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Original Article

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

Nobuhiro Hara, MD,[1] Takamichi Miyamoto, MD,[1] Takamasa Iwai, MD,[1] Junji Yamaguchi, MD,[1] Sadahiro Hijikata, MD,[1] Keita Watanabe, MD,[1] Yuichiro Sagawa, MD,[1] Ryo Masuda, MD,[1] Ryoichi Miyazaki, MD,[1] Naoyuki Miwa, MD,[1] Masahiro Sekigawa, MD,[1] Tetsuo Yamaguchi, MD,[1] Yasutoshi Nagata, MD,[1] Toshihiro Nozato, MD,[1] and Toru Obayashi, MD[1,2]

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 nonvitamin K antagonist oral anticoagulants against venous thrombosis has been reported[4)]; 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.

Materials and Methods

Patient population

The study enrolled a series of 53 patients with newly diagnosed VTE secondary to active malignancy who visited the Japanese Red Cross Musashino Hospital between September 2014 and August 2015. Forty-eight patients were treated with oral edoxaban, three with warfarin, and two with physical therapy. In these patients, VTE was newly diagnosed using computed tomography (CT) or ultrasonography of the veins of the lower extremities. Ten patients (20.8%) were asymptomatic. Subjects who had a history of hypersensitivity to edoxaban, active bleeding (intracranial, retroperitoneal, or other internal bleeding), acute bacterial endocarditis, or were determined ineligible for anticoagulation therapy by the attending physician were excluded from the study. Patients were treated with edoxaban following an initial injection of UFH (10 patients, 20.8%) or with edoxaban alone (38 patients, 79.2%). The dosage of edoxaban was set at 60 mg/day. Half the set dose (30 mg/day) was administered to patients weighing ≤60 kg; those receiving concomitant

[1] *Department of Cardiology, Japanese Red Cross Musashino Hospital, Tokyo, Japan*
[2] *Department of Health Science, Gunma Paz College, Takasaki, Gunma, Japan*

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Corresponding author: Nobuhiro Hara, MD. Department of Cardiology, Japanese Red Cross Musashino Hospital, 1-26-1 Kyonan-cho, Musashino, Tokyo 180-8610, Japan
Tel: +81-422-32-3111, Fax: +81-422-32-3130
E-mail: hara-nobuhiro@hotmail.co.jp

quinidine 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 ≤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 ≥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 ± 3.5 months).

Statistical analyses

All continuous variables were presented as mean ± 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±12
Male (%)		22 (45.8)
Body weight, kg		57±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±33
Blood cell counts		
	RBC, ×10⁴/μL	380±60
	Ht, %	35.0±5.0
	Hb, g/dL	11.7±1.8
	WBC, /μL	6,700±3,400
	Plt, ×10⁴/μL	23.6±12.9
PE with DVT (%)		14 (29.1)
PE without DVT (%)		4 (8.3)
DVT (%)		30 (62.5)
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		29 (60.4)
During chemotherapy		35 (72.9)

Values are presented as mean±standard deviation (SD) values or as n (%). For the stage classification, brain tumor was excluded. All continuous variables are presented as mean±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.

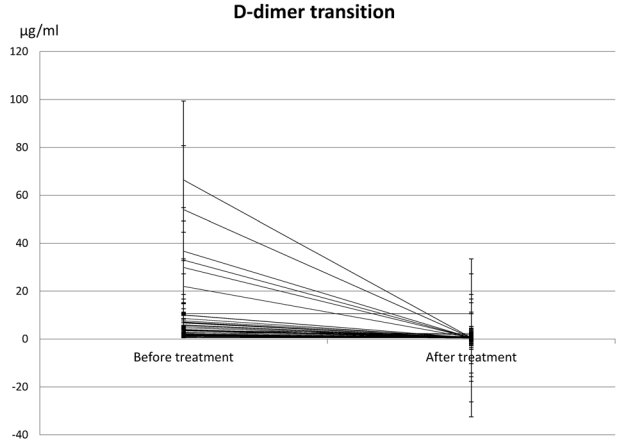

Fig. 1 Changes in the D-dimer level before and after the treatment. A significant decrease was observed in the mean D-dimer level (Wilcoxon signed rank test; P<0.05).

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.[5] 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.[6] Intravenous 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.[7] 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.[7] In addition, warfarin is not recommended because it interacts with several chemotherapeutic agents.[8,9] 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.[10–12] However, there are few patients with active malignancy even in large-scale clinical studies (81–353 subjects)[13–15] (**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[13]	Edoxaban (%)	109	4 (3.7)	5 (4.6)
Einstein-PE, DVT[14]	Rivaroxaban (%)	353	16 (4.5)	8 (2.3)
AMPLIFY[15]	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.[11] 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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