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What is the Best Treatment for a Cancer Patient with Thrombosis?

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ABSTRACT: The relationship between venous thromboembolism and cancer has been known for many years, and there is solid scientific evidence addressing the adequate treatment of this condition in oncology patients. However, established prescribing habits, individual patient challenges, and uncertainty concerning treatment justifies poor adherence to published guidelines. This paper reviews venous thromboembolism treatment while focusing on vitamin K antagonists, low-molecular-weight heparins, and novel oral anticoagulants, namely in terms of their efficacy and limitations.

KEYWORDS: venous thromboembolism, cancer, thrombosis, vitamin K antagonists, low-molecular-weight heparin, oral anticoagulants

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Cancer and Thrombosis

The relationship between cancer and thrombosis has been well established and has been known for over 100 years.[1] Venous thromboembolism (VTE), and pulmonary embolism (PE) in particular, are increasingly frequent complications in patients with malignancy, representing the second most common cause of death, following cancer itself.[2,3] Despite this fact, the reported frequency of VTE in cancer patients is probably underestimated, given that autopsy rates of VTE can be as high as 50% compared with clinical rates of 4%–20%.[4]

Compared with patients who do not have cancer, oncology patients are at a substantially higher risk for new and recurrent VTE – a conclusion that can be drawn from the fact that the incidence of VTE that is associated with cancer increased in late 1980s and 1990s when compared to a stabilization in the incidence of VTE in noncancer patients during the same period.[5]

The pathogenesis of hypercoagulability in malignancy involves a profound interaction among cancer cells, host cells, and the coagulation system. Specifically, tumor cells express tissue factor (TF), a procoagulant molecule related to the continuous activation of coagulation and increased thrombin generation. The upregulation of TF is associated with the production of the proangiogenic cytokine vascular endothelial growth factor (VEGF), which increases vascular permeability, allowing incremental exposure to coagulation factors and thus exacerbating the procoagulant environment.[6]

Not all oncology patients face an equal risk for thrombotic events. Factors such as cancer type, clinical setting, comorbid conditions, and therapeutic procedures are associated with different probabilities of developing VTE.[7] This risk is increased for those who are undergoing surgery (fivefold), those who are receiving chemotherapy (sixfold), those with previous VTE, and those who carry certain genetic mutations.[8]

The incidence of VTE may be closely associated with characteristics of tumor biology – namely, the rate of growth and spread of the cancer – suggesting that specific cancer types are associated with an increased risk of VTE.[9] For example, the cumulative incidence of VTE from the date of the cancer diagnosis in California (accrued over 3 years) was 6.9% in brain tumors, 5.3% in pancreatic cancer, 4.5% in gastric malignancy, 3.7% in acute myelogenous leukemia, 3.6% in esophagus cancer, and 3.5% in renal cell carcinoma.[10] Among hospitalized cancer patients, the sites of cancer with the highest rates of VTE include the pancreas (8.1%), kidney (5.6%), ovary (5.6%), lung (5.1%), myeloma (5%), stomach (4.9%), non-Hodgkin lymphoma (4.8%), and Hodgkin disease (4.6%).[2]

The increased risk of recurrent VTE in cancer patients is greatest in the first few months after the diagnosis of a malignancy and can persist for many years after an initial episode of symptomatic deep venous thromboembolism (DVT).[8] The risk of VTE varies over the natural history of cancer, with the highest risk occurring during hospitalization and following the development of metastatic disease.[9]

Systemic anticancer treatment (namely, chemotherapy and hormonal therapy) can further increased the risk of VTE by directly inducing endothelial cell injury[11] and decreasing the levels of protein C and S, thus contributing to a hypercoagulable state.[12] Saphner et al[12] reported a 5.4% frequency of thromboembolic complications, both venous and arterial combined, in patients with breast cancer who received adjuvant treatment (chemotherapy and hormonal therapy), and 1.6% among patients on observation ($P = 0.0002$). The combination of chemotherapy and tamoxifen was associated with more venous and arterial thromboembolic complications than was chemotherapy alone in premenopausal patients (2.8% versus 0.8%; $P = 0.03$), and with more venous thrombi than tamoxifen alone among postmenopausal patients (8.0% versus 2.3%; $P = 0.03$) or those who were observed (8.0% versus 0.4%; $P < 0.0001$).[12]

