CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will recognize the importance of searching for cancer in patients with idiopathic VTE and of managing VTE in patients with cancer

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Cancer and clots: All cases of venous thromboembolism are not treated the same

ABSTRACT

Idiopathic venous thromboembolism (VTE) can be the first sign of cancer, although how extensively one should search for cancer in a patient with idiopathic VTE is not clear. Treating VTE is more complex in cancer patients than in those without cancer. The authors discuss their approach to searching for undiagnosed cancer in patients with idiopathic VTE and to managing VTE in patients with cancer.

KEY POINTS

We recommend judiciously screening for cancer with age- and sex-specific tests in patients with idiopathic VTE.

Patients with VTE and cancer have a higher risk of both VTE recurrence and bleeding complications of anticoagulant therapy than do VTE patients without cancer.

Either unfractionated heparin or a low-molecular-weight heparin (LMWH) should be started as soon as VTE is confirmed or even strongly suspected, while still awaiting confirmation.

The current (grade 1A) recommendations for treating VTE in cancer patients are to use LMWH monotherapy for at least 3 to 6 months. Anticoagulation is necessary indefinitely when there is ongoing cancer treatment or persistent risk of VTE.

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VENOUS THROMBOEMBOLISM (VTE) has various differing causes, so its treatment is not necessarily the same in all cases. Most cases of VTE are related to an easily identified risk factor. In patients with an apparently idiopathic event, identifying an underlying cause may alter therapy. In particular, identification of a malignancy may affect the choice of therapy and the duration of treatment.

In this review, we explore the role of cancer screening in patients with idiopathic VTE, then highlight the treatment for VTE in patients with cancer.

'IDIOPATHIC' VTE CAN BE DUE TO CANCER

Most patients with venous thrombosis have one of the components of Virchow's triad: a hypercoagulable state, venous injury, or venous stasis. Those without identifiable risk factors for VTE are considered to have idiopathic VTE. In these patients, a search for a contributing factor may be indicated.

In 1861, the astute clinician Dr. Armand Trousseau noted a link between deep venous thrombosis and pancreatic cancer, stating that if cancer of an internal organ is suspected but the diagnosis cannot be verified, the diagnosis may be confirmed by the sudden, spontaneous appearance of thrombophlebitis in a large vein.[1]

Today, from 2% to 25% of patients with id-

*Dr. Carman has indicated that she has received honoraria from the sanofi-aventis corporation for teaching and speaking.

iopathic VTE are found to have cancer within 24 months of the diagnosis of VTE.[2–11] The goals of cancer screening in idiopathic VTE are to detect cancer at an early, treatable stage and to optimize the VTE therapy to decrease the risks of recurrence and anticoagulation-associated complications in patients who are found to have cancer. However, several questions must be considered first:

- What are the risks and costs of the screening?
- Will discovering the cancer sooner benefit the patient in terms of survival?
- If cancer is found, what are the possible complications or risks of the additional procedures, interventions, or treatments required?
- What is the psychological impact of the screening?

EVIDENCE SUPPORTING CANCER SCREENING AFTER IDIOPATHIC VTE

Piccioli et al[12] recently performed a randomized, controlled trial comparing cancer-related death rates in 99 patients with idiopathic VTE screened for malignancy vs 102 patients with idiopathic VTE who were not screened. The screened group underwent:

- Abdominal and pelvic ultrasonography and computed tomography (CT)
- Gastroscopy or double-contrast barium-swallow evaluation
- Colonoscopy or sigmoidoscopy followed by barium enema
- Testing for fecal occult blood
- Sputum cytology
- Measurement of carcinoembryonic antigen, alpha-fetoprotein, and cancer antigen 125.
- Mammography and Papanicolaou smears (women)
- Ultrasonography of the prostate and prostate-specific antigen testing (men).

