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Thirty-day mortality rate in women with cancer and venous thromboembolism. Findings from the RIETE Registry

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ABSTRACT

The influence of the site of cancer on outcome in cancer women with venous thromboembolism (VTE) is poorly understood. Reliable information on its influence might facilitate better use of prevention strategies.

We assessed the 30-day outcome in all women with active cancer in the RIETE Registry, trying to identify if differences exist according to the tumor site.

Up to May 2010, 2474 women with cancer and acute VTE had been enrolled. The most common sites were the breast (26%), colon (13%), uterus (9.3%), and haematologic (8.6%) cancers. During the 30-day study period, 329 (13%) patients died. Of them, 71 (2.9%) died of pulmonary embolism (PE), 22 (0.9%) died of bleeding. Fatal PE was more common in women with breast, colorectal, lung or pancreatic cancer (59% of the fatal PEs). Fatal bleeding was more frequent in women with colorectal, haematologic, ovarian cancer or carcinoma of unknown origin (55% of fatal bleedings).

Introduction

Cancer patients with venous thromboembolism (VTE) have an increased incidence of VTE recurrences and anticoagulant-related bleeding complications compared with those without cancer [1–5]. They also are a very heterogeneous group due to differences in tumor site, extent or time interval between diagnosis of cancer and diagnosis of VTE. Some of these variables may vary according to gender, and may likely influence on outcome. Reliable information on the factors determining the risk for dying of pulmonary embolism (PE) or bleeding may facilitate better use of therapy by improving selection of patients in whom its benefit will likely outweigh the risk, and by identifying those who may benefit from careful management. In addition, early detection and prompt therapy of complications with supportive measures might reduce mortality.

The RIETE Registry is an ongoing, international, multicenter, prospective registry of consecutive patients presenting with symptomatic acute VTE confirmed by objective tests [6–9]. In this analysis of the RIETE Registry we assessed the 30-day outcome in all VTE women with active cancer, trying to identify if differences exist according to the tumor site.

Patients and methods

Inclusion criteria

Consecutive patients with symptomatic, acute deep venous thrombosis (DVT) or PE, confirmed by objective tests were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with blind medications. All patients provided oral or written consent to their participation in the registry, according to the requirements of the ethics committee within each hospital.

Follow-up

Patients were managed according to the clinical practice of each participating hospital and were not subject to any predetermined intervention. After VTE diagnosis, all patients were followed-up for at least 30 days. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted.

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Table 1
Clinical characteristics of 2,474 women with cancer and venous thromboembolism.

	N	Age	Pulmonary embolism	Metastases	Post-operative	Immobility ≥4 days	Non-provoked
Patients, N	*2474*	*68±14*	*1266 (51%)*	*1271 (51%)*	*380 (15%)*	*515 (21%)*	*1620 (65%)*
Breast	654	68±13	349 (53%)	284 (44%)‡	72 (11%)‡	102 (16%)‡	486 (74%)‡
Colorectal	324	71±12	154 (47%)	176 (55%)	85 (26%)‡	62 (19%)	183 (57%)‡
Uterus	229	66±15	104 (45%)	123 (55%)	39 (17%)	46 (20%)	147 (64%)
Haematologic	214	67±17	93 (44%)*	57 (33%)‡	9 (4.2%)‡	55 (26%)	151 (71%)
Lung	171	63±14	108 (63%)‡	132 (79%)‡	8 (4.7%)‡	36 (21%)	128 (75%)†
Ovary	167	63±14	100 (60%)*	112 (69%)‡	28 (17%)	30 (18%)	112 (67%)
Brain	131	63±14	74 (57%)	10 (7.9%)‡	51 (39%)‡	45 (34%)‡	41 (31%)‡
Pancreas	106	71±11	62 (59%)	85 (80%)‡	8 (7.5%)*	25 (24%)	75 (71%)
Stomach	97	69±13	48 (50%)	65 (68%)†	21 (22%)	26 (27%)	54 (56%)*
Unknown	94	72±14	43 (46%)	85 (93%)‡	1 (1.1%)‡	23 (25%)	70 (75%)
Bladder	50	78±10	20 (40%)	14 (28%)‡	12 (24%)	16 (32%)	24 (48%)*
Kidney	47	70±11	26 (55%)	26 (55%)	12 (26%)	13 (28%)	23 (49%)*
Biliary system	37	73±7	14 (38%)	30 (81%)‡	3 (8.1%)	6 (16%)	28 (76%)
Sarcoma	22	55±20	9 (41%)	15 (71%)	6 (27%)	3 (14%)	14 (64%)
Vulva–vagina	21	74±13	4 (19%)†	11 (58%)	0	7 (33%)	14 (67%)
Thyroid	16	68±14	9 (56%)	6 (38%)	5 (31%)	1 (6.3%)	10 (63%)
Skin	14	81±10	11 (79%)	3 (23%)*	2 (14%)	5 (36%)	8 (57%)
Oesophagus	13	66±13	7 (54%)	8 (62%)	2 (15%)	5 (39%)	7 (54%)
Ear–neck–larynx	12	67±13	8 (67%)	4 (33%)	6 (50%)†	0	6 (50%)
Melanoma	12	64±11	9 (75%)	7 (58%)	1 (8.3%)	2 (17%)	9 (75%)
Liver	11	70±14	1 (9.1%)†	5 (46%)	2 (18%)	2 (18%)	7 (64%)
Urothelium	6	73±10	3 (50%)	0*	3 (50%)*	1 (17%)	3 (50%)
Other	26	68±16	10 (38%)	13 (52%)	4 (15%)	4 (15%)	20 (77%)

