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Rivaroxaban Treatment in Acute Proximal DVT Patients with Malignancy

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Abstract

Background: The primary objective of this study was to evaluate efficacy and safety of rivaroxaban treatment in patients with active malignancy and acute proximal deep vein thrombosis (DVT).

Methods: This study comprised 34 patients with active cancer and acute proximal DVT, who received rivaroxaban treatment for at least 5 months. The study endpoints included the rate of thrombus regression, treatment efficacy and safety, which were assessed with frequent duplex ultrasounds, plethysmography, and commutated tomography. The mean duration of the follow-up was 25.2 months.

Results: Of 34 patients with cancer, 31 suffered from active malignancy. 15 patients had breast carcinoma, and 5 had lung cancer in this study. At 3, 6, 12, and 24 months, cumulative patency was observed in 11.8%, 38.2 %, 44.1%, and 55.90% of all patients. Femoral valvular incompetence was found in 21 (61.8%) patients. 19 patients developed post thrombositc syndrome (PTS) at 12 months, and the mean PTS score was 5.9 ± 3.3. Of 34 patients, 9 patients had bleeding events. 9 (26.5%) patients developed recurrent deep vein thrombosis, and 3(7.5%) had pulmonary embolism during follow-up.

Conclusion: This study indicated extended-duration rivaroxaban therapy should be considered for acute unprovoked proximal DVT. Large-scale prospective studies should be conducted in cancer associated DVT patients in the future.

Keywords: Deep vein thrombosis; Post-thrombotic syndrome; Valvular incompetence

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Introduction

Venous Thrombo Embolism (VTE) is a potentially progressive disease with complex clinical sequelae, such as Pulmonary Embolisms (PE) and Deep Vein Thrombosis (DVT). Thrombosis may precede the diagnosis of malignancy by months or years, or it may only occur during treatment or hospitalization. Patients with malignancy are in a hypercoagulable state and are more likely to develop VTE during the course of their illness compared to those without malignancy. Particularly, patients receiving intravenous chemotherapy have risk of VTE is six-fold higher [1,2]. The American College of Chest Physicians (ACCP) Guideline provides recommendations that low-molecular-weight heparin remains standard of care for management of acute VTE in cancer patients. In addition, the ACCP 2016 guidelines do not state VKA versus rivaroxaban are superior to LMWHs for patients with cancer-associated VTE [3-6]. Individuals with cancer may also have a higher risk of bleeding with anticoagulation, making decisions about the use of prophylactic anticoagulants more challenging. For a decade, new oral anticoagulants (such as rivaroxaban, apixaban, or edoxaban) have been announced and replacing LMWH or UFH followed by oral anticoagulation in the majority of VTE patients with cancer [2,3,7-9]. Rivaroxaban was effective for the treatment of proximal DVT and prevention of recurrent VTE in patients receiving complete six to twelve months of anticoagulant therapy [10]. However, little information regarding the rivaroxaban treatment for acute VTE patients with malignancy has been described. The study was to assess safety and efficacy of rivaroxaban alone treatment in such patients.

Methods

The study was approved by the International Review Board of the Taipei Veteran General hospital, Taiwan (IRB Number 2015-03-015AC). This study was carried out on 46 patients with

Table 1: Demographic and clinical characteristics of the study patients.

Characteristic	Enrolled patients (n=34)
Age, mean ± SD years	70.4 ± 12.7
Female Gender, n (%)	22(64.7%)
DVT of left leg	24(70.6%)
Duration of symptoms (days)	10.9 ± 2.6
Clot locations, n (%)	
Iliofemoral	21(61.8%)
Femoropopliteal	13 (38.2%)
Predisposing factors	
Active malignancy	31(91.2%)
Breast	15
Lung	5
Cervix	3
Others	8
Smoking	4(11.8%)
Immobilization	10(29.4%)
Thrombophilia	8(23.5%)
Recent surgery	5(14.1%)
Recent trauma	2(5.9%)
Hypertension	16(47.1%)
Hyperlipidemia	13(38.2%)
Arrhythmia	8(23.5%)
DM	8(23.5%)
CAD	3(8.8%)
CVA	4(11.8%)

Recent trauma was defined as trauma that occurred 14 to 30 days before the onset of DVT. Previous orthopedic surgery was defined as surgery experienced 30 to 90 days before the onset of DVT. The scope for a classification of immobilization was 4 to 30 days before the onset of DVT. Thrombophilia was defined as documented biochemical hypercoagulable disorders, such as protein C or S deficiency and Factor V Leiden

acute proximal DVT with less than 21 days of symptom duration. The primary symptoms were limb swelling, discoloration, pain, and venous claudication in the majority of patients. Duplex sonography was first used to diagnose DVT and then to confirm the extent of DVT among the patients. Acute DVT was first diagnosed using duplex sonography, venography and or MRI.

