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Original article

Comparison of the effects of edoxaban, an oral direct factor Xa inhibitor, on venous thromboembolism between patients with and without cancer

Satoshi Ikeda (MD, PhD, FJCC)*, Seiji Koga (MD, PhD, FJCC), Yuki Yamagata (MD), Masamichi Eguchi (MD, PhD), Daisuke Sato (MD), Takahiro Muroya (MD, PhD), Tsuyoshi Yonekura (MD), Akira Tsuneto (MD, PhD, FJCC), Tsuyoshi Yoshimuta (MD, PhD), Yuji Koide (MD), Hiroaki Kawano (MD, PhD, FJCC), Koji Maemura (MD, PhD, FJCC)

Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

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Background: Venous thromboembolism (VTE) is a frequent and serious complication of cancer. The current guidelines in the USA and Europe recommend low-molecular weight heparin (LMWH) for the treatment of cancer-associated VTE. In Japan, LMWH is not given for the treatment of VTE; instead edoxaban, an oral direct factor Xa inhibitor, was approved for the treatment of VTE in September 2014. However, the efficacy and safety of the factor Xa inhibitor in cancer patients have not been fully elucidated.

Methods: Patients' charts were reviewed retrospectively, and 125 VTE patients (61 cancer patients) in whom edoxaban therapy was started between September 2014 and September 2016 were included in this study. Patients' demographics, changes in VTE amount, VTE recurrence, clinically relevant bleeding, and outcomes until February 2017 were examined.

Results: Patients' characteristics, including age, sex, weight, creatinine clearance, and duration of administration of edoxaban were comparable between cancer and non-cancer patients. No parenteral anticoagulant pretreatment before edoxaban was given in 37.5% and 55.7% of non-cancer and cancer patients, respectively. The incidence of pulmonary embolism was also similar in the two groups. The amount of thrombosis decreased ("improved") or disappeared ("normalized") in 89.6% and 94.1%, respectively, of non-cancer and cancer patients who underwent at least two imaging tests. The frequencies of recurrence of VTE and clinically relevant bleeding were not significantly different between the two groups ($p = 0.414$ and 0.516, respectively). However, 21 cancer patients died, 17 of whom died of cancer, while none of the non-cancer patients died.

Conclusion: The present study showed that the efficacy and safety of edoxaban for the treatment of VTE is comparable between cancer and non-cancer patients. Edoxaban may be a clinically useful therapy for VTE in Japanese cancer patients.

Introduction

Venous thromboembolism (VTE) is a common complication of cancer that has a significant impact on morbidity and mortality in cancer patients [1]. Cancer patients have a four to seven-fold greater risk of VTE compared to patients without cancer [2,3]. Among VTE patients, cancer patients account for as much as 20% of the total burden of VTE [4]. In Japan, Nakamura et al. showed that a history of cancer was the most common risk factor of VTE, present in 27.0% of VTE patients [5,6]. Kabuki et al. also showed a high prevalence of malignant tumors (26%) in patients with acute VTE [7]. Furthermore, the risk of recurrent VTE while on anticoagulant treatment is particularly high in patients with cancer, as is the risk of bleeding complications [8–11]. Using a Japanese healthcare database, Nakamura et al. also demonstrated

* Corresponding author at: Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
E-mail address: sikeda@nagasaki-u.ac.jp (S. Ikeda).

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that malignant disease was a predictor of recurrent VTE as well as bleeding [12].

Low-molecular-weight heparins (LMWHs) have been shown to be more effective than and as safe as conventional anticoagulation with initial LMWH followed by vitamin K antagonists [13–15]. Several guidelines from the USA and Europe, namely, from the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), American College of Chest Physicians (ACCP) [16], and the National Comprehensive Cancer Network (NCCN), recommend LMWH-based therapy over warfarin-based therapy as the preferred VTE treatment in cancer patients,both for initial therapy and for long-term (6–12 months) management [17]. However, in Japan, LMWHs are not used for such treatment, and the oral direct factor Xa inhibitors (Xa inhibitors), edoxaban, rivaroxaban, and apixaban, have been approved for the treatment of VTE. These Xa inhibitors, which do not require laboratory monitoring or dose adjustment, have been shown in trials to be as effective as and probably safer than conventional anticoagulation (unfractionated heparin or LMWHs, followed by warfarin) for the treatment of VTE [18–21]. Their fixed-dose regimens and oral administration make Xa inhibitors clinically attractive drugs for the treatment of VTE in patients with cancer. However, the proportion of patients with cancer in previous trials was small [8]. In addition, no clinical trial has compared the use of LMWHs versus Xa inhibitors in cancer patients. Therefore, their effectiveness and safety in cancer patients have not been fully elucidated. Among these drugs, edoxaban was first approved for VTE treatment in September 2014 in Japan. In the present study, we examined whether the efficacy and safety of edoxaban for the treatment of VTE differs between patients with and without cancer.

