A Study on the Efficacy and Safety of Rivaroxaban in Urologic Cancer-Associated Venous Thromboembolism

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Purpose: Although direct oral anticoagulants (DOACs) are recommended as an alternative to low-molecular weighted heparin for cancer-associated venous thromboembolism (VTE), there is no firm evidence on the efficacy and safety of DOACs in patients with urologic cancer. Therefore, we compared the efficacy and safety of rivaroxaban and dalteparin for treating cancer-associated VTE in urologic cancer.

Materials and Methods: We reviewed the medical records of 124 eligible VTE patients with urologic cancers who were treated with dalteparin or rivaroxaban. The primary outcome was the composite event of clinically relevant bleeding or VTE recurrence. The secondary outcomes were VTE recurrence, clinically relevant bleeding events, and all-cause mortality.

Results: During anticoagulation period, there was no significant difference in primary and secondary outcomes between the groups. In Cox proportional hazards model for composite events, although there was no statistical significance, rivaroxaban presented lower hazard ratio (HR) than dalteparin (HR, 0.472; 95% confidence interval [CI], 0.210–1.060; $p=0.069$ in univariate analysis; HR, 0.505; 95% CI, 0.206–1.234; $p=0.134$ in multivariate analysis). In clinically relevant bleeding events, there was no significance difference between rivaroxaban and dalteparin (HR, 0.568; 95% CI, 0.238–1.358; $p=0.203$ in univariate analysis; HR, 0.617; 95% CI, 0.232–1.636; $p=0.331$ in multivariate analysis).

Conclusions: Rivaroxaban can be regarded as a valuable option for VTE in urologic cancer. Further prospective studies are warranted to prove the safety or efficacy of rivaroxaban for treating VTE in patients with urologic cancer. (Korean J Urol Oncol 2019;17:178-185)

Key Words: Anticoagulants • Dalteparin • Rivaroxaban • Urologic neoplasm • Venous thromboembolism

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INTRODUCTION

Cancer-associated venous thromboembolism (VTE) is one of the most common and fatal complications of malignancy.^{1,2} The incidence of VTE is relatively low in urologic cancer compared with other cancer types.³⁻⁵ However, the adequate management of cancer-associated VTE is important to prevent patient mortality. Anticoagulation is the mainstay of VTE treatment in which anticoagulants are ap-

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appropriately decided by the clinicians to prevent bleeding events in patients. After CLOT trial, low-molecular-weight heparin (LMWH) is regarded as the standard therapy for cancer-associated VTE.⁶ Ascribed to its convenient use, some clinicians prefer to prescribe direct oral anticoagulants (DOACs) for treating cancer-associated VTE.⁷

There are following 2 types of DOACs: direct factor Xa (rivaroxaban, edoxaban, and apixaban) and direct thrombin inhibitor (dabigatran).⁸ Currents guidelines for the treatment of VTE have listed DOACs as one of the standard therapies in the general population.⁹ However, there is no firm evidence supporting the use of DOACs in patients with cancer.¹⁰ In addition, studies have reported that DOACs increase gastrointestinal and genitourinary tract bleeding compared with other anticoagulants.¹¹⁻¹⁴

There are 2 randomized controlled trials (RCTs) suggesting DOACs as reasonable alternatives to LMWH.^{2,15-18} There were no differences in VTE recurrence and major bleeding between DOACs and LMWH, but clinically relevant nonmajor bleeding events increased in the DOACs group. There were several studies that clinically relevant nonmajor bleeding events were increased due to included patients with gastrointestinal cancer.^{19,20} Clinically relevant nonmajor bleeding is one of the deciding factors for the discontinuation or decreasing doses of anticoagulants. In addition, urologic cancer occupied only about 10% in all patients. Therefore, conclusions of both studies cannot be equally applied to all patients with urologic cancer. Because visceral malignancies with mucosal lesion could increase bleeding risk in patients with cancer, studies on the safety and efficacy of DOACs for treating urologic cancer are necessary.²¹

This study aimed to compare the efficacy and safety of rivaroxaban and dalteparin for the treatment of cancer-associated VTE in patients with urologic cancer.

