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Original Article

Effect of Switching from the Initial Direct Oral Anticoagulant to Another One on Exacerbation of Venous Thromboembolism in Patients with Cancer: A Retrospective Study

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Objective: To determine the effect of switching from the initial direct oral anticoagulant (DOAC) to another DOAC on exacerbation of deep vein thrombosis (DVT).

Materials and Methods: We retrospectively reviewed the data of patients with advanced cancer who experienced exacerbated DVT during initial treatment with DOAC due to new venous thromboembolism (VTE). After switching to another DOAC for VTE recurrence, changes in the thrombus and bleeding were evaluated for 3 months. Eighteen patients met these criteria. We compared the effect of anticoagulant switching on the switched-drug group in those 18 patients with the effect of no anticoagulant switching on the single-drug group of patients (n=78) with a similar background.

Results: The recurrence rate of VTE in the switched-drug group was 6%. Non-major bleeding occurred in 11% of patients. Recurrent VTE occurred in 6% of patients in both the switched-drug and single-drug groups, respectively [risk ratio (RR): 0.9, 95% confidence interval (CI): 0.11–7.6]. Non-major bleeding occurred in 11% and 14% of patients in the switched-drug and single-drug groups, respectively (RR: 0.79, 95%CI: 0.19–3.2).

Conclusion: Switching DOAC may be a treatment option for exacerbation of DVT in patients with advanced cancer.

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Introduction

The American College of Chest Physicians guideline states that in patients who have recurrent venous thromboembolism (VTE), while receiving warfarin therapy or direct oral anticoagulant (DOAC) therapy, treatment should be switched to a low-molecular-weight heparin (LMWH), at least temporarily.[1)] Although LMWH is recommended, there is no insurance coverage for this treatment of VTE in Japan. Therefore, switching the anticoagulant to another DOAC or warfarin is considered for the recurrence of VTE when the patient is already receiving treatment with DOAC. No study in PubMed (National Center for Biotechnology Information) has been published about the effectiveness of switching the initial DOAC to another one (anticoagulant switching) for VTE.

Cancer is a risk factor for thrombosis, and patients with cancer are 4–7 times more likely to have a VTE than patients without cancer.[2,3)] The recurrence rate of VTE is reported to be three times higher in patients with cancer than in patients without.[4,5)] Furthermore, it is usually difficult to control the warfarin level of patients with cancer because of drug interactions and anorexia.[6,7)]

In this study, we evaluated the effect of anticoagulant switching on exacerbation of deep vein thrombosis (DVT) in patients with cancer receiving initial therapy with a DOAC.

Materials and Methods

We retrospectively reviewed the data of patients with advanced cancer who experienced exacerbated DVT during initial treatment with DOAC due to new VTE between September 2015 and October 2017 at Shizuoka Cancer Center. VTE was defined as proximal DVT and/or pulmo-

nary thromboembolism (PE).

After anticoagulant switching, changes in the thrombus and bleeding were evaluated for 3 months. A patient in whom the thrombus increased or appeared new was regarded as having a recurrence of DVT. The thrombus was evaluated by echography or contrast-enhanced computed tomography (CT). We categorized bleeding as confirmed major bleeding and non-major bleeding.[8,9] DOAC was administered according to the drug package insert.

We compared the effect of anticoagulant switching on the switched-drug group in 18 patients with the effect of no anticoagulant switching in the single-drug group (first-line therapy with a DOAC) of another group of patients with a similar background that we analyzed previously using the same endpoints of the switched-drug group.[10] The endpoints were the bleeding rate and recurrence rate for 3 months after the start of treatment. Patients in whom thrombosis was not evaluated by echography or CT after 3 months were excluded from the assessment of VTE recurrence.

Statistical analysis

To analyze differences in patient background characteristics, Fisher's exact test or Wilcoxon's rank sum test was used. The difference between each patient group was evaluated using Fisher's exact test. Statistical significance was set at $p<0.05$. The analysis was performed with JMP 9 (SAS Institute Inc., Cary, NC, USA).

