Thrombosis Research 164 (2018) S124–S129

Contents lists available at ScienceDirect

Thrombosis Research

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

Full Length Article

Apixaban for the prevention of venous thromboembolism in high-risk ambulatory cancer patients receiving chemotherapy: Rational and design of the AVERT trial

Miriam Kimpton[a], Philip S. Wells[b], Marc Carrier[b,*]

[a] Division of Hematology, Department of Medicine, University of Toronto, Toronto, Canada
[b] Department of Medicine, University of Ottawa, Ottawa Hospital Research Institute, Ottawa, Canada

ARTICLE INFO

Keywords:
Venous thromboembolism
Venous thrombosis
Thromboprophylaxis
Neoplasm
Haemorrhage

ABSTRACT

Patients with active cancer have a heightened risk of venous thromboembolism (VTE). This risk is further increased by the initiation of chemotherapy. Although previous studies have suggested that the use of parenteral thromboprophylaxis in all ambulatory cancer patients receiving chemotherapy significantly decreases the rate of VTE, current clinical practice guidelines do not recommend routine use of thromboprophylaxis in this patient population. A major criticism of these studies has been the inclusion of patients at lower risk for VTE, which may have diluted the potential beneficial effect of the parenteral thromboprophylaxis. It is therefore imperative to appropriately risk stratify ambulatory cancer patients using a validated scoring system (e.g. Khorana risk score) in order to identify those most likely to benefit from thromboprophylaxis. Direct oral anticoagulants, such as apixaban, may offer a convenient and safe option for thromboprophylaxis. As such, AVERT will randomize 574 ambulatory cancer patients receiving chemotherapy who are at high-risk for VTE (as defined by a Khorana score of ≥ 2) to Apixaban 2.5 mg BID versus placebo. The primary study outcome will be the first episode of objectively documented symptomatic or incidental VTE (deep vein thrombosis and/or pulmonary embolism) within the first 6 months (180 days ± 3) following initiation of the blinded study drug for both intervention and placebo groups. The secondary safety outcomes include major bleeding, clinically relevant non-major bleeding, and overall survival rates. This study will hopefully offer evidence regarding the benefit of apixaban in ambulatory patients at high risk for VTE receiving chemotherapy.

1. Introduction

Patients with active cancer have a heightened risk of venous thromboembolism (VTE). Overall, cancer patients have a risk of having a VTE of 24.6 per 1000 per year, as compared to 2 per 1000 per year in non-cancer patients [1]. The use of chemotherapy is an important risk factor that can potentially increase the risk for VTE up to an annual rate of 15%, depending on the type and combination of agents, or the addition of radiotherapy [2].

Management of cancer is now largely being provided in the outpatient setting and VTE has been shown to be an important cause of morbidity and mortality in this patient population [3]. A study has previously reported a significantly lower one-year overall survival rate (12% vs. 36%; $p < .01$) among patients with active cancer and VTE when compared to matched cancer patients without a VTE [4]. Furthermore, anticoagulated cancer patients with VTE are more likely to have recurrent events (i.e. therapeutic failures) as well as bleeding complications compared to non-cancer patients [5]. These complications in addition to other chronic consequences of VTE including post-thrombotic syndrome or chronic pulmonary hypertension may lead to increased morbidity by limiting the daily activities and quality of life of these patients [5–8]. Given the major impacts on both morbidity and mortality in cancer patients who do develop VTE during their treatment, strategies to prevent VTE in this patient population are desperately needed.

Several studies have assessed the use of thromboprophylactic doses of parenteral anticoagulation (ultra-low-molecular-weight-heparin (u-LMWH) or LMWH) in ambulatory cancer patients undergoing chemotherapy treatment (see Table 1). The largest trial randomized 3212 patients with various cancers to receive a u-LMWH (semuloparin 20 mg daily) or placebo [9]. Overall, 1.2% of patients receiving the u-LMWH and 3.4% receiving placebo developed a VTE during the follow-up period (HR, 0.36; 95% CI, 0.21 to 0.60; $p < .001$). There was no significant difference in the rate of major bleeding complications between

* Corresponding author at: The Ottawa Hospital, General Campus, Department of Medicine, Division of Hematology, 501 Smyth Road, Box 201A, Ottawa ON K1H 8L6, Canada.
E-mail address: mcarrier@toh.ca (M. Carrier).

https://doi.org/10.1016/j.thromres.2018.01.018
Received 16 November 2017; Received in revised form 9 January 2018; Accepted 10 January 2018

Table 1
Summary of studies assessing parenteral thromboprophylaxis.

