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ORIGINAL ARTICLE

# Use of direct oral anti-coagulants for the treatment of venous thromboembolism in patients with advanced cancer: a prospective observational study

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## Abstract

**Background** The efficacy of direct oral anti-coagulants (DOACs) for the treatment of venous thromboembolism (VTE) in Japanese patients with advanced cancer is largely unknown.

**Methods** This prospective single-center observational study enrolled Japanese patients with unresectable advanced cancer who started DOAC treatment for new-onset VTE between December 2015 and May 2018. Patients were followed for 3 months to evaluate bleeding and VTE recurrences. The primary study endpoint was major and non-major bleeding.

**Results** One hundred and forty-five of 147 enrolled patients were analyzed. Of these, 8 [5.5%, 95% confidence interval (CI) 2.8–10.5] and 29 patients (20%, 95% CI 14.3–27.2) experienced major and non-major bleeding, respectively. Patients with bleeding were more likely to have a poor performance status (PS) [hazard rate (HR) 2.04, 95% CI 1.15–3.63] and more frequent use of non-steroidal anti-inflammatory drugs (NSAIDs) (HR 2.75, 95% CI 1.62–4.67) relative to those without bleeding. In a multivariate analysis, combined DOAC and NSAID use correlated significantly with bleeding (odds ratio 4.63, 95% CI 1.70–12.9, $p = 0.003$). Among 105 of 145 patients included in the VTE recurrence assessment, 9 experienced a VTE recurrence (8.6%, 95% CI 4.6–15.5).

**Conclusions** Our findings confirm the risk of bleeding during DOAC treatment for VTE in Japanese patients with advanced cancer, particularly those with poor PS and those using NSAIDs. The risk of bleeding in these patients may be reduced by avoiding the combined use of DOACs and NSAIDs.

**Keywords** Advanced cancer · Venous thromboembolism · Pulmonary thromboembolism · Direct oral anti-coagulant · Bleeding · Cardio-oncology

## Introduction

Cancer is a risk factor for thrombosis. Therefore, cancer patients face a high risk of developing venous thromboembolism (VTE), the incidence of which is four–sevenfold higher in this population relative to non-cancer patients [1, 2]. Among cancer patients, those with metastatic advanced cancer face a higher risk of VTE, compared to patients with local disease [3].

Currently, VTE is treated using anti-coagulation therapies. However, cancer patients were reported to have a relatively higher risk of VTE recurrences and bleeding,

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compared to non-cancer patients [4–6]. Accordingly, low-molecular-weight heparin is recommended for the treatment of VTE in cancer patients. However, this treatment is not currently covered by the Japanese health insurance system [7, 8].

Regarding other options, direct oral anti-coagulants (DOACs) were associated with a lower risk of bleeding relative to warfarin in a phase III trial of VTE treatment [6, 9], and a similar outcome was observed in a subgroup analysis of cancer patients in phase III trials [10, 11]. Furthermore, the results of a randomized phase II trial of apixaban and placebo for the prevention of VTE in patients with advanced or metastatic cancer demonstrated that a 3-month course of apixaban was well tolerated in this population [12].

The above findings suggest that DOACs may be useful for the treatment of VTE in Japanese patients with advanced cancer. However, this topic has not previously been reported. Therefore, we conducted a prospective single-center observational study to evaluate the risk of bleeding during DOAC therapy for VTE in Japanese patients with advanced cancer (V LEAD study).

## Patients and methods

### Patient selection

Patients older than 20 years of age, patients with advanced metastatic cancer, those with incurable cancer, deep vein thrombosis (DVT) and/or pulmonary thromboembolism, confirmation of thrombus by echography or contrast-enhanced computed tomography (CT) on the day before VTE treatment initiation and planned to use a DOAC were deemed eligible for the study. All participants provided consent to participate in the examination. Patients who used anti-coagulant medications other than DOACs or anti-platelet drugs, had diseases other than VTE for which anti-coagulation therapy was required (e.g., atrial fibrillation, mechanical valve replacement), had a history of intracranial hemorrhage or active bleeding, were scheduled to receive thrombolytic therapy, had severe renal dysfunction (serum creatinine: 1.5 mg/dL or more) or a platelet count of ≤ 100,000/μL, or were otherwise deemed unsuitable for safe participation by a physician were considered ineligible and excluded from this study.

The initial diagnosis of DVT included a non-compressible vein at ultrasonography and an intraluminal filling defect on contrast-enhanced CT of the legs. The initial diagnosis of pulmonary thromboembolism was defined as an intraluminal filling defect in the pulmonary artery on contrast-enhanced CT [6].

