Dose Appropriateness, Efficacy, and Safety of Rivaroxaban and Apixaban in the Treatment of Cancer-related Venous Thromboembolism: A Retrospective Study at a Single Center

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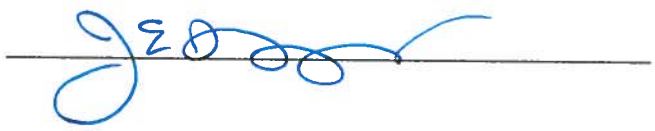


Abstract

Background

Malignancy is a major risk factor for developing venous thromboembolism (VTE), and thus cancer patients are at high risk for deep vein thrombosis (DVT) and/or pulmonary embolism (PE). While the guideline-recommended anticoagulant for the treatment of cancer-associated VTE is low-molecular-weight heparin (LMWH), direct oral anticoagulants (DOAC) such as rivaroxaban and apixaban are often prescribed for various reasons including patient preference, convenience, and cost. The purpose of this study was to retrospectively assess the appropriateness of rivaroxaban and apixaban dose as well as rate of VTE recurrence and bleeding outcomes in patients with cancer-related VTE treatment.

Methods

From April 2014 to April 2016, adults aged over 18 years old diagnosed with cancer (ICD-9 codes 140. to 239.) and prescribed rivaroxaban or apixaban in both inpatient and outpatient settings for the treatment DVT and/or PE were included in this study. Among additional exclusions, subjects excluded had a concomitant diagnosis of atrial fibrillation/flutter and were on treatment for less than six months. From the time of initiation to up to six months, each subject's chart was reviewed to assess potential need for dosage adjustment or any unindicated dosage adjustments. Any recurrent VTE events or bleeding events from the time of initiation to up to six months were noted for the outcome analysis.

Results

Of 82 subjects assessed, an inappropriate initial dose was prescribed in 26 subjects and 24 subjects for rivaroxaban and apixaban respectively. During the six months after initiation, no other dosage-adjustments occurred nor were any warranted. Rivaroxaban patients had a lower rate of VTE recurrence but a higher rate of major bleeding at six months than in other published studies. Apixaban patients had a lower rate of both VTE recurrence as well as major bleeding and clinically relevant non-major bleeding than in other published studies.

Conclusion

Despite guideline recommendations, some providers prescribe rivaroxaban or apixaban for cancer-associated VTE. Our analysis demonstrated that both rivaroxaban and apixaban are often initially dosed inappropriately and dose adjustment for renal or hepatic dysfunction or drug interactions is commonly disregarded. Future analyses of this dataset will compare these subjects' outcomes, such as recurrent VTE and bleeding, based upon appropriateness of dosing.

Introduction

Malignancy is a hypercoagulable state that leads to a four to seven-fold increased risk for VTE[1]. A population study at Olmsted County, Minnesota showed that cancer presented a fourfold increased risk of VTE (odds ratio (OR) 4.1, 95% CI: 1.9-8.5)[2]. In the United Kingdom, a cohort study using Cancer Registry data linked to Hospital Episode Statistics found a relative risk (RR) of VTE of 4.7 in cancer patients (95% CI: 4.5-4.9)[3]. It is estimated that four to twenty percent of patients with cancer will experience a cancer-related thrombosis (CAT) event[4]. Moreover, in cancer, VTE and thrombotic complications are the second most frequent cause of mortality and these patients have shorter life expectancies than cancer patients without VTE[1].

The hypercoagulable state in cancer is a complex interdependent mechanism involving interactions among cancer cells, host cells, and the coagulation system[1]. Tumor cells are thought to have the ability to activate the coagulation system and interact with hematopoietic cells, thus altering the balance between endogenous coagulants and anticoagulants[1]. Specifically, factors that contribute to the prothrombotic state in cancer are also the same characteristics that contribute to tumor progression[1]. These factors include the production by tumor of microparticles, proangiogenic factors, inflammatory cytokines, and tumor cell adhesion molecules that bind platelets and leukocytes[1]. As a result, increased clot formation and activation of coagulation eventually lead to thrombotic vascular events. Venous manifestation of CAT includes DVT, PE, or visceral vein thrombosis. Arterial manifestation includes stroke or myocardial infarction.

