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Management of recurrent venous thromboembolism in cancer patients

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KEYWORDS

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ABSTRACT

Cancer is one the most prevalent risk factors in patients diagnosed with deep vein thrombosis or pulmonary embolism. Patients with cancer and venous thromboembolism have a higher risk of mortality when compared to patients with cancer without venous thromboembolism and a higher risk of recurrent thrombosis when compared with patients with venous thromboembolism without cancer. This increased risk of recurrence is not only observed after anticoagulant treatment is stopped, but also during anticoagulant treatment. Clinical trials have shown that the use of low molecular weight heparin during the first three to six months after venous thrombosis in patients with cancer is associated with a significantly lower risk of recurrence than the use of vitamin K antagonists and, thus, low molecular weight heparin is currently recommended as the treatment of choice by international guidelines. Unfortunately, the optimal management of recurrent venous thromboembolism during anticoagulant treatment remains poorly defined. In general, patients should firstly be assessed for treatment compliance, for the occurrence of heparin-induced thrombocytopenia, and for the presence of mechanical compression from tumour masses. Possible strategies include switching to a different anticoagulant drug, in particular from vitamin K antagonists to low molecular weight heparin; increasing the dose of the anticoagulant drug; or inserting an inferior vena cava filter. The results of recent registries show that the current approach to cancer patients with recurrent venous thromboembolism in routine clinical practice is highly heterogeneous.

The risk of recurrent venous thromboembolism in cancer patients and recommended therapeutic strategies

The association between cancer and venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is well established. VTE is reported to occur in up to 20% of patients with cancer [1]. The occurrence of VTE in patients with cancer is associated with a shorter overall survival than in cancer patients without VTE, even after matching for tumor stage and anti-neoplastic treatment [2]. In addition, patients with VTE associated with cancer are at a higher risk for recurrent venous thromboembolism than patients with VTE without cancer not only after anticoagulant treatment has been stopped, but also during anticoagulation. This increased risk may be related to the release of procoagulants by tumor cells that could make patients with cancer resistant to the usual intensities of anticoagulant drugs [3-5].

This higher risk of recurrent events in patients with cancer was reported nearly 20 years ago, by the Columbus study investigators [6]. In this study that compared low molecular weight heparin (LMWH) with unfractionated heparin (UFH) for the initial treatment of VTE, 8.6% of patients with cancer had symptomatic recurrent VTE as compared to 4.1% of patients without cancer (p=0.009) [6]. Subsequently, other studies have assessed the incidence of recurrent thrombosis during anticoagulation in cancer patients. In a study aimed at assessing factors associated with recurrent VTE during the first 3 months of anticoagulant therapy in a cohort of 1021 patients affected by VTE, cancer was independently associated with recurrence at multivariate analysis (odds ratio [OR] 2.72: 95% confidence intervals [CI] 1.39-5.32) and resulted as the strongest risk factor for recurrent VTE [7].

In a retrospective cohort study of 1303 patients on vitamin K antagonists (VKAs) for the secondary prevention of VTE, the risk of both recurrent VTE and bleeding complications was significantly higher in patients with cancer than in patients without cancer (27.1 vs 9.0 per 100 patient-years and 13.3 vs 2.1 per 100 patient-years, respectively) [8]. In a prospective study of patients treated with warfarin, the rate of VTE recurrence was approximately six fold higher in patients with cancer compared with patients without cancer (1.2% vs 0.2% per treatment month) [9]. In the large Italian Study on Complications of Oral Anticoagulant Treatment (ISCOAT), patients with cancer had a higher rate of VTE recurrence compared with patients without cancer, although this difference was not statistically significant (6.8% vs. 2.7%, respectively; p=0.058). In patients with cancer, the relative risk (RR) for thrombosis recurrence with an INR of less than 2.0 compared with an INR of greater than 2.0 was 5.2 (CI 1.0 to 25.6; p<0.05), whereas in patients without cancer this RR was 3.0 (CI 1.5 to 6.0; p<0.01) [10]. Finally, Prandoni

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and colleagues reported on a large cohort of patients (842 patients, 181 with cancer) with a first episode of VTE who were treated with an initial course of intravenous standard heparin or weight-adjusted LMWH followed by warfarin started during the first week and continued for a period of at least 3 months [11]. They found that the 12-month cumulative incidence of recurrent thromboembolism was 20.7% (95% CI, 15.6-25.8%) in cancer patients versus 6.8% (95% CI, 3.9-9.7%) in patients without cancer. At the time of recurrence, the level of anticoagulation was within or above the therapeutic range in a higher number of patients with cancer (83.3%) than without cancer (57.6%). The frequency of recurrent VTE per 100 patient-years was 54.1 in patients with extensive neoplastic disease, 44.1 in patients with moderately extensive disease, and 14.5 in patients with less extensive disease. Compared to the rate observed in patients without cancer, the hazard ratios (HR) for recurrent VTE according to the severity of disease in patients with cancer were 4.6 (95% CI, 2.3-9.0), 5.3 (95% CI, 2.5-10.9), and 1.9 (95% CI, 0.8-4.2), respectively [11].

