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Clinical outcomes in cancer patients with concurrent venous thromboembolism: findings from the RIETE registry

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In cancer patients who develop venous thromboembolism (VTE) the risk of death is more than threefold higher than in patients without cancer who have VTE[1-3] and in those with cancer but no VTE.[4] The high mortality rate in cancer patients with VTE is probably due to both the VTE and the fact that malignancies associated with VTE appear to follow a more aggressive course. Identifying clinical characteristics that put cancer patients with VTE at increased risk of death, either due to PE or bleeding complications, is important if their outcomes are to be improved.

The Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) was initiated in March 2001 to prospectively record the current clinical management of VTE in Spanish hospitals. It is an ongoing, multicenter, observational registry of consecutively enrolled patients designed to gather and analyze data on treatment patterns and clinical outcomes in patients with symptomatic, objectively confirmed, acute VTE.[5-9]

The aim of the present study was to analyze the clinical characteristics and 3-month clinical outcomes of the patients with cancer enrolled in RIETE to try to identify which cancer patients with VTE are at a higher risk of death from either pulmonary embolism (PE) or bleeding.

Patients and methods

Consecutive patients with symptomatic, acute deep-vein thrombosis (DVT) or PE, confirmed by objective tests (contrast venography, ultrasonography, or impedance plethysmography for suspected DVT; pulmonary angiography, lung scintigraphy, or helical computed tomography scan for suspected PE), are enrolled in RIETE. Patients are excluded if they are participating in a therapeutic clinical trial or if they are not available for the 3-month follow-up. After hospital discharge, all patients were followed-up for at least 3 months. During each visit, any signs or symptoms suggesting either DVT or PE recurrence or bleeding complications were noted. Each episode of clinically suspected recurrent DVT or PE was documented by repeat compression ultrasonography, venography, lung scanning, helical CT scan or pulmonary angiography. Fatal PE was defined as any death occurring shortly after PE diagnosis, in the absence of an alternative cause of death.

Odds ratios and corresponding 95% confidence intervals were calculated using Confidence Interval Analysis software (version 2.0.0), and a P value less than 0.05 was considered to be statistically significant. The significance of a number of clinical variables on the risk of death from either PE or bleeding complications was tested by fitting bivariate proportional hazard models. Candidate variables were selected from clinical variables based on published literature and on expert opinion. A logistic regression model was used to examine the individual relationship between each variable and the risk of death due to PE or bleeding. Those variables identified by the univariate analyses as potential risk factors and achieving a significance level of less than 0.05 were considered for inclusion in a multivariate logistic regression analysis to determine the independent nature of the risk factors, while adjusting for other characteristics. Multivariate analysis was performed using the Statistical Package for Social Sciences (SPSS) program (version 11.5; SPSS Inc., Chicago, IL, USA). Only variables associated with a significance <0.05 were retained in the final multivariate model.

Results

Up to September 2004, a total of 8,845 patients with symptomatic acute VTE were enrolled in RIETE, of whom 1,758 (20%) had cancer. During the 3-month follow-up period, the rates of fatal PE (odds ratio 1.8, 95% CI [confidence interval] 1.3–2.5, $p<.001$) and fatal bleeding (odds ratio 3.5, 95% CI 1.9–6.5, $p<.001$) were significantly higher in patients with cancer than in

those without cancer. During follow-up, 49 patients (2.8%) with cancer and VTE died due to PE. Of these patients, 35 died from their initial acute PE during the first week of follow-up, while 14 died from recurrent PE. Of patients with fatal PE, 19 (39%) had localized (non-metastatic) cancer. Univariate analysis of data from the 1,758 cancer patients with VTE revealed that a recent episode of major bleeding (within the previous 30 days), abnormal creatinine levels, recent immobilization, an initial diagnosis of PE, and metastatic cancer were associated with a significantly higher risk of fatal PE. Multivariate analysis confirmed that only abnormal creatinine levels, recent immobilization, symptomatic PE on admission, and metastatic cancer were independently associated with a significantly higher risk of fatal PE.

Furthermore, 19 patients (1.1%) developed fatal bleeding, of whom only 3 died during the first week after enrollment. The most common sites of bleeding were the gastrointestinal tract (11 patients) and intracranial (4 patients). Of these patients, 5 (26%) had non-metastatic cancer. Univariate analysis revealed that recent major bleeding, abnormal creatinine levels, use of non-steroidal anti-inflammatory drugs (NSAIDs), recent immobilization, and metastatic cancer were associated with a significantly higher risk of fatal bleeding. Multivariate analysis confirmed that only recent major bleeding, abnormal creatinine levels, recent immobilization, and metastatic cancer were independently associated with a significantly higher rate of fatal bleeding.

Discussion

A number of studies have shown that cancer patients with VTE have a worse clinical outcome than those without cancer.[1,3] The data in this analysis, obtained from a large prospective series of consecutively enrolled patients in the RIETE registry, confirm that there are important differences in the prognosis of patients with cancer and VTE: the incidence of fatal PE reported during the 3 months following their VTE diagnosis is almost twice that of patients without cancer, while the incidence of fatal bleeding is more than threefold higher. Furthermore, abnormal renal function, metastatic disease, and recent immobilization are factors independently associated with a significantly increased risk of both fatal PE and fatal bleeding. In addition, a recent episode of major bleeding and use of NSAIDs were found to be independent risk factors for fatal bleeding, while PE diagnosis on admission was an independent risk factor for fatal PE.

The influence of the majority of these conditions on the clinical outcome of VTE patients are well known. A recent major bleeding, renal insufficiency, and use of NSAIDs have all been associated with an increased risk of bleeding complications.[10-12] The increased risk of fatal PE in patients with these risk factors may be linked to the fact that lower doses of heparin are often used in such patients because physicians are concerned about safety. However, the increased rate of both fatal PE and fatal bleeding in non-surgical cancer patients with VTE and recent immobilization has not been previously reported.

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