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PROTOCOL PAPER

Prospective Registry of Rivaroxaban Management of Cancer-Associated Venous Throboembolism (PRIMECAST) Study

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Background: The incidence of thromboembolism in patients with cancer is approximately 11%, and the risk of thrombosis in patients with malignant tumors is 6-fold higher than that in healthy persons. Thrombosis not only disrupts the treatment of cancer but also induces deterioration of quality of life (QOL). Knowledge about thrombus treatment is limited, and evidence is scarce. Clarification of the status and safety of venous thromboembolism (VTE) treatment in patients with cancer will contribute to active intervention and improvement of prognosis and QOL. In this study, the therapeutic effects of a non-vitamin K antagonist oral anticoagulant for VTE and the prognosis of cancer after treatment will be examined to establish a therapeutic method for VTE in patients with cancer.

Methods and Results: A multicenter, non-interventional, observational study will be conducted in patients with cancer who developed VTE and underwent anticoagulant therapy with rivaroxaban (group A) or warfarin (group B) for 24 weeks. The primary endpoint will be the recurrence/aggravation of symptomatic VTE or occurrence/aggravation of deep vein thrombosis. Registration of 500 patients is needed in order to calculate the 95% confidence interval of the event rate at ±1% precision.

Conclusions: The investigation period will run from January 2019 to December 2023 with ongoing selection of patients. Trial registration: no. 5-18-32 (approved 1 August 2018).

Key Words: Anticoagulant therapy; Cancer; Rivaroxaban; Venous thromboembolism; Warfarin

In cancer patients, the risk of venous thrombosis has risen due to multiple factors such as accelerated coagulability by direct enhancement of thrombin production by cancer cells; along with the addition of repair factors for thromboembolism due to vascular invasion, bedrest and infection, surgery and drugs.[1]

Thromboembolism appears in a wide range of patients, from those who are asymptomatic to those with life-threatening situations such as pulmonary embolism.[2] The incidence of thromboembolism in carcinoma patients is approximately 11%, and the risk of thrombosis in patients with malignant tumors is 6-fold higher than in healthy persons.[2,3] Thus, cancer is a risk factor for the development of thrombosis.[4] Because of this, anticoagulant therapy is recommended, even though there is limited knowledge about the appropriate treatment for this specific group of patients.

The use of low-molecular-weight heparin (LMWH) is recommended in the acute stage,[5] but the treatment evidence for non-vitamin K antagonist oral anticoagulants, which are recommended for general venous thromboembolism (VTE), is limited in cancer patients. In Japan, LMWH is not approved for VTE treatment, therefore the classical warfarin treatment is still used for cancer-VTE patients.

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After the approval of non-vitamin K antagonist oral anticoagulants in Japan, however, the treatment strategy is changing. The usage of warfarin has decreased, therefore it is important to clarify in Japan which kind of patients are given non-vitamin K antagonist oral anticoagulants for cancer-VTE treatment.

This is a prospective observational study of non-vitamin K antagonist oral anticoagulants for the treatment of VTE in cancer patients. We will examine the effects of drug treatment on VTE and on prognosis, as well as the incidence of hemorrhagic adverse events and hemorrhagic risks, in order to establish the best treatment method for VTE in cancer patients. We will also compare the backgrounds of patients undergoing treatment with rivaroxaban or warfarin. The study cohort will consist of the patients who present in hospital with acute pulmonary thromboembolism (PE) and/or symptomatic deep vein thrombosis (DVT). The primary endpoint in patients who receive rivaroxaban is recurrence/aggravation of VTE in ≤24 weeks.

The success of non-vitamin K antagonist oral anticoagulants for the treatment of VTE in comparison with warfarin has been demonstrated in international cooperation studies,[6] and, their safety has also been shown in Japan,[7] but the efficiency and safety findings in cancer patients are limited.[8] Because of this, clarification of the current status and safety of VTE treatment in cancer patients is expected to contribute to active intervention in the future, as well as to improvement of prognosis and of QOL, and to the collection of extremely useful information that will enable identification of unmet medical needs in the treatment of VTE. Furthermore, we can also assess the difference in patient background in terms of rivaroxaban and warfarin use (e.g., cancer type, renal dysfunction etc.).

Methods

This is a multicenter, prospective, non-interventional, observational study of cancer patients who have developed VTE and who have undergone anticoagulant therapy for a period of 24 weeks with rivaroxaban (group A) or warfarin (group B). The primary endpoint is the recurrence/aggravation of symptomatic VTE or occurrence/aggravation of symptomatic DVT in the rivaroxaban group.

Subjects will be enrolled consecutively in the study centers according to the inclusion and exclusion criteria.

