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Risk factors of occult malignancy in patients with unprovoked venous thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) can occur as the first manifestation of an underlying occult malignancy. It remains unclear whether or not a better selection of high risk patients might lead to more efficient occult cancer screening strategies.

Our aim was to assess the predictors of occult malignancy diagnosis in patients with unprovoked VTE.

Univariate analyses were performed to assess the effect of candidate predictors on occult cancer detection in patients enrolled in a prospective, multicenter, randomized, controlled study (MVTEP study) whose primary aim was to compare a limited screening strategy with a strategy combining limited screening and FDG PET/CT in patients with unprovoked VTE. This trial is completed and registered with ClinicalTrials.gov, number NCT00964275.

Between March 3, 2009, and August 18, 2012, 399 patients were included. Five patients withdrew consent and refused the use of their data, and no VTE was confirmed in 2 patients who were excluded from this analysis. A total of 25 (6.4%) out of the 392 analysed patients received a new diagnosis of malignancyduring the 2-years follow-up. Age ≥ 50 years ($p = 0.01$), male gender ($p = 0.04$), leukocytes count (p = 0.01), and platelets count ($p = 0.03$) were associated with occult cancer detection. Patients with leukocytosis or thrombocytosis had a risk of cancer way above 10%. Previous VTE and smoker status (combining previous and current smokers) were not associated with occult cancer diagnosis ($p > 0.05$).

Demographic characteristics (age and sex), and laboratory tests (high platelets and leukocytes counts) may be associated with cancer detection in patients withunprovoked VTE.

Introduction

Venous thromboembolism (VTE) can occur as the first manifestation of an underlying occult malignancy [1]. It was previously demonstrated that between 6% to 15% of patients presenting with unprovoked VTE will be diagnosed with cancer in the year following the diagnosis of an unprovoked VTE episode (i.e. venous thromboembolism not provoked by a major risk factor) [2–8]. However, recently published studies indicate a lower incidence of occult cancer in this population of patients, with an incidence of about6% [9,10].

Screening for occult malignancy at the time of VTE is appealing, with the hope to be able to detect and treat these malignancies as early

Abbreviations: ALK, alkaline phosphatase; ALT, alanine amino transferase; DVT, Deep Vein Thrombosis; FDG PET/CT, ^{18}F–Fluorodesoxyglucose Positron-Emission-Tomography combined with Computed-Tomography; GGT, gamma-glutamyl transpeptidase; PE, Pulmonary Embolism; VTE, Venous Thromboembolism

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as possible in order to improve prognosis. Clear guidelines for the investigation of occult malignancy after unprovoked VTE are not yet available. Different screening strategies have been proposed [9–13]. However, recently published studies have reported that an extensive screening does not provide clinically valuable benefit for patients [9–11]. Moreover, the low incidence of cancer in those studies limits the clinical relevance and cost efficacy of extensive cancer screening. It remains unclear whether or not selecting"high risk"patients might lead to more efficient occult cancer screening strategies.

To fill this knowledge gap, the aim of this study was to assess the predictors of occult malignancy diagnosis in a population of patients with unprovoked VTE enrolled in the MVTEP study.

Methods

Study population.

This is a post-hoc analysis of an open label, multicenter, randomized study that compared a screening strategy based on FDG PET/CT with a limited screening strategy for detection of occult malignant disease in patients with unprovoked VTE. Methods have been previously described in detail [10].

Patients aged 18 years or older, diagnosed with unprovoked VTE were invited to participate in the study if they did not present any exclusion criteria: ongoing pregnancy, active malignancy (defined as known malignancy, active and/or treated during the previous five years), unable or unwilling to give consent.

Study design.

Patients were randomized into two arms. In the limited screening arm, patients underwent medical history, complete physical examination, routine laboratory tests including complete blood count, erythrocyte sedimentation rate or C-reactive protein, transaminases, alkaline phosphatase, calcium, chest X-ray, and recommended age- and gender-specific cancer screening tests (i.e. prostate-specific antigen in men over 50 years of age, mammography in women over 50 years of age and Pap-smear in all women). In the limited plus FDG PET/CT arm, patients underwent the same limited screening plus a FDG PET/CT. In case of positive finding on initial screening, patients were referred for appropriate diagnostic procedures at the discretion of the treating physician.