Patients were followed for 2 years. The screening uncovered cancer in 13 patients. Cancer developed in one other patient in the screening group during follow-up; in the control group, 10 patients developed symptomatic cancer during follow-up. Overall, the time to cancer diagnosis was 11.6 months in the unscreened group vs 1 month in the screened group ($P < .001$). Nine of the 14 patients with cancer in the screened group had T1 or T2 disease without local or distant metastasis vs 2 of the 10 control patients with cancer ($P = .047$). Unfortunately, this study did not have adequate power to detect the effect of screening on survival.

Di Nisio et al[13] used data from this trial to perform a decision analysis for cancer screening. They calculated that abdominal and pelvic CT, with or without mammography and with or without sputum cytologic testing, would cost the least per life-year gained and would harm the fewest number of patients. They also suggested that substituting CT of the chest for sputum cytology may provide additional diagnostic benefit.

However, this strategy has not been clinically tested. Given the limited number of patients and the short follow-up in this initial trial, larger trials are needed to look at the cost-effectiveness of this screening model and whether it increases survival.

Our recommendations

Because the data are limited, our approach to looking for an early, treatable malignancy in patients with idiopathic VTE follows the current consensus:

- A thorough history and physical, including an extensive review of systems
- Basic laboratory testing with a complete blood cell count, comprehensive metabolic profile, and urinalysis
- Chest radiography
- Other age- and sex-specific cancer screening tests.

Adding CT of the abdomen, pelvis, or chest to this evaluation may be considered. However, tumor marker testing, which typically has high false-positive rates, is not routinely warranted.[13] Additional investigation should be considered if abnormalities are detected during the initial evaluation or in patients with recurrent VTE during therapy.

While this strategy may be most cost-effective, Monreal et al[14] suggest that it may miss up to half of cancers ultimately discovered.

Treating venous thrombosis in cancer patients requires a tailored risk-to-benefit analysis

MANAGING VTE IN PATIENTS WITH KNOWN CANCER

Managing VTE is far more complex in cancer patients than in patients without cancer. Also,

cancer patients with VTE have lower rates of survival than cancer patients without VTE and are at greater risk of adverse outcomes such as anticoagulant-associated bleeding and recurrent venous thrombotic events.[15–17]

Up to 21.5% of patients with VTE have another event within 5 years,[18] but the risk is two to three times higher if they also have cancer.[16,18] The risk of recurrence may be linked to the location of the thrombus and to the extent of the malignancy.

In one study, the 3-month rate of recurrence was up to 5.1% if the clot was in the popliteal vein, 5.3% if in the femoral vein, and 11.8% if in the iliac vein.[19]

Prandoni et al[16] found that the risks of VTE recurrence and bleeding were higher in patients with extensive cancer than in those with less-extensive cancer. In this study, major bleeding was documented in 12.4% of patients with cancer vs 4.9% of patients without cancer. Compared with patients without cancer, the hazard ratio for a major bleeding event was 4.8 in patients with extensive cancer and 0.5 in patients with less-extensive cancer.

In addition, not all patients with bleeding had excessive levels of anticoagulation, and not all patients with recurrent events had subtherapeutic levels.[16,17] Therefore, treatment of venous thrombosis in cancer patients requires a careful, individualized risk-to-benefit decision analysis.

ACUTE THERAPY FOR VTE: PARENTERAL AGENTS

Treatment in the first several hours or days after a thromboembolic event is with short-acting parenteral agents: unfractionated heparin; one of the low-molecular-weight heparins (LMWHs), ie, dalteparin (Fragmin), enoxaparin (Lovenox), or tinzaparin (Innohep); or fondaparinux (Arixtra).

Before starting anticoagulation, consider:

- Does the patient have severe chronic kidney disease (ie, a creatinine clearance < 30 mL/min)? If so, unfractionated heparin may be better than an LMWH or fondaparinux, which are cleared by the kidney.
- Does he or she need inpatient care? If not, LMWH therapy at home may be appropriate.
- Are there concerns about the ease of anticoagulation administration (ie, whether the patient can give the injections or have a family member do it), the cost of the drugs, or the ability to reverse the anticoagulant effect, if necessary? If so, unfractionated heparin may be more appropriate.