Risk factors for CAT can be characterized into three main categories: patient-dependent, tumor-related, or treatment-related. According to the Registry of Patients with Venous Thromboembolism (RIETE) investigators, women were found to have a lower rate of DVT recurrences (HR 0.78, 95% CI: 0.67-0.91) but a higher mortality due to PE (HR 1.24, 95% CI: 1.04-1.47) when compared to men[5]. Other patient-specific factors include older age, race, comorbidities such as obesity, diabetes, previous VTE, and decreased performance status[1]. In addition, hematologic malignancies and distant metastatic disease were found to have a higher rate of thrombosis events compared to local cancer diseases, a 10.3% VTE incidence compared to 5.6% in localized disease in a multicenter retrospective study of hospitalized cancer patients (RR 1.92, 95% CI: 1.21-3.04)[6]. Furthermore, chemotherapy has been linked to a two- to six-fold increase in VTE occurrence[2]. Other treatment-related factors include use of central venous catheters, hospitalization, and medications such as bevacizumab, tamoxifen, and growth factors[1].

Cancer patients with initial VTE may require extended anticoagulant therapy, though the optimal duration is not fully elucidated. According to the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), routine outpatient thromboprophylaxis is not recommended[7,8]. Thromboprophylaxis throughout hospitalization is recommended and patients undergo major cancer surgery should receive prophylaxis starting before surgery and continuing up to four weeks post-operation[7,8]. The risk of recurrence VTE in cancer patients is approximately three times that of non-cancer patients (HR 3.2, 95% CI: 1.5-

5.4)[1]. In addition, a few risk assessment scores are available to help predict the risk of CAT, although they are not commonly utilized in thromboprophylaxis evaluation. For instance, NCCN and ASCO panel recommend the use of a validated tool called Khorana Score to differentiate between high- and low-risk patients[7,8]. This risk score was originated from a development cohort of 1,365 patients from a prospective registry and externally validated by the Vienna CATS consortium and other retrospective cohort studies[9]. The following table lists the current recommendations from major oncology guidelines regarding antithrombotic therapies for acute VTE as well as duration for long-term anticoagulants.

Table 1: Major Guidelines Acute VTE Treatment and Duration Recommendations

	Acute VTE	**Long-term Anticoagulation**	**Duration**
ASCO[7] (2014)	LMWH preferred over UFH for initial 5-10 days of treatment	LMWH preferred over VKA, with VKA as acceptable alternative DOACs not recommended	At least 6 months
NCCN[8] (2016)	LMWH, UFH, or fondaparinux	LMWH preferred over VKA, with VKA as acceptable alternative DOACs not recommended	Minimum 3 months to indefinitely in patients with persistent risk factors
ACCP[10] (2016)	Not addressed	LMWH over VKA and DOACs, with no preference to VKA DOACs if LMWH is not used	Continue same agent for the first 3 months
ITAC-CME[11] (2016)	LMWH is preferred over UHF and fondaparinux	LMWH preferred over VKAs DOACs can be considered for VTE treatment of patients with stable cancer not receiving systemic anticancer therapy	Minimum of 3 months

ACCP = American College of Chest Physicians, ITAC-CME = International Initiative on Thrombosis and Cancer, VKA = Vitamin-K antagonist

LMWH is recommended as first-line for VTE treatment through findings from the Low Molecular Weight Heparin Versus Oral Anticoagulant Therapy for Long Term Anticoagulation in Cancer Patients with Venous Thromboembolism (CLOT)[12] trial in 2003. In this study, LMWH (dalteparin) was shown to be superior to warfarin in term of recurrent VTE rate reduction at 6 months without statistically significant difference in the rate of bleeding or mortality[12]. In 2015, the Comparison of Acute Treatments in Cancer Hemostasis (CATCH)[13] trial was conducted to further support recommendations for LMWH use in CAT. However, the study failed to detect significant difference in VTE recurrence after 6 months[13]. This was attributed to a "healthier" patient population with fewer VTE risk factors such as higher performance status, less metastatic disease, less systemic anticancer treatment, and less extensive history of thrombosis.

