Assessment of the Safety and Efficacy of Edoxaban for the Treatment of Venous Thromboembolism Secondary to Active Malignancy

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Objective: To assess the safety and efficacy of edoxaban for the treatment of venous thromboembolism (VTE) secondary to active malignancy.

Materials and Methods: We enrolled 48 patients with newly diagnosed VTE secondary to active malignancy that was treated with oral edoxaban for 1 year between September 2014 and August 2015. We retrospectively examined the presence or absence of recurrent symptomatic VTE, VTE-related mortality, and bleeding events.

Results: No recurrent symptomatic VTE or VTE-related deaths were recorded, enabling efficient assessment. Treatment safety was determined based on the reports of bleeding. Bleeding was reported in two patients, with serious bleeding in one of them.

Conclusion: Edoxaban is safe and effective for the treatment of VTE secondary to active malignancy.

Keywords: edoxaban, DOAC, venous thromboembolism, malignancy

Introduction

Venous thromboembolism (VTE) is an important factor affecting the prognosis of patients with malignancy. In Western countries, the risk of VTE is 5–7 times higher in patients with malignancy than in those without malignancy.1 In Japan, 27% of the patients with VTE of known cause had malignancy.2 In a report of 4,622 outpatients with malignancy, the rate of VTE-related mortality was 9%, second only to cancer-related deaths.3 Anticoagulant therapy is the fundamental treatment of choice for the initial management of VTE. In Japan, unfractionated heparin (UFH) has been used as an injectable medication and warfarin as an oral medication. In September 2014, edoxaban, a nonvitamin K antagonist oral anticoagulant, became available for the treatment of VTE. The usefulness of non-vitamin K antagonist oral anticoagulants against venous thrombosis has been reported4; however, few reports have evaluated the treatment outcomes of edoxaban for VTE secondary to active malignancy. Therefore, we examined the efficacy and safety of edoxaban for the treatment of VTE secondary to active malignancy.
quciniidine sulfate, verapamil hydrochloride, erythromycin, and cyclosporine; and those with creatinine clearance between 30 mL/min and 50 mL/min, as calculated using the Cockcroft–Gault formula. Patients received no other antithrombotic drugs except for edoxaban during the follow-up period. Chronic kidney disease was defined as a creatinine clearance of $\leq$ 60 mL/min.

**Follow-up**

For the assessment of treatment efficacy, the presence or absence of recurrent symptomatic VTE and VTE-related mortality were evaluated in all patients. Pulmonary embolism was considered the cause of death if there was objective documentation or if death could not be attributed to any other documented cause and pulmonary embolism could not be excluded. D-dimer levels, CT scan images, and ultrasonographic images of the veins of the lower extremities were examined within 1–3 months of treatment initiation. For assessing treatment safety, possible hemorrhagic complications were assessed. Massive bleeding events were defined based on the following criteria given by the International Society on Thrombosis and Haemostasis (ISTH): (1) decrease in the hemoglobin level by $\geq$ 2 g/dL; (2) the need for at least two units of packed red blood cell transfusion; (3) bleeding at one or more intracranial, intraspinal, intraocular, intrapericardial, intraarticular, intramuscular (with compartmental syndrome), or retroperitoneal sites; and (4) clinically apparent acute bleeding, equivalent to lethal bleeding events. Patients were followed up for 1 year, and the treatment efficacy and safety were assessed (mean follow-up: 10.2 $\pm$ 3.5 months).

**Statistical analyses**

All continuous variables were presented as mean $\pm$ standard deviation (SD) and dichotomous data as percentages. Nonparametric data were expressed as medians [interquartile range]. The Wilcoxon signed rank test was used to analyze changes in the D-dimer level before and after the treatment. A P-value of < 0.05 was considered statistically significant. Statistical analyses were performed using the Microsoft Excel statistics software, ver. 2012.

**Ethics**

This study was approved by the Ethics Committee of Japanese Red Cross Musashino Hospital and was conducted in accordance with the principles of the Declaration of Helsinki.