Bevacizumab, a monoclonal antibody directed toward the VEGF with documented activity in combination with chemotherapy in patients with colorectal, nonsquamous-cell lung, breast, renal, and ovarian cancer, is associated with an increased risk of arterial thromboembolic events (twofold) and VTE (relative risk [RR] of 1.33) compared with chemotherapy alone.[13,14] It is thought that bevacizumab exerts this effect by reducing the production of nitric oxide and prostacyclin, and it simultaneously exposes subendothelial procoagulant phospholipids, predisposing an individual to thromboembolic events.[14]

Recombinant human erythropoietins increase hemoglobin levels and reduce the need for blood transfusions in cancer patients, but as Bohlius et al[15] demonstrated in a meta-analysis that included 35 trials with 6,769 patients, these agents are associated with a 67% increase in the RR of a VTE.[15]

Central venous catheters (CVCs), commonly used in patients with cancer, were required for infusion chemotherapy and for the intravenous administration of supportive care treatments that are frequently associated with thrombosis. The reported incidence of CVC-associated thrombosis varies widely between studies, ranging from 4%–5% for symptomatic occurrences, to 30% for asymptomatic events.[16] A recent large, prospective study of 2,144 patients with peripherally inserted CVCs found a 3% rate of thrombosis.[17]

There is also an inherit risk of VTE related to each individual patient. Older age, race (higher risk in African Americans and lower risk in Asian—Pacific Islanders), comorbid conditions (namely obesity, infections, or renal or pulmonary disease), prior history of VTE, or heritable prothrombotic mutations are all conditions that enhance the probability of a thromboembolic event.[4] In addition to the epidemiologic risk factors, laboratory parameters such as high platelet count, high leukocyte count, elevated levels of the cell adhesion molecule soluble P-selectin, high levels of D-dimer, and the prothrombin fragment 1 + 2 have been associated with an increased risk of cancer-associated thrombosis.[18]

Venous thromboembolism and survival. The risk of death is significantly increased among patients with DVT/PE and malignant disease compared with noncancer patients with DVT/PE. According to Levitan et al,[19] the probability of death within 183 days of initial hospitalization is 0.94 for those with malignant disease versus 0.29 for those without cancer ($P = 0.001$). This study suggests that patients with concurrent DVT/PE and malignancy have a threefold higher risk of recurrent thromboembolic disease and death than do patients with DVT/PE without malignancy.[19]

Moreover, a diagnosis of thromboembolism within 1 year of a cancer diagnosis is a significant predictor of death. Sørensen et al[20] studied the prognosis of oncology patients diagnosed during or after an episode of VTE. Based on the Danish National Registry of Patients, the authors compared the survival of patients who received a diagnosis of cancer at the same time or after an episode of VTE with that of patients with cancer who did not have VTE (control patients); patients were matched by the type of cancer, age, sex, and year of diagnosis. A total of 44% of patients with cancer at the time of an episode of DVT had distant metastasis, as compared to 35% of the control patients. Patients in whom cancer was diagnosed within 1 year after an episode of VTE had a relatively low rate of survival at 1 year (38% versus 47% in the control group; $P < 0.001$). The authors conclude that cancer diagnosed at the same time or within 1 year after an episode of VTE is associated with an advanced stage and a poor prognosis.[20] The cause for such a strong association between VTE and decreased survival is not clear. Patients with thromboembolism may have a more biologically aggressive disease, more serious underlying comorbidities, or they may simply die earlier because of complications associated with thromboembolism and/or its treatment.[21]