For acute treatment, the 2008 guidelines of the American College of Chest Physicians[20] (ACCP) recommend using an LMWH in a weight-based dose; unfractionated heparin given intravenously; unfractionated heparin given subcutaneously with monitoring and dosing adjustments; unfractionated heparin given subcutaneously at a fixed dose; or fondaparinux (grade 1A recommendation). The 2007 National Comprehensive Cancer Network (NCCN) guidelines[21] recommend an LMWH, fondaparinux, or unfractionated heparin. Treatment should start promptly after the diagnosis of VTE is confirmed. However, if VTE is strongly suspected and a delay in diagnostic testing is anticipated, therapy should be started while awaiting the test results.

LONG-TERM THERAPY: LMWH OR WARFARIN

If testing for VTE is delayed, start anticoagulation while awaiting the test results

The ACCP and the NCCN guidelines recommend LMWH monotherapy for extended treatment of VTE in patients with active malignancy, when appropriate.[20,21] However, if long-term LMWH is not appropriate, then oral anticoagulation with a vitamin K antagonist, such as the coumarin derivative warfarin (Coumadin), is an alternative and should be started on the same day as the heparin. The heparin and the warfarin therapy must overlap for a minimum of 4 or 5 days and until a stable, therapeutic level of anticoagulation is achieved, ie, an international normalized ratio (INR) of 2 to 3 for 2 consecutive days.[20]

The duration of anticoagulant therapy depends on comorbidities and the patient's underlying predisposition for VTE. In patients with limited disease, the guidelines recommend continuing anticoagulation for a minimum of 3 to 6 months for deep venous thrombosis and pulmonary embolism.[20–21] Patients with active malignancy, ongoing treatment for the cancer, or continued risk factors may need indefinite treatment. In some circumstances, such as

catheter-associated deep venous thrombosis, anticoagulation should continue for as long as the catheter is in place and for 1 to 3 months after its removal.[21]

WARFARIN CAN BE DIFFICULT TO USE

In 1954, the US Food and Drug Administration (FDA) approved the vitamin K antagonist warfarin for medical use in humans. Experience has shown it to be effective in preventing and treating VTE. However, it can be somewhat difficult to use, for several reasons:

- A narrow therapeutic window
- Genetic polymorphisms and variability in dose response
- Drug interactions and dietary considerations
- The need for laboratory monitoring and dose adjustment
- Patient noncompliance or miscommunication between the patient and physician.[22]

In cancer patients, the response to warfarin may be unpredictable because of poor nutrition, interactions with chemotherapy and antibiotics, and comorbid conditions.[22] Furthermore, its onset of action can be delayed and its clearance may be prolonged, further increasing the risk of complications, especially in patients prone to developing chemotherapy-related anemia or thrombocytopenia.[22] Bleeding risk is the highest in the first 3 months of therapy. In addition, the risk of bleeding is higher in older patients, women, and patients with a history of gastrointestinal bleeding, stroke, recent myocardial infarction, diabetes, renal insufficiency, malignancy, or anemia.[23,24]

LMWHs can be given safely at home, thus enhancing quality of life

ADVANTAGES AND DISADVANTAGES OF LMWH

The advantages of the LMWHs over unfractionated heparin include a lower risk of heparin-induced thrombocytopenia, greater bioavailability when given subcutaneously (which also permits once-daily or twice-daily dosing), and no need for laboratory monitoring in most patients. LMWHs have a short half-life, so omitting one or two doses will adequately interrupt therapy. Also, LMWHs have been shown to be as safe and effective as unfractionated heparin in treating VTE. They can be given safely at home, thus enhancing quality of life.[25–31]