### Study treatment

Anti-coagulant therapy was administered to eligible patients. Apixaban was administered according to the manufacturer's instructions as follows: 10 mg per os (po) twice daily (BID) for 7 days, and 5 mg po BID thereafter. Edoxaban was administered at a dosage of 60 mg po daily for patients with a body weight ≥ 60 kg or 30 mg po daily for those with a body weight < 60 kg or impaired renal function, according to the manufacturer's instructions. Rivaroxaban was administered as follows: 15 mg po BID for 21 days, and 15 mg po daily thereafter. Patients in the edoxaban group were administered pre-treatment with unfractionated heparin or fondaparinux for a maximum of 7 days. Anti-coagulants were discontinued when necessary.

### Outcome measures

Endpoint assessment was conducted after 12 weeks in a previous study involving DOAC use in patients with advanced or metastatic cancers [12]. Therefore, the present study applied an observational period of 12 weeks (± 14 days) from the date of DOAC treatment initiation. If DOAC treatment was discontinued within 12 weeks from the treatment start date, the observation period was defined from the date of initiation to the date of discontinuation of DOAC treatment.

The primary endpoint of this study was the incidence of major and non-major bleeding during the observation period after the initiation of DOAC treatment. We also evaluated minor bleeding episodes. Major bleeding was defined as visible bleeding, signs of bleeding, and obvious bleeding that could be confirmed by ultrasonography, CT, and MRI along with one of the following conditions: a decrease in hemoglobin levels of ≥ 2.0 g/dL; requirement for > 2 units of erythrocyte blood transfusion; intracranial, intrathecal, intraocular, retroperitoneal, or intraarticular bleeding; epicardial hemorrhage; intramuscular hemorrhage with compartment syndrome, or bleeding associated with mortality [13]. Non-major bleeding was defined as an episode affecting hemodynamics or requiring hospitalization, subcutaneous hematoma ≥ 25 $cm^2$ or traumatic subcutaneous hematoma ≥ 100 $cm^2$, intramuscular hematoma confirmed by ultrasonography, epistaxis (more than twice in 24 h) lasting ≥ 5 min or requiring treatment, naturally appearing gum hemorrhage (not caused by meals or toothpaste) or gingival bleeding for ≥ 5 min, naturally appearing macroscopic hematuria or hematuria persisting for ≥ 24 h after urinary catheter insertion, gastrointestinal bleeding, melena, hematemesis, rectal bleeding (indicated by spotty

bleeding on toilet paper), hemoptysis, and other bleeding requiring medical intervention, unexpected patient consultation because of bleeding, telephone contact, unexpected anti-coagulant interruption, and bleeding with effects on daily life (e.g., pain and functional disorders) [14]. Minor bleeding was defined as all minor and non-clinically problematic bleeding episodes that did not meet the definitions of major and non-major bleeding.

Furthermore, we evaluated recurrences of VTE, as well as potential factors contributing to bleeding events. VTE recurrence was defined as a recurrence of PE objectively confirmed by imaging, a recurrence of DVT, or death due to PE. A PE recurrence was diagnosed from the new onset of contrast deficiency in the pulmonary blood vessel on contrast-enhanced CT. DVT recurrence was defined as the appearance of a new uncompressed vein on ultrasonography or a thrombus that increased by ≥4 mm in diameter at full compression [14]. Patients in whom VTE recurrence was not evaluated were excluded from our assessment of this parameter.

### Statistical methods

A previous phase III trial of edoxaban reported an overall bleeding rate was 8.5% and a rate of 18.3% in a subgroup of patients with active cancer [6]. Therefore, we set the overall bleeding rate threshold and expected bleeding rate at 8.5% and 18.3%, respectively, in the present study. To reach a significance level of 5% (two-sided) and statistical power of 90%, we calculated the minimum required sample size of 123 patients. As the aforementioned phase III trial reported a DOAC discontinuation rate of 11.8% within 3 months [6], we calculated a planned sample size of 147 patients with the assumption of a 20% exclusion rate.

For the statistical analysis, we confirmed the number of bleeding and recurrent VTE events, determined the corresponding frequencies, and calculated the 95% confidence intervals (CIs). We also evaluated factors related to bleeding. Wilcoxon's rank-sum test or Fisher's exact test was used for comparisons between the two groups. A multiple logistic regression analysis was used to conduct a multivariate analysis of potential factors affecting bleeding. A $P$ value $<0.05$ was considered to indicate statistical significance. Data were analyzed using JMP 9 software (SAS, Institute Inc., Cary, NC, USA).

### Ethics

Our institutional review board approved the design of this study. All enrolled patients provided written informed consent.

