Thrombosis Research 164 (2018) S172–S177

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Management of recurrent venous thromboembolism in patients with cancer: A review

Siavash Piran, Sam Schulman*

Department of Medicine, Division of Hematology and Thromboembolism, Thrombosis and Atherosclerosis Research Institute, McMaster University, Canada

ARTICLE INFO

Keywords:
Venous thromboembolism
Anticoagulation
Cancer
Recurrence

ABSTRACT

Venous thromboembolism (VTE) occurs in 10–20%% of patients with cancer and is associated with significant mortality and morbidity in these patients. The current standard of care recommended by international guidelines is to use low-molecular-weight heparin (LMWH) for 6 months for the management of cancer-associated thrombosis (CAT), which is based on evidence from randomized controlled trials demonstrating that LMWH significantly reduced the risk of recurrent VTE compared with vitamin K antagonists. However, patients with CAT have a high risk of VTE recurrence of up to 20% despite receiving anticoagulation. Reasons for recurrent VTE may include non-compliance, temporary cessation of therapy due to bleeding or for procedures, inadequate dosing, cancer progression, and the presence of heparin-induced thrombocytopenia. Management of patients with CAT and recurrent VTE is not well defined. Management strategies for recurrent VTE include switching to LMWH if an oral anticoagulant is employed, dose escalation of LMWH, or as a last resort option consider insertion of a vena cava filter. In this review, we discuss the acute, long-term, and extended management of CAT, risk factors for recurrent VTE, and management of recurrent VTE.

1. Introduction

Patients with cancer have 4–7 fold higher risk of having venous thromboembolism (VTE) compared with the general population [1–2]. Patients with cancer-associated thrombosis (CAT) have a higher mortality rate than those with VTE without cancer [3–4]. Furthermore, VTE is the second leading cause of mortality in patients with cancer [5] and is a significant predictor of reduced survival within 1 year for all cancer types [6]. Therefore, treatment of VTE is vital in this high-risk population.

The aim of this review is to (1) summarize the evidence on treatment of CAT, (2) describe the potential risk factor for recurrent VTE in patients with CAT, and (3) review the possible management strategies of recurrent VTE.

2. Management of cancer-associated thrombosis

Management of CAT is divided into three phases of acute, long-term, and extended treatment (> 6 months). In early 2000's, two randomized controlled trials (RCTs), the CLOT trial and the CANTHANOX trial, compared low-molecular-weight heparin (LMWH) to vitamin K antagonists (VKAs) for the acute and long-term treatment of CAT [7–8]. The CANTHANOX trial compared treatment with enoxaparin or warfarin for 3 months in 146 patients with CAT [7]. There was no significant difference in the combined outcome of recurrent VTE or major bleeding (21% versus 10.5% for warfarin versus enoxaparin, respectively) [7]. However, there were significantly more cases of fatal major bleeding in the warfarin group compared with the enoxaparin group (6% versus 0%) [7]. The CLOT trial was a multi-center randomized trial of 672 patients with CAT that compared 6 months of therapy with warfarin with dalteparin [8]. Dalteparin significantly reduced the incidence of recurrent VTE by 52% compared with VKA (dalteparin 9% versus warfarin 17%; hazard ratio (HR), 0.48, 95% confidence interval (CI), 0.30–0.77) [8]. There were no significant differences in rates of major bleeding or mortality between the two groups [8]. Since the early 2000's, 3 major RCTs have compared LMWH with warfarin for treatment of CAT: one trial showed a trend towards reduction in rate of recurrent VTE at 3 months, a significant reduction in rate of recurrent VTE at 12 months, and no difference in bleeding or mortality [9]; one showed no difference in any outcome [10]; and the 2015 CATCH trial of 900 patients with CAT showed a non-significant reduction in incidence of recurrent VTE with no significant difference in major bleeding or mortality but a lower rate of clinically relevant non-major bleeding in patients who received LMWH [11]. The details of these 5 trials are listed in Table 1. A 2014 meta-analysis of RCTs involving 1908 patients with CAT reported that long-term treatment with

* Corresponding author at: Thrombosis Service, McMaster Clinic, HHS - General Hospital, 237, Barton Street East, Hamilton, ON L8L 2X2, Canada.
E-mail address: schulms@mcmaster.ca (S. Schulman).

https://doi.org/10.1016/j.thromres.2017.12.019
Received 24 November 2017; Accepted 28 December 2017

Table 1
Low-molecular weight heparin versus vitamin K antagonists for treatment of VTE in cancer patients in randomized controlled trials.