Materials and methods

Patients' charts were reviewed retrospectively, and 165 consecutive patients (82 with cancer and 83 without cancer) who either started edoxaban (Lixiana®, Daiichi-Sankyo, Tokyo, Japan) therapy for the treatment of VTE or were switched from other oral anticoagulants to edoxaban for the treatment of VTE from September 2014 to September 2016 at Nagasaki University Hospital were initially recruited. VTE was confirmed by ultrasonography of the lower extremities, contrast-enhanced computed tomography, or magnetic resonance imaging. VTE was classified into 2 groups [deep vein thrombosis (DVT) and pulmonary thromboembolism (PE) with and without DVT], and the site of DVT was classified into 3 sites according to its location (between the inferior vena cava and knee joint as proximal DVT; below the knee joint as distal DVT; and between the superior vena cava and upper extremities as upper DVT). Hematological data from within 1 week before starting the administration of edoxaban or VTE occurrence were obtained. Active cancer was defined as a diagnosis of cancer within 6 months before edoxaban therapy, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer [22].

To examine the direct effects of edoxaban in patients with and without cancer, patients who switched from warfarin to edoxaban for continuing anticoagulant therapy, those who stopped taking edoxaban within 1 week of commencement of its administration, and those who had non-active cancer were excluded. Finally, 125 patients (64 non-cancer and 61 cancer patients) were included in analyses of recurrence of VTE, clinically relevant bleeding, and death. Among them, 82 patients (48 non-cancer and 34 cancer patients) who underwent at least two imaging tests, such as ultrasonography of the lower extremities and contrast-enhanced computed tomography, before and after administration of edoxaban for more than 1 week and who had taken edoxaban for more than half of the duration between the two imaging tests were analyzed for the effects of edoxaban on changes in the amount of thrombosis (Fig. 1).

Recurrence of VTE was defined as confirmed symptomatic recurrence of DVT or PE. Clinically relevant bleeding was defined as major or clinically relevant non-major bleeding according to previous papers [19]. Major bleeding was defined if it was overt and was associated with a decrease in hemoglobin of 2 g per deciliter or more, or required a transfusion of 2 or more units of blood, occurred at a critical site, or contributed to death. Clinically relevant non-major bleeding was defined as overt bleeding that did not meet the criteria for major bleeding, but was associated with the need for medical intervention, contact with a physician, interruption of the study drug, or with discomfort or impairment of activities of daily life. These events were examined during the administration of edoxaban. The occurrence of death was examined from the initiation of drug administration to February 28, 2017. When the status of survival or death was unknown, as in patients who transferred to other hospitals, they were defined as "uncertain".

Changes in the amount of thrombosis were classified as normalized (no thrombus in the legs and lungs), improved

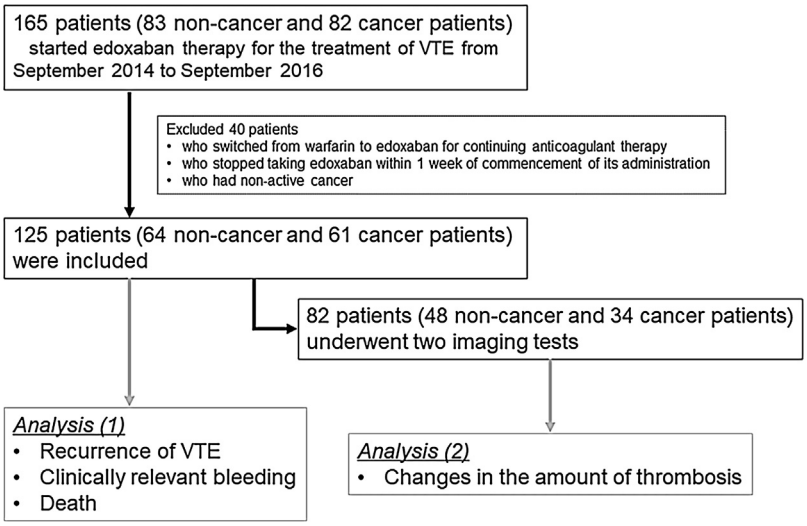

Fig. 1. Flow chart of patient enrollment. VTE, venous thromboembolism.

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