to LMWH when the patients are on oral anticoagulant therapy, increasing the dose or frequency of administration of LMWH for those patients already on LMWH and introducing an inferior vena cava filter (58). Also, it is recommended to test the patient for acquired or inherited thrombophilia causes (19). The benefits of switching to a direct oral anticoagulant in this population are still unknown.

Thromboprophylaxis during chemotherapy. Chemotherapy represents a risk factor for VTE, although current clinical guidelines do not recommend routine use of thromboprophylaxis in ambulatory patients. Given the fact that included patients were not stratified by using risk scores for VTE, the benefit of parenteral anticoagulant treatment needs to be assessed.

The SAVE-ONCO trial indicated a reduced incidence of VTE in this particular category of patients, with no significant increase in major hemorrhagic events, during the administration of semuloparin, an ultra-low-molecular-weight heparin, in

doses of 20 mg daily versus placebo. Patients with advanced or metastatic cancer of the lung, colon/rectum, stomach, ovary, pancreas or bladder who were starting a new chemotherapy course were included in this trial (59).

Weight-adjusted dalteparin for 12 weeks reduced VTE incidence during gemcitabine treatment for pancreatic cancer in FRAGEM trial (60) and nadroparin in patients with advanced stage lung, breast, gastrointestinal, ovarian or head and neck cancer undergoing chemotherapy in the PROTECHT trial (61).

DOACs could be a more suitable option, thus creating the premise of many trials, which compared apixaban and rivaroxaban versus placebo in thromboprophylaxis of high-risk patients (as defined by a Khorana score of ≥ 2) receiving chemotherapy [NCT02048865 (62), NCT02555878 (63)].

However, some chemotherapy agents can interfere with DOAC pharmacokinetics (rivaroxaban, apixaban), due to cytochrome P450 3A4-related drug-drug interactions, with the effects of either increasing toxicity and bleeding risk (many tyrosine kinase inhibitors) or decreasing effectiveness of DOACs (64-68).

Perioperative anticoagulant therapy. Major surgery for cancer represents an indication of prophylaxis before surgery and for at least 7-10 days after, with extended therapy up to four weeks being considered in abdominal and pelvic high-risk cancer surgery (20,69-71).

Prevention of VTE with DOACs in patients who are scheduled to surgery represents a bold purpose, given the fact that this treatment improves patient adherence and would decrease VTE monitoring and complications (72-74). Cancer surgery increases the risk of thrombosis, especially in older patients, those with recurrent VTE, or prolonged immobilization. Several ongoing trials compare the efficacy and safety of using fondaparinux, LMWH (first and second generation), UFH following major orthopedic and abdominal cancer surgery [NCT01444612 (75), NCT00219973 – bempiparin (76)] and even DOACs [NCT02366871-apixaban (77)].

Brain-tumor patients. The VTE risk in patients with brain tumors is increased up to 60%, after surgery, with an incidence of 20-30% per year of survival (78-80). Although thromboprophylaxis is necessary, its use is still controversial, due to increased risk of intracranial hemorrhage demonstrated in some studies (81-83).

Patients with increased bleeding risk. Chemotherapy-induced thrombocytopenia increases the risk of bleeding events. The anticoagulant treatment decision is problematic, due to lack of evidence, mainly because of the exclusion of this category of patients from clinical trials. Bleeding risk was assessed in patients with thrombocytopenia who continued to receive lower doses of enoxaparin in case series and a small retrospective study, with promising results (84,85).

8. Future treatments

Isoquercetin, a flavonoid that targets endothelial-produced protein disulfite isomerase, thus preventing platelet aggregation, fibrin addition and platelet-dependent thrombin

generation via blocking of platelet factor Va (86,87), could represent a viable option to prevent VTE in metastatic cancer, such as unresectable or metastatic pancreatic adenocarcinoma, stage III or IV non-small cell lung cancer unresectable, or stage IV colorectal cancer (NCT02195232, CAT IQ, N=618). In this study, the administration of isoquercetin 500 mg and 1000 mg for 56 days, with vascular ultrasound screening, led to an important decrease in platelet-dependent thrombin production, decreased plasmatic D-dimer concentration by a median of -21.9% (P=0.0002), without primary VTE events or major bleeding events observed (88,89). Statins are also investigated for the potential prophylactic effect on VTE, especially in high-risk cancer patients who receive chemotherapy (NCT01524653, DISOLVE) (90).

9. Conclusions

Direct anticoagulants could represent a more appealing alternative to low-molecular-weight heparin in paraneoplastic VTE, due to patient comfort, easy administration of the drug and emerging studies that prove similar efficacy and safety as the standard treatment. The increasing number of clinical trials that aim to prove this point is the result of shifting to the need to recommend a simpler, safer and efficient treatment for patients with active cancer or during chemotherapy.

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Authors' contributions

RAI, OGB, TC and RDM collected, analyzed and interpreted the patient data regarding the venous thromboembolism in patients with cancer. DLDM, CCD, MAG and BS had substantial contribution to the conception of the study and interpretation of data; also, they drafted the manuscript and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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