The inclusion criteria are as follows: (1) age ≥18 years at the time of informed consent; (2) solid cancer; (3) development of VTE (acute PE or acute DVT) after cancer incidence and initiation of treatment with the study drugs; (4) confirmation of VTE, whether central or peripheral, symptomatic or asymptomatic, on diagnostic imaging; and (5) written consent for participation in this study ≤12 weeks after the start of the study drugs.

The exclusion criteria are as follows: (1) ≥2 weeks between VTE diagnosis and the start of anticoagulant therapy; (2) contraindication to the study drugs according to the package inserts; (3) active hemorrhage at the time of diagnosis of VTE; (4) judged to be inappropriate by the physician in charge; (5) no possibility of receiving anticoagulant therapy in the next 3 months.

The observation period of the cohort is set at 24 weeks from the start of treatment with the study drugs; and the follow-up period is 2 years from the end of the initial 24 weeks.

The information of all patients who meet the inclusion criteria for registration and who do not meet the exclusion criteria will be registered ≤1 week after obtaining written consent, which is to be obtained from the subject him/herself or legal representative ≤12 weeks after the start of treatment with the study drugs. The anticoagulants will be given according to the approved dosage based on the attached package inserts. If the dosage and treatment are adjusted at the discretion of the investigator, the adjusted dosage and the reason will be documented. The background subject information before the start of prescription of the study drugs will be collected and entered as needed for the initial 12 weeks from the start of the treatment, and thereafter, at the times of general investigation (every 6 months for 2 years from the start of the study and at the end of the investigation period in the 3rd year).

In this study, the primary endpoint and secondary efficacy endpoints will be analyzed in all the patients registered. The incidence of an event is defined as the proportion obtained by dividing the number of patients who developed one event or more by the target population. The incidence rate of an event is defined as the number of events divided by the cumulative number of patients in the analysis, set in the period with the risk; and is analyzed using the Kaplan-Meier method. The 95% confidence intervals of these values will also be presented. The safety endpoints and adverse events will be analyzed similarly in the safety analysis set, consisting of the patients who have taken either study drug at least once after enrollment in the study. The continuous variables will be presented as mean±SD and categorical variables as the number of patients and the percentage. Patient background will be summarized using descriptive statistics. The patients will be classified into subgroups by age, underlying tumor type, details of anticoagulant therapy, renal function, presence or absence of risk factors for VTE, presence or absence of pretreatment and their details, and the severity of PE at the time of diagnosis, based on the information at the time of registration to investigate each event. The events will also be analyzed according to the dosage and treatment implemented, considering the possibility that the study drugs used were not compliant with that described in the package insert. In relation to the subgroup analysis of tumor type, although we are planning to present component of tumor types, there is no plan to compare all of these groups now, because each group might have a small sample size, especially regarding rare cancers. A statistical analyst will be assigned to the study to perform the statistical analysis independently. The software to be used in the statistical analysis is still not assigned (JMP, SPSS, or other).

This study will be conducted in accordance with the ethical principles in the Declaration of Helsinki and "Ethical Guidelines for Medical and Health Research Involving Human Subjects (MECSST/MHLW Notification No. 3, 2014)".

The study personnel will hand the written information and informed consent form approved by the review board to the subjects (including legal representatives where necessary, the same hereinafter), give sufficient explanation in writing and orally, and obtain freely given written consent from the subjects. The study personnel will make an effort to obtain informed assent from the subjects who are judged in an objective way to be incapable of giving informed consent. When information that may affect consent is obtained, or a change in the protocol that may affect consent is made, the study personnel will promptly provide

Table. Observation List

Evaluation timing	Start of treatment	After 12 weeks	After 24 weeks	At recurrence, aggravation, or interruption	Every 6 months up to 2 years from the end of the initial 24 weeks
	At registration	Observation period			Follow-up period
Informed consent†	○				
Registration‡	○				
Eligibility	○				
Patient background§	○				
Vital signs	○	○	○	○	
PS	○	○	○	○	○
CT	○	○	○	○	
Lower-extremity venous ultrasound	○	○	○	○	
Echocardiography	○	Δ¶			
ASCO risk of thrombosis	○				
Hematology tests††	○	○	○	○	
Coagulation abnormality‡‡	Δ§§			○¶¶	
Clinical events†††		○	○	○	○
Adverse events‡‡‡		○	○	○	○
Concomitant drugs§§§	○	○	○	○	○
Compliance check¶¶¶		○	○		

