Original Article

Venous thromboembolism in cancer patients: report of baseline data from the multicentre, prospective Cancer-VTE Registry

Yasuo Ohashi1,*, Masataka Ikeda2, Hideo Kunitoh3, Mitsuru Sasako4, Takuji Okusaka5, Hirofumi Mukai6, Keiichi Fujiwara7, Mashio Nakamura8, Mari S. Oba9, Tetsuya Kimura10, Kei Ibusuki10, and Masato Sakon11

1Department of Integrated Science and Engineering for Sustainable Society, Chuo University, Tokyo, Japan, 2Division of Lower Gastrointestinal Surgery, Hyogo College of Medicine, Nishinomiya, Japan, 3Department of Medical Oncology, Japanese Red Cross Medical Center, Tokyo, Japan, 4Department of Surgery, Yodogawa Christian Hospital, Osaka, Japan, 5Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, 6Division of Breast and Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan, 7Department of Gynecologic Oncology, Saitama Medical University International Medical Center, Hidaka, Japan, 8Department of Internal Medicine, Pediatrics and Cardiology, Nakamura Medical Clinic, Kawanana, Japan, 9Department of Medical Statistics, Faculty of Medicine, Toho University, Tokyo, Japan, 10Medical Science Department, Daiichi Sankyo Co. Ltd., Tokyo, Japan and 11Department of Gastrointestinal Surgery, Osaka International Cancer Institute, Osaka, Japan

*For reprints and all correspondence: Yasuo Ohashi, Department of Integrated Science and Engineering for Sustainable Society, Chuo University, 1-13-27 Kasuga Bunkyo-ku, Tokyo 112-8551, Japan. E-mail: ohashiy.00e@g.chuo-u.ac.jp

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Abstract

Background: The Cancer-VTE Registry evaluates the occurrence and management of venous thromboembolism in Japanese participants with major solid tumors. Using Registry data, we evaluated the frequency of concurrent venous thromboembolism in cancer patients prior to treatment initiation by cancer type.

Methods: The Cancer-VTE Registry is an ongoing (March 2017–September 2020) prospective cohort study using a nationwide, multicentre clinical registry. Participants aged ≥20 years with colorectal, lung, stomach, pancreatic, breast or gynecologic cancer, confirmed staging, ≥6 months life expectancy post-registration and who had undergone venous thromboembolism screening were managed with routine clinical care. Venous thromboembolism frequency at registration was evaluated.

Results: Of 9735 participants, 571 (5.9%) had venous thromboembolism at baseline, including asymptomatic [5.5% (n = 540)] and symptomatic venous thromboembolism [0.3% (n = 31)]. Most participants with venous thromboembolism (n = 506, 5.2%) had deep vein thrombosis only; 65 (0.7%) had pulmonary embolism with/without deep vein thrombosis. The prevalence of distal and proximal deep vein thrombosis was 4.8% (n = 466) and 0.9% (n = 83), respectively. The highest prevalence of venous thromboembolism was for pancreatic cancer (8.5%) and the lowest for breast cancer (2.0%). Venous thromboembolism prevalence increased as cancer stage advanced.

Conclusions: Although there was a marked difference in venous thromboembolism by cancer type, the data suggest that cancer stage is an important risk factor for venous thromboembolism.
Introduction
Venous thromboembolism (VTE) comprises pulmonary embolism (PE) and deep vein thrombosis (DVT). VTE is associated with a considerable disease burden, including long-term complications and significant morbidity (1–3). Notably, among patients with cancer, the risk of VTE is estimated to be four- to seven-fold that of the general population (4–6). Furthermore, in cancer patients, VTE is associated with worse prognosis (7–10) and increased medical costs (11,12). Among 4466 cancer patients in the United States, VTE was observed to be the second most common cause of death (8).