MATERIALS AND METHODS

1. Study Design and Patients

This was a single-center retrospective study at Asan Medical Center (a 2,700-bed referral hospital in Seoul, Korea). From the electronic medical record system, patients with history of rivaroxaban or dalteparin treatment for urologic cancer were selected. Urologic cancer included blad-

der cancer, prostate cancer, kidney cancer, testicular cancer, and other urinary tract cancers. There were 3 inclusion criteria in this study: (1) diagnosis of primary urologic cancer, (2) diagnosis of pulmonary embolism (PE) and/or deep vein thrombosis (DVT) and (3) treatment of VTE with rivaroxaban or dalteparin between 1 January 2012 and 31 December 2017. Exclusion criteria were (1) prescription of rivaroxaban or dalteparin for 7 days or less without bleeding events; (2) no follow-up visits after the first visit; (3) rivaroxaban or dalteparin firstly prescribed at other institutions; (4) VTE lesions removed by thromboembolectomy; and (5) changing of the anticoagulant dose during therapeutic periods.

Because there was no recommendation for the treatment of cancer-associated VTE in Asan Medical Center, anticoagulant prescription was decided on clinical judgement made by responsible clinicians considering patients' condition, preference of clinicians or patients, comorbidity and so on. In rivaroxaban group, cancer-associated VTE is treated with oral rivaroxaban 15 mg twice daily for 21 days followed by 20 mg once daily. In dalteparin group, patients subcutaneously injected dalteparin 200 IU/kg once daily.

This study was approved by the Institutional Review Board of the Asan Medical Center (IRB no. 2017-0652). The requirement for informed consent was waived due to the retrospective nature of this study.

2. Measurement

We collected the patient clinical characteristics and study outcomes through retrospective review of their electronic medical records. Additionally, we calculated the score of bleeding risk factors. Bleeding risk factors included surgical history 2 weeks before anticoagulant use, concurrent use of antiplatelet agents, accompaniment of a primary or metastatic brain tumor, regionally advanced or metastatic cancer, coexisting gastrointestinal or urothelial cancer, and bevacizumab use in 6-week period before anticoagulant use.¹⁷

VTE included PE and/or DVT. PE was diagnosed by certificated radiologists via computed tomography or ventilation-perfusion scanning. Doppler ultrasonography or computed tomography venography was used for the diagnosis of DVT. Follow-up examinations were performed when clinicians suspected recurrence of VTE or prescribed imaging study for regular evaluation of cancer status.

The composite event, including any events of major bleeding, clinically relevant nonmajor bleeding events or recurrence events during anticoagulant therapy, was selected as the primary outcome in this study. We defined VTE recurrence as computed tomographic or ultrasonographic evidence of an increased extent or new occurrence of VTE during anticoagulant therapy.¹⁷ The evaluation of VTE recurrence was performed when VTE recurrence was suspected or periodical examination to assess the cancer status. Clinically relevant bleeding events were regarded as major bleeding events during anticoagulant therapy when one of the following criteria was met: (1) death-related, (2) VTE occurrence at a fatal site (intracranial, intraocular, retroperitoneal, intraspinal or pericardial) and (3) required a

transfusion of at least 2 units of packed red blood cells or a hemoglobin decrease of at least 2.0 g/dL.²² Any other clinically relevant events which were not included in the major bleeding events were regarded as clinically relevant nonmajor bleeding. Secondary outcomes included VTE recurrence rate, bleeding event during anticoagulant therapy and death until 31 March 2019.

For subgroup analysis, we defined that urothelial cancer included bladder cancer, kidney cancer and other urinary tract cancer. Other urinary tract cancer included ureter cancer and urethral cancer.

3. Statistical Analysis

Differences in categorical variables were analyzed by

Table 1. Baseline characteristics of the study cohort

Characteristic	Dalteparin (n=61)	Rivaroxaban (n=63)	p-value
Male sex	48 (78.7)	55 (87.3)	0.201
Age	68.74±9.58	68.05±11.17	0.713
Smoking			0.304
Current	11 (18.0)	6 (9.5)	
Ex-smoker	19 (31.1)	18 (28.6)	
GFR < 50 mL/min/1.73 m ²	7 (11.5)	6 (9.5)	0.723
Platelet count < 100,000/μL*	2 (3.3)	2 (3.2)	> 0.999
Cancer type			0.795
Bladder cancer	25 (41.0)	20 (31.7)	
Prostate cancer	13 (21.3)	19 (30.2)	
Kidney cancer	16 (26.2)	17 (27.0)	
Testicular cancer	1 (1.6)	1 (1.6)	
Other urinary tract cancer	6 (9.8)	6 (9.5)	
Metastasis	49 (80.3)	37 (58.7)	0.009
Coexisting cancer*	8 (13.1)	2 (3.2)	0.052
Brain lesion*	4 (6.6)	3 (4.8)	0.715
History of chemotherapy	47 (77.0)	36 (57.1)	0.018
History of radiotherapy	12 (19.7)	12 (19.0)	0.930
Pulmonary embolism	39 (63.9)	37 (58.7)	0.552
History of VTE*	0 (0)	4 (6.3)	0.119
Recent operation*	1 (1.6)	6 (9.5)	0.115
IVC filter insertion	8 (13.1)	13 (20.6)	0.264
Antiplatelet agent*	4 (6.6)	8 (12.7)	0.248
Therapeutic duration	66.78±58.49	120.57±96.14	< 0.001
Risk factors for bleeding			0.015
0	8 (13.1)	15 (23.8)	
1	41 (67.2)	26 (41.3)	
2-3	12 (19.7)	22 (34.9)	

