The Efficacy and Safety of Rivaroxaban and Dalteparin in the Treatment of Cancer Associated Venous Thrombosis

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Abstract Venous thromboembolism (VTE) is a complication of malignancy that is associated with significant mortality. The CLOT trial showed superiority of dalteparin in comparison to warfarin in preventing VTE recurrence. Rivaroxaban has been approved for treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE). In the absence of large randomized trials in the oncology population, the efficacy and safety of rivaroxaban for the treatment of VTE in cancer patients needs to be assessed. A single-center retrospective chart review was conducted to assess the efficacy and safety of rivaroxaban compared with dalteparin in cancer-associated thrombosis. Out of 671 patients identified, 286 patients (107 in the rivaroxaban group and 179 in the dalteparin group) were eligible for analysis. The rivaroxaban group had a rate of VTE recurrence at 6 months of 4.9 versus 11.1% with dalteparin ($p = 0.252$). The incidence of recurrent DVT at 6 months

was lower in patients treated with rivaroxaban (0%) compared with dalteparin (8.2%) at 6 months ($p = 0.025$). Incidence of recurrent PE in the rivaroxaban group (5%) versus dalteparin group (3.1%) at 6 months was not statistically significant ($p = 0.675$). No significant difference was identified between the rivaroxaban group and dalteparin group in the rate of major bleeding (2.8 vs. 1.1%, respectively). Rivaroxaban was comparable to dalteparin in prevention of VTE recurrence while having no significant differences with major or minor bleeding.

Keywords Venous thrombosis · Cancer associated thrombosis · Venous thromboembolism · Thrombosis · Novel anticoagulants

Introduction

Venous thromboembolism (VTE), in the form of a deep vein thrombosis (DVT) or pulmonary embolism (PE), is a common disorder with an annual incidence of approximately 1–2 cases per 1000 persons in the general population [1]. An increased risk of VTE has been associated with specific sites of cancer, cancer treatments, surgery, and metastatic disease [2, 3]. The annual incidence of VTE is approximately 1 in 200 cancer patients. In the National Comprehensive Cancer Network (NCCN) guidelines, VTE is broadly defined to include DVT, PE, superficial vein thrombosis (SVT), and thrombosis in other vascular territories and is said to increase the likelihood of death in cancer patients by two- to sixfold [4]. Chemotherapy, vessel stasis from direct compression, surgery, and prolonged immobilization are thought to all play roles in this increased risk [5, 6]. Treatment options for VTE include low-molecular-weight heparins [dalteparin (Fragmin®) and

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enoxaparin (Lovenox[®]), factor Xa inhibitors [fondaparinux (Arixtra[®]), edoxaban (Savaysa[®]), rivaroxaban (Xarelto[®]), and apixaban (Eliquis[®])], unfractionated heparin, vitamin K antagonists (warfarin), and direct thrombin inhibitors [dabigatran (Pradaxa[®])].

Prior to the CLOT trial, cancer patients with a diagnosis of VTE were treated similarly to patients with other hypercoagulable disease states. Generally, these patients received intravenous heparin, low-molecular-weight heparin (monotherapy or bridge therapy), or warfarin [7]. The CLOT trial, published in 2003, consisted of 676 adult patients with active cancer and newly diagnosed, symptomatic proximal DVT, PE, or both. The study demonstrated that dalteparin was superior to oral vitamin K antagonist in preventing recurrent VTEs in the setting of malignancy (9 vs. 17%). There was no significant difference between the two therapies with regard to the risk of major bleeding (6 vs. 4%) or any bleeding (14 vs. 9%) [8]. This important study showed that, in the setting of acute VTE associated with malignancy, treatment with a low-molecular-weight heparin is more effective than an oral vitamin K antagonist without any increased risk of bleeding. Thus, low-molecular-weight heparin is currently the preferred treatment of cancer-associated thrombosis. However, the cost of these medications can often be prohibitive for some patients, depending on their insurance carrier; in addition, with the need for daily subcutaneous injections, patient compliance may be reduced.