There are several pathways that can result in an increased risk of VTE in cancer patients (13), including increased blood coagulability resulting from the release of inflammatory cytokines from cancer cells (14–16). The risk of developing VTE during cancer treatment may depend on patient-related (including age, body mass index, performance status, smoking and concomitant medical comorbidities), tumor-related (cancer type and stage) and treatment-related factors (such as surgery, use of chemotherapy, hormone therapy or immune-checkpoint inhibitor and placement of a venous catheter) (17,18). Although the association between cancer and VTE is well recognized, information on Japanese or Asian patients with cancer and VTE is currently scarce. No data from large-scale, reliable and prospective studies evaluating the frequency (prevalence and/or incidence) of VTE and treatment status have been reported in this population. Thus, the relative VTE frequencies according to different types of cancer and risk factors are not yet understood.

The Cancer-VTE Registry aimed to determine the prevalence of VTE at treatment initiation and the cumulative incidence of VTE after 1 year in patients according to cancer type (colorectal, lung, stomach, pancreatic, breast or gynecologic), to investigate risk factors associated with VTE manifestation and to clarify the current treatment landscape of VTE in cancer patients, as well as survival status. The study is ongoing. Here, we address the first of these objectives by evaluating baseline data and the prevalence of VTE prior to treatment initiation in participants enrolled in the Cancer-VTE Registry.

Patients and methods
Study design
The full details of the Cancer-VTE Registry design have been reported previously (19). In brief, this is a prospective cohort study based on a nationwide, multicentre clinical registry (Supplementary Fig. S1).

As far as possible, all eligible patients were consecutively registered. Registered patients were managed with routine clinical care, and no interventions were specified.

The study was initiated in March 2017 and will be completed in September 2020. Enrollment ended in January 2019, and the data discussed herein are derived from the baseline demographic and clinicopathologic information submitted at registration. For gynecologic cancers, participants were separately enrolled in an investigator-initiated study with an intervention; the data from that study were added to those of the main registry in an integrated analysis. The data cut-off for this analysis was 9 August 2019 for colorectal, lung, stomach, pancreatic and breast cancers and 30 May 2019 for gynecologic cancers.

Ethics
The study was conducted according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the ethical principles originating from the Declaration of Helsinki. The protocol, amendments and participant consent forms were approved by the institutional review board/independent ethics committee at each site prior to study commencement. All participants provided written informed consent at the time of registration. All participant information has been anonymized to ensure privacy.

Participants
Enrollment details for the Cancer-VTE Registry have been published (19). All patients were registered before initiating planned cancer treatment (including chemotherapy, radiation therapy or surgery). Eligibility criteria included age ≥20 years and a diagnosis of colorectal, lung, stomach, pancreatic, breast or gynecologic cancer (comprising endometrial, cervical, ovarian, fallopian tube, and peritoneal tumors). Patients with recurrent cancer (defined as patients for whom all planned cancer treatments had been completed and who had at least 6 months of stable disease before disease progression was detected), who had previously received treatment (including chemotherapy, radiation therapy or surgery) for the primary cancer, were also eligible for registration; cases of recurrence were handled as stage IV cases. Confirmation of stage II–IV cancer with planned initiation of cancer therapy was necessary for participation (stages I–IV for gynecological cancers and stages II–IV for lung cancer).

Participants could be outpatients or hospitalized, with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1 or 2 (for pancreatic cancer, a PS of 0 or 1 only was permitted), with a life expectancy of ≥6 months after registration and had undergone VTE screening [lower extremity venous ultrasonography or computed tomography (CT) angiography] in the 2 months prior to registration. Venous ultrasonography of the lower extremity was standardized with the aid of the Japan Society of Ultrasonics in Medicine guidelines (20). However, VTE screening was not required if patients had a D-dimer concentration of ≤1.2 µg/ml after cancer diagnosis (regarded as non-VTE) (21). When PE was suspected due to subjective or other findings, its presence or absence was confirmed by conducting diagnostic imaging tests (such as contrast CT) at the physician’s discretion.

Patients with active double cancer were excluded, although multiple intramucosal cancers in one organ could be registered. There were no other specific exclusion criteria, although the investigator could...
Figure 1. Participant flow.