All patients underwent clinical follow-up every 6 months for 24 months. All patients provided written informed consent. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki, Good Clinical Practice, and relevant French regulations regarding ethics and data protection. The protocol was approved for all study sites by our institutional Ethics committee (Comité de Protection des Personnes Ouest VI, 2008–541). The study was registered on clinicaltrials.gov (NCT00964275).

Risk factors analysis.

The impact of the following candidate predictors on occult cancer detection were analysed: demographic characteristics (age and sex), episode of VTE (deep vein thrombosis (DVT), pulmonary embolism (PE) ± deep vein thrombosis), medical history (tobacco use combining previous and current smokers), oral contraceptives, familial history of cancer, previous malignancy, prior VTE, alcohol intoxication (> 3 standard drinks per day (30 g) for men, > 2 standard drinks per day (20 g) for women), asbestos exposition, asthenia and anorexia), laboratory tests (hemoglobin, hematocrit, leukocytes, platelets, liver function tests (alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and alkaline phosphatase (ALK)).

Statistical analysis

General characteristics of the population were described using median (IQR) or numbers and proportions, as appropriate. We conducted univariate analyses of the association between each of the predictors and cancer diagnosis, using chi-2 test or Fischer exact test when appropriate for categorical variables and Student *t*-test for continuous variables. All analyses were performed using IBM SPSS Statistics (version 24.0).

Table 1
General characteristics of the population.

Characteristics	*N* = 392
Age, years	63 (49–76)
50 years or older	291 (74%)
Sex	
Male	206 (53%)
Female	186 (47%)
Venous thromboembolism	71 (18%)
- Deep vein thrombosis (DVT)	
- Pulmonary embolism (PE) ± DVT	321 (82%)
Tobacco use	67 (17%)
Oral contraceptives	25 (6%)
Familial history of cancer	128 (33%)
Previous malignant disease	22 (6%)
Previous venous thromboembolism	116 (30%)
Alcohol intoxication	34 (9%)
Asbestos exposition	27 (7%)
Asthenia	52 (13%)
Anorexia	7 (2%)

Results

Between March 3, 2009, and August 18, 2012, 748 patients were assessed for eligibility, and 399 were included and randomized to one of the two study groups. 200 patients were allocated to the FDG PET/CT group, and 199 to the limited screening group. Five patients, three in the FDG PET/CT group and two in the limited screening group, withdrew consent and refused the use of their data. In two patients of the FDG PET/CT group, no venous thromboembolism was confirmed, these two patients were excluded from this analysis.Thus, 392 patients were analysed.

General characteristics of the population are presented in Table 1. Median age was 63 years (IQR 49–76).

(Abbreviations: DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism).

A total of 25 (6.4%) out of the 392 analysed patients received a new diagnosis of malignancy at initial screening and during the 2-year follow-up. In our population, 24 out of the 25 occult cancers were diagnosed in patients aged 50 years or more.

The association between potential predictors and cancer is shown in Table 2. Age ≥ 50 years and male gender were associated with occult cancer detection ($p < 0.05$). Complete blood counts and liver function tests were available in 386 patients (98%) and in 336 patients (86%) respectively. Leukocytes count (missing values, $n = 9$) and platelets count (missing values, $n = 6$) were associated with occult cancer diagnosis ($p < 0.05$).

Type of VTE, medical history (oral contraceptives, familial history of cancer, previous malignancy, prior VTE, smoker status, alcohol intoxication, asbestos exposition, asthenia and anorexia), other laboratory tests (hemoglobin, hematocrit, liver function tests) were not associated with occult cancer ($p > 0.05$).

(*: statistically significant difference).

(Abbreviations: ALK: alkaline phosphatase; ALT: alanine aminotransferase; DVT: Deep Vein Thrombosis; GGT: gamma-glutamyltranspeptidase; PE: Pulmonary Embolism).

Risk of occult cancer in patients with unprovoked VTE based on gender, age, leukocytes and platelets counts are shown in Table 3. Patients with leukocytosis (≥ 10G/l) had a risk of cancer of 12.9% (12/93), and patients with thrombocytosis (≥ 350G/l) had a risk of cancer of 15.4% (6/39).