Comparisons between patients with or without the variable: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

Each episode of clinically suspected recurrent DVT or PE was documented by repeat compression ultrasonography, venography, lung scanning, helical CT scan or pulmonary angiography.

Study endpoints

Only women with acute VTE and active cancer were considered for this study. The major outcomes were the development of fatal PE or fatal bleeding during the first 30 days of therapy. The causes of death were assigned by their attending physicians. Fatal PE, in the absence of autopsy, was defined as any death appearing shortly after PE diagnosis, in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring shortly after a major bleeding episode. Bleeding complications were classified as 'major' if they were overt and required a transfusion of 2 units of blood or more, or were retroperitoneal, spinal or intracranial, or when they were fatal.

Study variables and definitions

The following parameters were recorded in RIETE: patient's baseline characteristics; clinical status including any coexisting or underlying conditions; clinical characteristics of the malignancy (site, extent, time interval between diagnosis of cancer and diagnosis of VTE); additional risk factors for VTE; the treatment received upon VTE diagnosis; and the outcome during the first 3 months of therapy. For this study, only women with active cancer (defined as newly diagnosed cancer [up to 3 months before VTE diagnosis] or cancer that is being treated [i.e. surgery, chemotherapy, radiotherapy, hormonal, support therapy, or combined therapies] or have distant metastases) were considered. Immobilized patients were defined as non-surgical patients who had been immobilized (i.e., total bed rest with bathroom privileges) for ≥4 days in the 2-month period prior to VTE diagnosis. Surgical patients were defined as those who underwent surgery in the 2 months prior to VTE.

Statistical analysis

Odds ratios and corresponding 95% confidence intervals were calculated using the Epidat 3.1 program, and a p value <0.05 was considered to be statistically significant. The characteristics of the variables of women with a specific site of cancer were compared with those of other sites using the Student's t test or χ^2 test in case of quantitative or qualitative variables. These analyses were completed with the Statistical Package for Social Sciences (SPSS) program (version 13.0. for Windows, 2004 SPSS Inc. Chicago. IL, USA).

Results

Up to May 2010, 2474 women with cancer and acute VTE had been enrolled. The most common sites of cancer were the breast (26%), colon (13%), uterus (9.3%), haematologic (8.6%), lung (6.9%) and the ovary (6.8%). Their mean age was 68±14 years, 1266 (51%) initially presented as PE, 1271 (51%) had metastases, 380 (15%) had postoperative VTE, and 515 (21%) developed the VTE after immobilization for ≥4 days (Table 1).

Most patients (91%) received initial therapy with low-molecular-weight heparin (LMWH) at doses of 182±42 IU/kg/day. Then, 848 (34%) switched to vitamin K antagonists (Table II). During the 30-day study period 329 women (13%) died; of these 71 (2.9%) died of PE, 22 (0.9%) had fatal bleeding. Other common causes of death were: disseminated malignancy (4.3%), unknown reason (1.9%), respiratory insufficiency (0.9%), and infection (0.5%).