## Results

### Patients

One hundred and forty-seven patients were enrolled from December 2015 to May 2018. Of these, 145 patients were examined; one patient refused participation while another patient was excluded because the dosage was beyond the protocol treatment. The characteristics of these 145 patients are shown in Table 1. Notably, 122 and 23 patients had performance status (PS) of 0–1 or 2–3, respectively. Lung and colorectal cancers were most common, affecting 54 and 23 patients, respectively. Apixaban, edoxaban, and rivaroxaban were administered to 68, 63, and 14 patients, respectively, and non-steroidal anti-inflammatory drugs (NSAIDs) were administered to 20 patients.

Thirteen patients died within the observation period due to cancer progression. Nine patients stopped DOAC therapy before 12 weeks due to bleeding, while 21 stopped DOAC before 12 weeks for other reasons including, cancer death ($n=10$), cancer progression ($n=4$), recurrence of DVT ($n=4$), patient's decision ($n=1$), patient's decision due to the adverse event of dizziness ($n=1$), and death by pulmonary thromboembolism ($n=1$).

### Outcomes

Bleeding was assessed in all 145 patients. The primary outcomes, major and non-major bleeding, occurred in 8 (5.5%, 95% CI 2.8–10.5) and 29 patients (20%, 95% CI 14.3–27.2), respectively, while minor bleeding occurred in 44 patients (30.3%, 95% CI 23.4–38.3) (Table 2). The sites of major and non-major bleeding are presented in Table 3. In this study, major bleeding events except intracranial hemorrhage were accompanied by blood transfusion or a reduction in hemoglobin levels (≥2.0 g/dL). No fatal bleeding events were recorded. In a comparison of patients without bleeding, those with major or non-major bleeding had significantly worse PS (2.3) [hazard ratio (HR) 2.04, 95% CI 1.15–3.63, $p=0.034$] and had more frequently used NSAIDs (HR 2.75, 95% CI 1.62–4.67, $p=0.002$). In a multivariate analysis, the combined use of DOACs and NSAIDs correlated significantly with bleeding (odds ratio 4.63, 95% CI 1.70–12.9, $p=0.003$).

VTE recurrence was evaluated in 105 of 145 patients. An assessment revealed that 9 patients (8.6%, 95% CI 4.6–15.5) developed recurrent VTE (Table 4). One patient died due to pulmonary thromboembolism.

**Table 1** Characteristics of patients at baseline

| Patient characteristics | | |
|---|---|---|
| Age | Median (range), years | 68 (33 88) |
| Sex | Male | 58 |
| | Female | 87 |
| Performance status | 0 | 48 |
| | 1 | 74 |
| | 2 | 19 |
| | 3 | 4 |
| | 4 | 0 |
| Body weight | Mean (standard deviation) kg | 56.3 (10.0) |
| Body mass index | Mean (standard deviation) $kg/m^2$ | 22.2 (3.6) |
| Creatinine | Mean (standard deviation) mg/dL | 0.69 (0.20) |
| Platelet count | Mean (standard deviation) $10^4/L$ | 25.2 (10.6) |
| Hemoglobin | Mean (standard deviation) g/dL | 11.6 (1.6) |
| Chemotherapy | Present at time of venous thromboembolism (n) | 93 |
| | Absent at time of venous thromboembolism | 52 |
| Anti-coagulant drug | Apixaban | 68 |
| | Edoxaban | 63 |
| | Rivaroxaban | 14 |
| Pulmonary thromboembolism | Yes | 42 |
| | No | 103 |
| Type of cancer | Lung | 54 |
| | Colorectal | 23 |
| | Gastric | 12 |
| | Pancreatic | 11 |
| | Ovarian | 10 |
| | Others | 35 |

**Table 2** Outcomes of bleeding events

| | *n* | % | 95% Confidence interval |
|---|---|---|---|
| Major bleeding | 8 | 5.5 | 2.8–10.5 |
| Non-major bleeding | 29 | 20.0 | 14.3–27.2 |
| Minor bleeding | 44 | 30.3 | 23.4–38.3 |

**Table 3** Types of bleeding lesions (with some patient overlap)

| Bleeding | Site | *n* |
|---|---|---|
| Major bleeding | Tumor | 2 |
| | Melena | 2 |
| | Intracerebral | 1 |
| | Gastrointestinal | 1 |
| | Hematuria | 1 |
| | Hemoptysis | 1 |
| Non-major bleeding | Melena | 12 |
| | Tumor | 4 |
| | Hematuria | 4 |
| | Epistaxis | 4 |
| | Bleed of instillation site | 3 |
| | Others | 5 |

## Discussion

In this V LEAD study, 5.5% and 20% of patients experienced major and non-major bleeding events, respectively. Among the 8 patients with major bleeding, one patient developed major bleeding in the context of intracerebral hemorrhage while all other cases involved bleeding with blood transfusion or with decreased hemoglobin level. No fatalities associated with bleeding occurred during the study.