On the other hand, these drugs cost more than unfractionated heparin or warfarin, their dosage must be adjusted in patients with renal insufficiency, their anticoagulant effect can be reversed only to a limited extent, and their dose must be adjusted according to weight in morbidly obese or in very thin patients.[32,33]

LMWHs are expensive, but may be worth it

As initial therapy, the LMWHs are cost-effective compared with unfractionated heparin in patients with VTE.[34,35] However, they cost more with extended use. A cost-effectiveness analysis comparing 6 months of LMWH therapy to standard warfarin concluded that LMWH therapy was more costly.[35] However, the impact of fewer hospitalizations, probably fewer bleeding complications, and better quality of life are difficult to analyze in this decision model and should also be considered when deciding about therapy for an individual patient.[35]

LMWHs are cleared by the kidney

All LMWHs are renally cleared, so patients with significant renal insufficiency (creatinine clearance < 30 mL/min) are at greater risk of bleeding complications. The rate below which clearance is impaired varies among the different LMWHs. Only enoxaparin has approved dosing regimens for use in patients with renal impairment.

If the patient has renal insufficiency, the ACCP guidelines suggest using unfractionated heparin, or if using LMWH, monitoring anti-factor Xa levels to avoid drug accumulation and increased bleeding risk.[25] If bleeding occurs, LMWHs have limited reversibility with protamine sulfate, which is estimated to neutralize about 60% of the anti-factor Xa activity of LMWHs.[25]

Adjusting LMWHs for body weight

In the *Registro Informatizado de la Enfermedad Tromboembólica* (RIETE),[33] patients weighing less than 50 kg had a higher risk of bleeding than patients weighing 50 to 100 kg, so in thinner patients the risk of bleeding from LMWH vs oral anticoagulation must be considered carefully and monitored prudently.

Although there is little evidence to suggest a higher bleeding risk in morbidly obese patients (> 150 kg), they may be at risk of subtherapeutic treatment, and monitoring with anti-factor Xa assays is recommended.[25,32,33]

LMWH VS WARFARIN FOR VTE IN CANCER PATIENTS

LMWHs are the first-line treatment for VTE in cancer patients.[20,21] Several randomized controlled trials compared the efficacy of LMWH vs warfarin in patients with cancer.

Meyer et al[36] randomized patients to receive either warfarin for 3 months at an INR between 2 and 3, or enoxaparin 1.5 mg/kg subcutaneously daily. Seventy-one patients received warfarin and 67 received enoxaparin. Fifteen (21%, 95% confidence interval [CI] 12%–32%) of the 71 patients assigned to warfarin experienced one major outcome event, defined as major bleeding or recurrent VTE, compared with 7 (10.5%) of the 67 patients assigned to receive enoxaparin (95% CI 4%–20%, P = .09). Six patients in the warfarin group died of bleeding vs none of the patients in the enoxaparin group. Overall, the warfarin group had a higher rate of bleeding, although this did not reach statistical significance. Despite weekly INR measurements, only 41% of the measured values were within the therapeutic range during the 3 months of treatment.[36]

Lee et al[37] randomized cancer patients with deep venous thrombosis, pulmonary embolism, or both to receive 6 months of dalteparin alone, dosed at 200 IU/kg daily for 1 month, then decreased to 75% to 80% of the original dose (150 IU/kg) daily for the duration of therapy, or dalteparin followed by warfarin. During the 6-month follow-up, 17.4% of patients in the warfarin group had a recurrent thromboembolic event vs 8.8% in the dalteparin group (P = .0017). No statistically significant difference was noted in rates of major bleeding, minor bleeding, or death.[37]

Hull et al[38] reported statistically significantly fewer episodes of recurrent VTE at 12 months in cancer patients treated with once-daily tinzaparin vs warfarin. In the tinzaparin group the recurrence rate was 7%, vs 16% in the warfarin group (P = .044). No difference in rates of bleeding or death were found.

