REVIEW ARTICLE

Vitamin K antagonists in anticoagulant therapy of patients with cancer

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KEY WORDS

anticoagulant therapy, antivitamins K, cancer, low-molecular weight heparin

ABSTRACT

Venous thromboembolism (VTE) is a common complication of cancer. Prolonged use of low-molecular-weight heparin in cancer patients provides better VTE prophylaxis compared with vitamin K antagonists. Both therapeutic options have a similar safety profile. If patients on long-term oral anticoagulation are diagnosed with cancer, they should continue treatment with vitamin K antagonists.

Armand Trousseau, one of the "founding fathers" of modern clinical medicine, was perhaps the first to recognize, in 1865, the association of abdominal cancer with superficial vein thrombosis, and 2 years later he diagnosed himself with this syndrome. Since then, there has been extensive research on to cancer-related venous thromboembolism (CRVTE). The factors determining CRVTE have been well summarized recently (TABLE 1).[1,2] Malignancy is associated with a 7-fold higher overall risk of venous thromboembolism compared with individuals free of cancer.[3] The highest risk of venous thrombosis is observed in the first few months after the diagnosis of malignancy (adjusted odds ratio [OR], 53.5; 95% confidence interval [CI], 8.6–334.3).[3] The risk was higher in patients with cancer with distant metastases compared with patients without distant metastases (adjusted OR, 19.8; 95% CI, 2.6–149.1).[3] The thrombotic risk of cancer is considerably increased with the presence of the factor V Leiden mutation.[3]

The prevalence of CRVTE is difficult to estimate because most cases are asymptomatic. Fatal pulmonary embolism was revealed in cancer patients in 33% to 45.5% of autopsy studies before thromboprophylaxis was prevalent.[4] Currently, venous thrombosis is responsible for 46.3% of postoperative deaths in cancer patients.[5]

The incidence of symptomatic CRVTE in various cancer registries ranges from 1% to 13%.[6-9] In the cohort of 66,329 cancer patients, the highest risk was associated with bone, ovary, brain, and pancreatic cancer (7.54%, 6.52%, 6.42%, and 4.54% per year, respectively).[6] Among outpatients of the Sloan Kettering Memorial Cancer Center, independent risk factors for CRVTE were gastroesophageal cancer (hazard ratio [HR], 2.76 [1.41–5.38]; P = 0.003), pancreatic cancer (HR, 2.26 [1.06–4.80]; P = 0.05), use of white cell growth factors (HR, 1.69 [1.09–2.64]; P = 0.02), and irinotecan therapy (HR, 1.89 [1.29–3.59]; P = 0.05).[9]

The significance of CRVTE will be even greater considering longer survival of cancer patients possible due to modern cancer therapy,[11] which, on the other hand, also contributes to CRVTE (TABLE 2). In a large cohort of patients with breast cancer, the risk of pulmonary embolism was 2- to 3-fold higher before hospitalization, 23.5-fold higher during hospitalization, and was still 3.6 times higher 12 months after hospitalization.[10]

Khorana et al.[12] proposed and validated a multivariate risk model to predict the risk of CRVTE[12] in cancer patients undergoing chemotherapy (TABLE 3).

CVRTE is an independent predictor of a poor prognosis in this vulnerable population. The Analysis of the Danish Cancer Registry revealed that a 1-year survival rate after the incidence of CRVTE was 12%, compared with 36% in cancer patients without this complication (P <0.001).[6] In the California Cancer Registry, CRVTE contributed to the relative risk (RR) of death by 3.7.[7]

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TABLE 1 Determinants of cancer-related venous thromboembolism

tissue factor released by malignant cells
microparticles of tumor origin
platelet activation by tumor cells

Multiple trials confirmed the benefits of long-term anticoagulant prophylaxis in patients with CRVTE. The pivotal CLOT trial (Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) compared low-molecular-weight heparin (LMWH) – dalteparin – with vitamin K antagonists (VKAs), within 6 months of the secondary VTE prevention in patients with cancer. The trial showed a 49% RR reduction of recurrent deep-vein thrombosis (DVT) with dalteparin compared with VKA.[13] Major bleeding occurred in 6% of the patients in the dalteparin group and in 4% of the patients in the VKA group (any bleeding in 14% and 19%, respectively; both comparisons were statistically nonsignificant).[13]

The comparison of LMWH with VKA as long-term prophylaxis after CRVTE was the subject of a recent Cochrane meta-analysis that included 7 randomized clinical trials. The overall result was that LMWH, compared with VKA, provided no statistically significant survival benefit (HR, 0.96; 95% CI, 0.81–1.14) but a statistically significant reduction in VTE recurrence (HR, 0.47; 95% CI, 0.32–0.71).[14] The authors concluded that selection of an anticoagulant for a long-tem treatment of VTE is ambiguous and should include the patient's preferences.[14]

These doubts were not taken into account by the authors of all current guidelines, including the American College of Chest Physicians, who unanimously recommend treatment of CRVTE with LMWH for at least 6 months and continuation of a not specified anticoagulant therapy indefinitely or until the cancer is cured.[15-17]

For the delivery of chemotherapeutics, most patients with cancer need central vein catheter. Its presence is associated with frequent thrombosis.