Venous thromboembolism as a chronic disease in cancer patients. VTE should be considered a chronic disease for which the risk of recurrence persists for many years after the initial event.[22] A prospective follow-up study conducted by Prandoni et al[23] evaluated the risk for recurrent VTE or bleeding during anticoagulant treatment in 842 patients with DVT (with and without cancer) receiving anticoagulant therapy. Among 181 patients who had known cancer upon study entry, the incidence of recurrent VTE was increased 3.2-fold compared with those without cancer (20.7% versus 6.8%, respectively). The cumulative incidence of major bleeding was also increased 2.2-fold among patients with cancer compared to those without (12.4% versus 4.9%, respectively).[23] These data suggest that many patients with cancer with an initial episode of VTE may require extended, sometimes lifelong,

antithrombotic therapy, but the risks of bleeding must be carefully weighed against the thromboprophylactic benefit associated with treatment.[22]

Treatment of Thrombosis in Cancer Patients

The treatment of VTE in cancer patients aims at reducing mortality and morbidity and improving quality of life, but there are some potential problems involved – namely hemorrhagic risk, the high rate of recurrence, and difficulties related to diagnosis. Until the mid-2000s, the standard treatment for acute VTE consisted of initial therapy with low-molecular-weight heparin (LMWH) or unfractionated heparin followed by long-term therapy with an oral anticoagulant, namely vitamin K antagonists (VKAs).[24] The use of VKAs is, at present, still widespread, but these drugs are difficult to manage in oncology patients; drug interactions, malnutrition, and liver dysfunction can lead to fluctuations in the international normalized ratio (INR). Oncology patients have a higher rate of VTE recurrences during oral anticoagulant therapy with VKAs and a higher anticoagulation-associated hemorrhagic risk as compared with noncancer patients.[25] Warfarin therapy interacts with many chemotherapy agents, and INR control is difficult to achieve in cancer patients.[26,27] The frequent need for invasive techniques and coordination of warfarin therapy interruption with these procedures is notoriously challenging.[28] Finally, the association between VKAs and genetic determinants has been consistently identified. Namely, polymorphisms in the *CYP2C9* gene can interfere with initial anticoagulation control, and polymorphisms in the *VKORC1* gene can determine the eventual stable dose of warfarin. Undoubtedly, the complexities of warfarin pharmacogenetics can influence different outcomes.[29]

Dalteparin. The fist study to demonstrate that a specific LMWH, namely dalteparin, was more effective than oral anticoagulation in reducing the risk of recurrent thromboembolism in cancer patients without increasing the risk of bleeding was the CLOT study.[24] In this multicenter, randomized, open-label clinical trial, 676 adult patients with active cancer and newly diagnosed, symptomatic proximal DVT, PE, or both were assigned to receive subcutaneous dalteparin or an oral anticoagulant. The patients randomized to the dalteparin group received 200 IU of dalteparin/kg (maximal daily dose, 18,000 IU) once daily for the first month. For the remaining 5 months, patients were treated with 75%–83% of the full dose (approximately 150 IU/kg). The patients assigned to the oral-anticoagulant group received dalteparin initially for 5–7 days and a VKA, mainly warfarin, for 6 months. The primary efficacy outcome was the first episode of objectively documented, symptomatic, recurrent DVT, PE, or both during the 6-month study period. Secondary outcome events included clinically overt bleeding (both major bleeding and any bleeding) and death. The probability of recurrent thrombosis at 6 months was 9% in the dalteparin group, as compared with 17% in the oral-anticoagulant group. The hazard ratio (HR) for recurrent thromboembolism in the dalteparin group as compared with the oral-anticoagulant group was 0.48 (95% confidence interval [CI]: 0.30–0.77; $P = 0.002$) over the 6-month study period. No differences were found between groups concerning bleeding rates (14% versus 19%; $P = 0.09$) or mortality rates at 6 months (39% versus 41%; $P = 0.53$). The authors concluded that long-term self-injection of dalteparin was acceptable to patients, and it significantly reduced the risk of recurrent VTE without increasing the risk of bleeding.[24]

