Thrombosis Research 151, Suppl. 1 (2017) S16–S20

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Gender differences in patients with venous thromboembolism and five common sites of cancer

Francisco Martín-Martos [a], Javier Trujillo-Santos [a], Jorge del Toro [b], Alessandra Bura-Riviere [c], Alicia Lorenzo [d], Giovanni Barillari [e], Silvia Soler [f], Isabelle Mahè [g], Joan Carles Sahuquillo [h], Manuel Monreal [i,*], and the RIETE Investigators**

[a]Department of Internal Medicine, Hospital General Universitario Santa Lucía, Murcia, Spain
[b]Department of Internal Medicine, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[c]Department of Vascular Medicine, Hôpital de Rangueil, Toulouse, France
[d]Department of Internal Medicine, Hospital Universitario de La Paz, Madrid, Spain
[e]Department of Internal Medicine, Ospedale Santa Maria della Misericordia, Udine, Italy
[f]Department of Internal Medicine, Hospital Olot i Comarcal de la Garrotxa, Gerona, Spain
[g]Department of Internal Medicine, Hôpital Louis Mourier, Colombes (APHP), University Paris 7, France
[h]Department of Internal Medicine, Hospital Municipal de Badalona, Barcelona, Spain
[i]Department of Internal Medicine, Hospital Universitario Germans Trias i Pujol de Badalona, Barcelona, Universidad Católica de Murcia, Spain

ARTICLE INFO

Keywords:
Venous thromboembolism
Gender
Cancer
Anticoagulant drugs
Recurrence
Hemorrhage
Mortality

ABSTRACT

Background: The outcome of cancer patients with venous thromboembolism (VTE) may differ according to gender.
Methods: We used the RIETE database to compare the rate of VTE recurrences, major bleeding and mortality in patients with lung, colorectal, pancreatic, hematologic or gastric cancer during the course of anticoagulation, according to gender.
Results: As of January 2016, 11,055 patients with active cancer were enrolled: 1,727 had lung cancer, 1,592 colorectal, 840 hematologic, 517 pancreatic and 459 had gastric cancer. Compared with men ($N = 3,130$), women ($N = 2,005$) were more likely to have colorectal, pancreatic or hematologic cancer, and less likely to have lung cancer. Most patients (91%) were initially treated with low-molecular-weight heparin (LMWH), but women received higher daily doses per body weight. Then, 66% kept receiving LMWH for long-term therapy. During the course of anticoagulation, 302 patients developed recurrent VTE, 220 bled and 1,749 died. Compared with men, women had a similar rate of VTE recurrences or major bleeding, and a lower mortality (risk ratio [RR]: 0.90; 95% CI: 0.82–0.99). When separately comparing outcomes according to cancer site, women with lung cancer had a lower mortality (RR: 0.79; 95% CI: 0.70–0.92), those with colorectal cancer had a higher mortality (RR: 1.25; 95% CI: 1.02–1.54) and those with gastric cancer had a higher rate of VTE recurrences than men (RR: 2.47; 95% CI: 1.04–5.89).
Conclusions: VTE women with lung, colorectal, pancreatic, haematological or gastric cancer experienced a similar outcome during the course of anticoagulant therapy than men with similar cancers.

1. Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE) is a frequent condition with significant morbidity and mortality, particularly in patients with cancer [1–4]. In a first study using the RIETE database, we found that women (with or without cancer) had a lower rate of DVT recurrences and a higher rate of major bleeding during the course of anticoagulant therapy than men [5]. In a subsequent study including only patients with active cancer, we found a number of gender-differences in their clinical characteristics, treatment and outcome [6]. Compared with men, women had a significantly lower rate of fatal bleeding and all-cause mortality. However, since the sites of cancer largely vary according to gender, and the site of cancer greatly influences on outcome [7], any difference could be attributed to differences in cancer sites.

The RIETE (Registro Informatizado de Enfermedad Trombo-Embólica) Registry is an ongoing, multicenter, international (Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Czech Republic, Macedonia, United States, Canada, Brazil and Ecuador), observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE (ClinicalTrials.gov identifier: NCT02832245).

* Corresponding author: Professor Manuel Monreal, MD, PhD, Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, 08916 Badalona (Barcelona), Spain.
E-mail address: mmonreal.germanstrias@gencat.cat (M. Monreal).
** A full list of RIETE investigators is given in the appendix.