*Includes endometrial, cervical, ovarian, fallopian tube and peritoneal cancers.

| Includes endometrial, cervical, ovarian, fallopian tube and peritoneal cancers. | No data available. |

Endpoints

The overall outcome measures for the study have been defined previously (19).

This article will present data derived from baseline participant registration information, including baseline demographic and clinical characteristics and an assessment of the prevalence of VTE [including symptomatic/incidental PE, and symptomatic/asymptomatic DVT (proximal and distal)] among participants with six different cancer types.

The definitions of PE and DVT have been described (19); details are also provided in Supplementary Table S1.

Statistical analyses

The planned sample size, which was based on estimated cancer incidences among the Japanese population (22), included a total of 10 000 participants (colorectal cancer: 2500; lung cancer: 2500; stomach cancer: 2000; pancreatic cancer: 1000; breast cancer: 1000; and gynecologic cancers: 1000). Baseline demographic and clinico-pathologic characteristics were reported using descriptive statistics (frequency, mean and standard deviation). All analyses (including data access, extraction and management) were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) by an external company (Mediscience Planning Inc., Tokyo, Japan).

Results

Participants

Between March 2017 and February 2019, 10 202 participants were registered at 162 sites in Japan, achieving both the overall target of 10 000 participants and the targets for each cancer type. At the time of registration, before the start of cancer treatment, VTE was confirmed by imaging examinations, and the VTE status at baseline was clarified. Herein, we report the results based on confirmed baseline data, which included a total of 9735 participants. The study flow is shown in Fig. 1.

Baseline demographic and clinical characteristics are shown in Table 1. The proportion of males was 51.4%, the mean age was 66.7 years and the mean body mass index was 22.6 kg/m². Most participants (95.5%) had a primary cancer, while just 4.5% had cancer recurrence. The ECOG PS was 0 in 74.3% of participants. Regarding cancer stage, 35.2% had stage II, 29.8% had stage III and 24.0% had stage IV cancer. Around half of the participants had lymph node metastasis (54.5%), but only a quarter (23.0%) had distant metastasis. The most frequently observed complications were hypertension (39.0%) and diabetes (18.9%), and 18.9% had a history of organ resection.

Baseline prevalence of VTE

The baseline prevalence of VTE is shown in Table 2. Overall, 571/9735 (5.9%) participants were found to have VTE at baseline. Most participants (n = 506, 5.2%) had DVT alone, and 65 (0.7%)
Prospective cancer-VTE registry baseline data

Table 1. Baseline clinical characteristics

| Characteristic                  | Baseline analysis set N = 9735 |
|---------------------------------|---------------------------------|
| Sex, male                       | 5001 (51.4)                     |
| Age, years, mean (SD)           | 66.7 (11.9)                     |
| ≥65 years                       | 6246 (64.2)                     |
| Weight, kg, mean (SD)           | 58.1 (12.0)                     |
| BMI, kg/m², mean (SD)           | 22.6 (3.9)                      |
| Cancer occurrence               |                                 |
| Primary                         | 9300 (95.5)                     |
| Recurrence                      | 435 (4.5)                       |
| ECOG PS                         |                                 |
| 0                               | 7235 (74.3)                     |
| 1                               | 2164 (22.2)                     |
| 2                               | 336 (3.5)                       |
| Cancer stage                    |                                 |
| I                               | 615 (6.3)                       |
| IB                              | 460 (4.7)                       |
| II                              | 3425 (35.2)                     |
| III                             | 2902 (29.8)                     |
| IV                              | 2333 (24.0)                     |
| Presence of lymph node metastasis| 5309 (54.5)                     |
| Presence of distant metastasis  | 2238 (23.0)                     |
| Complications/comorbidities     |                                 |
| Hypertension                    | 3800 (39.0)                     |
| Diabetes                        | 1837 (18.9)                     |
| Ischemic heart disease          | 459 (4.7)                       |
| Atrial fibrillation             | 319 (3.3)                       |
| Liver dysfunction               | 280 (2.9)                       |
| Peptic ulcer                    | 281 (2.9)                       |
| Heart failure                   | 42 (0.4)                        |
| VTE risk factors                |                                 |
| Surgery                         | 391 (4.0)                       |
| General anesthesis              | 340 (3.5)                       |
| Central vein port placement     | 211 (2.2)                       |
| Steroid use                     | 184 (1.9)                       |
| Central venous catheterization  | 154 (1.6)                       |
| Bed rest for 4 days or more     | 118 (1.2)                       |
| Current smoker                  | 1308 (13.4)                     |
| Medical history                 |                                 |
| Organ resection                 | 1844 (18.9)                     |
| Cerebral infarction             | 397 (4.1)                       |
| Gastrointestinal bleeding       | 175 (1.8)                       |
| Intracranial hemorrhage         | 121 (1.2)                       |
| VTE                             | 80 (0.8)                        |
| TIA                             | 49 (0.5)                        |
| Myocardial infarction           | 11 (0.1)                        |