Enoxaparin. The evidence concerning the efficacy of enoxaparin, another LMWH, in cancer-related thrombosis came from two randomized controlled studies: the CANTHANOX[30] and ONCENOX trials.[31] In the first study, 146 patients with cancer of any type and PE or DVT were randomized to either treatment with warfarin or treatment with enoxaparin at a fixed dose of 1.5 mg/kg subcutaneously once daily for 3 months without dose adjustment. Seven patients (10.5%) assigned to receive enoxaparin experienced major hemorrhage or recurrent thromboembolism (95% CI: 4.3%–20.3%) compared with 15 patients (21.1%) assigned to receive warfarin (95% CI: 12.3%–32.4%; $P = 0.09$) (RR: 2.02; 95% CI: 0.88–4.65). No fatal bleeding was observed in patients assigned to receive enoxaparin (95% CI: 0%–5.1%), whereas 6 patients (8.0%) in the warfarin group died of bleeding

Table 1. Key trials of anticoagulation drugs in cancer patients.

REFERENCES	DRUGS	PATIENTS ENROLLED	TREATMENT PERIOD	RECURRENT VTE	HAZARD RATIO	BLEEDING (MAJOR*)
Lee et al, 2003	Dalteparin versus warfarin#	676	6 months	9% versus 17%	0.48 ($P = 0.002$)	6% versus 4% ($P = 0.27$)
Meyer et al, 2002	Enoxaparin versus warfarin	146	3 months	2.8% versus 4.0%	0.7	7% versus 16% ($P = 0.09$)
Deitcher et al, 2006	Enoxaparin versus warfarin	101	6 months	5.1% versus 10%	0.49	8.8% versus 2.9%
Hull et al, 2006	Tinzaparin versus warfarin#	200	3 months	7% versus 16% ($P = 0.04$)	0.44	0% versus 2.1%

Notes: *Major bleeding – bleeding event associated with death, occurred at a critical site (intracranial, intraspinal, intraocular, retroperitoneal, or pericardial area), resulted in a need for a transfusion of at least two units of blood, or led to a drop in hemoglobin of at least 2.0 g/dL. #Studies in which recurrent venous thromboembolisms were the primary outcomes.

(95% CI: 3.0%–16.6%; $P = 0.03$). This study highlights the difficulties related to oral anticoagulation with warfarin: even with weekly INR monitoring in the VKA group, therapeutic INR was only achieved during 41% of the treatment period – a fact probably explained by the hepatic dysfunction induced by chemotherapy and/or other medications. The authors concluded that a full dose of enoxaparin is at least as effective and may be safer than warfarin for the long-term treatment of VTE in cancer patients.[30]

In the ONCENOX trial,[31] 101 cancer patients with acute symptomatic VTE events were randomized to one of three treatments: group 1A received subcutaneous twice-daily enoxaparin (1.0 mg/kg) for 5 days, followed by once-daily enoxaparin (1.0 mg/kg) for 175 days; group 1B received subcutaneous twice-daily enoxaparin (1.0 mg/kg) for 5 days, followed by once-daily enoxaparin (1.5 mg/kg) for 175 days; and group 2 received subcutaneous twice-daily enoxaparin (1.0 mg/kg) for a minimum of 5 days until achievement of a stable INR between 2 and 3, and they started warfarin on day 2 and continued for a total of 180 days. The frequency of recurrent VTE during anticoagulant treatment was of 10.3% (three patients) in the warfarin group and 5.1% in both enoxaparin groups, without statistical significance observed between groups. The authors concluded that treatment with enoxaparin was feasible, generally well tolerated, and effective over a 180-day period in the secondary prevention of VTE in patients with active cancer.[31]

Tinzaparin. Tinzaparin sodium is a LMWH produced by enzymatic depolymerisation of unfractionated porcine heparin. In the multicenter, randomized, open-label, clinical trial, LITE,[32] 200 cancer patients with acute symptomatic proximal-vein thrombosis were treated with long-term VKA therapy or with long-term therapeutic tinzaparin subcutaneously once daily for 3 months. Outcomes were assessed at 3 months and 12 months. No significant difference was found at 3 months, but at 12 months, the group treated with VKA had an excess of recurrent VTE: 16% versus 7% ($P = 0.044$; RR = 0.44). Bleeding, largely minor, was not significantly different between groups: 27% in patients receiving tinzaparin and 24% in patients receiving warfarin.[32] The authors concluded that long-term LMWH tinzaparin is more effective than VKA therapy for preventing recurrent VTE in patients with cancer and proximal venous thrombosis.