Results

Among 18 patients, the median age was 67 years, mean (±2 standard deviation); body weight was 55.0 (12.5) kg; and creatinine level was 0.70 (0.26) mg/dL. Fifteen patients had undergone chemotherapy, and eight were complicated with PE at the start of anticoagulant switching. Types of cancer were lung cancer (n=6), pancreatic cancer (n=3), colorectal cancer (n=2), and other (n=7). The recurrence of VTE with anticoagulant switching occurred in one patient (6%). There was no incidence of major bleeding. Non-major bleeding occurred in two patients (11%) (**Table 1**). The treatment effects of anticoagulant switching were as follows: thrombus reduction, 10 patients; no thrombus change, seven patients; and thrombosis exacerbation, one patient (**Table 2**). Non-major bleeding included melena and hematuria. In patients with thrombus reduction or disappearance, DOAC was changed as follows: from apixaban to 60 mg edoxaban (n=1), 60 mg edoxaban to apixaban (n=1), 30 mg edoxaban to apixaban (n=5), rivaroxaban to 60 mg edoxaban (n=1), and rivaroxaban to 30 mg edoxaban (n=2). In patients without thrombus change, DOAC was changed as follows: from apixaban to 60 mg edoxaban (n=2), 30 mg edoxaban to apixaban (n=2), rivaroxaban to apixaban (n=1), and rivaroxaban to 30 mg edoxaban (n=2). In patients with thrombus propagation, DOAC was changed from apixaban to 30 mg edoxaban (**Table 3**).

Next, we compared the effect of anticoagulant switching on the switched-drug group with that of no anticoagulant switching on the single-drug group (first-line DOAC treatment) in our hospital.[10] Patient background charac-

Table 1 VTE recurrence and bleeding in second-line therapy after switching the direct oral anticoagulant (N=18)

	n	%
VTE recurrence	1	6
Non-major bleeding	2	11
Major bleeding	0	0

VTE: venous thromboembolism

Table 2 Treatment effect after switching the initial DOAC to a second DOAC (anticoagulant switching)

Treatment effect after switching the DOAC	n	%
Thrombus reduction or disappearance	10	56
No thrombus change	7	39
Thrombus propagation	1	6

DOAC: direct oral anticoagulant

Table 3 Details of the initial and switched direct oral anticoagulant treatment

	Initial anticoagulant	Switched anticoagulant	n	%
Thrombus reduction or disappearance	Edoxaban (60 mg)	Apixaban	1	6
	Edoxaban (30 mg)	Apixaban	5	28
	Rivaroxaban	Edoxaban (60 mg)	1	6
		Edoxaban (30 mg)	2	11
	Apixaban	Edoxaban (60 mg)	1	6
No thrombus change	Edoxaban (30 mg)	Apixaban	2	11
	Rivaroxaban	Edoxaban (30 mg)	2	11
		Apixaban	1	6
	Apixaban	Edoxaban (60 mg)	2	11
Thrombus propagation	Apixaban	Edoxaban (30 mg)	1	6

Table 4 Comparison of patient background characteristics between the switched-drug and single-drug groups

		Switched-drug group (n=18)	Single-drug group (n=78)	p-value
Age, years	Median (range)	67 (42–77)	65.5 (47–94)	0.85
Sex	Male/female	10/8	40/38	0.80
Body weight	Mean (standard deviation), kg	55.0 (12.5)	57.7 (10.3)	0.30
Creatinine level	Mean (standard deviation), mg/dL	0.70 (0.26)	0.70 (0.20)	0.93
Hemoglobin level	Mean (standard deviation), g/dL	9.9 (1.5)	11.6 (2.2)	0.001
Serum platelet count	Mean (standard deviation), 10^4/μL	25.3 (12.2)	20.9 (8.4)	0.16
Chemotherapy	Treated/not treated	15/3	42/36	0.03
Pulmonary thromboembolism	Yes/no	8/10	39/39	0.80

Table 5 Comparison of VTE recurrence and bleeding in the switched-drug and single-drug groups