0049-3848/$ – see front matter

It started in Spain in 2001, and 6 years later the database was translated into English, aimed to expand the Registry to other countries, ultimately allowing physicians worldwide to use the database to select the most appropriate therapy for their patients. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, major bleeding and mortality, and risk factors for these outcomes [8–11]. The aim of the current study was to assess if there were gender-differences in the rate of VTE recurrences, major bleeding or death during the course of anticoagulation in patients with 5 common cancer sites: lung, colorectal, pancreas, hematologic or stomach.

2. Patients and methods

Consecutive patients with symptomatic, acute DVT or PE confirmed by objective tests (contrast venography or ultrasonography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography scan for suspected PE), were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent to their participation in the registry, in accordance with local Ethics Committee requirements.

In the RIETE registry, participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating centre through a secure website. The study coordinating centre assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

2.1. Study design and definitions

For this analysis, only patients with lung, colorectal, pancreatic, hematologic or gastric cancer were considered. The major outcome was the development of VTE recurrences, major bleeding events or death during the course of anticoagulant therapy. Major bleeding was defined as an overt bleed that required a transfusion of two or more units of blood, was retroperitoneal, spinal or intracranial, or was fatal. Fatal PE, in the absence of autopsy, was defined as any death occurring within 10 days after PE diagnosis, in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death.

2.2. Study variables

The following parameters were recorded: patient's characteristics at baseline, cancer characteristics (including site, presence or absence of metastases, elapsed time from cancer diagnosis to VTE, and treatment received), additional risk factors for VTE, other coexisting or underlying conditions, diagnostic tests, the type and dose of treatment received upon VTE diagnosis and their outcome during at least the first 3 months. Immobilized patients were defined in this analysis as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for $\geq$4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who had undergone an operation in the 2 months prior to VTE diagnosis.

2.3. Treatment and follow-up

Patients were managed according to the clinical practice of each participating hospital (i.e., there was no standardization of treatment). The type, dose and duration of anticoagulant therapy, as was the insertion of an inferior vena cava filter, were recorded. After discharge, all patients were followed-up for in the outpatient clinic. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was investigated by repeat ultrasonography, venography, lung scanning, helical-CT scan or pulmonary angiography as appropriate. Most outcomes were classified as reported by the clinical centres. However, if staff at the coordinating centre were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (less than 10% of events).

2.4. Statistical analysis

Student t-tests and nonparametric tests were used to compare means and medians of continuous variables. Categorical variables were compared using the chi-square test (two-sided) and Fisher's exact Test (two-sided). Incidence rates of recurrent VTE, major bleeding and death were calculated as cumulative incidence (events/100 patient-years). We compared the cumulative incidence of these events according to sex using the Kaplan-Meier technique. A SPSS software (version 15, SPSS Inc., Chicago, Illinois) was used for the statistical management of the data, and a two-sided $p < 0.05$ was considered to be statistically significant.

3. Results

As of January 2016, 11,055 patients with active cancer were enrolled in RIETE. Of these, 1,727 (16%) had lung cancer, 1,592 (14%) colorectal, 840 (7.6%) hematologic, 517 (4.7%) pancreatic and 459 (4.2%) had gastric cancer. Compared with men (N = 3,130), women (N = 2,005) were older, weighed less, and were less likely to have chronic lung disease or anaemia but more likely to have renal insufficiency (Table 1). As to the cancer characteristics, women were more likely to have colorectal, pancreatic or hematologic cancer than men, and less likely to have lung cancer. They also were less likely to have metastatic cancer. Among patients initially presenting with PE, there were no gender differences in the clinical signs of severity (arterial hypotension, tachycardia or hypoxemia).

The majority of patients (91% in both subgroups) were initially treated with low-molecular-weight heparin (LMWH), but women received higher daily doses per body weight (Table 2). Then, most (66%) kept receiving LMWH for long-term therapy. During the course of anticoagulation (mean duration: 150 days), 302 patients developed recurrent VTE (recurrent PE 132, recurrent DVT 170), 220 bled and 1,749 died (122 died of PE, 48 died of bleeding). Compared with men, women had a similar rate of DVT recurrences, PE recurrences or major bleeding, but had a lower mortality rate (risk ratio [RR]: 0.90; 95% CI: 0.82–0.99), as shown in Table 3.

When separately comparing outcomes according to cancer site, women with lung cancer had a lower mortality rate (RR: 0.79; 95% CI: 0.70–0.92), those with colorectal cancer had a higher mortality (RR: 1.25; 95% CI: 1.02–1.54) and those with gastric cancer had a higher rate of VTE recurrences than men (RR: 2.47; 95% CI: 1.04–5.89) (Table 4).

4. Discussion

Our data, obtained from a large series of consecutive patients with active cancer and acute VTE, reveal a number of gender differences in the clinical characteristics and treatment. Compared