In order to add significant data to the knowledge on the efficacy, safety, and cost-effectiveness of LMWHs in the prevention of recurrent VTE, an open-label, randomized study of tinzaparin versus warfarin is currently recruiting 900 patients with active cancer and symptomatic DVT and/or PE. In this CATCH trial,[33] tinzaparin is given at full treatment doses (175 IU/kg once daily) for 6 months in the experimental arm, and initial tinzaparin treatment for 5–10 days followed by dose-adjusted warfarin (target INR: 2.0–3.0) is given for 6 months in the control arm. The primary composite outcome is time to VTE recurrence, including incidentally diagnosed VTE and fatal PE. The trial is currently recruiting individuals from approximately 160 sites in 25 countries across four continents. It is worth mentioning that the CLOT,[24] CANTHANOX,[30] ONCENOX,[31] and LITE[32] studies did not address important questions such as postthrombotic syndrome frequency, quality of life, or LMWH monotherapy cost-effectiveness, all of which are important considerations for long-term therapy in patients with reduced life expectancy.[33]

Compared with other LMWHs, tinzaparin does not exhibit significant accumulation in patients with renal impairment, allowing for utilization without dose adjustment.[34] The difference favoring tinzaparin clearance in patients with severe renal insufficiency compared to other LMHWs is possibly related to the drug's metabolism by hepatic mechanisms due to the higher molecular weight of tinzaparin.[35,36] This is not a minor feature; indeed, abnormal renal function is a common condition in patients with malignancy.[37] According to the Renal Insufficiency and Anticancer Medications study group,[3] 50%–60% of patients with solid tumors, including the most common cancers including lung, breast, and prostate cancer, have abnormal renal function or renal insufficiency – a fact that may prove crucial when choosing the most appropriate LMHW for an individual patient.[3]

Low-molecular-weight heparins as standard of care. In 2006, Hull et al[32] published a summary of the randomized clinical trials comparing long-term LMWH treatment with VKA treatment in cancer patients with VTE. The summary treatment effect for recurrent VTE favored long-term LMWH therapy with an HR of 0.50 (95% CI: 0.33–0.72). Differences found in the bleeding rate between treatments also favored LMWHs over VKA, with an HR of 0.80 (95% CI: 0.61–1.05). The authors concluded that long-term LMWH offers an alternative strategy to usual care with VKA therapy without the need for anticoagulant monitoring, and that the improved efficacy observed in cancer patients is strongly supported by the literature and offers hope for improved quality of life, particularly in patients without additional risk factors for bleeding.[32]

The strength of these data allowed for the establishment of LMWH monotherapy (ie, dalteparin, enoxaparin, or tinzaparin) as the current standard of care for VTE treatment in oncology patients. The most important guidelines, namely from the American Society of Oncology, the European Society of Medical Oncology, the American College of Chest Physicians, and the National Cancer Comprehensive Network, all recommend LMWH-based therapy over warfarin-based therapy as the preferred VTE treatment in cancer patients.[4,25,38,39] Of note, the duration of treatment is longer in the oncology setting; a VTE in a cancer patient should be treated with a LMWH for a period between 3–6 months, but in patients receiving chemotherapy in a palliative setting or in patients achieving complete remission with a very high risk of recurrence, an indefinite course of treatment should be considered.[25] A VTE in a noncancer patient can be treated with a

VKA for 3–6 months, depending on the location of the VTE (ie, proximal versus distal DVT) and on the cause of the VTE (ie, provoked or unprovoked.