Deitcher et al[39] compared enoxaparin with long-term warfarin in 102 patients. While this trial did not have the power to detect clinical differences in recurrent thromboembolic events or bleeding complications, at 180 days they noted 97% compliance with once-daily or twice-daily enoxaparin therapy.

Noble and Finlay,[40] in another small study, found LMWH therapy to be qualitatively more acceptable for palliative-care cancer patients than oral therapy.

In general, long-term therapy with once-daily or twice-daily LMWH is well tolerated. Currently, dalteparin is the only LMWH approved by the FDA for extended monotherapy in cancer-related VTE.

DO LMWHs AFFECT CANCER?

In vitro and animal studies indicate that LMWH may have antimetastatic and antiangiogenic properties.[41–44]

Altinbas et al[45] reported significantly better chemotherapy-induced tumor response rates and survival rates in patients with small cell lung cancer randomized to receive combination chemotherapy plus prophylactic dalteparin 5,000 IU daily compared with combination chemotherapy alone. However, as provocative as these results may be, we need to test the effects of LWMHs on different cancer types in a prospective clinical trial. For now, this area remains controversial.

In thinner patients, bleeding risk with LMWH is higher, requiring close monitoring

It has been suggested that anticoagulants may improve survival in patients with nonmetastatic cancer. Supporting this observation, a post hoc analysis of the trial by Lee et al[37] found a statistically significantly lower cancer-specific mortality rate in nonmetastatic cancer patients treated with dalteparin vs oral therapy with a coumarin derivative. In patients without metastatic disease, the death rate at 12 months was 36% in patients treated with oral therapy vs 20% in patients treated with dalteparin (P = .03).[46]

These findings are consistent with those of the Fragmin Advanced Malignancy Outcome Study (FAMOUS),[47] the first randomized, placebo-controlled trial of dalteparin 5,000 IU daily in patients with advanced solid tumors and without evidence of underlying thrombosis. Overall, dalteparin prophylaxis did not

increase survival. However, in a subgroup of patients with a better prognosis and who were alive 17 months after diagnosis, survival was statistically significantly longer in patients treated with dalteparin.

Another small trial showed similar survival benefits in cancer patients without VTE.[48] The results may suggest a long-term favorable effect of LMWH on tumor cell biology, which could translate into a favorable outcome in some patients. It is important to note, however, that not all trials have shown this same clinical benefit.[49]

In general, the growing body of laboratory and clinical data indicates that LMWHs may suppress tumor growth and metastasis. However, definitive conclusions about these effects are not yet possible because of variations in study design, tumor type, and patient populations. Further investigations into the role of LMWHs in the treatment of VTE and in cancer progression are ongoing.

THE EVIDENCE IN PERSPECTIVE

Illness and the recurrence of VTE in patients with cancer depend on the location and extent of the underlying cancer. Rates of death are higher in VTE patients with cancer than in VTE patients without cancer. Patients with limited or localized disease may not die of the cancer itself but of complications of acute pulmonary embolism. Therefore, it is important to recognize the different options for and the potential side effects of treating VTE.

If patients are hospitalized for an acute thromboembolic event and unfractionated heparin is chosen as the initial anticoagulant, using a weight-based nomogram has been shown to achieve therapeutic levels within 24 hours and reduce the rates of recurrence of thromboembolic events.[50]

Warfarin treatment may pose a particular challenge for both cancer patients and physicians, since multiple drug interactions, anorexia, and comorbid conditions contribute to an unpredictable response.

The risk of bleeding is higher in cancer patients than in the general population, and the decision to start anticoagulants should be based on an individualized risk-benefit profile. Several trials have shown LMWH to be more effective and safer than warfarin in cancer patients.

These considerations, along with the other advantages of LMWHs (ease of use, less need for laboratory monitoring, and better patient tolerance), make LMWHs a good choice for initial therapy. Extended LMWH therapy is currently favored for initial management in patients with cancer. Trials are under way to further assess the antitumor properties and potential survival benefit in patients with selected solid tumors.

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