Values are presented as number (%) or mean±standard deviation.

GFR: glomerular filtration rate, VTE: venous thromboembolism, IVC: inferior vena cava.

Difference between both groups was analyzed by the chi-square test, Fisher exact test, or independent 2-sample t-test.

*Fisher exact test.

chi-square test or Fisher exact test. Independent 2-sample t-test was used to analyze the differences in continuous variables. The time to composite event or clinically relevant bleeding event was analyzed using the Cox proportional hazard model. Time to event curves was calculated by Kaplan-Meier curves with a log-rank test. Multivariate analyses were performed to adjust the differences in clinical and demographic characteristics between dalteparin and rivaroxaban groups. History of chemotherapy, coexisting cancer and score of bleeding risk factors were included as co-variables for multivariate analysis, because they were statistically different between both study groups ($p < 0.1$).

Statistical significance was set at p -value < 0.05 . We used IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA) analytic software for statistical analysis.

RESULTS

A total of 151 patients with urologic cancer were diagnosed with PE and/or DVT between January 1, 2012 and December 31, 2017. Total 27 patients were excluded from the study, 12 were prescribed with rivaroxaban or dalteparin for 7 days or less without bleeding events, 7 were transferred to other hospitals without visiting our institute, 5 were firstly prescribed at other institutions, dose of anticoagulants was changed during anticoagulant therapy in 2, and VTE lesions in 1 were removed by pulmonary thromboembolism. Among 124 patients, 61 were included in dalteparin group and 63 in rivaroxaban group.

Fig. 1. Kaplan-Meier cumulative event rates for the composite event during 200 days.

Table 1 presents the baseline characteristics of patients in dalteparin and rivaroxaban groups. Patients in the dalteparin group had metastasis and history of chemotherapy, whereas those in the rivaroxaban group underwent respective anticoagulant therapy longer than that in dalteparin group. Patients with one bleeding risk factor were included in dalteparin group, other patients more included in rivaroxaban group.

There was no statistical difference in the composite event between the 2 groups during anticoagulant therapy (dalteparin vs. rivaroxaban group=23.0% vs. 22.2%, $p=0.923$). Kaplan-Meier curve with a log-rank test for time to composite event presented no statistical significance between the 2 groups ($p=0.063$) (Fig. 1). Other end points, such as bleeding events and mortality, did not present statistical difference between both groups (Table 2). We performed subgroup analyses for urothelial cancer and nonurothelial cancer (Tables 3, 4). There were no significant differences in primary and secondary outcomes between rivaroxaban and dalteparin in both subgroup analyses.

In the univariate analysis by Cox proportional hazards model for composite events, rivaroxaban presented 0.472-fold hazard ratio (HR) without significance (95% confidence interval [CI], 0.210–0.160, $p=0.069$) (Table 5). After adjusted for history of chemotherapy, coexisting cancer and bleeding risk factors, rivaroxaban did not present statistical significance difference in composite events (HR, 0.505;

Table 2. Primary and secondary endpoints in both groups

Variable	Dalteparin (n=47)	Rivaroxaban (n=43)	p-value
Composite event	14 (23.0)	14 (22.2)	0.923
Recurrence*	3 (4.9)	2 (3.2)	0.677
Symptomatic recurrence*	1 (1.6)	1 (1.6)	> 0.999
Bleeding	11 (18.0)	13 (20.6)	0.714
Major bleeding*	4 (6.6)	3 (4.8)	0.715
CRNM bleeding	7 (11.5)	10 (15.9)	0.477
All-cause mortality	44 (72.1)	41 (65.1)	0.398
Bleeding-related mortality*	3 (4.9)	0 (0)	0.116

Values are presented as number (%).

CRNM: clinically relevant nonmajor.

Difference between both groups was analyzed by the chi-square test or Fisher exact test.

*Fisher exact test.