Before the treatment, the extent of DVT was confirmed in all of patients. A Thrombus Scoring (TS) classification was assigned to each segment based on the modified criteria of Porter et al [11,12].

Rivaroxaban dosage and duration

All patients were hospitalized and administered subcutaneously with low-molecular-weight heparin (LMWH such as Enoxaparin twice daily at 1 mg/kg) without routine anti-factor Xa monitoring for at most three days. All patients were followed by rivaroxaban treatment (15 mg b.i.d. during the first 3 weeks, then 15-20 mg q.d. later on). Elastic bandage or graduated elastic compression stockings were applied on all patients, and ambulation was also initiated as soon as possible. The treatment duration was 3 months to 12 months on the basis of sonographic finding and clinical conditions. Patient characteristics and clinical parameters are assessed and summarized in (Table 1). The relevant medical history, physical examinations,

Table 2: Inclusion and exclusion criteria.

Inclusion criteria
Age 20–90 years
Onset of symptoms <21 days
First time verified deep vein
Thrombosis limited to femoropopliteal and, iliofemoral segments
Informed consent obtained.
Exclusion criteria
Bleeding diathesis
Hemorrhagic stroke
Severe renal failure - estimated creatinine clearance <25 ml min^{-1}
Severe Anemia (hemoglobin <8 gdL^{-1}
Thrombocytopenia (platelets <100 x 10^9L^{-1}

Table 3: Venous outcomes and PTS at 12 months after treatment.

Outcomes	Enrolled patients (n=34)
Cumulative patency, n (%)	
3- month	4(11.8%)
6-month	13(38.2%)
12-month	16(47.1%)
24-month	19(55.9%)
Lysis rate. (%)	
1 month	22.9 ± 16.9
3 month	46.5 ± 31.6
6 months	71 ± 28.9
12 months	77.6 ± 24.2
Femoral venous insufficiency	21 (61.8%)
1 second >RD ≧ 0.5 second	8
RD ≧ 1 second	13
12-month Post thrombotic syndrome	21 (61.8%)
12-month Villalta score	5.9 ± 3.3

RD: Reflux Duration

and diagnostic testing, including phlebography and color duplex ultrasounds, were reviewed in all patients. The complete inclusion and exclusion criteria are presented in (Table 2).

Study end points

The study endpoints were evolution of DVT, treatment safety, and efficacy. These endpoints were assessed via clinical findings, laboratory tests, and vascular laboratory instruments at pre-established times (i.e. baseline, 7 days, and the first, third, and sixth month). The tests included liver function, renal function, fibrinogen, Prothrombin Time (PT), a PTT, D-dimer, and blood and platelet counts. The safety endpoints included bleeding and serious adverse events. Major bleeding was defined as obvious bleeding, such as intracranial bleeding, gastrointestinal bleeding, and retroperitoneal hematoma, which resulted in either hemodynamic instability, a need for a blood transfusion of more than 2U, surgery, or death. All other bleeding events were regarded as minor episodes. The efficacy endpoints included early and immediate venous patency and venous functioning, which were evaluated using a Duplex ultrasound, plethysmography and Commutated Tomography (CT) plus venography, and pulmonary embolism was documented by lung scan or chest CT. All of the patients were regularly followed up

Table 4: Anatomic characteristics documented by CT venography.

Anatomic characteristics, n (%)	Femoropopliteal DVT (n=17)	Iliofeamoral DVTT(n=17)	P value
Lesion sites (left), N (%)	11(64.7)	14(82.3)	0.438
Patency, N (%)	10(58.3)	5(29.4)	0.166
Obstructive, N (%)	7(41.2)	12(70.6)	
Narrowing (small calibre, irregular wall)	3(17.6)	2(11.8)	
Occlusion (total or partial)	4(23.5)	10(58.8)	
Involved anatomic location			
Inferior vena cava	0	2	
Iliofemoral segment	0	7	
Common femoral segment (including saphenofemoral junction)	0	8	
Femoropopliteal segment	7	3	

after one week, and one, three, six twelve months. The color Doppler ultrasound was performed by vascular physicians and experienced technicians. The standardized and reproducible definitions of the degree of thrombi, identification of the five proximal deep vein segments (external iliac, common femoral,