A. VTE recurrence

	Switched-drug group (n=18)	Single-drug group (n=65)	Risk ratio (95% confidence interval)	p-value
VTE recurrence	6%	6%	0.90 (0.11–7.6)	1.00

B. Bleeding

	Switched-drug group (n=18)	Single-drug group (n=78)	Risk ratio (95% confidence interval)	p-value
Non-major bleeding	11%	14%	0.79 (0.19–3.2)	1.00
Major bleeding	0%	0%	—	—

VTE: venous thromboembolism

teristics showed a significant difference in the hemoglobin level and history of chemotherapy (**Table 4**). Compared with the single-drug group, the switched-drug group had a lower hemoglobin value and more of them were undergoing chemotherapy. In the single-drug group, 65 patients were evaluated for the recurrence of VTE because the change in the thrombus was not evaluated at 3 months in 13 patients. Recurrent VTE in the switched-drug and single-drug groups occurred in 6% of patients [risk ratio (RR): 0.9, 95% confidence interval (CI): 0.11–7.6] (**Table 5A**). Non-major bleeding occurred in 11% and 14% of patients in the switched-drug and single-drug groups, respectively (RR: 0.79, 95%CI: 0.19–3.2). There were no significant statistical differences in data between these treatment groups. There was also no incidence of major bleeding (**Table 5B**).

Discussion

In our small retrospective cohort, the recurrence of VTE after anticoagulant switching was 6%. The switched-drug group, which was treated using a different DOAC for VTE recurrence, showed similar results to those of the single-drug group for newly diagnosed VTE in the therapeutic effect and bleeding ratio. These findings suggested that switching DOAC may be effective for preventing the recurrence of VTE.

In atrial fibrillation, switching DOAC was effective for patients in whom left atrial thrombus developed during the oral administration of DOAC.[11,12] Pharmacological properties of each DOAC are different.[13] Therefore, patients with cancer, who usually have changes in renal function, body weight, and concomitant drugs, may achieve a therapeutically effective plasma level of anticoagulation by switching to a different DOAC.

Edoxaban is administered at a reduced dose for a body weight of ≤60 kg. When the patient's body weight is ≤60 kg, changing edoxaban to apixaban or rivaroxaban has the effect of increasing the DOAC dose. However, if the patient's body weight is ≤60 kg, changing DOAC to edoxaban has the effect of reducing the DOAC dose. In this study, thrombus propagation was found when DOAC was switched to one with a reduced dose. The American College of Chest Physicians guideline states that in patients who have recurrent VTE and have been taking long-term LMWH, the LMWH dose should be increased by about one-quarter to one-third.[1] At the time of recurrence of VTE, increasing the doses of medication is recommended so it may be better to avoid switching DOAC to one with a reduced dose. In addition, patients who newly

experienced non-major bleeding in the switched-drug group were all patients who were switched to a DOAC with an increased dose.

This study has some limitations. For VTE in patients with cancer, the recurrence of VTE was 7.9% with treatment with edoxaban.[14] As described earlier, the number of patients with VTE recurrence while receiving DOAC treatment was small, and the number of patients in this study was very small. In order to confirm the effect of anticoagulant switching, a comparison between switching from one DOAC to another and switching from DOAC to LMWH or warfarin is essential. In the future, prospective studies with more cases are needed.

Conclusion

In patients with advanced cancer and exacerbation of DVT, a thrombus recurrence rate of 6% was observed after anticoagulant switching for VTE. Switching DOAC may be a treatment option for exacerbation of DVT in patients with advanced cancer. With the advent of DOAC therapy, the options for VTE treatment have increased. It is necessary to confirm the effectiveness of secondary therapy for recurrent VTE, including switching DOACs.

Disclosure Statement

The authors declare no conflict of interest.

Author Contributions

Study conception: TO, KI
Analysis: TO
Investigation: TO, KI
Writing: TO
Critical review and revision: all authors
Final approval of the article: all authors
Accountability for all aspects of the work: all authors

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