

Variables Influencing Outcome in Cancer Patients with Venous Thromboembolism: Data from the RIETE Registry

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INTRODUCTION

Current guidelines from the American College of Chest Physicians, based on evidence from clinical trials, recommend that patients with venous thromboembolism (VTE) be treated initially with heparin, followed by long-term treatment with a vitamin K antagonist (VKA) [1]. However, patients with active cancer are often excluded from clinical trials of anticoagulant therapy because of short life expectancy, inability or unwillingness to attend for regular laboratory monitoring during VKA therapy, or contraindications to therapy, which means that treatment regimens based on the results from clinical trials might not be suitable for many VTE patients with cancer.

The “Registro Informatizado de la Enfermedad TromboEmbólica” (RIETE) was initiated in March 2001 to prospectively record the current clinical management of patients with symptomatic, objectively confirmed, acute VTE in Spanish hospitals. Currently it is an ongoing, international (Spain, France, Italy, Israel, Argentina and Brazil), observational registry of patients designed to gather and analyze data on treatment patterns and clinical outcomes in patients with VTE. So far it contains data from over 25,000 patients, followed-up for at least 3 months, from 186 hospitals.

The RIETE registry provides data on the treatment of VTE in a real-world situation with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies (and this is important because our patient population reflects routine, unmonitored medical practice involving a broad spectrum of patients with VTE). It can, therefore, provide insights into the natural history of

VTE in patients with cancer. It can also help to identify practices for providing treatment to patients, and factors associated with better or worse patient outcomes. Data from the registry are hypothesis-generating and provides feedback from real-world clinical situations which may be of help when designing new randomized clinical studies.

In this article we will review the influence of a number of variables on outcome during the first 3 months of anticoagulant therapy in cancer patients with VTE.

1. HIDDEN CANCER IN PATIENTS WITH VTE

Although usually developing in advanced stages of the disease, VTE may also appear before the cancer has become symptomatic and may lead to an earlier diagnosis of cancer. This association is greatest within the first few months after VTE, thus suggesting these cancers are present at the time of diagnosis. One clinical implication of a high risk of occult cancer in these patients could be an extensive diagnostic workup at the time of presentation. The usefulness and the extension of such screening has been long debated: while several investigators advise only a basic screening by means of a thorough clinical history, physical examination, simple laboratory tests and a chest X-ray [2], others advocate a more extensive workup [3, 4]. However, although extensive screening may result in early identification of hidden cancer, it is unknown whether the clinical course of these patients may be favourably influenced.

We compared the incidence of VTE recurrences, major bleeding complications, and death during the first 3 months of therapy, in patients with hidden cancer with those in whom no symptoms of cancer were noted [5]. Of 17,475 patients with acute VTE, 2852 (16%) had cancer diagnosed before VTE or during admission. Hidden cancer was detected in 178 (1.2%) of the remaining 14623 patients. The most common sites were the lung, prostate, and colon, or were haematologic malignancies, and 51% had metastases.

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Compared with patients in whom no symptoms of cancer were noted, those with hidden cancer had an increased incidence of recurrent VTE (11.4% vs 2.1%; $p < 0.001$), major bleeding (5.1% vs 2.1%; $p = 0.007$), and mortality (20% vs 5.4%; $p < 0.001$).

Our data reveal that VTE patients with hidden cancer have an increased incidence of recurrent VTE, major bleeding or death, compared with those in whom no symptoms of cancer were noted. Four randomized trials have demonstrated that LMWH can be used for the long-term therapy of VTE, resulting in significantly reduced rates of recurrent VTE compared with standard oral anticoagulation, without any increase in bleeding [6-9]. Accordingly, we hypothesize that early detection of cancer has the potential to identify a subgroup of patients who may benefit from the long-term LMWH therapy instead of anti-vitamin K drugs.

2. PREDICTING RECURRENCES OR MAJOR BLEEDING COMPLICATIONS

Cancer patients with VTE have an increased incidence of VTE recurrences and anticoagulant-related bleeding complications compared with those without cancer [10-13]. Reliable information on the factors determining the risk for VTE recurrences or major bleeding complications 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. A number of variables (including age, cancer, renal insufficiency, recent bleeding or the clinical presentation of VTE) have been associated with a worse outcome in patients with VTE. However, those with cancer are an heterogeneous group due to differences in tumor site, therapy, extent or time interval between diagnosis of cancer and diagnosis of VTE. Some of these variables might also influence the outcome in cancer patients with VTE.