When compared to warfarin, DOACs have favorable profile in term of drug-drug interaction, dosing convenience, and no required therapeutic drug monitoring. The CHEST 2016 Guideline recommends DOACs over warfarin for the treatment of VTE in non-cancer patients[14]. Landmark trials for DOACs have established efficacy and safety in this population. Specifically, rivaroxaban was compared to enoxaparin and warfarin in the EINSTEIN-DVT and EINSTEIN-PE trials[15]. Apixaban was compared to enoxaparin and warfarin in the AMPLIFY trial[16]. The following table summarizes the pharmacokinetics and pharmacodynamics of DOACs.

Table 2: Summary of the Pharmacokinetics and Pharmacodynamics of DOACs

	Dabigatran[17] (Pradaxa®)	**Rivaroxaban[18] (Xarelto®)**	**Apixaban[19] (Eliquis®)**	**Edoxaban[20] (Savaysa®)**
Approval Date	2010	2011	2012	2015
Drug Class	Direct thrombin inhibitor	Factor Xa inhibitor		
Half-life	12-17 hrs	5-9 hrs	12 hrs	10-14 hrs
Metabolism	P-gp, hydrolysis	P-gp, CYP3A4/5, CYP2J2, and hydrolysis	Mainly via CYP3A4, P-gp	Remains mostly as unchanged drug in plasma, P-gp
Renal Excretion	80% of absorbed dose	66% of total dose (36% as unchanged drug)	27% of total dose	50% of total dose
Food Effects	May be taken with or without food	10-mg tablet may be taken with/without food 15-mg and 20-mg tablets should be taken with the largest meal of the day	Bioavailability not affected by food	Can be administered without regard to food
VTE Dosing	10 mg daily x7 days, then 5 mg BID	15 mg BID x21 days, then 20 mg daily	10 mg daily x7 days, then 5 mg BID	60 mg daily <60 kg: 30 mg daily
VTE Dose Renal Adjustment	CrCl < 30 ml/min: avoid	CrCl <30 ml/min: avoid	CrCl < 15 ml/min: avoid	CrCl 15-50 ml/min: 30 mg daily CrCl <15 ml/min: avoid
VTE Dose Hepatic Adjustment	None Recommended	Avoid in Child-Pugh Class B/C	Avoid in Child-Pugh Class C	Avoid in Child-Pugh Class B/C

CrCl = Creatinine clearance

While the guideline-recommended anticoagulant for the treatment of cancer-associated VTE is LMWH[21], DOACs are often prescribed off-labeled for various reasons including patient preference, convenience, and cost. There are pending trials aiming to assess efficacy and safety of DOACs for VTE treatment in cancer patients. Results of the first of such trials involved

edoxaban's and was published late 2017. The authors of this study concluded that oral edoxaban was non-inferior to subcutaneous dalteparin with respect to the composite outcome of recurrent VTE or major bleeding. However, the rate of major bleeding was higher with edoxaban[22]. In addition, a recent meta-analysis suggests DOACs are comparable to vitamin K antagonists (VKA) for preventing VTE recurrence and bleeding events in cancer patients[23].

Methods

Study Objective:
The objective of this study is to retrospectively assess the appropriateness of dose as well as efficacy and safety of rivaroxaban and apixaban in patients with cancer-related VTE treatment at UNC Medical Center.

Study Design:
This is a non-interventional, retrospective study in patients initiated with rivaroxaban or apixaban for the treatment of cancer-related VTE.

Study Endpoints
The primary endpoints of this study include appropriateness of rivaroxaban and apixaban dose for VTE treatment, recurrent of VTE and bleeding outcomes at 6 months.