Regarding the treatment of VTE in active cancer patients, the Hokusai VTE cancer study reported that major bleeding and non-major bleeding by edoxaban were 6.9% and 14.6%, respectively, by at least 6 months and up to 12 months. Furthermore, that study reported a major bleeding of 6.2% rate in a subgroup of patients with metastatic cancer [15]. Furthermore, a study of rivaroxaban (SELECT-D study) reported major bleeding and

**Table 4** Outcomes of recurrences of venous thromboembolism

| VTE recurrence | *n* |
|---|---|
| Death due to PE | 1 |
| Recurrence of DVT | 8 |

*VTE* venous thromboembolism, *PE* pulmonary thromboembolism, *DVT* deep vein thrombosis

non-major bleeding rates of 6% and 13%, respectively, in active cancer patients undergoing treatment for VTE, although the dosage used in that study differs from the available dosage in Japan [16]. We note that the SELECT-D study did not report the results only for patients with advanced cancer. The differences in the study methods and observation periods made it impossible to compare our results with those of the Hokusai VTE cancer or SELECT-D studies. However, we observed a non-major bleeding rate of 20% in a 3-month period, which is higher than the rates reported by the previous two studies. Active cancer is generally defined as recurrent, local, and early cancers, in addition to advanced cancer [15, 16]. The Hokusai VTE cancer study and SELECT-D study reported that advanced cancer patients with metastasis comprised 52.5% and 58% of the study populations, respectively. By contrast, our study included only patients with advanced metastatic cancer. As cancer patients face a higher risk of bleeding as the disease progresses [17], we considered bleeding to be more likely in a population comprising only patients with advanced cancer, compared to all patients with active cancer. Furthermore, we noted that the Hokusai VTE cancer study reported an average patient body weight of 78.8 kg, while the SELECT-D study reported an average BMI of 26.7 kg/m$^2$. Our study involved only Japanese patients and observed a mean body weight of 56.3 kg and mean BMI of 22.2 kg/m$^2$, both of which were lower than the corresponding values in previous studies. These factors may explain the high rate of non-major bleeding in our study.

In this V LEAD study, using NSAIDs was related to major and non-major bleeding. An increased risk of bleeding has been observed in patients with atrial fibrillation who are treated with a combination of anti-coagulant therapy and NSAIDs [18]. Furthermore, the combination of rivaroxaban and NSAIDs during the treatment of VTE led to a significant increase in bleeding [19]. Currently, NSAIDs are often used to treat cancer pain in patients with advanced cancer. Therefore, avoiding the use of NSAIDS or switching NSAIDs to other analgesics during DOAC therapy may help to reduce bleeding events during the treatment of VTE in patients with advanced cancer.

In this study, patients with poor PS more frequently experienced bleeding, compared to patients with a good PS. As the PS usually deteriorates as cancer progresses, the high rate of bleeding associated with a poor PS may overlap with the increased risk of bleeding in patients with more advanced or more serious cancer [17]. Furthermore, current recommendations regarding VTE treatment in cancer patients suggest the continuation of anti-coagulant therapy, regardless of the risk of bleeding [20, 21]. However, as patients with advanced cancers experience a decrease in PS with disease progression, prophylactic anti-coagulation therapy against VTE should potentially be avoided during hospitalization for palliative treatment [22]. However, the criteria for discontinuing anti-coagulant therapy for VTE in patients with worsening PS have not been clarified. In the future, these criteria should be evaluated for patients experiencing cancer progression or a decline in PS.

This study had several limitations of note. First, as we included only advanced cancer patients with metastasis, the primary outcome was evaluated only during a period of 3 months. Therefore, the risks associated with longer-term DOAC treatment remain unknown. Second, it will be necessary to compare the results of DOACs, and of different types of DOACs, with those of warfarin in a Japanese study to confirm the usefulness of the former in patients with advanced cancer. A retrospective study of Japanese patients with advanced cancer found that DOAC may be associated with relatively fewer bleeding or VTE recurrence events, compared to warfarin [23]. Currently, we are awaiting the results of a comparative study of DOAC versus warfarin or DOAC versus another DOAC for the treatment of VTE in Japanese patients with advanced cancer. Third, the risk of VTE, as well as the clinical course and cancer treatment, differ depending on cancer type [24, 25]. Therefore, studies of cancer-related VTE should assess the effect of cancer type. Fourth, it is difficult to distinguish non-bleeding adverse events caused by DOACs from events caused by anti-cancer drugs or cancer-related events. Therefore, we were unable to evaluate non-bleeding adverse events.

## Conclusions

This study confirmed the risk of bleeding during VTE treatment in patients with advanced cancer. In this population, the bleeding rate may be reduced by avoiding the combined use of DOACs and NSAIDs.

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### Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest.

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