**Results**

Demographic and clinical data of the subjects are shown in Table 1. The study population included 18 patients with pulmonary thromboembolism, one with submassive pulmonary thromboembolism, and 17 with nonmassive pulmonary thromboembolism. No recurrent symptomatic VTE or VTE-related deaths were recorded. During follow-up, 12 patients (25%) died of malignancy. The D-dimer level was measured in 46 patients (96%) before and after the treatment, and a significant decrease from 3.75 (5.5) µg/mL to 0.5 (0) µg/mL (Wilcoxon signed rank test,

| Table 1  | Baseline characteristics of the study participants (n=48) |
|----------------------|-----------------|
| Age, years | 66 $\pm$ 12 |
| Male (%) | 22 (45.8) |
| Body weight, kg | 57 $\pm$ 12 |
| Smoking history (%) | 17 (35.4) |
| Hypertension (%) | 15 (31.3) |
| Diabetes (%) | 6 (12.5) |
| Dyslipidemia (%) | 6 (12.5) |
| Atrial fibrillation (%) | 0 (0) |
| Cardiovascular disease (%) | 2 (4.2) |
| Cerebral vascular disease (%) | 3 (6.3) |
| Chronic kidney disease (%) | 12 (25) |
| Creatinine clearance, mL/min | 81 $\pm$ 33 |

| Site of primary malignancy (%) |
|--------------------------------|
| Stomach | 8 (16.7) |
| Colon | 7 (14.6) |
| Gynecologic | 11 (22.9) |
| Lung | 7 (14.6) |
| Breast | 4 (8.3) |
| Brain | 4 (8.3) |
| Prostate | 4 (8.3) |
| Pancreas | 1 (2.1) |
| Kidney | 1 (2.1) |
| Lymphoma | 1 (2.1) |
| Unknown | 1 (2.1) |

| Stage (%) |
|---------|
| I | 16 (36.4) |
| II | 3 (6.8) |
| III | 2 (4.5) |
| IV | 23 (52.3) |

| Surgery history | During chemotherapy |
|-----------------|---------------------|
| 29 (60.4) | 35 (72.9) |

Values are presented as mean $\pm$ standard deviation (SD) values or as n (%). For the stage classification, brain tumor was excluded. All continuous variables are presented as mean $\pm$ SD and dichotomous data as percentages. RBC: red blood cell count; Ht: hematocrit; Hb: hemoglobin; WBC: white blood cell count; Plt: platelet count; PE: pulmonary thromboembolism; DVT: deep vein thrombosis.
P < 0.05) was observed (Fig. 1). The D-dimer level was normalized (≤ 0.5) in 42 patients (91.3%). After treatment, CT scanning, ultrasonography of the veins of the lower extremities, or both was performed in 33 patients (75%). On evaluating the post-treatment CT scan images of 19 patients (40%), resolution and reduction of pulmonary thrombosis was observed in 12 and two patients, respectively, and disappearance and reduction of deep vein thrombosis (DVT) was observed in three and two patients, respectively. Ultrasonography of the veins of the lower extremities was performed in 24 patients (50%). Disappearance of thrombosis was confirmed in 14 patients, residual mural thrombosis in eight, and reduction of thrombosis in two. In all the 10 asymptomatic patients, the D-dimer level normalized. Although no patient experienced recurrent VTE, cerebral infarction (Trousseau syndrome) was detected in two patients during edoxaban administration. Bleeding was reported in two patients (4.2%). Of these two patients, one (2.1%) experienced severe bleeding from the digestive tract 2 months after edoxaban administration. This patient had local recurrence of colorectal cancer in addition to multiple metastases (stage IV) and died 6 months after edoxaban discontinuation. However, this patient had no recurrent symptomatic VTE. The other patient had stage I renal carcinoma and experienced mild bleeding from the digestive tract 3 months after edoxaban administration. This patient had no recurrent symptomatic VTE at 12 months after edoxaban discontinuation.

**Discussion**

**Main findings**

Although this study was performed in patients with active malignancy and > 50% had stage IV malignancy, none had recurrent symptomatic VTE after the initiation of edoxaban, and only one had serious bleeding. Based on these results, edoxaban was considered safe and effective for the treatment of VTE secondary to active malignancy.