Study Population

a. **Inclusion criteria:**
   - At least 18 years old diagnosed with cancer (ICD-9 codes 140.xx to 239.xx)
   - Prescribed rivaroxaban (April 2014 – October 2015) or apixaban (April 2014 – April 2016) for VTE treatment at UNC Medical Center

b. **Exclusion criteria:**
   - Treated with rivaroxaban or apixaban for less than 6 months
   - Had concomitant atrial fibrillation or flutter
   - Had VTE prior to cancer diagnosis
   - Diagnosed clotting disorder
   - Benign cancerous lesion
   - Failed treatment with a different anticoagulant prior to rivaroxaban or apixaban initiation
   - Lost to follow-up

Statistical Methods

a. **Study size**: Given the solely descriptive nature of the study objectives, the sample size was not based on formal statistical hypothesis testing. Sample size was planned to be approximately 35 to 50 patients where all patients who met eligibility criteria would be included in the analysis.
b. **Main summary measurements:** Descriptive statistics (percent, means, medians, range, standard deviations) were used to describe patient demographic/clinical characteristics, treatment dose, and clinical outcomes.

Result

Of all 1,576 rivaroxaban orders from April 2014 to October 2015, 192 subjects had ICD-9 codes from 140. to 239. Further exclusion based on benign lesions, on therapy prior to study dates, lost to follow up, or on therapy for less than six months resulted in 50 subjects eligible for data analysis. Of all 1,813 apixaban orders from April 2014 to April 2016, 1,585 were excluded based on ICD-9 codes having benign lesions, atrial fibrillation, or unknown. Additional 196 subjects further excluded based on all remaining exclusion criteria, resulting in 32 eligible subjects for data analysis.

Respectively of rivaroxaban and apixaban, the study population was comprised predominantly of white (64% and 81%) females (60% and 53%) with a mean age of 57.9 and 67.3 years old. About one third patients of each group are obese. The majority of patients had hematologic cancers, Child-Pugh Class A, and normal renal function. Some patients' data were not available for renal and hepatic function assessment based upon lab availability at UNC Medical Center within two months of initiation. Among rivaroxaban patients, one patient was on both aspirin 81 mg and NSAID around-the-clock. Among apixaban patients, two patients had CrCl less than 25 ml/min.

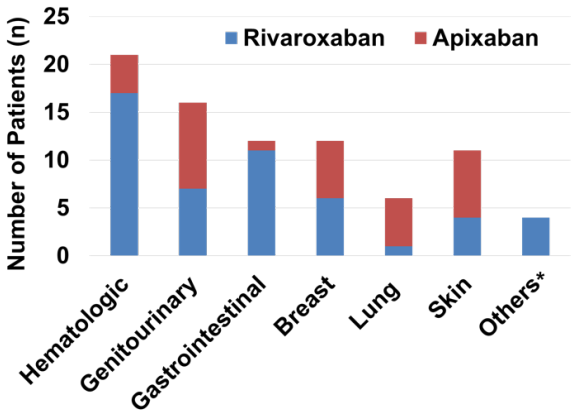
Table 3: Baseline Characteristics

Patient Characteristics	**Rivaroxaban (n = 50)**	**Apixaban (n = 32)**
Age (years), mean (range)	57.9 (19-89)	67.3 (40-88)
Female, n (%)	30 (60)	17 (53)
BMI > 30 kg/m^2, n (%)	17 (34)	10 (31)
Race		
African American, n (%)	18 (36)	6 (19)
White or Caucasian, n (%)	32 (64)	26 (81)
Others, n (%)	-	-
Diagnosis		
DVT only, n (%)	17 (34)	17 (53)
PE only, n (%)	17 (34)	7 (22)
DVT and PE, n (%)	16 (32)	8 (25)
Active Chemotherapy, n (%)	22 (46%)	13 (38%)
CrCl (ml/min)		
< 30, n (%)	1 (2)	4 (12)
30-60, n (%)	14 (28)	6 (19)
> 60, n (%)	33 (66)	22 (69)
Not Available, n (%)	2 (4)	-
Child-Pugh Class		
Class A, n (%)	36 (72)	14 (44)
Class B, n (%)	5 (10)	1 (3)
Class C, n (%)	-	-
Not Available, n (%)	9 (12.5)	17 (53)

Concomitant Medications		
Aspirin, n (%)	5 (10)	8 (25)
P2Y12 Inhibitor, n (%)	2 (4)	1 (3)
NSAID (ATC), n (%)	2 (4)	1 (3)
NSAID (PRN), n (%)	3 (6)	1 (3)
Prescribing Specialties		
Hematology/Oncology, n (%)	32 (64)	12 (37)
Surgery, n (%)	3 (6)	1 (3)
Other Medicines, n (%)	15 (30)	19 (60)

ATC = around the clock, DDI = drug-drug interaction, NSAID = nonsteroidal anti-inflammatory agent, PRN = as needed.