Recurrence of VTE in a cancer patient, even on LMWH treatment, is possible, and if it happens, it should alert the physician to a possible recurrence of the disease. Carrier et al[40] reported a retrospective cohort study of 70 consecutive cancer outpatients referred for the management of symptomatic, recurrent VTE while receiving an anticoagulant. At the time of recurrence, 67% of patients were receiving LMWH and 33% were receiving a VKA. Confirmed episodes of recurrent VTE were treated with either dose escalation of LMWH (increasing the weight-adjusted dose by 20%–25% for at least 4 weeks) or the initiation of a therapeutic dose of LMWH in patients who were taking a VKA. A total of six patients had a second recurrent VTE during the 3-month follow-up period. Three patients (4.3%; 95% CI: 1.5%–11.9%) experienced bleeding complications. The authors concluded that escalating the dose of LMWH can be effective for treating cases that are resistant to standard, weight-adjusted doses of LMWH.[40]

Although evidence-based treatment guidelines recommend LMWH monotherapy for cancer-associated VTE, warfarin-based treatment remains the most common strategy.[41,42] The use of LMWH monotherapy for the first-line treatment of VTE in patients with advanced-stage solid tumors in a large, geographically heterogeneous population was evaluated in a study published by Delate et al.[43] Overall, 25% of the 1,089 eligible patients received LMWH monotherapy as the primary VTE treatment. The percentage increased steadily over time, from 18% among patients diagnosed in 2000 to 31% among those diagnosed in 2007, although the majority of patients still received warfarin-based therapy across all years (74% overall). Patients who received LMWH monotherapy were younger and more likely to have been diagnosed with VTE in the latter years of the study period. Patients with nonsmall-cell lung cancer, metastatic disease, and a history of prior stroke, VTE, or invasive surgery in the 90 days following VTE diagnosis were also more likely to receive LMWH monotherapy. The authors concluded that prescribers were either unaware of VTE outpatient treatment guidelines in cancer patients, or they made a conscious decision to ignore these recommendations. Elaborating upon the reasons why a physician might choose to prescribe the warfarin-based therapy, the authors noted the prolonged use of this agent in VTE treatment, the fact that warfarin is inexpensive, the widespread anticoagulation monitoring services that result in a high level of physician comfort with this therapeutic option and patient refusal of self-injection, among others.[43] Interestingly, there is evidence that terminally ill cancer patients prefer daily LMWH injections to the rigors and uncertainties of warfarin therapy.[44]

Recently, Kleinjan et al[45] presented a similar review based on the Dutch Pharmo database and reached similar conclusions: LMWH monotherapy for the first-line treatment of PE in patients with advanced cancer increased over time from 2% in 1998 to 32% among those diagnosed in 2008. Remarkably, however, only 14% of cancer patients with PE received extended treatment with LMWH – emphasizing the urgent need for improved VTE outpatient treatment guideline adherence.[45]

Novel Oral Anticoagulants

Recently, factor-specific oral anticoagulants were developed that directly inhibit thrombin (for example, dabigatran etexilate) or factor Xa (for example, rivaroxaban, apixaban, edoxaban, or betrixaban). Unlike LMWHs and warfarin, which inhibit multiple coagulation factors, novel oral anticoagulants (NOAs) target specific clotting cascade factors; they do not require laboratory monitoring to achieve therapeutic anticoagulation, they can be taken orally in fixed doses, and they have minimal food and drug—drug interactions. NOAs do require routine safety monitoring, albeit not as frequent as is required with VKAs; their major limitation is the lack of specific antidotes to reverse the anticoagulant effect and the absence of readily available assays to measure the anticoagulant effect, which can be an issue when facing bleeding events or treatment failure.[37]

Although approved for stroke prevention in atrial fibrillation (dabigatran and rivaroxaban), orthopedic prophylaxis (dabigatran, rivaroxaban, apixaban, and edoxaban), and VTE treatment (rivaroxaban), there is almost no data available for cancer patients.[46,47] The ADVOCATE study[48] evaluated whether apixaban would be well tolerated and acceptable in cancer patients receiving chemotherapy. The rate of major bleeding in the 93 apixaban patients was 2.2% (95% CI: 0.26–7.5%). The authors concluded that these results supported further study of apixaban in Phase III trials.[48] Phase III trials in VTE treatment have included only a small number of cancer patients (less than 5% of the enrolled population) and there is no specific trial investigating the role of these agents in VTE treatment in the malignancy setting. Subgroup analyses from existing Phase III studies suggest a potential clinical benefit for NOAs that warrants further investigation; however, the small sample size precludes definitive conclusions and, therefore, should be interpreted as hypothesis-generating only. It must be kept in mind that these trials were noninferiority studies in which the comparator arm consisted primarily of VKAs. Given that we now know that LMWHs are superior to VKAs in the treatment of malignancy-associated VTE, future studies should evaluate the efficacy of NOAs in direct comparison with LMWH – an assumption that, until the present day, has not been tested.[49]