Data are shown as n (%) unless otherwise stated. SD, standard deviation; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; VTE, venous thromboembolism; TIA, transient ischemic attack.

aGynecologic cancers only.

bLung cancer only.

had PE with or without DVT. The prevalence of asymptomatic and symptomatic VTE was 540 (5.5%) and 31 (0.3%), respectively. Of the 549 participants with DVT, 466 (4.8%) had distal and 83 (0.9%) had proximal DVT.

Analysis of VTE prevalence by cancer type and stage

Figure 2A and B shows the VTE prevalence by cancer type and stage. The numbers of patients with PE (with or without DVT) and DVT and those with symptomatic or asymptomatic VTE are also described in Supplementary Table S2. The highest VTE prevalence was found in pancreatic cancer (8.5%) and the lowest in breast cancer (2.0%); the prevalence in other types of cancer was similar (5.1–6.9%). VTE prevalence appeared to increase as the cancer stage increased, reaching a level of 11.2% at stage IV.

Further, the prevalence of VTE increased rapidly for patients with advanced stomach cancer, lung cancer and pancreatic cancer (i.e. stage III or higher stages) (Fig. 3). The prevalence of VTE with confidence intervals by cancer type and stage is also shown in Fig. 3.

The regression coefficients and odds ratios of the logistic regression model obtained as a result of variable selection are shown in Supplementary Table S3. It was confirmed that female sex and higher age were independent risk factors, in addition to the combination of cancer type and stage. Applying variable selection (backward elimination) to assess the influence of other background factors on VTE and using the Akaike Information Criterion (AIC), sex, age, metastasis, history of VTE, bed rest for ≥4 days and D-dimer level were confirmed to be independent risk factors. The C-index was 0.898. The Hosmer–Lemeshow test, which was 5.81 (8 degrees of freedom; P = 0.67), indicated a good fit.