Trial	CANTHANOX [9]	CLOT [10]	LITE [11]	ONCENOX [12]	CATCH [13]
Number of patients	146	676	200	122	900
LMWH type and dose	Enoxaparin 1.5 mg/kg OD for 3 months	Dalteparin 200 IU/kg OD for one month then 150 IU/kg OD for 5 months (total of 6 months)	Tinzaparin 175 IU/kg OD for 3 months	Enoxaparin 1 mg/kg BID for 5 days then enoxaparin 1 mg/kg or 1.5 mg/kg OD for a total of 6 months	Tinzaparin 175 IU/kg OD for 6 months
Recurrent VTE LMWH versus VKA (N; %)	2/71 (2.8) vs 3/75 (4)	27/336 (8)[a] vs 53/336 (15.8)	3 months: 6/100 (6) vs 10/100 (10); 12 months: 7/100 (7) vs 16/100 (16)[a]	Enoxaparin 1 mg vs 1.5 mg vs VKA: 2/29 (6.9) vs 2/32 (6.3) vs 3/30 (10)	31/449 (6.9) vs 45/451 (10)
Major bleeding LMWH versus VKA (N; %)	5/71 (7) vs 12/75 (16)	19/338 (5.6) vs 12/335 (3.6)	7/100 (7) for both groups	Enoxaparin 1 mg vs 1.5 mg vs VKA: 2/31(6.5) vs 4/36 (11.1) vs 1/34 (2.9)	12/449 (2.7) vs 11/451 (2.4)

BID, twice daily; LMWH, low-molecular weight heparin; N, number; OD, once daily; VKA: vitamin K antagonist; VTE, venous thromboembolism.
[a] Statistically significant difference between the two groups.

LMWH compared with VKAs significantly reduced the rate of recurrent VTE by 53% (HR 0.47, 95% CI 0.32–0.71) [12]. There was no difference in mortality or major bleeding [12].

Treatment duration in these 5 trials was limited to 6 months of therapy; however, cancer patients often receive extended anticoagulation if there is evidence of active disease or ongoing cancer treatment. The DALTECAN study examined the safety of extending treatment with dalteparin in 334 patients with CAT for 12 months [13]. Recurrent VTE occurred in 37 of 334 patients (11.1%): the rate was the highest in the first month (5.7%), 3.4% for months 2–6, and 4.1% for months 7–12 [13]. Similarly, the rate of major bleeding was the highest in the first month (3.6%) and declined in months 2–6 (1.1%) and 7–12 (0.7%) [13]. The recently published TiCAT study also examined the safety of extended treatment with tinzaparin in 247 patients with CAT for 12 months [14]. Recurrent VTE occurred in 13 of 247 patients (5.3%): incidence was 4.5% for months 1–6 and 1.1% for months 7–12 [14]. Major bleeding occurred in 12 of 247 patients (4.9%): the rate was 2.8% for months 1–6 and 2.1% for months 7–12 [14]. Based on the results of the DALRECAN and TiCAN studies, extended treatment with LMWH seems safe, although the available data is only up to 12 months.

Society guidelines issued by the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) recommend using LMWH for the acute and long-term management of CAT, and continuing anticoagulation if cancer is active, there is high risk of recurrence, or in the setting of ongoing cancer treatment [15–18]. Of these 4 guidelines, only the ESMO guidelines suggest dose reduction to 75–80% during the long-term management [18]. It might be reasonable to consider full dose LMWH in patients at high risk of VTE recurrence (see below for section on VTE recurrence risk factors).

3. Risk factors for recurrent venous thromboembolism

The risk of recurrent VTE in cancer patients can be up to 20% despite therapeutic anticoagulation [8,19], which is associated with increased morbidity and mortality [20–21]. Risk factors for recurrence identified in the RIETE registry of 3805 cancer patients were younger (< 65 years old), pulmonary embolism (PE) at study entry, and newly diagnosed cancer (< 3 months) [22]. Other risk factors identified include cancer site (brain, lung, myeloproliferative neoplasms or myelodysplastic disorders, ovarian cancer, stage IV pancreatic cancer), cancer stage (other stage IV cancer, cancer progression, metastatic disease), and histology (adenocarcinoma type) as risk factors for VTE recurrence [20,23]. Furthermore, in a recently published large population-based cohort study, 733 patients with an initial VTE (110 had overt cancer and 40 had occult cancer) were followed for a median of 3.2 years for recurrent events [24]. The authors reported that patients with occult-cancer related first VTE had the highest risk of recurrence (HR 12.4, 95% CI 5.9–26.3), followed by patients with overt cancer (HR 4.3, 95% CI 2–9.2) than patients with no cancer [24]. The high recurrence rate in those with occult-cancer related VTE recurrence may have been related to the cancer site (lung and gastrointestinal) and the cancer stage (advanced stage), and most of the recurrences occurred shortly after the cancer diagnosis [24].

Although most clinicians do not routinely perform an ultrasound at the end of treatment of a cancer-associated deep vein thrombosis (DVT) and management is mainly guided by symptoms, a study of 347 patients with DVT (DACUS-cancer) who were treated for 6 months with LMWH reported that those that had no residual vein thrombosis (RVT) on ultrasound had a significantly lower risk of VTE recurrence compared to those with RVT while off of anticoagulation at one year (2.8% versus 21.9%) [25]. Extended treatment with LMWH for up to 1 year in those with RVT did not significantly reduce the rate of VTE recurrence [25].

An Ottawa risk stratification model was developed by Louzada et al. determine the risk of VTE recurrence in cancer patients as low and high