Rivaroxaban, a factor Xa inhibitor, is approved for treatment and secondary prevention of VTE and may be an appealing oral choice for cancer patients. Rivaroxaban does not require routine monitoring of blood levels and has less drug–drug/drug–food interactions compared with warfarin. The EINSTEIN-PE and EINSTEIN-DVT trials are landmark clinical trials that investigated the efficacy of enoxaparin plus warfarin versus rivaroxaban in preventing recurrent thrombosis. Both trials evaluated safety through the incidence of clinically relevant and major bleeding during VTE treatment. However, the major limitation of the EINSTEIN trials, particularly in the setting of malignancy, is that only about 4–6% of the study participants had active cancer [9, 10]. In the absence of large randomized trials in the oncology population, studies like this one are needed to determine the efficacy and safety of rivaroxaban for the treatment of VTE in cancer patients.

Methods

The study was a single-center retrospective chart review conducted at H. Lee Moffitt Cancer Center between May 1, 2010, and June 30, 2015, following approval by the Institutional Review Board. Patients were included if they were

at least 18 years of age, had a diagnosis of cancer and concurrent diagnosis of DVT or PE, and were prescribed treatment with either rivaroxaban or dalteparin during the study period. Patients were excluded if the length of anticoagulation therapy was < 30 days, if therapy with dalteparin or rivaroxaban was initiated more than 6 months after DVT or PE diagnosis, or if they did not receive therapeutic doses of therapy. The primary efficacy outcome was the incidence of new or recurrent DVT or PE. The secondary endpoint of the study was to compare the safety of rivaroxaban versus dalteparin in cancer patients for the treatment of DVT or PE. Safety was determined by the incidence and severity of bleeding, based on the International Society of Thrombosis and Hemostasis (ISTH) definition. Major bleeding was defined as clinically overt if it was associated with a drop in hemoglobin of ≥ 2 g/dL, required transfusions of ≥ 2 units of packed red blood cells, involved critical site bleeding (intracranial, intraspinal, intraocular, retroperitoneal, or pericardial area), or if it contributed to death. Minor bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact with a physician, interruption or discontinuation of anticoagulation treatment, or associated with any discomfort or impairment of activities of daily life [11].

Patients who received anticoagulation therapy with dalteparin or rivaroxaban from May 1, 2010, to June 30, 2015, were identified using a generated report from inpatient pharmacy department charge codes. Out of 671 patients identified, 286 patients (107 in the rivaroxaban group and 179 in the dalteparin group) were eligible for analysis based on exclusion criteria. The following information was extracted from the medical record for each eligible patient: age, gender, body mass index, laboratory results at time of VTE diagnosis, cancer type, presence of active cancer, active chemotherapy, metastatic malignancy, comorbidities (coronary artery disease, hypertension, diabetes, renal insufficiency), prior history of VTE, surgery within 30 days, or central venous catheter.

Patients who received therapeutic doses of rivaroxaban were matched with a similar population of patients who were treated with therapeutic doses of dalteparin in a 1:2 ratio. Wilcoxon rank sum test was performed to compare continuous variables. The Fisher exact test was performed to compare categorical variables. All data were analyzed using SAS 9.4 with a significance level of $\alpha = 0.05$.

Results

Our study cohort consisted of 286 patients, with 107 patients treated with rivaroxaban and 179 patients treated with dalteparin. Baseline characteristics, comorbidities,