**Treatment of VTE secondary to active malignancy**

Thrombogenesis is stimulated by various factors including age, sedentary lifestyle, as well as the increased rate of diagnosis due to advancements in imaging modalities, the increased use of hematopoietics, blood transfusion, and the use of invasive intravascular catheters. Furthermore, the influence of new antineoplastic drugs has also been implicated. The treatment of VTE secondary to active malignancy involves the management of thrombosis along with the treatment of the underlying malignancy. Treating patients with malignancy is challenging because of complications such as bleeding and VTE recurrence. Intra-venous fondaparinux, an indirect inhibitor of factor Xa, was used for prophylaxis against VTE after orthopedic surgery. Since September 2014, edoxaban has been used for the treatment of VTE. However, since March 2017, therapeutic low molecular weight heparin has been used for the treatment of patients with VTE and malignancy as per the American guidelines; this treatment cannot be used in Japan. Therefore, the treatment of choice in Japan is parenteral unfractionated heparin, oral warfarin, or direct oral anticoagulants (DOACs).

**Advantages of DOACs for VTE**

DOACs are currently not recommended by the above-mentioned guidelines for the treatment of patients with malignancy and VTE. In addition, warfarin is not recommended because it interacts with several chemotherapeutic agents. Moreover, frequent blood sampling and dose adjustment are required to achieve the optimal target international normalized ratio. Recent studies have reported that DOACs are beneficial for the secondary prevention of VTE in patients with malignancy. However, there are few patients with active malignancy even in large-scale clinical studies (81–353 subjects) (Table 2). It has also

**Table 2** Treatment outcomes for VTE secondary to active malignancy in previous studies

| Study or subgroup | DOACs       | Number of cases | Recurrent symptomatic VTE | Major bleeding |
|------------------|-------------|-----------------|---------------------------|---------------|
| Hokusai-VTE      | Edoxaban (%) | 109             | 4 (3.7)                   | 5 (4.6)       |
| Einstein-PE, DVT | Rivaroxaban (%) | 353            | 16 (4.5)                  | 8 (2.3)       |
| AMPLIFY          | Apixaban (%) | 81 or 87        | 3/81 (3.7)                | 2/87 (2.3)    |

DOACs: direct oral anticoagulants; VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep vein thrombosis
been reported that DOACs might be as efficacious and safe as warfarin in patients with malignancy; however, further studies are warranted to confirm this finding. Moreover, this report did not investigate the treatment outcomes of edoxaban. Although all previous studies have compared heparin and warfarin, we did not perform this comparison because warfarin was administered to only three patients. Although the guidelines recommend initiating edoxaban therapy following heparin bridging, some patients in this study were administered only edoxaban as per the instructions of the attending physician, based on the extent of thrombosis determined according to symptoms, vital signs, and imaging results. Some patients with malignancy and poor prognosis were enrolled at the time of VTE diagnosis in this study, and imaging studies were conducted after the treatment in 75% of the patients. Therefore, symptom-based treatment was provided. Since the D-dimer levels normalized post-treatment in all the patients (n = 10) who were asymptomatic from the onset, we concluded that there was no thrombosis recurrence. In this study, although no patient experienced recurrent symptomatic VTE, cerebral infarction (Trousseau syndrome) was detected in two patients during edoxaban administration. Therefore, careful follow-up of the anticoagulant therapy is necessary. Few studies have investigated the use of DOACs for the treatment of VTE secondary to active malignancy. Further, to our knowledge, no study has examined the factors involved in VTE recurrence and bleeding; therefore, further research in this field is warranted.

**Limitations**

This retrospective study was performed in a single institution. Therefore, the efficacy and safety of the treatment were compared to those reported by previous studies. Future prospective comparative studies that use low molecular weight heparin are warranted.

**Conclusion**

Edoxaban is safe and effective for the treatment of VTE secondary to active malignancy.

**Disclosure Statement**

The authors declare that there is no conflict of interest.

**Author Contributions**

Manuscript preparation: TM
Data collection and interpretation: all authors

**Critical revision of manuscript: all authors**

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