Study	Type of cancer	N	Intervention	Primary outcome	Comparison of thrombotic events (treatment group versus non-treatment group)
Agnelli [9]	Lung, pancreas, stomach, colon, rectum, bladder, ovary	3212	Semuloparin 20 mg daily	Composite outcome of symptomatic DVT, any nonfatal PE or deaths related to VTE	1.2% vs 3.4% (HR, 0.36; 95% CI, 0.21 to 0.60; p < .001)
Agnelli [10]	Lung, stomach, colon, rectum, pancreatic, breast, ovarian, head and neck, other	1150	Nadroparin 3800 IU daily	Composite of symptomatic VTE, acute cardiovascular, acute PAT, and unexplained death	2.0% vs 3.9% (single-sided p = .02)
Altinbas [30]	SCLC	84	Dalteparin 5000 IU daily	Overall survival	0% vs 2.5%
Elit [31]	Epithelial ovarian cancer	77	Dalteparin 50, 100 or 150 IU/Kg daily	50% or greater reduction in the CA125 level from baseline, maintained for at least 28 days	0% (within 7 days of treatment discontinuation)
Haas [32]	Breast	351	Certoparin 3000 IU daily	Symptomatic or asymptomatic VTE	4.0% vs 4.0% (OR 1.02; 95% CI 0.30–3.48, p = 1.000)
Haas [32]	NSCLC	532	Certoparin 3000 IU daily	Symptomatic or asymptomatic VTE	4.5% vs 8.3% (OR 0.52; 95% CI 0.23–1.12, p = .078)
Khorana [15]	Gynecologic, gastrointestinal, lung, genitourinary, lymphoma, breast, pancreatic, other	98	Dalteparin 5000 IU daily	Symptomatic and asymptomatic VTE	12% vs 21% (HR 0.69, 95% CI 0.23–1.89) majority of outcomes detected by screening
Lecumberri [33]	SCLC	38	Bemiparin 3500 IU daily	Progression-free survival	0% vs 22% (p = .04)
Macbeth [11]	Lung cancer	2202	Dalteparin 5000 IU daily	Overall survival	5.5% vs 9.7% (HR 0.57; 95% CI, 0.42 to 0.79; p < .001)
Perry [34]	Glioma	186	Dalteparin 5000 IU daily	Symptomatic VTE	9% vs 15% (HR 0.51, 95% CI: 0.19–1.4, p = .29)
Van Doormaal [35]	Prostate, NSCLC, pancreatic	503	Nadroparin, weight-adjusted once daily dosing	All-cause mortality	6.6% vs 5.8%

IU: international units; NSCLC: non-small cell lung cancer; PAT: peripheral arterial thromboembolism; SCLC: small cell lung cancer; vs: versus; VTE: venous thromboembolism.

the two groups. Two large randomized trials assessing the use of thromboprophylactic doses of LMWH reported similar findings [10, 11]. In a recent trial of 2202 lung cancer patients, the LMWH dalteparin at a dose of 5000 IU was associated with a reduction in the risk of VTE from 9.7% to 5.5% (HR, 0.57; 95% CI, 0.42 to 0.79; p < .001) over follow-up of approximately 2 years [11]. Again, there was no increase in the risk of major bleeding (1.1% in the dalteparin group vs. 0.7% in the control group). Two additional studies have assessed full or intermediate dose of LMWH in pancreatic cancer patients receiving chemotherapy (see Table 2) [12, 13]. Both studies reported a lower rate of VTE complications without an increase in the rate of major bleeding events among patients receiving LMWH.

The use of parenteral pharmacological prophylaxis (u-LMWH, LMWH) in ambulatory cancer patients remains controversial due to concerns over the risk-to-benefit ratio, the cost, and the inconvenience of parenteral therapy. A major criticism of previous clinical trials has been the overall consistently low risk of VTE in the studied population [14, 15]. This observation has raised concerns that the low risk of VTE in these patients might have diluted the benefit of thromboprophylaxis and caused an unfavorable risk-to-benefit ratio. This issue has led to the suggestion that risk stratification for VTE at the time of cancer diagnosis may play a decisive role in the assessment of the benefits and risks for thromboprophylaxis in cancer patients [14, 16]. Stratification for VTE among ambulatory cancer patients undergoing chemotherapy is challenging because not all patients have the same risk factors. A clinical prediction model with the aim to risk-stratify a broad range of ambulatory cancer patients has been previously derived and validated. The Khorana risk score combines the tumor types, a complete blood count and the body mass index (BMI) to stratify patients according to their underlying risk of VTE. The Khorana risk score has been subsequently validated using a large prospective cohort [16]. In the Vienna cohort study, the risk of VTE complication was 9.4% for patients with a Khorana risk score of 2 or more over a 6-month follow-up period [16]. Multiple other cohort studies have validated this score further [17]. Based on these results, the 2015 ASCO VTE Guidelines suggest to clinicians to use risk scores to identify high-risk patients [18]. A recent Cochrane review reported a relative risk (RR) of 0.36 (95% CI: 0.22 to 0.60) for symptomatic VTE in patients receiving u-LMWH with an intermediate risk for VTE (defined as rates of symptomatic VTE of 2 to 7%) when compared to placebo [19]. The risk of major bleeding or clinically relevant non-major bleeding (CRNMB) were not significantly increased with a RR of 1.05 (95% CI: 0.55 to 2.0) and of 1.40 (95% CI: 0.90 to 2.19), respectively. In patients at high risk for VTE (defined as rates of symptomatic VTE of ≥7%) receiving LMWH, the RR for symptomatic VTE when compared to no prophylaxis was 0.54 (95% CI: 0.38 to 0.75). The risk of major bleeding was not statistically-significantly increased with a RR of 1.44 (95% CI: 0.98 to 2.11), but the risk of CRNMB was increased at RR of 3.40 (95% CI: 1.20 to 9.63). Therefore, current clinical practice guidelines do not recommend routine parenteral thromboprophylaxis for ambulatory cancer patients [18, 20].

The use of oral anticoagulants as thromboprophylactic agents in ambulatory cancer patients undergoing chemotherapy may offer important advantages regarding route of administrations and cost. Two studies have previously assessed thromboprophylaxis using low-dose warfarin or apixaban in this patient population (see Table 3). A phase 2 trial assessing the use of apixaban, a direct Xa inhibitor, has shown promise. A total of 125 cancer patients were randomized to receive 5 mg, 10 mg, and 20 mg of apixaban per day or placebo. None of the patients receiving apixaban had VTE complication as compared to 3 in the placebo group [21]. Rates of major bleeding were low in all three apixaban groups, but were more significant in the apixaban 20 mg group (6.3%). None of the patients receiving 5 mg of apixaban per day had a major bleeding episode and only one had a CRNMB [21]. Therefore, the AVERT trial (NCT02048865) is a double-blind randomized controlled trial comparing 2.5 mg of apixaban twice daily versus