Proximal and middle femoral, and popliteal), the four distal deep vein segments (two posterior and two anterior tibial veins), and the three superficial vein segments (long saphenous vein above and below the knee, and lesser saphenous vein). The scores for the degree of venous obstruction (i.e. 0= open vein completely free of thrombus, 1= partially occluded vein with a flow Doppler signal present, and 2= completely occluded vein with no flow signal) were determined. The TS classification assigned to each segment was based on the modified procedures of Haenen et al. and Porter et al. In each leg, a total thrombus scores before and after rivaroxaban treatment was calculated by adding the TS of all 12 vein segments (TStotal). A progression of DVT was considered when TStotal increased, a regression (i.e. complete lysis or incomplete lysis) was considered when TStotal decreased, and no changes in DVT were considered when TStotal remained the same at follow-up. Venous insufficiency was also evaluated with Doppler ultrasound, and valvular reflux of greater than 0.5 second was considered as a valve incompetence of the involved segment [13,14]. Venous Outflow Resistance (VOR) was assessed via air plethysmography [15]. A year after treatment, PTS was assessed using the Villalta scale, which comprises five symptoms (pain, cramps, heaviness, pruritus, and paraesthesia) and six signs (pretibial Oedema, skin induration, hyperpigmentation, venous ectasia, redness, and compression pain). A total score of 5-9 was considered mild PTS; 10-14 was moderate PTS; and, 15 was severe PTS [16].

Statistical analysis

The continuous data are presented as mean ± Standard Deviation (SD), and the categorical data are expressed as numbers and percentages. Differences between the femorpopliteal and iliofemoral groups were determined via a Fisher's exact test for dichotomous variables. A *P* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using statistical analysis software (SPSS 22).

Results

From January 2013 through October 2017, 46 cancers with Acute DVT of less than 21 days, who received rivaroxaban treatment, were enrolled at our institution. Of 46 patients of this study

Table 5: Bleeding and serious adverse events that occurred during the study period.

Events	No (%)
Bleeding event	9(26.5)
Major bleeding	4(11.8)
GI bleeding	3
Gross hematuria	1
Minor bleeding	15
Skin ecchymosis	4
Oral bleeding	1
Recurrent deep vein thrombosis	7(20.6)
Pulmonary embolism	3(7.5)

with symptomatic proximal deep vein thrombosis, 17 (37%) had femoropopliteal vein thrombosis, and 29 (63%) had iliofemoral vein thrombosis. During the follow-up, 12 of 46 patients were excluded in this study due to death, lost to follow -up, and incomplete treatment. Finally, 34 of all enrolled patients comprised 22 women and 12 men, with a mean age of 70.4 ± 12.7 years (20 to 90 years). Of 34 patients with cancer, 31 suffered from active malignancy. 15 patients had breast carcinoma this study. The baseline demographics and clinical characteristics of these patients were listed in (Table 3). At 3, 6, 12, and 24 months, cumulative patency was observed in 11.8%, 38.2 %, 44.1% and 55.90% of all patients. Femoral valvular incompetence was found in 21 (61.8%) patients. 19 patients developed PTS at 12 months, and the mean PTS score was 5.9 ± 3.3. Venous outcomes and PTS at 12 months was listed in (Table 4) According to the TS, lysis rate of thrombi was 46.5%, 71% and 77.6% at three, six and twelve months, respectively. All patients were examined using CT venography at 24-month follow-up. Of all 34 patients, 19 had obstructive veins, including narrowing (5) and vein occlusion (14). The19 patients had significant anatomic abnormalities, including iliofemoral narrowing and obstruction (7), left common iliac vein compression by the right common iliac artery and May–Thurner syndrome (n=2), venous stricture of the common femoral vein near the inguinal area (n=8), and inferior vena cava (IVC) (n=2), and irregular obstruction of femoropopliteal veins (n=10). Of 34 patients, 9 patients had bleeding events, including gross hematuria, ecchymosis, gingival bleeding, and UGI bleeding. All patients of this study had fresh venous thromboembolism. 9 (26.5%) patients developed recurrent deep vein thrombosis, and 3 (7.5%) had pulmonary embolism during follow-up. Four of nine patients developed a progression of thrombosis

during treatment, and five patients developed recurrent DVT within six months after treatment. The adverse effect during follow-up was present in (Table 5).