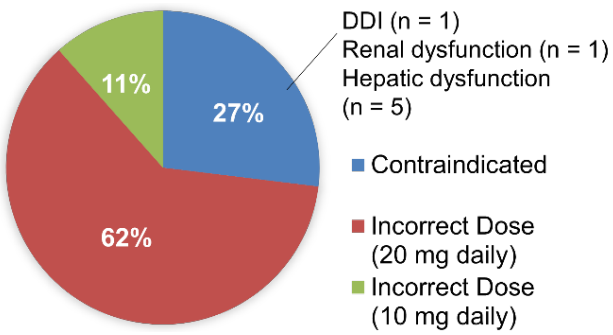
Figure 1: Types of Cancer



*Others include connective tissue and brain cancers

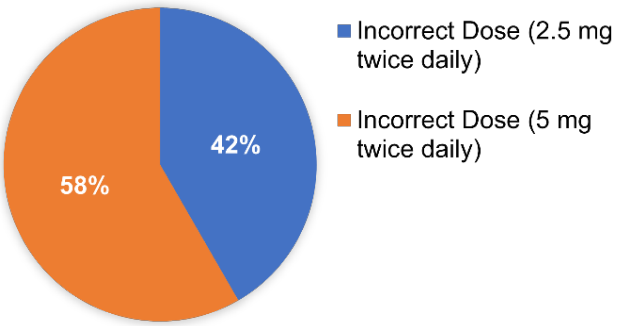
In term of appropriateness of dose, for rivaroxaban, twenty-six (52%) patients were initially prescribed inappropriate doses. At time of initiation, seven (14%) patients were inappropriately prescribed based on contraindications (DDI with itraconazole, renal and hepatic dysfunction). After 21 days, seven (14%) patients were not appropriately dose-reduced to 20 mg by mouth (PO) daily. After initiation, one patient had a potential DDI identified with fluconazole; however, the dose was not adjusted. During the six months, no other dosage-adjustments occurred. The following graph illustrates reasons for inappropriate initial apixaban dose

Figure 2: Reasons for Inappropriate Initial Rivaroxaban Dose (n = 26)



For apixaban, twenty-four (75%) patients were initially prescribed inappropriate doses; however, none of these patients had contraindications to therapy. After 7 days, all patients were appropriately dose-reduced to 5 mg PO twice daily. After initiation, one patient was dose-adjusted from 5 mg PO daily to 2.5 mg PO daily due to sign of bleeding (bruising). During the six months, no other dosage-adjustments occurred. The following graph illustrates reasons for inappropriate initial rivaroxaban dose

Figure 2: Reasons for Inappropriate Initial Apixaban Dose (n = 24)



In addition, rivaroxaban VTE recurrence and major bleeding rates at 6 months are 6.3% and 12.5% respectively. Apixaban VTE recurrence and major bleeding rates at 6 months are 2.9% and 5.9% respectively. The following tables list the rates from major clinical trials for rivaroxaban (EINSTEIN PE/DVT) and apixaban (AMPLIFY) VTE treatment.