Conclusion

In conclusion, the incidence of VTE in cancer patients is higher than in the general population, and the risk of VTE relates with cancer type, stage of the disease, and patient-related factors. LMWH is the standard of care for VTE

treatment in oncology patients with a low incidence of side effects. LMWH treatment should be delivered for an extended period between 3–6 months, or even indefinitely, in the presence of active oncology disease or a very high risk of recurrence. At the present day, only a minority of cancer patients diagnosed with VTE are treated with LMWH – a fact that, according to the highest level of scientific evidence available, should be changed.

Author Contributions

Conceived the concept: MB. Analyzed the data: MB. Wrote the first draft of the manuscript: MB. Made critical revisions: MB. The author reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the author has provided signed confirmation of compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

REFERENCES

1. Khorana AA. Venous thromboembolism and prognosis in cancer. *Thromb Res*. 2010;125(6):490–3.
2. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer patients. *Cancer*. 2007;110(10):2339–46.
3. Scotté F, Rey JB, Launay-Vacher V. Thrombosis, cancer and renal insufficiency: low molecular weight heparin at the crossroads. *Support Care Cancer*. 2012;20(12):3033–42.
4. Lyman GH, Khorana AA, Falanga A, et al; American Society of Clinical Oncology. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol*. 2007;25(34):5490–505.
5. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. *Am J Med*. 2006;119(1):60–8.
6. Siegal DM, Garcia D. Anticoagulants in cancer. *J Thromb Haemost*. 2012;10(11):2230–41.
7. Khorana AA. Targeted prophylaxis in cancer: the evidence accumulates. *Intern Emerg Med*. 2013;8(3):187–9.
8. Khorana AA. Cancer and thrombosis: implications of published guidelines for clinical practice. *Ann Oncol*. 2009;20(10):1619–30.
9. Lyman GH. Venous thromboembolism in the patient with cancer: focus on burden of disease and benefits of thromboprophylaxis. *Cancer*. 2011;117(7):1334–49.
10. Wun T, White RH. Epidemiology of cancer-related venous thromboembolism. *Best Pract Res Clin Haematol*. 2009;22(1):9–23.
11. Hall IE, Andersen MS, Krumholz HM, Gross CP. Predictors of venous thromboembolism in patients with advanced common solid cancers. *J Cancer Epidemiol*. 2009;2009:182521.
12. Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. *J Clin Oncol*. 1991;9(2):286–94.
13. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst*. 2007;99(16):1232–9.
14. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA*. 2008;300(19):2277–85.
15. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst*. 2006;98(10):708–14.
16. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *J Clin Oncol*. 2003;21(19):3665–75.
17. Evans RS, Sharp JH, Linford LH, et al. Risk of symptomatic DVT associated with peripherally inserted central catheters. *Chest*. 2010;138(4):803–10.
18. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood*. 2010;116(24):5377–82.
19. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. *Medicine (Baltimore)*. 1999;78(5):285–91.
20. Sørensen HT, Mellemkjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med*. 2000;343(25):1846–50.
21. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*. 2006;166(4):458–64.
22. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. *Br J Cancer*. 2010;102 Suppl 1:S2–S9.
23. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood*. 2002;100(10):3484–8.
24. Lee AY, Levine MN, Baker RI, et al. Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349(2):146–53.
25. Mandalà M, Falanga A, Roila F; ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2011;22 Suppl 6:vi85–vi92.
26. Masci G, Magagnoli M, Zucali PA, et al. Minidose warfarin prophylaxis for catheter-associated thrombosis in cancer patients: can it be safely associated with fluorouracil-based chemotherapy? *J Clin Oncol*. 2003;21(4):736–9.
27. Hill RR, Martinez KD, Delate T, Witt DM. A descriptive evaluation of warfarin use in patients receiving hospice or palliative care services. *J Thromb Thrombolysis*. 2009;27(3):334–9.
28. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):454S–545S.
29. Jorgensen AL, Al-Zubiedi S, Zhang JE, et al. Genetic and environmental factors determining clinical outcomes and cost of warfarin therapy: a prospective study. *Pharmacogenet Genomics*. 2009;19(10):800–12.
30. Meyer G, Marjanovic Z, Valcke J, et al. 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*. 2002;162(15):1729–35.
31. Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J. ONCENOX Investigators. 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*. 2006;12(4):389–96.
32. Hull RD, Pineo GF, Brant RF, et al. LITE Trial Investigators. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med*. 2006;119(12):1062–72.
33. Lee AY, Bauersachs R, Janas MS, et al. CATCH: a randomised clinical trial comparing long-term tinzaparin versus warfarin for treatment of acute venous thromboembolism in cancer patients. *BMC Cancer*. 2013;13(1):284.
34. Mousa SA, Petersen LJ. Anti-cancer properties of low-molecular-weight heparin: preclinical evidence. *Thromb Haemost*. 2009;102(2):258–67.
35. Garcia DA, Baglin TP, Weitz JI, Samama MM. American College of Chest Physicians. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e24S-43S.
36. Johansen KB, Balchen T. Tinzaparin and other low-molecular-weight heparins: what is the evidence for differential dependence on renal clearance? *Exp Hematol Oncol*. 2013;2(1):21.
37. Lee AY. Treatment of established thrombotic events in patients with cancer. *Thromb Res*. 2012;129 Suppl 1:S146–S153.
38. Kearon C, Akl EA, Comerota AJ, et al. American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e419S—e494S.
39. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Venous Thromboembolism Disease version 2. 2013. Accessed September 20, 2013. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#supportive.
40. Carrier M, Le Gal G, Cho R, Tierney S, Rodger M, Lee AY. Dose escalation of low molecular weight heparin to manage recurrent venous thromboembolic events despite systemic anticoagulation in cancer patients. *J Thromb Haemost*. 2009;7(5):760–5.