Fatal PE was thus the second most common cause of death, and it was particularly common in women with pancreatic cancer

Table 2
Treatment strategies and 30-day outcome

	N	Initial therapy, LMWH	Long-term therapy, LMWH	Overall death	Fatal PE	Fatal bleeding
Patients, N	*2474*	*2259 (91%)*	*1383 (56%)*	*329 (13%)*	*71 (2.9%)*	*22 (0.9%)*
Breast	654	598 (92%)	312 (50%)‡	46 (7.0%)‡	16 (2.4%)	0†
Colorectal	324	300 (93%)	189 (62%)	32 (9.9%)	11 (3.4%)	3 (0.9%)
Uterus	229	210 (93%)	138 (66%)	35 (15%)	6 (2.6%)	0
Haematologic	214	187 (%)*	93 (48%)‡	25 (12%)	4 (1.9%)	3 (1.4%)
Lung	171	153 (90%)	114 (77%)‡	30 (18%)	8 (4.7%)	1 (0.6%)
Ovary	167	156 (93%)	98 (64%)	21 (13%)	5 (3.0%)	3 (1.8%)
Brain	131	122 (93%)	85 (70%)*	12 (9.2%)	2 (1.5%)	1 (0.8%)
Pancreas	106	94 (89%)	67 (74%)*	34 (32%)‡	7 (6.6%)	1 (0.9%)
Stomach	97	92 (95%)	67 (77%)†	24 (25%)†	4 (4.1%)	2 (2.1%)
Unknown	94	84 (89%)	52 (66%)	29 (31%)‡	6 (6.4%)	3 (3.2%)*
Bladder	50	45 (92%)	26 (62%)	10 (20%)	0	2 (4.0%)
Kidney	47	46 (98%)	27 (60%)	5 (11%)	1 (2.1%)	0
Biliary system	37	36 (97%)	25 (76%)	8 (22%)	1 (2.7%)	1 (2.7%)
Sarcoma	22	20 (91%)	13 (62%)	1 (4.5%)	0	0
Vulva–vagina	21	19 (91%)	15 (75%)	4 (19%)	0	1 (4.8%)
Thyroid	16	15 (94%)	8 (53%)	0	0	0
Skin	14	11 (79%)	4 (31%)*	2 (14%)	0	0
Oesophagus	13	10 (77%)	9 (69%)	2 (15%)	0	0
Ear–neck–larynx	12	12 (100%)	5 (46%)	1 (8.3%)	0	0
Melanoma	12	9 (75%)	8 (80%)	2 (17%)	0	0
Liver	11	10 (91%)	6 (67%)	2 (18%)	0	1 (9.1%)
Urothelium	6	6 (100%)	4 (80%)	1 (17%)	0	0
Other	26	24 (92%)	18 (69%)	3 (12%)	0	0

Abbreviations: LMWH, low-molecular-weight heparin; PE, pulmonary embolism.
Comparisons between patients with or without the variable: *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.

(6.6%), carcinoma of unknown origin (6.4%) or lung cancer (4.7%). The incidence of fatal PE outweighed that of fatal bleeding in all subgroups, with the only exception of women with cancer of the bladder or in the vulva (Table 2). Fatal bleeding was more common in women with bladder cancer (4.0%) or carcinoma of unknown origin (3.2%). Interestingly, no women with breast cancer and only one in 171 women (0.6%) with lung cancer had fatal bleeding.

Discussion

Our data, obtained from a large prospective series of consecutive series of women with cancer and VTE, reveal that PE was the second cause of death in this patient population (accounting for one in every 4–5 deaths), and bleeding was the fourth cause (one in every 15 deaths). Interestingly, is some patients (those with breast or lung cancer) the risk of fatal PE clearly outweighed that of fatal bleeding, but in others (gastrointestinal, genitourinary or haematologic malignancies) both risks were more balanced.

Accumulating evidence suggests that both the intensity and duration of treatment should be tailored to the risk of recurrences or bleeding in an individual patient, particularly in those with cancer, renal insufficiency, or very elderly [10–15]. In the overall population of patients with VTE we recently reported that some variables at entry (age, recent bleeding, cancer, renal insufficiency, PE at baseline and anemia) may be useful to identify those at an increased risk for major or fatal bleeding [16,17]. However, in VTE patients with cancer the presence of anemia seems to have little influence on outcome. Alternatively, the presence of metastases and the time interval between diagnosis of cancer and diagnosis of VTE proved to have more influence on outcome. Thus, our findings may be of added value in comparison with a model applicable to all patients with VTE.