Table 3. Primary and secondary endpoints in both groups with urothelial cancer

Variable	Dalteparin (n=61)	Rivaroxaban (n=63)	p-value
Composite event	11 (23.4)	11 (25.6)	0.810
Recurrence*	3 (6.4)	1 (2.3)	0.618
Symptomatic recurrence*	1 (2.1)	1 (2.3)	>0.999
Bleeding	8 (17.0)	10 (23.3)	0.460
Major bleeding*	4 (8.5)	2 (4.7)	0.679
CRNM bleeding	4 (8.5)	8 (18.6)	0.159
All-cause mortality	35 (74.5)	29 (67.4)	0.463
Bleeding-related mortality*	3 (6.4)	0 (0)	0.243

Values are presented as number (%).

CRNM: clinically relevant nonmajor.

Difference between both groups was analyzed by the chi-square test or Fisher exact test.

*Fisher exact test.

Table 4. Primary and secondary endpoints in both groups with nonurothelial cancer

Variable	Dalteparin (n=14)	Rivaroxaban (n=20)	p-value
Composite event*	3 (21.4)	3 (15.0)	0.672
Recurrence*	0 (0)	1 (5.0)	>0.999
Symptomatic recurrence*	0 (0)	0 (0)	>0.999
Bleeding*	3 (21.4)	3 (15.0)	0.672
Major bleeding*	0 (0)	1 (5.0)	>0.999
CRNM bleeding*	3 (21.4)	2 (10.0)	0.627
All-cause mortality	9 (64.3)	12 (60.0)	0.800
Bleeding-related mortality*	0 (0)	0 (0)	>0.999

Values are presented as number (%).

CRNM: clinically relevant nonmajor.

Difference between both groups was analyzed by the chi-square test or Fisher exact test.

*Fisher exact test.

Table 5. Hazard ratio for the composite event in the Cox proportional hazards model

Covariate	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Anticoagulants				
Dalteparin	1		1	
Rivaroxaban	0.472 (0.210-1.060)	0.069	0.505 (0.206-1.234)	0.134
History of CTx	1.465 (0.583-3.684)	0.417	1.284 (0.490-3.366)	0.611
Coexisting cancer	1.104 (0.259-4.709)	0.893	0.703 (0.157-3.147)	0.645
Bleeding risk factor				
0	1		1	
1	1.645 (0.601-4.500)	0.332	1.414 (0.493-4.047)	0.518
2-3	1.320 (0.396-4.405)	0.652	1.376 (0.339-4.287)	0.607

HR: hazard ratio, CI: confidence interval, CTx: chemotherapy.

Table 6. Hazard ratio for the clinically relevant bleeding event in the Cox proportional hazards model

Covariate	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Anticoagulants				
Dalteparin	1		1	
Rivaroxaban	0.568 (0.238-1.358)	0.203	0.617 (0.232-1.636)	0.331
History of CTx	1.482 (0.542-4.053)	0.443	1.307 (0.456-3.748)	0.619
Coexisting cancer	1.318 (0.306-5.674)	0.711	0.938 (0.203-4.346)	0.935
Bleeding risk factor				
0	1		1	
1	1.272 (0.456-3.547)	0.646	1.127 (0.383-3.312)	0.828
2-3	1.041 (0.298-3.644)	0.949	1.072 (0.303-3.800)	0.914

HR: hazard ratio, CI: confidence interval, CTx: chemotherapy.

Table 7. Bleeding site in both groups

Site	Total (n=24)	Dalteparin (n=11)	Rivaroxaban (n=13)
GI tract bleeding	6 (25.0)	2 (18.2)	4 (30.8)
Hematuria	10 (41.7)	3 (27.3)	7 (53.8)
Intramuscular bleeding	1 (4.2)	1 (9.1)	0 (0)
Petechiae	1 (4.2)	1 (9.1)	0 (0)
Epistaxis	1 (4.2)	0 (0)	1 (7.7)
Intracranial hemorrhage	1 (4.2)	1 (9.1)	0 (0)
Vaginal bleeding	1 (4.2)	0 (0)	1 (7.7)
Injection site bleeding	1 (4.2)	1 (9.1)	0 (0)
Hemoperitoneum	1 (4.2)	1 (9.1)	0 (0)
Operation site bleeding	1 (4.2)	1 (9.1)	0 (0)

Values are presented as number (%).

GI: gastrointestinal.

95% CI, 0.206–1.234; $p=0.134$). In addition, history of chemotherapy, coexisting cancer, and bleeding risk factors were not associated with the incidence of composite events.