†Obtaining consent after the start of treatment. ‡Registration ≤12 weeks after the start of treatment and ≤1 week after informed consent. §Age, sex, date of birth, body height, body weight, previous history, complications (cardiac diseases, hypertension, diabetes mellitus, hyperlipidemia). ¶Only in PE. ††Blood cell counts, D-dimer, renal functions (blood urea nitrogen; creatinine), hepatic functions (total bilirubin, alanine aminotransferase, aspartate aminotransferase). ‡‡Prothrombin time (s), international normalized ratio of prothrombin time, activated partial thromboplastin time, D-dimer. §§Data before the start of study drug treatment. ¶¶Confirm the time from the most recent study drug take-up to blood sampling. †††Discontinuation of anticoagulation therapy due to hemorrhagic adverse events, death due to venous thromboembolism, discontinuation of anticoagulation therapy upon judgment of low justification of the therapy by the physician in charge, recurrence/aggravation of venous thromboembolism, death (venous thromboembolism-related death, cardiovascular death and all death). ‡‡‡Clinically significant hemorrhagic events (events corresponding to ISTH criteria for major bleeding (1)). Clinically insignificant hemorrhagic events (hemorrhagic events other than clinically significant hemorrhages). Other (serious) adverse events (non-hemorrhagic adverse events). §§§Anticoagulant, anticancer agent, or hormone drug given as directed in the package insert. If you deviate from the package insert, the reason will be specified in the medical record. ¶¶¶Researchers should evaluate how many tablets are left during each visit to evaluate the drug compliance. ASCO, American Society of Clinical Oncology; CT, computed tomography; PS, performance status.

information to the subjects and reconfirm their willingness to continue participation in the study. In addition, the study personnel will revise the informed consent form with the approval of the review board in advance and obtain the consent of the subject again. Data will be evaluated for compliance with the protocol and accuracy according to source documents defined in the study-specific monitoring plan. The monitors will verify and report that all the data are generated, documented and recorded in compliance with the protocol.

Discussion

In the present study, the primary objective is to assess the effectiveness of rivaroxaban for the treatment of VTE in Japanese patients with active cancer. Therefore, we have first estimated the number of patients needed in the rivaroxaban group. The number of patients in this group was calculated based on precision, because this study is a non-interventional one and not intended for direct comparison of drug efficiency. The sample size calculation of the rivaroxaban group is as follows: in the integration analysis of the EINSTEIN DVT/PE study, recurrence/aggravation of symptomatic VTE set as the primary endpoint was reported at 2.1%.[9] In addition, the Japanese VTE population to be included in this study and the population in the EINSTEIN DVT/PE study[10] were compared and the registration of 500 patients was judged to be necessary to calculate the 95% confidence interval of the event rate at ±1% precision. A possible bias exists related to the sample recruitment between the rivaroxaban and the warfarin groups. We do not plan to compare treatment outcomes, and instead will be comparing the background of patients given rivaroxaban with that of those treated with warfarin, given that, because of bias, we know that we cannot directly compare the efficacy and safety of rivaroxaban with warfarin.

In this study, the data on course observation or information will be collected until the end of the investigation period for all patients, including those with efficacy or safety events, change of hospital, or who have discontinued or terminated prescription of the study drugs for some reason. Then information relating to the efficacy or safety endpoints will be entered in EDC at the times of general investigation. **Table** lists the observational data collected at each point.

The primary endpoints and secondary endpoints are applied to group A (rivaroxaban group) and are as follows. The primary endpoint is the recurrence/aggravation of symptomatic VTE (combined endpoint with occurrence/aggravation of symptomatic PE or occurrence/aggravation of symptomatic DVT) in the observation period of 24 weeks after initiation. The secondary endpoints are all clinically relevant or irrelevant bleeding events that require medical intervention, unscheduled consultation with a physician, temporary discontinuation of study treatment, pain, or impairment of daily activities. There will be an external event judgment committee to evaluate this type of

events independently.

The definition of VTE recurrence is as follows. DVT recurrence is the appearance of a new thrombus in a deep vein detected on contrast-enhanced computed tomography (CT) or lower extremity vein imaging; on ultrasonography vein imaging, the thrombus is confirmed on compression ultrasonography or the diameter has increased by 4 mm. Symptomatic PE recurrence is a new thrombus in the pulmonary artery (vessel diameter >2.5 mm), confirmed on contrast-enhanced CT or pulmonary arteriography associated with symptom suggesting PE. Incidental PE recurrence is a PE detected incidentally on imaging carried out for other purposes, such as staging a cancer, or PE confirmed on autopsy pathology at the time of death not due to a cancer, which is suspected to have caused the death.

Trial Status

The registration period started in January 2019 (after institution review board [IRB] approval) and will be ongoing until December 2021 (2 years). The investigation period is from January 2019 (after IRB approval) to December 2023 (≥24 weeks). The planned number of participating study sites is 20 Japanese hospitals. The study administrative office is at the International University of Health and Welfare approved 1 August 2018, No. 5-18-32.

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This study will be conducted using the fund provided by Bayer Yakuhin, within the range of the health insurance treatment and based on the agreement on the investigator-initiated study between International University for Health and Welfare and the company. The company will have no part in the study administration including the study conduct, data control, statistical analysis or publication of results. With regard to conflict of interest between the investigators and the company, the provisions set at each study site will be followed taking care not to deviate from them.

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