TABLE 2 Cancer drugs that carry the risk of cancer-related venous thromboembolism (adapted from Haddad TC and Greeno EW[11])

l-asparaginase
thalidomide, lenalidomide
anti-EGF, i.e., bevacizumab
bleomycin
carmustine
irinotecan
5-fluorouacil
vinca alcaloids
Tamoxifen
erythropoietin and darbopoetin
GSF

Abbreviations: EGF – epidermal growth factor, GSF – granulopoiesis-stimulating factor

No benefit of prophylactic anticoagulation either with LMWH or VKAs in central vein catheters in cancer patients has been proved so far.[18,19]

There have been numerous reports on increased risk of bleeding in patients with active cancer treated with VKAs.[20-25] Cancer itself is responsible for the increased risk of bleeding (TABLE 4), but the risk may be amplified by VKAs. In the Dutch cohort of patients treated with VKAs, the risk of bleeding was higher in cancer patients compared with those without cancer (13.3% vs. 2.1%, respectively, per 100 patient-years).[24] Frequent bleedings were noted in cancer patients even at the international normalized ratio (INR) below 2.0. It may be difficult to establish the therapeutic INR range in this patient group because of changes in diet, malabsorption, liver dysfunction, etc. Bona et al.[21] observed that therapeutic INR values are more difficult to obtain in cancer patients compared with noncancer patients (TTR 43.3% vs. 56.9%, P <0.0001).[21] Cancer patients required monitoring more often than noncancer patients (4.6 vs. 3.5 visits per treatment month; P <0.005).[21] Bleeding complications were often temporary and related to the initiation of cancer therapy.[22] In a large Italian registry of anticoagulated patients (20% treated with VKA), active

TABLE 3 Risk score for chemotherapy-related venous thromboembolism (adapted from Khorana et al.[12])

Variable		Score
site of primary cancer		
– very high risk (stomach, pancreas)		2
– high risk (lung, lymphoma, gynecologic, bladder, testicular cancers)		1
prechemotherapy platelet count ≥350 × 10^9/l		1
hemoglobin level <10 g/dl or use of red cell growth factor		1
body mass index ≥35 kg/m^2		1
prechemotherapy leukocyte count >11 × 10^9/l		1
Score	**Risk category**	**Risk of symptomatic venous thromboembolism, %**
0	low	0.3–0.8
1–2	intermediate	1.8–2.0
≥3	high	6.7–7.1

TABLE 4 Determinants of high bleeding risk in cancer patients

thrombocytopenia
enhanced tumor-induced fibrinolysis
increase in international normalized ratio due to interaction of warfarin with chemotherapeutics such as cisplatin
involvement of blood vessels in the cancer spread

cancer increased the risk of bleeding 4-fold.[20] In the RIETE registry, which included only patients with DVT, cancer increased the risk of bleeding 1.8-fold.[23] Increased 12-month cumulative incidence of major bleeding was higher in patients with DVT and cancer than in patients without cancer (12.4% vs. 4.9%).[20] Bleeding was related to cancer severity and occurred predominantly during the first month of anticoagulant therapy. It could not be explained by overanticoagulation, and was associated with the extent of cancer.[20] The Cochrane Collaboration did not find any differences between LMWH and VKAs in patients with cancer in terms of the risk of major bleeding (RR, 1.05; 95% CI, 0.53–20).[14]

Contemporary large registries of the populations of patients treated with VKAs, who mostly received the drug because of atrial fibrillation (AF), did not confirm that cancer is an independent risk factor for bleeding.[26-30] Furthermore, cancer was not included in the HASBLED bleeding score endorsed by the European Society of Cardiology.[30,31]

Of note, LWMH is not recommended for long-term thromboembolism prophylaxis in AF. It may be given only for the brief interruption of VKA therapy (i.e., perioperatively).[31] There are perhaps justified concerns about the long-term safety of LMWH because of the risk of type 2 heparin-induced thrombocytopenia (HIT). The incidence of HIT among inpatients with active cancer treated with LMWH was only 0.25%, and active cancer was not reported to be a significant risk factor for HIT.[28] In the Cochrane Collaboration, the risk of thrombocytopenia during treatment with LWMH was similar to that observed during administration of VKAs (RR, 1.02; 95% CI, 0.60–1.74).[14]

New oral anticoagulants, direct thrombin and activated coagulation factor X inhibitors, are now available for treatment of VTE, but evidence on their role in the treatment of CRVTE is scarce. The RE-COVER Study, which compared direct thrombin inhibitor, dabigatran, with warfarin in the treatment of DVT included only 4.8% of cancer patients.[29] Cancer was present in 6% of the participants in the EINSTEIN trial, in which active factor Xa inhibitor, rivoraxaban, was compared with warfarin in the treatment of VTE.[30] In both studies, new anticoagulant drugs proved to be more effective and as save as warfarin, although detailed data on the subgroups with cancer are not available yet.

In summary, cancer patients who develop VTE can be treated with VKAs and LMWH. The latter is more effective in reducing thromboembolic complications without prolonging overall survival. Risk of bleeding does not differ between the two therapies. Anticoagulant therapy should take at least 6 months. Patients treated with VKA for cardiac causes, such as AF or prosthetic heart valves, when diagnosed with cancer should continue to receive VKAs, with the exception of major surgery when VKA withdrawal with LWMH bridging therapy in high-risk patients is recommended.

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ARTYKUŁ POGLĄDOWY

Antywitaminy K w leczeniu przeciwkrzepliwym chorych na raka

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antywitaminy K, heparyna drobnocząsteczkowa, leki przeciwkrzepliwe, rak, żylna choroba zakrzepowo-zatorowa

STRESZCZENIE

Żylna choroba zakrzepowo-zatorowa (ŻChZZ) jest częstym powikłaniem choroby nowotworowej. Przedłużone stosowanie heparyn drobnocząsteczkowych u chorych na nowotwory złośliwe lepiej chroni przed nawrotem ŻChZZ niż leczenie antywitaminami K. Obie metody leczenia są w tej populacji chorych równie bezpieczne. Chorzy leczeni przewlekle antywitaminami K powinni w razie rozpoznania raka kontynuować to leczenie.

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