41. Imberti D, Agnelli G, Ageno W, et al; MASTER Investigators. Clinical characteristics and management of cancer-associated acute venous thromboembolism: findings from the MASTER Registry. *Haematologica*. 2008;93(2):273–8.
42. Wittkowsky AK. Barriers to the long-term use of low-molecular weight heparins for treatment of cancer-associated thrombosis. *J Thromb Haemost*. 2006;4(9):2090–1.
43. Delate T, Witt DM, Ritzwoller D, et al. Outpatient use of low molecular weight heparin monotherapy for first-line treatment of venous thromboembolism in advanced cancer. *Oncologist*. 2012;17(3):419–27.
44. Noble SI, Nelson A, Turner C, Finlay IG. Acceptability of low molecular weight heparin thromboprophylaxis for inpatients receiving palliative care: qualitative study. *BMJ*. 2006;332(7541):577–80.
45. Kleinjan AH, Di Nisio M, Kamphuisen PW. Anticoagulant treatment of cancer patients with pulmonary embolism in the real world. Presented at XXIV International Society on Thrombosis and Haemostasis Congress June 29-July 4, 2013, Amsterdam.; Abstract.
46. Bauersachs R, Berkowitz SD, Brenner B, et al. EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499–510.
47. Schulman S, Kearon C, Kakkar AK, et al. RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342–52.
48. Levine MN, Gu C, Liebman HA, et al. A randomized phase II trial of apixaban for the prevention of thromboembolism in patients with metastatic cancer. *J Thromb Haemost*. 2012;10(5):807–14.
49. Martin LK, Bekaii-Saab T. Management of venous thromboembolism in patients with advanced gastrointestinal cancers: what is the role of novel oral anticoagulants? *Thrombosis*. 2012;2012:758385.