Discussion

It has long been recognized that cancer patients have a high frequency (prevalence and/or incidence) of VTE, resulting in worse prognosis and high morbidity levels (7–10). However, data on the frequency and risk factors for VTE in Japanese cancer patients are currently lacking. The Cancer-VTE Registry was initiated to evaluate the frequency and management of VTE in Japanese participants with a range of solid tumors (19). The baseline data from this registry, which included 9735 participants with six cancer types, indicated that the prevalence of VTE prior to the initiation of cancer treatment was 5.9% overall. Notably, most of the cases of VTE detected at baseline were peripheral DVT; the clinical impact of DVT in these patients will be revealed after follow-up. Moreover, the frequency of VTE observed in this analysis should be interpreted with caution. To put this number into the context of previous research, it is necessary to consider several possible variables, including whether the frequency was calculated during VTE screening, how the flow of VTE diagnosis was applied and the differences in background characteristics of the target patients.
The prevalence of VTE varied considerably according to the type of cancer, with the highest rates of VTE observed in pancreatic cancer, followed by stomach, colorectal, gynecologic and lung cancers. When the cancer stage was considered, VTE prevalence was found to increase with stage. It was also observed that the prevalence of VTE increased sharply in patients with stage IV stomach cancer, lung cancer and pancreatic cancer. These results are in line with data from analyses in cancer patients of other ethnicities, in which the frequency of VTE was also found to be highest in pancreatic cancer (23–26) and in tumors at a higher stage (23,25,27). Furthermore, the analysis results of risk factors affecting VTE prevalence showed that cancer stage was the dominant factor, rather than cancer type. The prevalence of VTE in gynecological cancers seemed different when viewed before treatment. Asymptomatic VTE with a D-dimer ≤ 1.2 µg/ml may be underestimated, and asymptomatic PE without thrombosis in the lower leg may not be detectable.
only by cancer type (Fig. 2A) and by cancer stage (Fig. 3). In fact, the prevalence of VTE among patients with gynecological cancer was the highest at every stage compared with other cancer types. There was a large proportion of stage I gynecologic cancers in this study, which may explain these findings. Other reasons may be that gynecologic cancers often present peritoneal metastasis, and tumors tend to be large in size (28). Thus, from the present results, it can be inferred that metastasis (i.e. advanced cancer stage) is a critical risk factor of VTE. The high prevalence of VTE in patients with pancreatic cancer may be attributable to the fact that this cancer type is commonly detected at advanced stages. In addition, mucin expression during pancreatic cancer progression may be associated, in part, with higher VTE risk (29).

The major strength of this study is the large number of patients included from real-world clinical practice, which allows the data to be extrapolated across the spectrum of Japanese cancer patients. This study has several limitations. First, only six cancer types were examined in this registry, and there are notable differences in baseline VTE risk between these six cancers; thus, further studies will be needed to expand the evidence-base and provide risk predictions for other cancer types. Second, because the registry was conducted within usual clinical practice, VTE screening was not carried out for all patients, and the screening methods used for PE were not pre-specified compared with those used for DVT. In accordance with local insurance regulations, the 5569 patients with D-dimer ≤1.2 µg/ml were not routinely screened for VTE; however, 694 of these patients underwent lower extremity venous ultrasonography or CT angiography. Of these, 33 participants were diagnosed with DVT. The prevalence of concurrent VTE in cancer patients may, therefore, be higher than the 5.9% recorded in this study.

As cancer progresses, patients undergo treatment, and follow-up is necessary. Herein, we report the prevalence of VTE prior to the initiation of cancer treatment, and subsequent publications will provide details of the course of the incidence of VTE during cancer treatment, information on VTE treatment and other cancer therapies (i.e. chemotherapy, radiotherapy and surgery) and overall survival rates. Moreover, in the future, we will examine patient background characteristics and analyze potential risk factors to further expand our understanding of VTE occurrence in cancer patients. It is expected that these data can be used to create a VTE risk score by examining the relationship between the frequency of VTE and potential VTE risk factors in cancer patients, thereby informing treatment decisions for physicians and improving outcomes for patients. We expect that further analysis of the obtained data will yield valuable information on VTE and cancer. As the data on the subject are limited, the forthcoming information that will result from these analyses is eagerly anticipated.

Conclusions

For the first time in Japan, the prevalence of VTE in cancer patients prior to treatment initiation has been demonstrated. There was a marked difference in the VTE prevalence between the various cancer types. The present data suggest that cancer stage is the dominant
risk factor for VTE rather than cancer type. From this, we inferred that metastasis, a key characteristic of advanced cancer stage, is an important risk factor for VTE.

**Supplementary data**

Supplementary data are available at JJCO online.

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**Conflict of interest statement**

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Mini-abstract
Cancer-VTE Registry data showed that 371/9735 participants (5.9%) had venous thromboembolism at baseline. Thromboembolism prevalence was highest for pancreatic cancer and lowest for breast cancer and increased as cancer stage advanced.