Discussion

The trial included patients with predominantly active malignancy and acute symptomatic proximal deep vein thrombosis. Although numerous studies demonstrate that rivaroxaban has significant effect on the prevention of recurrent DVT and compatible bleeding events [7,10], rare and definitive information has been known regarding regression of thrombus, and venous outcome. A review of the relevant literature suggests that LMWH greatly act on thrombus regression and prevention of recurrent DVT. The regression rate of thrombus was previously found to be roughly 50% to 70% for enoxaparin and less than 50% for UFH after six month [13,15,17-19]. This study found rivaroxaban treatment appears to achieve stable treatment of DVT and prevention of recurrent VTE and no-inferior bleeding events in the acute setting compared to anticoagulants alone [7,9,10]. According to the TS, our results showed re-canalization rate occurred in 22.9%, 46.5%, 71% and 77.6% of all patients at one week, three months, six and twelve months, respectively, and the re-canalization with rivaroxaban developed progressively and greatly after three months. Several studies suggested the resolution rate of thrombus would likely be correlated with a reduction in recurrent DVT and the prevention of PTS [20-23]. The present study indicated the resolution rate of thrombus was 77% at twelve months, and the recurrent DVT, and PTS rate was 20.6% and 61.8%, respectively. Because little knowledge about venous outcomes in DVT patients with cancer treated with rivaroxaban, the relationships between re-canalization and short-term functional venous outcomes or PTS prevention needs to be clarified in the future study.

Since there are no published randomized trials regarding rivaroxaban treatment entirely for cancer-associated DVT till now, ACCP guidelines recommend low-molecular-weight heparin remains standard of care for management of acute DVT in cancer patients. Furthermore, ACCP 2016 guidelines do not prefer VKA versus DOAC to LMWH for patients with cancer-associated DVT [3]. However, several studies found low rates of recurrent VTE (4.4, 3.8%, respectively) and major bleeding (1.3, 2.2%) in patients with active cancer and treated with Novel Oral Anti-Coagulants (NOAC) [24-27]. Similarly, major concerns regarding rivaroxaban treatment are bleeding complications and recurrent DVT. During up to five – month treatment, the incidence of major bleeding events was 11.8% (4/9), and the incidence of recurrent DVT was 20.6% (7). Both results were a bit higher than that reported by other studies. In this study, most patients (31/34) having active malignancy continued on intravenous or oral chemotherapy, and 70.6% of 34 patients received more than 6-month rivaroxaban was continued for treatment of VTE , prevention of recurrent VTE and thrombus progression. Till now, guidelines suggest LMWH should be considered in these patents at high risk and great benefit can be likely from continuing LMWH [26,27]. Further prospective larger-scale study is needed to clarify this difference.

Recent studies have demonstrated that rivaroxaban have significant effects on prevention of thrombus regression and recurrent DVT. However, to our best knowledge, few studies have reported on the venous function and patency on the thrombosed veins. Thus, only a head-to-head analysis using Doppler US and CT venography should provide substantial information regarding the evolution of DVT and the efficacy of the treatment. During follow-up, all patents were examined with computed tomography, and 19 of all DVT patients had vein obstruction compared to15 patients documented by Doppler ultrasonography plus D-dimer testing. Therefore, relative to CT venography, Doppler ultrasonography is also sensitive (89% to 100%) and specific (94% to 99%) for symptomatic DVT of the proximal veins.

The venography findings were consistent with those obtained via Doppler ultrasound. Doppler US can be conveniently and accurately used to evaluate the clot resolution during follow-up. 25-28 Among 19 obstructive patients, 12 were in the ilio feamoral lesion, and 7 were in the femoropopliteal lesion.

These 19 patients had significant anatomic abnormalities, including left common iliac vein compression by the right common iliac artery and May Thurner syndrome (n=2), venous stricture of the common femoral vein near the inguinal area (n=8), IVC (n=2) and narrowing or irregular obstruction of femoropopliteal veins (n=10) and iliofemoral veins (n=7). These findings showed that anatomic abnormality of the involved leg may influence vein patency and venous complications later in cancer patients with acute proximal DVT. Large-scale prospective randomized studies are required to determine whether alternative antithrombotic strategies are warranted in such patients.

This study has a potential limitation that should be addressed. First, this study is limited by the small sample size and the study design. Although a prospective medical database was used in this study, more longitudinal, comparative, clinical trials should be conducted with larger sample sizes to further explain the relative outcomes and safety issues in acute proximal DVT with active malignancy.

In summary, this trial enabled us to conclude that extended-duration oral rivaroxaban therapy should be considered for acute unprovoked proximal DVT. Due to the limited number of patients in the present study, large-scale prospective randomized studies that compare rivaroxaban to anticoagulant treatment alone are warranted in cancer –associated DVT patients in the future.

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