Rivaroxaban presented 0.568-fold HR for clinically relevant bleeding without statistical significance in univariate analysis (95% CI, 0.238–1.358; $p=0.203$) (Table 6). After adjusting for covariates in multivariate analysis, there was no statistical significance between the 2 groups (HR, 0.617; 95% CI, 0.232–1.636; $p=0.331$). Other covariates were not associated with the incidence of clinically relevant bleeding events in univariate and multivariate analyses.

Table 7 presents the bleeding sites in both groups. In dalteparin and rivaroxaban groups, urinary tract was the most common bleeding site (27.3% and 53.8%), followed by gastrointestinal tract bleeding (18.2% and 30.8%), respectively.

DISCUSSION

From the previous 2 RCTs that compared DOACs and LMWH for the treatment of cancer-associated VTE,^{17,18} patients with urologic cancer occupied only 10% of the study group, and the results shown could not be applied to patients with urologic cancer. We previously performed retrospective studies of the bleeding risk of rivaroxaban in patient with gastrointestinal, lung and gynecologic cancer.^{23–25} In these studies, rivaroxaban was associated with higher incidence of bleeding in treatment of gastrointestinal cancer, but not in lung cancer. These results imply that the efficacy

and safety of DOACs are needed to be evaluated in each cancer type. Therefore, this study compared the efficacy and safety of rivaroxaban and dalteparin for the treatment of urologic cancer-associated VTE. To the best of our knowledge, this is the first study to compare DOACs with LMWH in urologic cancer patients with VTE. In our study, rivaroxaban and dalteparin did not present statistical difference in composite events, recurrence, bleeding, and mortality. Because rivaroxaban results in higher bleeding tendency compared with other DOACs, the other types of DOACs could be used for the treatment of urologic cancer-associated VTE.⁸

Ascribed to the different therapeutic duration between dalteparin and rivaroxaban groups, we used Cox proportional hazards model to compare time to composite events and clinically relevant bleeding events. Univariate analysis revealed no significant difference between the 2 groups. Because there were significant differences in metastatic status, duration of anticoagulant therapy, and risk factors for bleeding between the 2 groups, we performed multivariate analysis. After adjusting for covariates, there was no significant difference between the groups. Although there was no statistical significance, rivaroxaban presented less HR compared with dalteparin. Analysis for clinically relevant bleeding events also presented similar results. These results suggest the noninferiority of DOACs compared with LMWH in the treatment of urologic cancer.

In both groups, urinary tract was the most common bleeding site, followed by gastrointestinal tract. There were 45.5% and 84.6% urinary tract and gastrointestinal bleeding cases in dalteparin and rivaroxaban groups, respectively. There are several explanations for the urinary tract and gastrointestinal bleeding observed. First, DOACs were alleged to increase gastrointestinal tract bleeding compared with other anticoagulants.^{19,26,27} This might be due to the activity of unabsorbed DOACs in gastrointestinal tract.^{28,29} Second, rivaroxaban is mainly excreted through the urinary tract rather than feces.²⁸ Compared with dalteparin, the higher anticoagulants activity of rivaroxaban was observed in the urine.³⁰ We speculate that these factors cause higher incidence of gastrointestinal and urinary tract bleeding in rivaroxaban compared with dalteparin. In addition, urinary tract and gastrointestinal bleeding have been observed in other cancer types.^{18,23,24} Thus, it possible that DOACs have

more effect on the gastrointestinal and urinary tract than LMWH in inducing bleeding, and other sites are less affected by DOACs than LMWH. Although we performed subgroup analysis to prove this hypothesis, there was no statistical difference. Because small population was included in this study, this assumption needs to be evaluated by further studies, especially for urinary tract bleeding.

There are several limitations of the study. Firstly, a retrospective study with relatively small number of patients might cause selection bias. To generalize the results of the study, a large RCT is preferred. Secondly, there were several differences between the groups. To adjust for these differences, we used multivariate analysis by Cox proportional hazards model. However, there was a possibility that it may not be enough to correct these differences. Finally, there were possibilities that we could not collect all composite events. We collected the data of VTE recurrence and bleeding events via the electronic medical records in Asan Medical Center. Additionally, we used insurance data for patient mortality. However, we could not get data of VTE recurrence and bleeding events that were not electronically recorded.

CONCLUSIONS

The present study shows that rivaroxaban is safe and efficacious for the treatment of VTE in patients with urologic cancer compared with dalteparin. In addition, rivaroxaban shows less HRs than dalteparin. Thus, DOACs can be regarded as a valuable option in treating urologic cancer-associated VTE. Further prospective studies with more patients are warranted to consolidate the safety and efficacy of rivaroxaban.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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