Up to May 2007, 3805 cancer patients had been enrolled in RIETE. During the first 3 months of follow-up after the acute, index VTE event, 90 (2.4%) patients developed recurrent PE, 100 (2.6%) recurrent DVT, 156 (4.1%) had major bleeding [14]. Forty patients (44%) died of the recurrent PE, 46 (29%) of bleeding. On multivariate analysis, patients aged < 65 years (odds ratio: 3.0; 95% CI: 1.9-4.9), with PE at entry (odds ratio: 1.9; 95% CI: 1.2-3.1), or with < 3 months from cancer diagnosis to VTE (odds ratio: 2.0; 95% CI: 1.2-3.2) had an increased incidence of recurrent PE. Those aged < 65 years (odds ratio: 1.6; 95% CI: 1.0-2.4) or with < 3 months from cancer diagnosis (odds ratio: 2.4; 95% CI: 1.5-3.6) had an increased incidence of recurrent DVT. Finally, patients with immobility (odds ratio: 1.8; 95% CI: 1.2-2.7), metastases (odds ratio: 1.6; 95% CI: 1.1-2.3), recent bleeding (odds ratio: 2.4; 95% CI: 1.1-5.1), or with creatinine clearance < 30 mL/min (odds ratio: 2.2; 95% CI: 1.5-3.4), had an increased incidence of major bleeding.

Our data reveal that with some variables available at entry it is possible to identify those patients at an increased risk for VTE recurrences or major bleeding during the first three months of anticoagulant therapy. In our series, recurrent PE appeared in 2.4% of patients, and 44% of them died. Major bleeding occurred in 4.1%, and 29% also died. Thus, its clinical impact is considerable. Our findings may be of

added value in comparison with a model applicable to all patients with VTE. Interestingly, we failed to find any influence of the tumor site on outcome. On univariate analysis patients with breast cancer bled less often, and those with lung cancer recurred more often, but these differences disappeared on multivariate analysis. This information has to be validated in further studies in order to help clinicians to weigh the risks and benefits of prescribing anticoagulant therapy in an individual patient.

3. ELEVATED WHITE BLOOD CELL COUNT AND OUTCOME

Accurate prediction of survival is necessary, especially in helping to avoid harm, discomfort, inappropriate therapies or to avoid unnecessary toxicity in terminally ill patients. Additionally, important personal decisions are influenced by prognostic information, and therefore, patients' autonomy can be enhanced by providing better prognostication [15]. However, prognostic accuracy in patients with cancer seems to be the exception rather than the rule [16]. Traditional prognostic factors (i.e., cancer stage, site, or patient status) can reasonably predict survival in early-stage disease but do not provide an adequate short-term prognosis in patients with advanced cancer [17, 18]. A significant association between elevated white blood cell (WBC) count and mortality in patients with cancer has been reported, but the predictive value of elevated WBC on mortality in cancer patients with acute VTE has not been explored. We compared the 3-month outcome of cancer patients with acute VTE according to their WBC count at baseline [19].

As of May 2007, 3805 patients with active cancer and acute VTE had been enrolled in RIETE. Of them, 215 (5.7%) had low- ($< 4,000$ cells/ μ l), 2403 (63%) normal- (4,000-11,000 cells/ μ l), 1187 (31%) elevated ($> 11,000$ cells/ μ l) WBC count. During the study period 190 patients (5.0%) had recurrent VTE, 156 (4.1%) major bleeding, 889 (23%) died (399 of disseminated cancer, 113 of PE, 46 of bleeding). Patients with elevated WBC count at baseline had an increased incidence of recurrent VTE (odds ratio: 1.6; 95% CI: 1.2-2.2), major bleeding (odds ratio: 1.5; 95% CI: 1.1-2.1) or death (odds ratio: 2.7; 95% CI: 2.3-3.2). Most of the reported causes of death were significantly more frequent in patients with elevated WBC count. Multivariate analysis confirmed that elevated WBC count was independently associated with an increased incidence of all three complications.

Our data reveal that cancer patients with elevated WBC count at the moment of VTE had an increased incidence of VTE recurrences, major bleeding or death than those with normal WBC count. This worse outcome was consistent among subgroups (i.e., clinical presentation as DVT or PE, spread of the malignancy) and persisted after multivariate adjustment. Interestingly, most of the reported causes of death (not only fatal PE or fatal bleeding) were more frequent in patients with elevated WBC count. To our knowledge, this is the first prospective study to demonstrate the relationship between WBC count and outcome in cancer patients with acute VTE. Accordingly, we suggest including—at least tentatively—the WBC count in future scores aiming at predicting outcome of cancer patients suffering from a VTE event.

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