Table 1 Patient baseline characteristics, comorbidities, and risk factors

Characteristic	Rivaroxaban n (%)	Dalteparin n (%)	<i>p</i> value
Number of patients treated for ≥ 30 days	107	179	
Number of patients treated for ≥ 3 months	88 (82.2%)	143 (79.9%)	
Number of patients treated for ≥ 6 months	60 (56.1%)	97 (54.2%)	
Age in years (MEAN $\pm$ SD)	62.20 $\pm$ 12.34	59.31 $\pm$ 12.02	0.022
Male gender	56 (52.3%)	91 (50.8%)	0.808
BMI (mean $\pm$ SD)	29.04 $\pm$ 5.78	28.59 $\pm$ 6.15	0.54
Hemoglobin (mean $\pm$ SD)	11.05 $\pm$ 1.90	11.09 $\pm$ 1.99	0.88
Platelet count (mean $\pm$ SD)	216.0 $\pm$ 115.5	219.8 $\pm$ 105.4	0.78
Leukocyte count (mean $\pm$ SD)	8.55 $\pm$ 5.76	7.79 $\pm$ 5.96	0.30
Active cancer	97 (90.7%)	170 (95%)	0.219
Hematologic malignancy	19 (19.6%)	47 (27.6%)	0.184
Metastatic malignancy	53 (67.9%)	93 (75.6%)	0.258
Chemotherapy	75 (70.1%)	131 (73.2%)	0.588
Coronary artery disease	6 (5.6%)	16 (8.9%)	0.365
Hypertension	55 (51.4%)	85 (47.8%)	0.625
Diabetes mellitus	14 (13.1%)	24 (13.4%)	1.000
Creatinine clearance 30–50	6 (5.6%)	14 (7.8%)	0.633
History of VTE	11 (10.3%)	8 (4.5%)	0.083
Surgery within 30 days	15 (14%)	17 (9.5%)	0.250
Central line	66 (61.7%)	113 (63.1%)	0.900
Khorana score ≥ 3 points	16 (15.0%)	15 (8.4%)	0.115

and risk factors for thrombosis are shown in Table 1. Indication for anticoagulation for our population included DVT only (56.6%), PE only (29.7%), or both DVT and PE (13.6%). Among the patients treated with rivaroxaban or dalteparin, 60 patients (56.1%) and 97 patients (54.2%) remained on treatment for at least 6 months, respectively. Most of our cohort had active malignancy at the time of VTE diagnosis (93.4%), including 51% patients with metastatic disease and 72% patients receiving chemotherapy. Patient characteristics were similar in both groups except for an older average age in the rivaroxaban group at 62.20 $\pm$ 12.34 years compared to 59.31 $\pm$ 12.02 years in the dalteparin group ($p = 0.022$). Risk factors for thrombosis such as personal history of VTE, surgery within 30 days, central line, and Khorana score were similar in both groups.

Table 2 shows a comparison of the incidence of VTE recurrence and bleeding events. Overall, rivaroxaban had a similar rate of VTE recurrence at 6 months with 3 (4.9%) events versus 11 (11.1%) events with dalteparin ($p = 0.252$). The incidence of recurrent DVT at 6 months was lower in patients treated with rivaroxaban (0%) compared to dalteparin (8.2%) at 6 months ($p = 0.025$). However, there was no statistical significant difference in the incidence of recurrent PE in patients treated with rivaroxaban (5%) compared to dalteparin (3.1%) at 6 months ($p = 0.675$).

No significant difference was identified between the rivaroxaban group and dalteparin group in the rate of major bleeding (2.8 vs. 1.1%, respectively) or minor bleeding (9.3 vs. 4.5%, respectively). Major bleeding events in the rivaroxaban group included three GI bleeds. The dalteparin major bleeding events included one GI bleed and one intraocular hemorrhage.

Discussion

Recurrent thromboembolism in patients with cancer is a serious problem that diminishes patient's life spans and quality of life [12]. To our knowledge our retrospective study of rivaroxaban versus dalteparin is the largest matched case control study comparing direct oral anticoagulants (DOACs) to low-molecular-weight heparin for the treatment of acute venous thromboembolism in patients with cancer. Previous trials have depicted that dalteparin reduces the risk of symptomatic recurrent thromboembolism among patients with active cancer compared with vitamin K antagonists [8]. Rivaroxaban in retrospective subgroup analysis has been shown to be safe in cancer patients [13]. No prospective studies have reported the treatment of venous thromboembolism in cancer patients utilizing dalteparin and DOACs, although there are several trials currently being conducted [14].