In this study, selection bias was avoided by including consecutive patients with objectively confirmed VTE, but it has potential limitations that should be addressed. First, the small percentage of events may imply overfitting, and hence overoptimistic results. Second, the risk of fatal PE or fatal bleeding is probably modified by characteristics that change during the course of therapy, such as differences in the intensity of anticoagulation when receiving anti-vitamin K drugs, the use of concomitant drugs, or the presence of intercurrent illnesses. Third, in RIETE we do not gather information on other potential risk factors, such as tumor histology and cancer treatment, that would likely influence the results.

In summary, we identified some differences in outcome according to the site of cancer that may help to identify those women with cancer and VTE at a higher risk for fatal PE or fatal bleeding. This information has to be validated in further studies in order to help clinicians to weigh the risks and benefits of prescribing long-term anticoagulant therapy in an individual patient.

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Conflict of Interest Statement

There are no conflicts of interest.

Appendix: RIETE Group

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References

[1] Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JGP, Büller HR. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: A retrospective analysis. J Clin Oncol 2000;18:3078–83.
[2] Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484–8.
[3] Geerts WH, Bergqvist D, Pineo GF, et al. American College of Chest Physicians. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):381S–453S.
[4] Kuijer PM, Hutten BA, Prins MH, Büller HR. Prediction of the risk of bleeding during anticoagulant treatment for venous thromboembolism. Arch Intern Med 1999;159:457–60.
[5] Monreal M, Falgá C, Valdés M, Suárez C, Gabriel F, Tolosa C, et al. For the RIETE Investigators. Fatal pulmonary embolism and fatal bleeding in cancer patients with venous thromboembolism: Findings from the RIETE Registry. J Thromb Haemost 2006;4:1950–6.
[6] Arcelus JI, Monreal M, Caprini JA, Gutiérrez Guisado J, Soto MJ, Núñez MJ, et al. Clinical presentation and time-course of postoperative venous thromboembolism: Results from the RIETE Registry. Thromb Haemost 2008;99:546–51.
[7] Muñoz FJ, Mismetti P, Poggio R, Valle R, Barrón M, Guil M, et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. Chest 2008;133:143–8.
[8] Trujillo-Santos J, Prandoni P, Rivron-Guillot K, Román P, Sánchez R, Tiberio G, et al. Clinical outcome in patients with venous thromboembolism and hidden cancer. Findings fro the RIETE Registry. J Thromb Haemost 2008;6:251–5.
[9] Laporte S, Mismetti P, Découssus H, Uresandi F, Otero R, Lobo JL, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism; Findings from the registro informatizado de la enfermedad tromboembólica venosa (RIETE) Registry. Circulation 2008;117:1711–6.
[10] López-Jiménez L, Montero M, González-Fajardo JA, Arcelus JI, Suárez C, Lobo JL, et al. For the RIETE investigators. Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE). Haematologica 2006;91:1046–51.
[11] Falgà C, Capdevila JA, Soler S, Rabuñal R, Sánchez JF, Gallego P, et al. For the RIETE Investigators. Clinical outcome of patients with venous thromboembolism and renal insufficiency. Findings from the RIETE Registry. Thromb Haemost 2007;98:771–6.
[12] Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med 1989;87:144–52.
[13] Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: Clinical epidemiology, prediction, and prevention. Am J Med 1993;95:315–28.
[14] White RH, Beyth RJ, Zhou H, Romano PS. Major bleeding after hospitalization for deep-venous thrombosis. Am J Med 1999;107:414–24.
[15] Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med 1999;159:445–53.
[16] Ruiz-Giménez N, Suárez C, González R, Nieto JA, Todolí JA, Sampériz AL, et al. Predictive variables for major bleeding in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost 2008;100:26–31.
[17] Nieto JA, Solano R, Ruiz-Ribó MD, Ruiz-Giménez N, Prandoni P, Kearon C, et al. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism. Findings from the RIETE Registry. J Thromb Haemost 2010;8:1216–22.