Given the high risk of VTE-recurrence during VKA therapy in cancer patient and in the light of the several management issues with the use of VKAs in this setting due to drug-drug interactions, malnutrition, vomiting, liver dysfunction, but also the need for invasive procedures and chemotherapy-induced thrombocytopenia, a number of clinical trials tested LMWH as an alternative treatment during the first 3 to 6 months after VTE [8]. Despite the inconvenience of the subcutaneous administration, LMWH has potential advantages over VKA including the more predictable pharmacokinetic properties and the weight adjusted dosage with no need for laboratory monitoring [12]. In the CLOT study, the authors compared dalteparin, administered at the full therapeutic dose for one month followed by 75% of the initial dose for additional 5 months, with VKA (warfarin or acenocoumarol) for the prevention of recurrent thrombosis in 676 patients with acute VTE and active cancer [13]. The incidence of recurrent thrombosis at six months was 9% in the dalteparin group and 17% in the control group, with a HR of 0.48, 95% CIs 0.30-0.77 [13]. In a meta-analysis of published randomized controlled trials comparing LMWH with VKA for the treatment and secondary prevention of VTE in patients with cancer, recurrent VTE was reduced by the use of LMWH by 53% (HR 0.47; 95% CI 0.32-0.71), without significant differences in major bleeding (RR 1.07; 95% CI 0.52-2.19) and mortality (HR 0.96; 95% CI 0.81-1.14) [14].

More recently, the LMWH tinzaparin was compared with VKA in the CATCH study, the largest randomized controlled trial in this setting [15]. In this study, the 6-month cumulative incidence of recurrence was 7.2% for tinzaparin vs 10.5% for warfarin (HR 0.65, 95% CI 0.41-1.03), while major bleeding rates were similar between the two groups [15].

Current guidelines from different scientific societies recommend LMWH as the treatment of choice for the first 3 to 6 months of anticoagulation, with UFH as an alternative [16-18]. The use of fondaparinux is also suggested, but with a lower level of evidence [16].

This recommendation is due to the fact that in all published randomized controlled trials, patients were treated for a maximum of 6 months. However, in most cases patients with active cancer need to continue their therapy beyond this period. The DALTECAN study was a multicentre, prospective cohort study aimed to assess the safety of dalteparin administered for up to 12 months after cancer-associated VTE [19]. The overall frequency of major bleeding was 10.2%, with a decreasing incidence over the 12 months (3.6% during the first month, 1.1% per patient-month during months 2 to 6, and 0.7% per patient-month during months 7 to 12). The incidence of VTE was as high as 11.1% despite active treatment over the entire treatment period, but it dropped from 9.1% during the first 6 months to around 4% thereafter. [19]. In the Cancer-DACUS study, all patients with DVT who received LMWH for 6 months underwent compression ultrasound to detect the presence of residual vein thrombosis [20]. Patients with residual vein thrombosis were then randomized to continue LMWH for an additional 6 months or to discontinue it. All patients without residual thrombosis discontinued treatment. Recurrence rates were 11.3 per 100 patient-years in patients who continued on LMWH and 26.7 per 11 patient-years in those with residual vein occlusion who stopped treatment. These rates were significantly lower in patients without residual vein obstruction (3.0 per 100 patient-years). Thus, the optimal therapeutic strategies for the long-term secondary prevention of VTE in patients with cancer are not sufficiently established, but in most patients the risk of recurrence remains high.

Management of recurrent VTE during anticoagulant treatment

Given the high risk of recurrence during anticoagulant treatment faced by patients with cancer, the application of adequate management strategies in these challenging circumstances becomes crucial. Unfortunately, the optimal management of recurrent VTE during anticoagulant therapy in cancer patients is poorly defined. In the absence of solid evidence, suggested approaches are based on expert opinions. In general, patients should firstly be assessed for treatment compliance, for the occurrence of heparin-induced thrombocytopenia, and for the presence of mechanical compression from tumour masses. Therapeutic management options then include the administration of higher doses of the ongoing treatment or the switch to a different anticoagulant agent. The guidelines of the American Society of Clinical Oncology suggest treatment with an alternative anticoagulant, increasing the dose of LMWH, or the insertion of a vena cava filter [17]. The Italian Society for Haemostasis and Thrombosis suggested as an alternative option the possible use of subcutaneous unfractionated heparin adjusted according to the activated partial thromboplastin time [21]. In another guidance document, the authors suggested a switch from VKA to LMWH or, in case of patients already treated with LMWH, an escalation of dosage [16]. Finally, in 2013 an international consensus working group of experts suggested three options, switching from VKA to LMWH in patients treated with VKA, increasing LMWH dose in patients treated with LMWH, or inserting a vena cava filter [22].

There are only few studies that have described the management of recurrent VTE in cancer patients in clinical practice and have reported on clinical outcomes thereafter. In a retrospective cohort study of 70 cancer patients with VTE recurrence while receiving anticoagulant treatment, 67% of patients were receiving LMWH and 33% were receiving a VKA at the time of the recurrence [23]. VTE recurrence was treated with either the initiation of LMWH treatment at a therapeutic dose in patients who were on VKA or with dose escalation of LMWH in patients already receiving LMWH, from subtherapeutic to therapeutic dose or from therapeutic dose to about 120% of the initial dose. All patients were followed-up for a minimum of 3 months after the diagnosis of recurrent VTE. During follow-up, the incidence of further recurrence was 9.9% per 100 patient-years, with a median survival rate or 11.4 months [23].

The International Society on Thrombosis and Haemostasis (ISTH) promoted an international registry aimed at exploring the different antithrombotic regimens used to manage patients with cancer and VTE during anticoagulation and the incidence of further recurrences of VTE and bleeding on these regimens [24]. Eligible patients were those with active cancer who developed an objectively verified recurrent venous thromboembolic event while receiving anticoagulant treatment with unfractionated heparin, LMWH, fondaparinux or a VKA. A total of 212 patients were followed-up for a maximum of 3 months. Most common sites of cancer were genito-urinary (24%), lung (21%), and colorectal (17%); in 59% of patients the cancer type was adenocarcinoma and in 73% of patients