Table 2 Comparing rates of VTE recurrence, major, and minor bleeding in rivaroxaban and dalteparin groups

Event	Rivaroxaban	Dalteparin	<i>p</i> value
Recurrent VTE while on therapy	4/107 (3.7%)	11/179 (6.1%)	0.427
Recurrent VTE in 30 days	1/107 (0.9%)	4/179 (2.2%)	0.655
Recurrent VTE in 3 months	1/88 (1.1%)	4/143 (2.8%)	0.652
Recurrent VTE in 6 months	3/60 (4.9%)	11/97 (11.1%)	0.252
Recurrent DVT while on therapy	1/107 (0.9%)	6/179 (3.4%)	0.263
Recurrent DVT in 30 days	0/107 (0%)	3/179 (1.7%)	0.298
Recurrent DVT in 3 months	0/88 (0%)	4/143 (2.8%)	0.300
Recurrent DVT in 6 months	0/60 (0%)	8/97 (8.2%)	0.025
Recurrent PE while on therapy	3/107 (2.8%)	4/179 (2.2%)	1.000
Recurrent PE in 30 days	1/107 (0.9%)	1/179 (0.6%)	1.000
Recurrent PE in 3 months	2/88 (2.3%)	1/143 (0.7%)	0.559
Recurrent PE in 6 months	3/60 (5%)	3/97 (3.1%)	0.675
Major bleeding	3/107 (2.8%)	2/179 (1.1%)	0.366
Minor bleeding	10/107 (9.3%)	8/179 (4.5%)	0.131

In our retrospective study, rivaroxaban has been shown to be an effective drug in active cancer patients. Rivaroxaban was utilized in a slightly older population at 62 years of age versus dalteparin at 59 years. There is no evidence that age either increases or decreases risks of thrombosis in cancer patients; hence, we do not believe that this was a significant finding in our study [1]. Most patients were undergoing treatment for a malignancy in either treatment arm.

At 30 days, the recurrent deep vein thrombosis risk was similar in the patient's treated with rivaroxaban compared with dalteparin. The 3-month data were also similar. The 6-month rivaroxaban-treated patients did have less recurrent deep vein thrombosis rate than those treated with dalteparin. These results could have been biased if there were fewer patients with metastatic disease in either treatment arm but our study did not have any statistically significant differences in metastatic disease in the rivaroxaban when compared to the dalteparin cohorts. Because this was the retrospective study, follow-up bias could have confounded the data. The recurrent pulmonary embolism rate was similar in both groups at 30 days, 3 months, and 6 months. Although this study is a retrospective study, the event rate of recurrent thromboembolism in the LMWH group is comparable with the prospective CATCH trial. In the CATCH study, the event rate was 7.2% (31/449) versus 6.1% (11/179) in our study [15]. The event rate was lower than the CLOT trial that had an event rate of 8% (27/336) [8].

There were no major bleeding differences between the dalteparin cohort and rivaroxaban cohort. The incidence of major bleeding in the dalteparin cohort (1.1%) was similar to the bleeding rate (2.7%) in the CLOT trial [8]. The CATCH trial did have an increase in major bleeding (6% in the dalteparin group) compared with our study [15]. As a

result of the retrospective nature of the study, a limitation could have been that patients with major bleeds and thromboembolism that led to mortality were admitted to another hospital and not included in the medical records. The cause of death could have been reported as due to malignancy; when indeed it was due to major bleeding or recurrent venous thromboembolism.

Although retrospective data lead to biases, a prospective strength of this data is that patients were evaluated under real world circumstances. As a result, the efficacy of dalteparin and rivaroxaban could be evaluated in patients undergoing treatment for their malignancies without stringent exclusion criteria in regard to types of malignancy. Our data included solid tumors and hematologic malignancies under real world conditions.

Another limitation of this retrospective trial is that the sample size is insufficient because of patient deaths and patients lost to follow up. Although this is a confounding factor, when dalteparin and rivaroxaban are utilized in real world situations, there will be patients who will survive less than 6 months, which was evident in this retrospective study. In conclusion, rivaroxaban appears to be safe in patients with active cancer for treatment of venous thromboembolism. Prospective trials are currently being done to address the efficacy of DOACs in cancer patients with low-molecular-weight heparin being utilized as the standard treatment arm [16].

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Compliance with Ethical Standards

Conflict of interest The authors declares that they have no conflicts of interest to disclose.

Human and Animal Rights Statement All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. For studies with human subjects include the following: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent All persons gave their informed consent prior to their inclusion in the study. Informed consent was obtained from all patients for being included in the study.

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