Table 4: Outcomes at 6 months for Rivaroxaban Patients

Study	Drug	6 Month VTE Recurrence	6 Month Major Bleeding
Our Study (n = 50)	Rivaroxaban	6.3%	12.5%
EINSTEIN PE/DVT (n = 354)[15]	Rivaroxaban	4.5%	2.3%
CLOT (n = 336)[12]	Dalteparin	8.0%	5.6%
CLOT (n = 336)[12]	Warfarin	15.8%	3.6%
CATCH (n = 449)[13]	Tinzaparin	6.9%	2.7%

Table 5: Outcomes at 6 months for Apixaban Patients

Study	Drug	6 Month VTE Recurrence	6 Month Bleeding*
Our study (n = 32)	Apixaban	2.9%	5.9%
AMPLIFY (n = 534)[16]	Apixaban	1.9%	8.1%
AMPLIFY (n = 534)[16]	Warfarin	6.3%	17.4%
CLOT (n = 336)[12]	Warfarin	15.8%	19%
CLOT (n = 336)[12]	Dalteparin	8%	14%

*Bleeding rate includes major bleeding and clinically relevant non-major bleeding

Discussion

Our analysis demonstrated that both initial and maintenance doses of rivaroxaban and apixaban are often inappropriately selected. A majority of rivaroxaban patients were initiated on 20 mg PO daily despite the correct VTE treatment dose is 15 mg PO twice daily for 21 days and then 20 mg PO once daily. In the same manner, the majority of apixaban patients were initiated on 5 mg PO twice daily despite the correct VTE treatment dose is 10 mg PO twice daily for 7 days and then 5 mg PO twice daily. Apixaban dosing for VTE treatment may be mistaken with dosing for stroke prevention in non-valvular atrial fibrillation (NVAF), which is 5 mg PO twice daily. Moreover, rivaroxaban was inappropriately prescribed in six patients with Child-Pugh Class B or impaired renal function (CrCl less than 30 ml/min). In contrast, no patients receiving apixaban had documented impaired hepatic. Two patients with CrCl less than 25 ml/min were initiated on apixaban. According to apixaban prescribing information, CrCl less than 15 ml/min is contraindicated. However, in the AMPLIFY study, subjects were excluded if having CrCl less than 25 ml/min. This was an interesting pattern observed in our apixaban cohort. In addition, no patients were inappropriately dose-adjusted during the six-month follow-up period as well as no adjustments warranted. One apixaban patient was dose-reduced from 5 mg PO daily to 2.5 mg PO daily due to signs of bleeding and this adjustment was subjective to the provider as no literatures or guidelines recommend on dosing adjustment due to sign of bleeding for VTE treatment.

Among patients receiving rivaroxaban, the risk of VTE recurrence in our cohort was lower however major bleeding rate was higher than in other published studies. Patients being actively treated with chemotherapy may be at a particular high risk of bleeding. In addition, among patients receiving apixaban, both the risk of VTE recurrence and bleeding, including major bleeding and clinically relevant non-major bleeding rates in our cohort were lower than in other published studies. Further characterization of bleeding events and bleeding rates in this dataset is forthcoming to better understand cofounders or risk factors contributing to a higher rate of bleeding in our rivaroxaban cohort.

Conclusion

Despite not being guideline recommended for cancer-associated VTE, rivaroxaban and apixaban continue to be frequently prescribed. Our study showed that initial and maintenance doses are often prescribed inappropriately and despite of contraindication to therapy. The primary limitation of this study included small sample size, single center, and retrospective design. The latter precluded inquiry of providers to identify intention for alternative DOAC dosing strategies. Future analyses of this data will compare these subjects' outcomes, such as recurrent VTE and bleeding, based upon appropriateness of dosing.

Potential Implications and Future Direction

This study was the first to examine the appropriateness of dose and outcomes of DOACs for cancer-related VTE treatment at UNC Medical Center. Due to the nature of retrospective design as discussed in our limitation, we were unable to further explain the observed dosing difference from the manufacturer's recommendation. However, this study's finding provides potential opportunities for provider education on appropriate VTE treatment dosing. In addition, we developed our inclusion and exclusion criteria with the purpose of minimizing confounders that might interfere with interpretation of outcomes and appropriateness of dose. In the future, we would like to collect platelet counts because providers may not initiate patients on a full anticoagulant dose due to a low baseline platelet. In addition, as discussed in the background section, we would also like to collect cancer treatment regimen as some chemotherapy put a patient at a higher risk of developing VTE. Overall, future direction will aim to identify and assess potential risk factors or baseline characteristics that put patients at a higher risk of having recurrence VTE or a bleeding event when they are prescribed with DOACs for cancer-related VTE treatment.

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